It is now more than 300 years since Harvey described the circulation of the blood. Three hundred years is not a long time, but it includes, according to historians, more than 90 per cent of the recorded scientific achievements of man. During these 300 years enormous effort has been expended in attempting to understand the properties and behavior of the cardiovascular system. It is perhaps significant in considering this effort, which was participated in by some of the world's most outstanding scientists, that we do not have a clue to the etiology of the major diseases of the cardiovascular system. Indeed, we cannot elaborate a reliable physiologic explanation for the cardiovascular response to any of man's stresses, such as exercise for example.

In sharp contrast to this lack of a satisfactory concept of how the system works as a system, much is known about the properties and behavior of a myriad of the pieces and parts that comprise the cardiovascular system (fig. 1).

A great stride in understanding the cardiovascular system would be made if we could put the pieces together instead of becoming lost among them. Putting pieces together implies that there is some logical arrangement into which they naturally fit. One way in which the behavior and properties of the cardiovascular system can be organized into a logical pattern is with regard to its regulation. To do this we must first define what we mean by regulation. We have chosen to adopt the definition of regulation used by most engineers, physical scientists, and many biologists. I am told that this rigorous definition is also applied by many sociologists and economists.

The principles of a regulated system can be illustrated by considering the regulation of the temperature of a house. Figure 2 is a schematic drawing representing the elements of a system that has been designed to regulate the temperature of a house. On the left wall of the house is a thermostat, which consists of 3 basic parts: a device to measure the actual temperature of the interior of the house (thermometer), a device that allows the occupant of the house to "set" the desired temperature, and a device that will generate some kind of signal (e.g., an electric voltage) that is proportional to the difference between the "set" temperature and the real temperature. This signal is called the "error," i.e., the error between the real temperature and the set temperature. The regulatory system is designed toward minimizing the error between the ideal or set temperature and the actual temperature, i.e., to regulate the temperature around the ideal value. The error signal from the

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thermostat then commands or controls the heat-producing device (furnace) and the heat-dissipating device (window). In this case, heat production is governed by controlling the motor that turns the valve, hence determining the fuel supply to the furnace. Heat dissipation is controlled by the motor that turns the gears, thus opening or closing the window. Thus, if the temperature is too low, i.e., lower than the "set" temperature, the thermostat generates an error signal that increases heat production and decreases the heat loss, hence raising the temperature of the house. Conversely, if the temperature is too high, an error signal commands the furnace and window mechanisms in such a way that the temperature will fall until it reaches the ideal level. Thus, it can be seen that the error may be either negative or positive and that there are mechanisms that can drive the temperature up or down.

There are certain important characteristics that must be present in such a system in order to establish that a function is regulated by the system:

1. We must identify the character of the function that is being regulated. In this case, it is the temperature of the interior of the house at the site of the thermometer.

2. The system must possess a mechanism for measuring the function that is being regulated, i.e., a sensor or receptor is required. In this case, it is a thermometer for measuring temperature.

3. The system must possess a device for setting the desired value of the regulated function. This value is called the ideal or "set" value. In this case, it is the temperature level selected by the occupant of the house and it is put into the thermostat by the setting of a dial.

4. The system must contain a device for comparing the real and ideal value and for generating a coded signal that is proportional to the difference.

5. The system must contain devices for changing the magnitude of the controlled function. In this case, for changing the temperature of the house, i.e., furnace and window.

6. In such a system all these functions are connected in the form of a closed loop or circuit. The furnace and window mechanisms are connected to the thermostat by wires and the thermostat is connected to the furnace and windows by the temperature of the air in the room.

7. The system should behave so that if the
magnitude of the regulated function is displaced from the ideal or set value, the system will respond so as to return the magnitude toward its ideal or set value. Furthermore, if the closed loop is opened or cut, the regulation will not persist.

It should be noted that the function of the circuit or closed loop arrangement of the system is to "feed" the value of the regulated variable "back" into the system in such a direction that the value of the variable (e.g., temperature) is controlled in such a way as to minimize the error. In other words, the variable itself is used to furnish the information by which control of itself is achieved and therefore it can be regulated. This form of feedback is called "negative feedback." If the direction of the feedback is such that the magnitude of the error is increased, e.g., by increasing the output of the furnace when the temperature rises, the process is called positive feedback.

Figure 3 is a schema that identifies the aspects of a regulatory system and indicates the form of the circuit or closed loop. Most regulatory systems perform their function by means of negative feedback. This applies to biologic systems as well as man-made systems. I should like to emphasize the difference in meaning between regulation and control: temperature is regulated, but the mechanisms (such as the furnace and window) for determining temperature are controlled. Another phenomenon that might be confused with reg-

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**Figure 3**
Schematic drawing of the general properties of a regulation system in order to emphasize its closed loop or circuit aspect. For description, see text.

**Figure 4**
Essentials of a "black box." Only the relationships between the input and output are considered. This relationship is called the transfer function. The mechanisms by which the output and input are related (transfer function) are the mechanism implied in the black box and are indicated by the diagonal line. For example, if \( x = \text{the input} \) and \( y = \text{the output} \), then \( y = 5x \) then the black box contains a mechanism for multiplying the input by 5 to get the output.
Schematic drawing of a temperature regulatory system for a house. The function of each element or black box according to its number is:

**Input**

1. Error signal (i)
2. Rotation of fuel valve motor (θ₁)
3. Heat (H) to air
4. Error signal (i)
5. Rotation of window motor (θ₂)
6. Heat loss (−H)
7. Temperature of room (T) determined by the relative amount of heat loss and heat production
8. Temperature of room (T)
9. Movement of mercury (X)
10. Coded information indicating temperature of the room is compared to coded information from the ideal temperature setting box
11. Setting of thermostat dial (X)
12. Distribution of error signal (i) to furnace and window motor

**Output**

- Rotation of fuel valve motor (θ₁)
- Heat production by furnace (+H)
- Temperature rise (+T)
- Rotation of window motor (θ₂)
- Heat loss from window (−H)
- Temperature drop (−T)
- Temperature of room (T) determined by the relative amount of heat loss and heat production
- Movement of mercury in thermometer (X)
- Signal that indicates mercury movement with respect to temperature (iₙ)
- Coded information indicating temperature of the room is compared to coded information from the ideal temperature setting box
- Coded information about setting (iₙ)
- Distribution of error signal (i) to furnace and window motor

I should like to introduce a scheme to this symposium that is used by many scientists and engineers. The scheme involves the use of what are called “black boxes.” A black box is an imaginary structure that carries out some function without indicating how the function is performed. Thus, only what goes into and what comes out of the box are considered. The advantage of the concept of the black box is that it identifies the function being considered in terms of what it puts out with respect to what it takes in, rather than how it does it. Figure 4 represents such a black box.

The black-box concept also suggests a very common technique of scientific thinking. Most
often a scientist begins his investigation of a system by considering what it does, i.e., its input and output, rather than by how it does it. Scientists call the functional relationship between input and output the **transfer function**. They may also develop their own input or stimulus, and then measure the system’s output or response to that stimulus. The black box can represent any scale of nature, e.g., from an atom to the universe. It may, for example, represent the furnace in which the input is fuel and the output is heat, or it may represent the fuel valve in which the input is an error signal from the thermostat and the output is the degree of opening of the valve. Figure 5 is an example of how the regulation of temperature of the house may be represented using black boxes. Any number of black boxes can be put into the scheme, depending upon the number of elements one wishes to consider. The closed-loop arrangement, which is one of our requirements of a regulation system, is apparent.

Many functions of the cardiovascular system have been said to be regulated. Some of these are indicated in figure 6. It is the purpose of this symposium to examine certain of these concepts in the light of today’s knowledge, 300 years after Harvey, and to see how the pieces fit together—which pieces are missing and to consider whether, indeed, these functions are regulated. The considerations are all germane to our basic understanding of normal and abnormal cardiovascular functions.

I have been asked to act as a moderator; I am not sure how a moderator fits into the schema of regulation. An analogy that troubles me is that the nerve bundles coming from the aortic arch and carotid sinus regions have been called moderator nerves, but they have also been called depressor nerves; to avoid the latter function, I shall merely serve to introduce the subject of this symposium and complete my role as moderator by outlining the schedule of the symposium.

**Summario in Interlingua**

In su remarques de introduction al presente symposio super le regulation del sistema cardiovascular, le autor lista le characteristicas que debe esser presente in un sistema particular ante que on pote asserer que un function particular es regulate per ille sistema.

1. Nos debe identificar le natura del function que se trova sub regulation.
2. Le sistema debe posseder un mechanismo pro le mesurasion del function que se trova sub regulation, i.e., un sensor o receptor es requisite.
3. Le sistema debe posseder un dispositivo pro fixar le desirato valor del function que se trova sub regulation. Iste valor es le "valor ideal."
4. Le sistema debe contener un dispositivo pro comparar le valor real e le valor ideal e pro generar un signal cifrato que es proportional al differentia inter le duo.
5. Le sistema debe contener dispositivos pro alterar le magnitude del function sub regulation.
6. In un tal sistema, omne le mentionate functiones es connectite in le forma de un circuito claudite.

7. Le sistema debe comportar se de maniera que quando le magnitude del function sub regulation es diaplanata ab le valor ideal, su responsa resulta in le retorno de ille magnitude a su valor ideal. In plus, si le circuito es aperite o disrupmite, le regulation non pote persistere.

In iste senso, multe functiones del sistema cardiovascular ha esse considere como regulate. Un lista de tales es presentate per le autor, incluse illos que forma le themas individual del presente symposio.