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**A REVIEW OF MODELS OF THE  
HUMAN TEMPERATURE  
REGULATION SYSTEM**

L. G. Meyer

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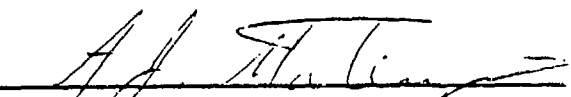


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## PREFACE

This review was undertaken as a preliminary investigation for the project entitled "Development of a Model to Predict the Endocrine and Circulatory Response to Cold." The model was developed as an independent research project, which resulted from an earlier study, "Endocrine and Circulatory Response to Acute Cold Exposure." Much of the credit for personal assistance and support in pursuing this work goes to Dr. W. G. Lotz and Dr. S. E. Shamma.

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## ABSTRACT

Over the last 100 years, models of temperature regulation have improved our understanding of the body's response to cold as much as scientific experimentation. Models have taken many forms, that is, verbal, pictorial, mechanical, mathematical, and have always been used to predict the body's thermal behavior in changing environmental conditions. Some models have been based on experimental data and some on theories of thermodynamics. As science has advanced, models have become increasingly more complex. However, the use of powerful, high-speed computers has enabled simulations to achieve a formidable level of predictability.

Despite the increasing number and sophistication of models of temperature regulation, we have not reached the point where the computer simulation predicts accurately and entirely the complex interactions of the human body. There are many gaps to be filled. This review highlights the development of different models of the biological process of temperature regulation. The objective is to demonstrate the remarkable achievements of models as contributions to the advancement of our knowledge of human temperature regulation, while, at the same time, suggest the need for more explicit and accurate models that include important and previously excluded interactions between physiological systems, such as the cardiovascular and endocrine systems.

## INTRODUCTION

The human temperature regulatory system is a complex of interrelated physiological functions that cannot be investigated entirely in the laboratory. The large number of variables and the numerous feedback control loops prohibit adequate research of all possible integrated mechanisms and responses. Additionally, ethical concerns for humans and animals limit the range of temperatures and time of exposure for experimentation. Yet, there is a need to extrapolate beyond permissible limits and examine combinations of specific components of these physiological reactions.

Models of temperature regulation in man have been used for both the theoretical analysis of experimental results and the evaluation of hypothetical concepts. Models provide insight into the fundamental mechanisms and formulation and tests of hypotheses together with experimental programs. Interest in the problem of biological temperature regulation is shared by engineers, biologists, psychologists, and physicians. The one area that provides a common meeting of these different points of view and allows the researcher unlimited latitude is the modeling of temperature regulation. Recent reviews (1-6) list over 250 papers and book chapters describing models of the human temperature regulatory system alone. Some models have been based on experimental results while others have been designed on theories of thermodynamics and transport processes. These models generally predict human temperature regulatory responses of the entire body or parts of it. Most models apply to a very restricted aspect of a particular system even though they may serve a variety of purposes. Often, there is a lack of data to validate the model.

A mathematical model has been defined as one that can be described symbolically and discussed deductively (7). Rather than describing the system, the model depicts the behavior of the system. Bligh (4) defines a mathematical model as "essentially a description of the relations between disturbance and response in very restricted experimental circumstances," yielding little insight into the nature of the controlling and the controlled aspects of the system. Often, a typical model of a complex biological system qualitatively characterizes the system in a single diagram that would otherwise require a lengthy mathematical or verbal explanation. The model becomes quantitative only when the system can be described mathematically. However, for researchers of temperature regulation, mathematical models have proved difficult because of the limitations in solving complex nonlinear equations in the explanation of the data. Fortunately, computers have made it possible to overcome this problem, and several valid mathematical models exist that reasonably explain the physiological responses to cold.

Grodins' (8) concept of a scientific model is much broader. His scheme depicts a science servosystem that compresses the maximum number of observations into the minimum number of conceptual principles (Fig. 1). This closed-loop system relies on valid and reliable observations of the real world which can be tested to obtain implications which then can be compared to nature. Grodins identifies a number of forms in which models can be expressed (Fig. 2). He suggests that the powerful and highly developed mathematical

model may be the best way to describe a system and understand its output. His diagram on the nature of the content of models is shown in Fig. 3. Grodins emphasizes in this conceptual scheme that physiological and engineering models are usually synthetic, that is, either empirical or theoretical, while an analytical model involves the building of a new structure or process as in theoretical physics.

A modification of Grodins' process for developing and using models in the study of temperature regulation is presented in Fig. 4 (3). This illustrates the particular types of models developed for temperature regulation and how they are used to make a comparison of the concept with the real world. As indicated, the experimenter has the option of the type of model to synthesize based on assumptions and personal satisfaction with the model. By continually conducting experiments to challenge the model and building new models, the researcher will benefit optimally from its use. It appears that this process has been successfully employed for many years by many scientists without much thought to what constituted modelling.

Early scientists used the word sparingly to describe their work, even though what they had accomplished was, in fact, modelling. In the last 30 years, there has been a dramatic increase in the popularity of describing a scientific system in terms of a model. A search of the recent literature finds that between 1960 and 1990, over 2500 papers with the word "model" in the title were published. Therefore, the increase in the modeling of temperature regulation seems to parallel the modeling trend in biological research in general.

Much has been published concerning the physiology of the human temperature regulatory system. There have been a number of comprehensive reviews that list more than 1500 papers and present a critical assessment of the historical development and current status of the work in that field (9-27). Over the last 40 years, many excellent reviews have dealt specifically with temperature regulation during exercise (28-56). Special treatment of the cardiovascular adjustments to exercise and thermal stress can be found in several recent reviews (24,25,41,57). Endocrine and neuroendocrine responses to cold stress and exercise in the cold have been sufficiently reviewed in previous reports (58-66).

This monograph reviews models of temperature regulation. Emphasis is placed on the physiological response to cold stress. The object is to discuss the contributions of models to our knowledge of the human temperature regulatory system while demonstrating that there is yet room for more complex and physiologically accurate models. Models will be discussed according to their classification, that is, pictorial, verbal, physical, neuronal, and mathematical.

## **BASIC TEMPERATURE REGULATORY CONTROL SYSTEMS**

The basic concept of a feedback or closed-loop control system (servosystem) can be depicted by the block diagram shown in Fig. 5 (67). The basic negative feedback control system contains an error detector, control

elements, a controlled system, and the feedback elements. The human temperature regulatory system is shown in a modification of a simple block diagram of short-term exposure to heat, cold, and exercise, Fig. 6 (68). Metabolic heat and environmental heat or cold displace body heat capacitance, which alters body temperature, the controlled variable. Hormonal or neuronal feedback information is then compared to reference information with the difference resulting in an error variable. The error stimulates a control center, which produces an opposing controlling action, shivering, sweating, or vasomotor action, which then modifies the regulated system with heat production or heat loss. A schematic of a long-term yet simple temperature regulating system is shown in Fig. 7 (69). The major feature of this diagram is the inclusion of adaptive changes affecting both the controlling and controlled parts of the system.

Central and peripheral sensors are incorporated in the block diagram in Fig. 8 (70). The central sensors are defined primarily as feedback controllers. The peripheral sensors, on the other hand, receive input from the environment and provide afferent information to the brain. In this figure, feedforward loops within the controllers are identified as II. Controlling action of the feedforward loop results from a combination of a time derivative of skin temperature and surface area of the exposed skin.

A scheme for the controlling and controlled systems for the regulation of internal body temperature is illustrated in Fig. 9 (13). This diagram portrays the involvement of the central temperature-sensitive structures, the thalamus, hypothalamus, cortex, and ascending reticular activating system in human temperature regulation. Additionally, endocrine and behavioral responses are portrayed in the controlling system. However, the roles of the receptors in the hypothalamus, the skin and subcutaneous areas, and other less well-defined areas of the body in the regulation of heat conductance and sweating during exposure to heat are controversial.

Some researchers claimed that temperature regulatory mechanisms are controlled solely by the temperature of the hypothalamic receptors (10). Conversely, many considered the temperature of the skin as the predominant influence on temperature regulation (71-73). Hardy (9) suggested that both the hypothalamus and the skin, and other regions of the body, harbored temperature receptors equally important in regulating temperature. Another report (74) also showed that both peripheral and central receptors played a role in regulation but that the temperature of the central receptors was more important. In support of this theory, Stolwijk and Hardy (69) concluded that the temperature receptors in the hypothalamus are about four times as effective as the receptors in the skin when exposed to heat and measuring sweat rate and heat conductance.

## VERBAL MODELS

The first models to be used were verbal models. The source and maintenance of body heat were speculated long before thermometry appeared in physiology early in the 17th century. In 1780, Lavoisier explained the source of body heat as due to the oxidation of food (3). Nearly 100 years later,

Claude Bernard stressed the importance of the biological regulation of the "milieu interieur" (75). At the same time, the brain was identified as important in temperature regulation from experiments on warm-blooded animals (76,77). Ott's concept (77) included "thermotaxic centers," which composed the thermogenic, thermoinhibitory, and thermolytic centers involved in temperature regulation.

Another early verbal model identified the ranges of ambient temperature that were thought to elicit chemical, physical, and metabolic regulation (78). Many of these concepts continue to be used to this day. Rubner (78) was also the first to relate the first law of thermodynamics to animal metabolism. Today, the study of energy balance during "negative" work begins with the first law and is based on the fact that energy may change form but none is created or lost in the process. In 1912, Barbour demonstrated for the first time that the hypothalamus actually functioned as a thermostat (79). Later work more clearly identified the functions of the central nervous system in temperature regulation (80-82).

An important verbal model that clearly restated much of Ott's concepts in modern terms proposed two sets of antagonistic functions with separate but integrated centers designated as warm (thermogenic) and cold (thermolytic) (83). In two separate studies, Bazett and Benzinger furthered Meyer's general concept, which resulted in the Ott-Meyer verbal model of temperature control accepted as the explanation of human temperature regulation and used widely in medical schools for years (84,85).

Verbal models have been used at one time or another by everyone interested in the problem of temperature regulation. The difficulty with verbal models is in qualitatively and quantitatively prioritizing one model ahead of another. It is virtually impossible to exclude other reasonable explanations for the control and regulation of body temperature because of the innate complexity of the system. Verbal models of temperature regulation become comparable and valid only when described in mathematical terms.

### PICTORIAL MODELS

No model is more effective as a teaching device than the pictorial model. The general purpose of a pictorial model is to merge the biological and conceptual components of a model in an easily comprehensible form (3). Though the concept of a pictorial model is often not contained in the diagram, anatomical and physiological arrangements of the components of the system are usually indicated. Therefore, anatomical sketches and block diagrams can be included under this heading.

One of the first pictorial models, Fig. 10, depicted the neurophysiological components of the temperature regulatory system and its connection to some of the control elements, sweat glands, blood vessels, and skeletal muscles (86). This model contained the basic knowledge of what is known today of the neurophysiology of temperature regulation. A subsequent model showed in more detail many physiological functions and processes with both stimulatory and inhibitory information channels (87). This model, Fig.

11, was a distinct departure from the Ott-Meyer concept in that it outlined a dual function for the brainstem centers, that is, temperature sensing and signal integration. The central components responded to blood temperature and integrated signals from the skin generating command signals for sweating, panting, shivering, and vasomotor control. This model prompted copious research directed towards the central sensors and the integration of temperature information in model building.

The pictorial model that gained the most exposure both in and out of the scientific community is shown in Fig. 12 (85). This model iterated the earlier idea of a sensing function for the brainstem limited to warmth perception and a regulatory function for the skin limited to cold perception. Sweating and vasodilation were controlled from the central sensor of warmth. Cold sensors in the skin prompted the shivering response via a "synaptic temperature insensitive center" in the posterior hypothalamus. The model proposed inhibitory pathways between the warmth sensors and the temperature insensitive center and between the sweat response and the cutaneous cold sensors. Benzinger boldly stated that physiological temperature regulation at rest and in exercise were both explained by his model (88).

Another verbal-pictorial model, which first proposed that behavioral and physiological temperature regulation had common origins, is shown in Fig. 13 (89). This model was based on the hypothesis that the motivation for behavioral temperature regulation originated in feelings of discomfort related to central and peripheral thermal stimulation and also to physiological responses. This simple model stimulated considerable research in behavioral temperature regulation by several authors (90,91).

### MECHANICAL MODELS

Physical analogues of temperature regulation were popular between 1920 and 1960. They were not truly representative of human physiology but attempted to depict man as a black box reacting to the environment. Other physiological systems, that is, the cardiovascular system, the renal system, and the digestive tract, had been successfully represented by mechanical models for teaching purposes for a number of years. Early attempts at modeling temperature regulation simulated heat-flow patterns from the skin (3). Among these were the wet and dry kata-thermometer proposed by Hill in 1923, the eupathoscope and thermointegrator used at the Pierce Foundation Laboratory in the 1930s and the Vernon black globe used to represent the radiation exchange between man and the environment in 1932. These models were designed to measure thermal stress without exposing man to extreme environments. They functioned adequately but were limited and failed to account for the rapid changes internally responsible for local temperature regulation.

Figure 14 illustrates a hydrodynamic model developed by Aschoff in 1958 for the study of counter current heat exchange (3). Within the extremity, glass tubes represented arteries and veins surrounded with cellulose in water. The flow of water through the system was controlled while the rate of perfusion of the hand was measured. Heat transfer into the hand and the

arterial-venous temperature difference were measured calorimetrically. This crude but important model demonstrated counter current heat transfer by the blood in the arm and hand.

Another interesting physical analog portrayed in Fig. 15 used an electrical circuit to model temperature regulation (92). Temperature was represented by electrical potential, and heat flow was defined by the electrical current. This model included a representation of a complete two-compartment control system with central and peripheral inputs to closed loops for sweat and vasomotor control. Using experimental data on men exercising in the heat, many qualitative similarities between the physiological data and the electrical system were deduced. This was one of the first predecessors to the later analog computer simulations of temperature regulation. Although these mechanical models were poor representations of the biological system, usually done in real time, they were important in furthering research and understanding of temperature regulation.

Another electrical analog to simulate physiologic temperature regulation in the nude man is shown in Fig. 16 (93). This model was constructed using the basic equations for heat balance taking into account heat losses by radiation, convection, and evaporation. The diagram shows 18 summing amplifiers, 4 high-gain amplifiers, 3 integrators, 2 square diode function generators, 2 electronic multipliers, 1 comparator, scaling potentiometers, diode limiters, and function switches. Body-temperature changes acted as a negative feedback controller in response to ambient temperature changes or temperature changes resulting from exercise.

Three basic types of control modes, proportional control, rate control, and on-off control, were used. Rate and proportionality constants were determined experimentally on the assumption that the regulated temperature was the average body temperature. Time constants for the various thermal changes were resolved from the thermal constants of tissue and the response times of the physiological variables of sweating, vasomotor activity, and change in metabolic rate. This model closely predicted steady-state conditions in rectal temperature, skin temperature, metabolic rate, vasomotor state, and evaporative heat loss at rest and during exercise.

### NEURONAL MODELS

For 100 years, it had been generally accepted that the brain was somehow involved in temperature regulation. It was virtually impossible to study directly the central complexes that relate the input from temperature sensors to the output of the temperature regulatory effectors. Therefore, temperature regulatory functions of the brain, like all other central nervous system functions, had initially been analyzed and described in terms of observed relationships between disturbances and responses and not in real terms of neuronal pathways. Only in the last 30 years have scientists begun to think seriously about the neuronal relationships that may be involved.

One of the first speculative attempts at understanding how the control of body temperature might be achieved neurally suggested that warm- and cold-

sensitive neurons in the hypothalamus may have different activity-related temperature characteristics (84). A later interpretation of this proposal, shown in Fig. 17 (94), describes neuronal involvement in terms of discharge frequencies of temperature sensors that rise to a peak and then decline as temperature rises. Assuming that the cold sensors are linked to the outflow to the heat production effectors and that warm sensors are linked to the outflow to the heat loss effectors, an upward displacement of core temperature would decrease heat production and increase heat loss. Conversely, a drop in core temperature below a set point would increase the activity of cold sensors, increase heat production, and decrease the activity of warmth sensors and heat loss effectors, driving the core temperature back up. It appeared that the set point was determined by the different characteristics of these two populations of primary temperature sensors. This was a simple but successful attempt to involve the temperature set point theory and sensor activity in the same model.

Guieu and Hardy reported on many different patterns of neuronal activity (95). They proposed that the primary warm sensors varied their activity positively and linearly with local temperature, while primary cold sensors showed a negative linear relation between activity and temperature. Other neurons that were altered by local temperature changes, but yielded a variety of biphasic relations between activity and temperature, were considered interneurons. These were directly influenced by local temperature changes acting on primary temperature sensors. A third class of temperature-insensitive neurons were considered to be concerned with set-point function.

Subsequent studies of the electrical activities of single hypothalamic neurons indicated that when temperature varied within the normal range of core temperature, some units showed a positive linear relationship between activity and temperature while others showed a negative relation over the same range (3). Indeed, the predicted bell-shaped curves of temperature/activity relations of temperature-sensitive hypothalamic neurons were confirmed over a wide range of temperatures with some activity peaking above and some below normal temperatures (96). This also suggested that the basic set-point mechanism of mammalian temperature regulation depended on the above characteristics with the overall heat balance at any level of hypothalamic temperature affected by the synaptic influence of peripheral thermosensitivity and other nonthermal influences. This point was argued at the time because of the uncertainty of the existence of substantial numbers of cold sensors in the hypothalamus. The debate over set-point control continues today.

An early study (97) of the electrical activity of single neurons in the preoptic area of the anterior hypothalamus found that only a few neurons responded to a rise in body temperature due to physical activity. Nakayama et al. (97) also reported that the activity of most hypothalamic neurons was unaffected by local peripheral temperature changes, indicating a possible division between central and peripheral receptors and effectors. Hammel (98) described both temperature-sensitive and temperature-insensitive neurons and postulated that the set point depended on the interaction of the two. The set point was considered to be that temperature at which the activities of the two neuronal populations were equal. Above the set point, the activity of the sensitive neurons was greater than the insensitive neurons, increasing the

drive to heat loss effectors and reducing the drive to heat producing effectors. When the core temperature was below the set point, the converse situation existed.

Apparently, changes in skin temperature also affected the regulation of body temperature (98). Hammel's neuronal model suggested that shifts in set point temperatures could account for immediate increases in heat loss in response to a rise in skin temperature. A reconstruction of this model, which used many of the same design attributes in neural pathways from sensors to effectors and their inhibitory connections, proved very reliable and valid when compared to actual experimental data (99).

Most of the initial attempts to model the neuronal interaction of temperature regulation were restricted to limited parts of the human body. The temperature regulatory responses of paraplegic men to pyrogens and local heating of hands and feet were reported in 1958 (100). In 1961, details of interneuronal connections of temperature-sensitive units in the preoptic area of the hypothalamus were first outlined (101). Experimental data on the responses of a variety of animals to selective heating and cooling of special areas of the central nervous system such as the hypothalamus, spinal cord, and scrotum have been reported (102). However, few models of the totally integrated neuronal composition of the system have been proposed beyond the pictorial state.

The model proposed by Hammel in 1965 was similar to the Hensel model previously described with two centers (inhibition and stimulation) but different in that the peripheral afferents modified the central error signal by adjusting the set-point temperature of the brain stem to produce the appropriate command or output (98). This adjustable set-point model added to the controversy among biologists and behavioral physiologists but was generally supported by neurophysiologists studying the interaction of peripheral thermal stimulation and single units of the hypothalamus (3).

Another neuronal model was based on data from experiments on single neuronal unit activity in response to local and peripheral temperature changes (103). This model, depicted in Fig. 18, attempted to fit all previously reported types of neuronal units, based on their response to temperature changes in the central nervous system, into a network. It did not, however, include single neuronal units responding to skin temperature as did an earlier model (104). The Hardy and Guieu model assumed at least two neurotransmitter substances were necessary for temperature regulation. Many thermal afferent units from various parts of the body were placed logically in the network with both cold and warm anterior hypothalamic output networks identified. Two separate but interacting networks greatly simplified the fitting process. The circuit diagrams indicated that the preoptic sensors of temperature were not affected by peripheral thermal stimuli but responded only to local temperature changes and provided independent inputs into the network. Figure 19 shows how the outputs W1, W2, W3, W4, C1, and C2 combined to describe the overall physiological response of temperature regulation (3).

Neuronal unit activity studies have provided evidence of a convergence of pathways from spinal, peripheral, and hypothalamic temperature sensors (4),

but, it is not clear at what point in the path this convergence occurred. The cutaneous, spinal, and hypothalamic sensors may all have been primary neurons that converged into a common pathway, or the hypothalamic neurons might have been interneurons between other temperature sensors. One report (105) indicated that the activities of some of the hypothalamic units were influenced by local and skin temperature changes, while other units were affected only by hypothalamic temperature changes. This same neuronal convergence was suggested in another model (106). In contrast, other studies argued either for the interaction of skin and hypothalamic neurons affecting hypothalamic cells (98) or against the involvement (107). Today, it is well known that the preoptic area of the hypothalamus, the skin, the spinal cord, the abdominal viscera, and tissues in and around the great veins all contain both warm and cold receptors.

Figure 20 details afferent pathways from both cold and warm sensors in the peripheral, spinal, and hypothalamic regions of temperature sensitivity (4). This composite neuronal model of mammalian temperature regulation was intended to express the variable and complex nature of the input to the pathways between temperature sensors and effectors, and the variable threshold temperatures for heat production and evaporative heat loss. The two additional inputs to each main pathway, one inhibitory and the other excitatory, were intended to represent all nonthermal disturbances that influenced the relation between sensors and effectors. The composite afferent input represented the various thermal and nonthermal influences on the balance between heat production and loss and, therefore, on steady-state core temperature. It did not account for threshold temperatures for the activation of evaporative heat loss by sweating or panting and heat production by shivering.

A more recent report (108) outlined an attempt to develop a time dependent model of shivering thermogenesis on the basis of neurophysiological evidence from the literature. Because of the extensive use of computers to formulate the complicated mathematical expressions based on thermodynamics, it would be easy to classify this model as a mathematical or engineering model and report it in a later section. However, its neuronal emphasis allows it to be included in this section. The model, Fig. 21, used existing stimulus-response expressions predicting thermogenesis based on static peripheral, core, and central temperatures. It incorporated the characteristics of thermosensitive neural structures of the body. Central and peripheral set points were established on the basis of the firing frequency of warm and cold receptors. The region of thermoneutrality where the firing frequencies of these receptors are identical was assumed to be the physiological set point. Data published in the literature were used to define receptor activities, dynamics of responses, regional summation, and set points. Metabolic heat generation was derived by integrating excitatory and inhibitory receptor stimuli from the various regions of the body. Actually, four different mathematical expressions were developed for shivering thermogenesis. A detailed comparative evaluation with previous studies (109,110) showed the Mekjavic and Morrison model generated significantly fewer errors and improved the overall prediction of shivering thermogenesis. Some of the other effector functions were not predicted as accurately. However, the model was successful in describing the body's temperature response to environmental changes.

Neurochemical, or chemical, models have been used in the past to describe the involvement of putative transmitter substances in the brain in biological temperature regulation. Some of the naturally occurring chemicals have distinct and reproducible effects on temperature regulatory effector functions and on core temperature when introduced into the brain. Feldberg and Myers suggested that body temperature was basically controlled by a balance of the neurotransmitters 5-hydroxytryptamine (5HT) and norepinephrine (NE) (111). Their concept was based on the fact that these substances were found in greater concentrations in the preoptic anterior hypothalamus than elsewhere in the brain. They discovered that when the ventricles of the brain were perfused with varying amounts of these chemicals, both hypo- and hyperthermia could be induced.

A subsequent model proposed the involvement of another chemical factor based on experiments that altered the sodium-calcium ratio in the posterior hypothalamus (112). This model, Fig. 22, was similar to the neuronal circuits proposed by Hammel with peripheral input to the anterior hypothalamus. Transmitter substances 5HT and NE facilitated the synapse with temperature-sensitive neurons. This area was depicted as the place of action of pyrogens, drugs, and temperature changes. The resulting activity was transmitted via acetylcholine (ACh) to the posterior hypothalamus. In this region, the set-point temperature of the body was added, but the sensitivity to the drugs, pyrogens, and blood temperature was lost.

Bligh (4) proposed another neurochemical model, which had much physiological data to support it. Many earlier findings in a number of species were clarified using a combination of ambient temperatures and centrally administered neural transmitters. Bligh's neuronal model was derived from synaptic interference studies with sheep. The model was intended to express the variable and complex nature of the input pathways between hypothalamic, spinal, and peripheral temperature sensors and regulatory effectors influencing panting or sweating, shivering, and vasomotor tone. Bligh described the model as simply an illustration of all the observations and rationalization of the functions of selected unit activity patterns. Other neurochemical models have dealt with particular subsystems of biological thermal regulation. One model accounted for peripheral vasomotor control by the sympathetic nervous system (113). Another model simulated the metabolic heat production in the cold from brown fat nonshivering thermogenesis (114).

### MATHEMATICAL MODELS

I have stated that the temperature regulatory functions of the brain had initially been analyzed and described in terms of the observed relationships between disturbances and responses. It has been difficult to study directly those central nervous complexes that relate the input from temperature sensors to the output of the temperature regulatory effectors. The physiological temperature regulator has been described as a "black box" that cannot be opened but can be analyzed for both qualitative and quantitative relationships between disturbances and responses. Assuming these relationships are regular and repeatable, they may be expressed easily in terms of mathematics. Many mathematical models have been constructed in attempts to define and quantify

these relationships and to demonstrate their orderliness. Because assumptions must be written in specific, mathematical language with logical solutions, mathematical models can be widely understood. The flexibility of the mathematical model allows changes to be made easily and test results to be obtained quickly. A mathematical model may provide results in the form of a time sequence or a deduction of a more complicated relationship between measured variables. High-speed computer simulation cannot replace laboratory experimentation, but it can overcome many of the practical constraints discussed previously.

Thermal and nonthermal influences vary from moment to moment and create such complex interactions between thermal disturbances and responses that it is impossible to express them in terms of relatively simple mathematical functions. This is true for the description and analysis of functions with both regular linear and curvilinear relationships. The complexity of the physiological relationships is minimized, however, when an organism is kept in a closely controlled environment. Stimuli and responses can be measured and expressed as equations. These mathematical models can be used to simulate experimental conditions and predict temperature regulatory responses beyond laboratory data. The challenge is to improve the predictive reliability of the model as the simulated thermal and nonthermal circumstances are moved further away from laboratory data.

A mathematical model is essentially a description of the relationships between disturbances and responses in very restricted experimental conditions. One of the most widely used mathematical models of temperature regulation is the expression for the First Law of Thermodynamics:

$$M \pm R \pm K \pm C - E \pm W \pm S = 0 \text{ (thermal balance)}$$

where M = metabolic heat transformation

R = radiative heat exchange with the environment

K = conductive heat exchange

C = convective heat exchange with the environment

E = evaporative heat loss to the environment

W = work accomplished (W = 0 at rest)

S = heat storage (negative for heat storage and positive for heat loss)

The equation is a descriptive mathematical model of temperature regulation based on a physical law, which implies that if during thermal equilibrium M, W, R, and C are known, then E is known (115). This quantitative relationship between the various energy flows in and out of the black box must hold true regardless of how the components of the black box function.

A mathematical model, or any model for that matter, is valuable only if it has been tested and proved to act like the system it is supposed to represent. A working model simulates the system it represents. Simulation provides an artificial reality for testing a model. Many experiments simulating various changes in parameters or extreme stresses not possible under normal conditions can be performed in a short time. The results of simulation can direct further research if necessary.

The U.S. Naval Air Development Center first suggested that analog simulation might be applied to human body thermal response (116). Soon after, followed the first successful computer simulation of human temperature

regulation (117). Another early mathematical model opened the door to new developments in temperature regulatory research (118). This model assumed the body to be a cylinder with uniform properties of density, specific heat, conductivity, and heat production per unit volume. Using Bessel functions for specific values of axial and skin temperatures, body temperatures at various distances from the center of the cylinder were predicted from initial immersion in 32.5 °C water followed by rapid heating of the water to 36 °C. Assuming that vasodilation increased the conductivity fourfold, the following predictions resulted from the model: (1) Complete adjustment of body temperature took a long time; (2) temperature of deep tissues would decrease first before increasing; (3) initial and final temperature profiles within the tissues were parabolic. These tenets were used to develop the powerful models that followed.

A steady-state model, which represented the heat balance of the human forearm, was proposed by Pennes in 1948 (119). He approximated the forearm as a cylinder and considered the following factors in developing the model: the radial conduction of heat; the metabolic heat generation in the tissue; convection of heat by the circulating blood; and heat loss from the surface of the skin by convection, radiation, and evaporation. This model was tested with numerous experimental data for the forearm, but it was essentially applicable to any cylindrical representation of an element of the body. Because the model was based on *in vivo* human data, it has served as a basis for temperature regulation model development for over forty years.

Machle and Hatch (120) introduced one of the first nonsteady-state models of the core and shell concept using measurements of rectal and mean skin temperatures, respectively. Starting with the basic heat balance equation and considering the rate of change of body heat content as a function of increments of rectal and mean skin temperatures, they developed a model that provided a relationship among skin temperature, partial skin wetness, local metabolic rate, and environmental parameters. Kerslake and Waddell (121) found the Machle and Hatch model unable to account for complete skin wetness. They extended the model to include complete skin wetness and were able to predict steady-state skin temperature from the local metabolic rate and the environmental condition.

As a result of the early attempts at mathematical modelling, many researchers found it useful to discuss temperature regulation simulation as having both controlled (passive) and controlling (active) parts of the system. The controlling parts of the system initially sensed the status of the controlled variable and then provided the necessary responsive action. The controlled system was concerned with heat flow and temperature distribution within the body as a result of a disturbance. A model of a controlled system of heat transfer through tissue conduction and the blood stream is shown in Fig. 23 (14). This human representation was arranged as a head, trunk, and limbs in six homogeneous cylindrical elements composed of bone and tissue covered with a layer of fat and skin. Heat transfer through the circulation connected the core (trunk) with the other components via arterial and venous channels, which allowed for countercurrent heat exchange. Metabolic reactions were assumed to generate heat uniformly in each section but with different rates. The capillary beds of each section were uniformly supplied with

arterial blood at a defined temperature. This computer model allowed for realistic predictions of heat exchanges and temperature gradients within the nude human body for cold exposure and both steady-state and transient conditions.

Wissler (122,123) later improved his model to include the following factors: (1) local generation of heat by metabolic reactions, (2) conduction of heat due to thermal gradients, (3) convection of heat by circulating blood, (4) the geometry of the body, (5) the existence of an insulating layer of fat and skin, (6) countercurrent heat exchange between adjacent large arteries and veins, (7) heat loss through the respiratory tract, (8) sweating, (9) shivering, (10) the storage of heat, and (11) the condition of the environment, including its temperature, wind speed, and relative humidity. This version of the model was more flexible and produced computed results that were consistent with experimental results reported in the literature. Wissler's model has continued to be used as a popular, valid and reliable predictor of the human body's response to environmental temperature changes.

Another model of the controlled system represented the body as a single cylinder containing four concentric layers (124). The four layers shown in Fig. 24 symbolized four different types of tissue: core of bone and viscera, muscle, deep skin and fascia, and the outer layer of skin. An independent central blood pool in the model collected blood returning from different areas, mixed it in the heart and lungs, and redistributed it. The model was essentially one-dimensional with no axial heat flow. Several other one-dimensional multilayered thermal models in the form of either a cylinder or a slab have been used (117,125,126). These models contributed significantly to the development of the equations for heat flow through different types of tissues.

A model of the controlling system in temperature regulation should identify the controlled variable, depict the behavior of the feedback elements, simulate the action of control elements, and provide a valid effect on the controlled system (5). Historically, the development of functional relationships between control actions and particular body temperatures through experimentation has occurred without knowing the relationship between those temperatures and the controlled variables. Black boxes were used liberally where questions existed. Atkins (127) designed a simulator to predict the reactions of men exposed to combinations of heat and work stress. His simulator contained function generators, which mimicked the relationship between deep-body temperature and skin temperature and between sweating and whole-body conductance. He found it unnecessary to model the mechanisms of the controlling system as long as the relationship between a disturbance and a particular physiological response was correctly predicted. The agreement between predicted and experimental data was good.

Several other attempts at modeling the controlling system added to the foundation that led to the development of the comprehensive analytical models of the last 10 years (68,126,128-130). However, Wyndham and Atkins (99) pointed out at that time the hazards of trying to write a mathematical equation for a control action as a function of body temperatures. The mathematics were correct, but the model was faulty. The reasons why so many

of the models of controlling systems failed were threefold. First, there was a tendency to build models according to theories of temperature regulation which were not necessarily correct or tested, for example, the uncertainty of the role of the brain and the spinal cord in regulation. Secondly, physiological information was inadequate. Lastly, most model builders failed to recognize the importance of the physiological information that was available such as the direct influence of local temperature on regulatory control. For many years, experimentalists outpaced the modelers. Fortunately, the technological boom of the computer age appears to have alleviated some of these concerns and allowed research in model building to address complicated, multifunctional areas of temperature regulation.

Because of slow and expensive computers, complete models with both controlled and controlling systems were not proposed initially. One of the first complete models of temperature regulation was a simple attempt by Smith and James (131) to predict heart rate for alternate periods of work and rest. A 6-cylinder model with a 15-19 compartment system was proposed initially. Heart rate was used as the index of thermal strain. The model allowed for heat exchange by countercurrent flow. The original concept represented the trunk as three cylinders comprised of compartments of core, a fatty layer, and an outer layer of skin. Standard heat equations were used for the heat balance of each of the compartments. Temperature regulation was controlled by local skin temperature from both the cutaneous blood flow and sweat rate through two positive feedback loops. The hypothalamic temperature was identified as a multiplier that determined the gain of the two loops. The central set-point temperature was 37 °C, and the local and central gain values were selected from the literature. The model included relationships between heart rate and cardiac output for muscle and blood flow. The model was tested with data from four subjects walking on a treadmill at 32 °C and roughly predicted the actual measurements.

Another early model to include both controlled and controlling systems assumed all regulation to be of central origin with the skin and muscle temperatures summing their signals with the hypothalamic temperature signals to control cutaneous blood flow, sweating, and shivering (117). Three set-points were required, one for the hypothalamus, one for the skin, and one for the muscle. Local skin temperature, however, was not used in the model. Heat loss was assumed equal to the metabolic rate. Steady-state calorimetric data of nude men at ambient temperatures of 22-35 °C were used to test the model. These empirical results were in good agreement with the predicted data.

Stolwijk and Hardy (69) contributed a mathematical model of temperature regulation for the purposes of theoretical analysis of experimental results and evaluation of hypothetical concepts. The human body was represented by three cylinders: the head, trunk, and extremities divided into two or more concentric layers to show the anatomical and functional differences important in temperature regulation (Fig. 25). A regulator was supplied with signals pertaining to temperature deviations in the brain and from the skin. The regulator then caused heat loss or heat production in the appropriate parts of the body. Using available experimental data, the authors showed good agreement between the predicted results and the quantitative data from measurements obtained in the laboratory. Stolwijk and Hardy stated, however,

that models of physiological processes and functions are useful to their originators only if there is a continual interchange with an experimental program. Mathematical models can be a very powerful tool in research when coupled with analog or digital simulation.

Based on his earlier model (123), Wissler (132) proposed an explicitly definitive mathematical model which could be adaptable to almost any homoiotherm and employed both a controlling and controlled system. Equations were adopted from several experiments on thermal regulation. A computer program written in Fortran was used to simulate heat production, heat transport, and heat loss. Experimentally obtained values for weighted body, mean skin, brain, trunk core, and central blood temperatures, skin blood flow, cardiac output, heat storage, heat production, and evaporative heat loss were in reasonable agreement with their predicted counterparts. This attempt focused on detailing the heat transfer rates between the individual compartments representing the body. A major problem encountered in the development of this model was defining the proper equations to validly describe the compartments because of the spatial variation of temperature within each compartment and the thermal flux along the boundary between the compartments. The solution for this problem was to define more compartments which increased the number of equations, complicating the model even more. With the use of a computer, the model proved to be capable of describing the response of the human temperature regulatory system under most situations.

Brown and Brengelmann (133) reported the results of an experiment that measured metabolic rate and skin, rectal, hypothalamic, and tympanic temperatures in a circulating water bath. Temperatures were recorded for 3 hours. Water temperature was held steady near body temperature then cooled rapidly to 28 °C. Several important conclusions were drawn, which have helped other scientists in subsequent attempts at developing valid models of temperature regulation. The presence of multiple feedback loops made the classical technique of evaluating system performance by the measurement of open loop gain difficult to apply. The concept of a floating set point did not follow unequivocally from experimental results. Brown and Brengelmann stated that cutaneous thermal transients were a potent input to metabolic heat output. The temperature regulation transient response was described as a combination of graphical and analytical expressions of a first order, nonlinear, lead-lag system. The model suggested that the input from the rate of change of body surface temperature promoted the functions of (1) anticipating the thermal stress, (2) stabilizing the system by compensating for inherent lags, and (3) contributing to the smoothing of response curves by rectification.

A review (1) of mathematical models of the human temperature system frequently used by engineers classified models in one of three categories. The models reviewed were based on experimental data or theories of thermodynamics and transport processes. The models were classified as representing a single element of the body or the entire body and either steady-state or nonsteady-state. A third class of mathematical models combined the human temperature regulating system with external temperature regulation devices, for example, cooling garments. This classification system was used by Shitzer (2) to identify additional published references of

engineering models of temperature regulation. He identified a number of mathematical models used by engineers primarily to describe the thermal response of living tissue to a localized heat source. These models were intended to facilitate the measurement of physical or physiological properties of the tissue.

Another review (6) of engineering models of the human temperature regulatory system emphasized the physiology of temperature regulation in mathematical models. This review was also intended to present an engineer's view of the literature on temperature regulation. Models were classified as one cylinder core and shell or multilayer, multisegment, or models with external temperature regulation systems. Some of the models reviewed had not been validated with experimental data. A major problem with many of the models was the use of inappropriate values for constants and parameters for the different theoretically reasoned empirical formulas. The reviewers found that many of the models did not incorporate any sort of limit on the physiological regulatory actions that affected the model's output. The models failed to consider the complication to temperature regulatory functions due to acclimatization. This critical review concluded that the mathematical model of such a complex system develops gradually and is never complete. The development of the model should be continuous and combined with experimental work.

Gordon et al. (134) published a mathematical model of the human temperature regulatory system that used finite difference techniques and included detailed anatomical and physiological information. The model had a passive system formulation and a cold-exposure control system. The proposed controller used head core temperature, mean skin temperature, and mean skin heat flux as input signals to control metabolism, skin blood flow, and extremity muscle blood flow. The body was defined as 14 major cylindrical and spherical segments (Fig. 26) differentiated by their characteristic thermophysical properties, anatomy, physiological attributes, and control system tendencies. Each segment consisted of several concentric tissue bands which simulated the anatomical structures found at different depths in the segment. A finite-difference formulation of the one-dimensional energy equation was written for each shell within each tissue band. All thermophysical and physiological properties were assumed to be uniform within each particular band. The control system (Fig. 27) changed individual tissue-band metabolism and blood flow rates depending on the input signals to the controller. The model simulated the experimental results well considering the large number of variables (seven temperatures, cardiac output, metabolism, and arm blood flow) modeled. In particular, it showed that skin heat flux provided an important feed-forward input to the regulatory system and confirmed the view that the change in heat flux from the body ultimately affects the core or hypothalamic temperature.

A recent study proposed a time-dependent model of shivering thermogenesis based on neurophysiological data from cold water immersion experiments (108). These data pertained to the response characteristics of thermosensitive neural structures in cats and primates and, therefore, had to be scaled to observations in humans. The thermogenic control system was categorized into three main components for temperature sensing, integration, and effecting

thermogenesis in response to the neural coded information. The general model shown in Fig. 21 considered shivering thermogenesis as a net result of thermoreceptor excitation and inhibition from various core and skin regions in the body. The thermogenic response was discussed as a function of the displacement of peripheral and core temperatures from predetermined set points based on the firing frequency of cold and warm receptors. The physiological set point was assumed to be the region of thermoneutrality where firing frequencies of the receptors were identical. The model suggested that displacement of peripheral and core temperatures were nonlinear and proportional to the static and dynamic properties of thermosensitive neural structures in the body. Prediction of metabolic heat generation was derived by integrating excitatory and inhibitory thermogenic drives from receptor stimulation in various regions of the body. Despite inadequacies in the prediction of thermogenesis from the assumptions made in the derivation of the model, it appeared to predict the thermogenic response during cold water immersion and rewarming with less error than other related models.

Another recent study (135) used data of resting nude subjects totally immersed in cold water to develop a model suitable for predicting temperature regulation. Transient changes in rectal temperature and metabolic rate were predicted accurately by including a shivering component responsive to skin temperature only, matching the measured and predicted initial core temperatures and metabolic rates, confining the initial shivering to the trunk region, and determining the steady-state convective heat loss to the water by using the heat storage equation. The model used was based on the Montgomery version (136) of the Stolwijk-Hardy model (69), which treats the body as a passive transfer system divided into six segments allowing heat to flow radially within each segment and between each segment through conduction via the central blood.

This model of nude immersion in cold water considered physiological responses not fully addressed in earlier models. Certain mechanisms adequate for less acute exposures were refined to model this response mathematically. In particular, mean body temperature was determined by weighing each model compartment temperature according to its heat capacity. Greater weight was given to core temperature with decreasing water temperature. The thermal neutral temperature profile and set-point values for regulation were determined according to preimmersion data of the subjects and not on theoretical standard values as other models had used. This assured that the subject was thermally neutral at the start of an exposure and that measured and predicted values of core temperature and metabolic rate were matched initially.

In this model by Tikuisis et al. (135), the efferent shivering command from the skin was necessary to predict the observed initial rapid rise in metabolic rate. The shivering command from the skin was dependent on the skin thermoreceptor output signal with a built-in delayed onset function for the limbs. This feature of the model showed good agreement with the measured metabolic and thermal response to cold water immersion.

## SUMMARY

As the historical development and use of models of the human temperature regulation system evolved, many different approaches to simulating the body's response to heat and cold have been proposed. Some have been complex while others have been simply a description of a single response to a disturbance in the environment. At times, the model preceded the actual discovery of the underlying physiological phenomena. More recently, complex physiological interactions of temperature regulation within the body have been studied, which allowed more sophisticated models to surface. However, despite the increasing number of simulations from many disciplines predicting human temperature regulation, there still remains a need for models to include the interactions of the different systems involved in the physiological response of the body.

For decades, scientists have used different types of models to represent and explain physiological functions. Models of the human temperature regulation system have been classified as verbal, pictorial, mechanical, physical, electrical, neuronal, fluid, chemical, engineering, and mathematical. Recently, with the aid of powerful computers, mathematical models have been developed using a variety of linear and nonlinear equations, differential equations, integrals, trigonometric functions, and combinations of these functions.

The popularity of developing models has been discussed. Models can be precise and flexible. However, in order to predict unobserved behavior, the model must be based on observed responses. It has to be adaptable to changing dynamic situations.

The steps usually accomplished in the mathematical simulation of a regulatory system such as the human temperature regulatory system consist of first reducing the system to a simple model, then deriving the equations for heat production, flow, and loss. A hypothesis for the mechanisms of controlling and controlled systems is defined in mathematical terms. Finally, the entire set of equations is solved on the computer. Unfortunately, model building is not always that simple. Often, models are not always complete or correct, and modeling without experimentation can lead to problems. The best way to assure the validity of a model is to compare its predictions with actual data from analogous experiments. Only then can a model become valuable in simulating reality and further our understanding of the physiology of the body.

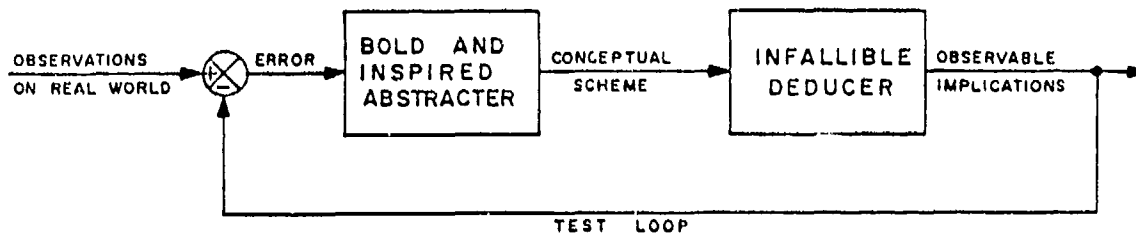


Figure 1. Closed-loop science servosystem (8) (Reprinted with permission).

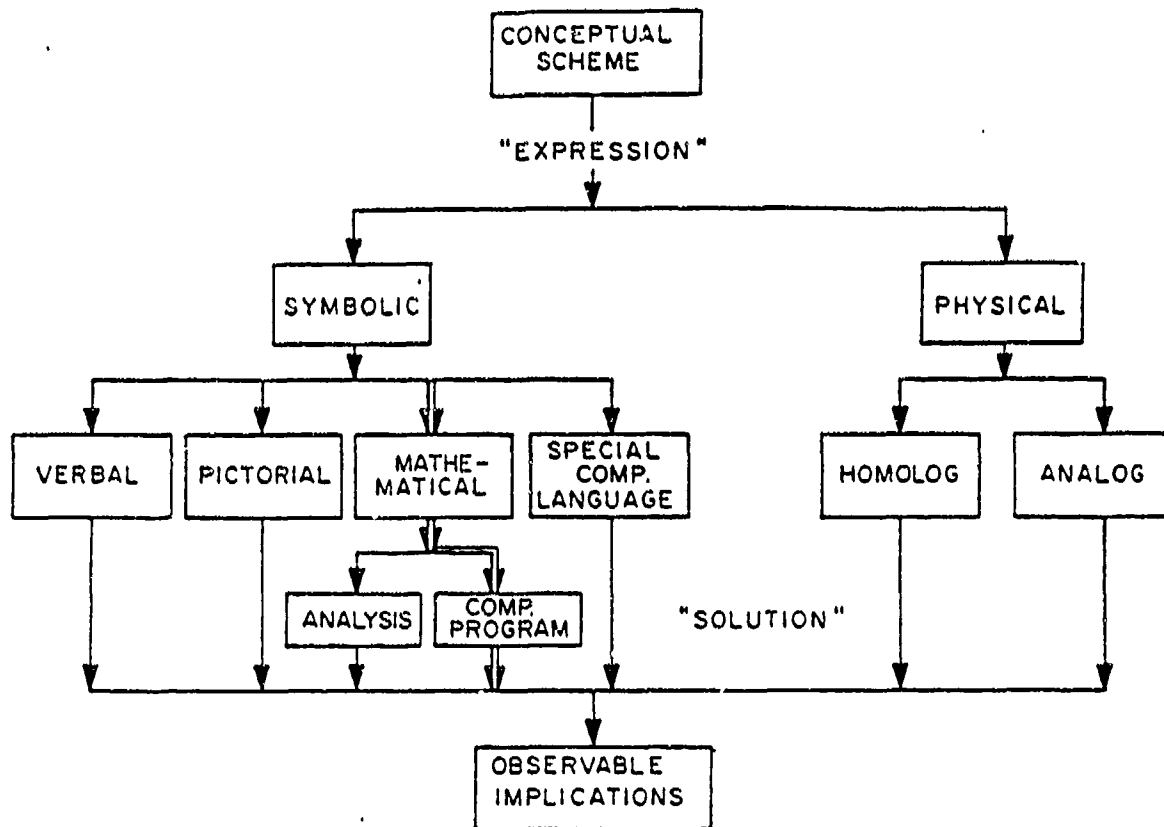


Figure 2. Modes of model expression and solutions (8) (Reprinted with permission).

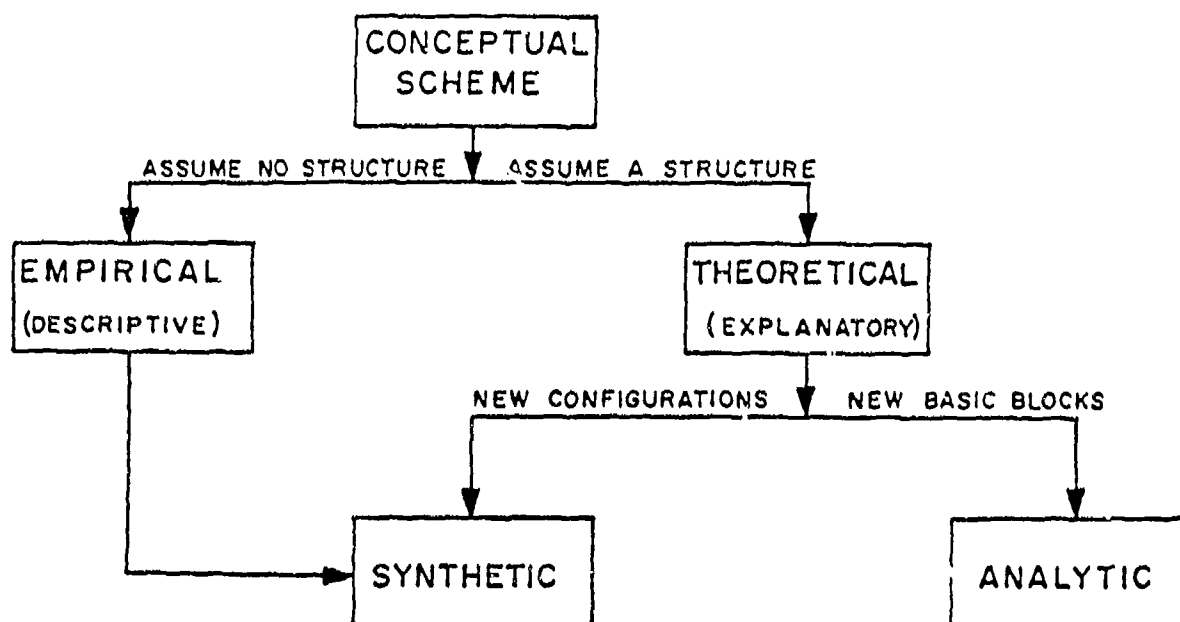


Figure 3. Contents of models (8) (Reprinted with permission).

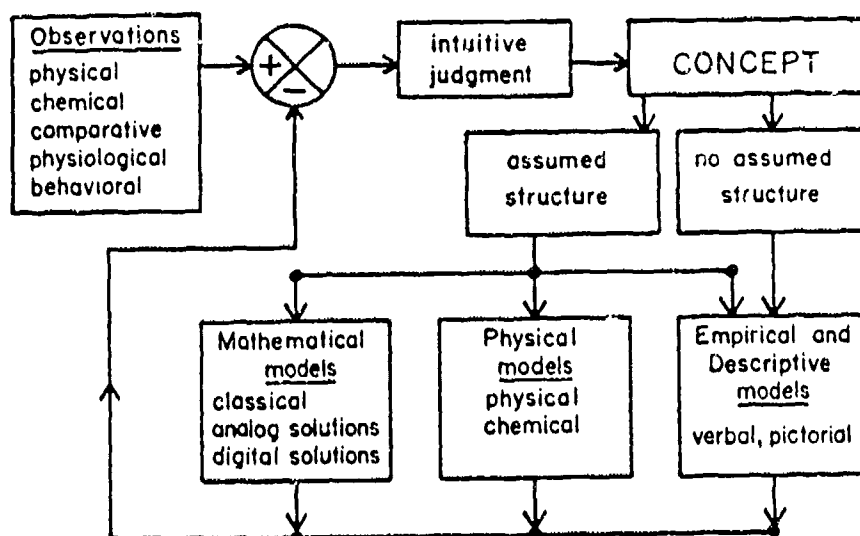


Figure 4. Models of temperature regulation and how they are used (3)  
(Reprinted with permission).

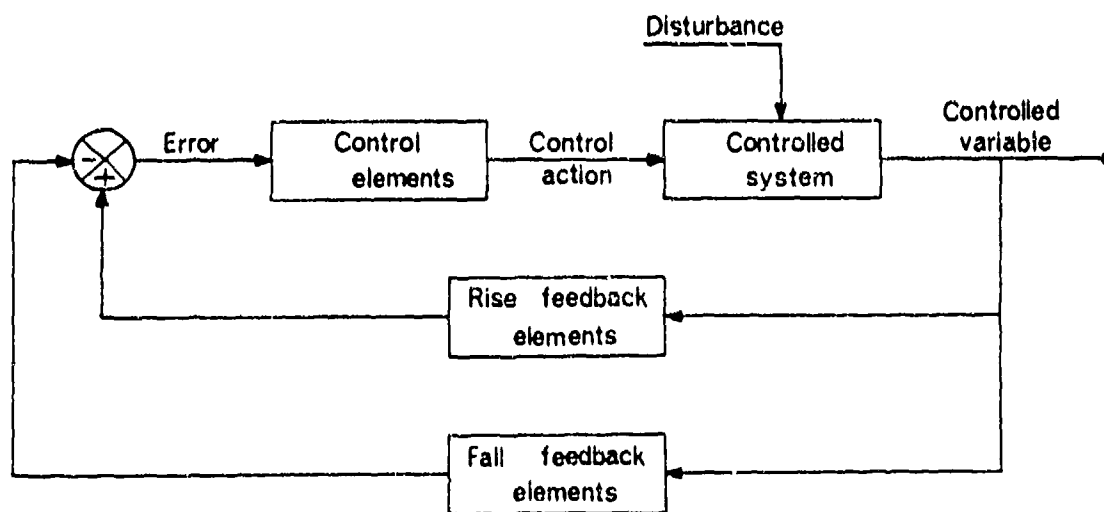


Figure 5. Basic negative feedback control system (67) (Reprinted with permission).

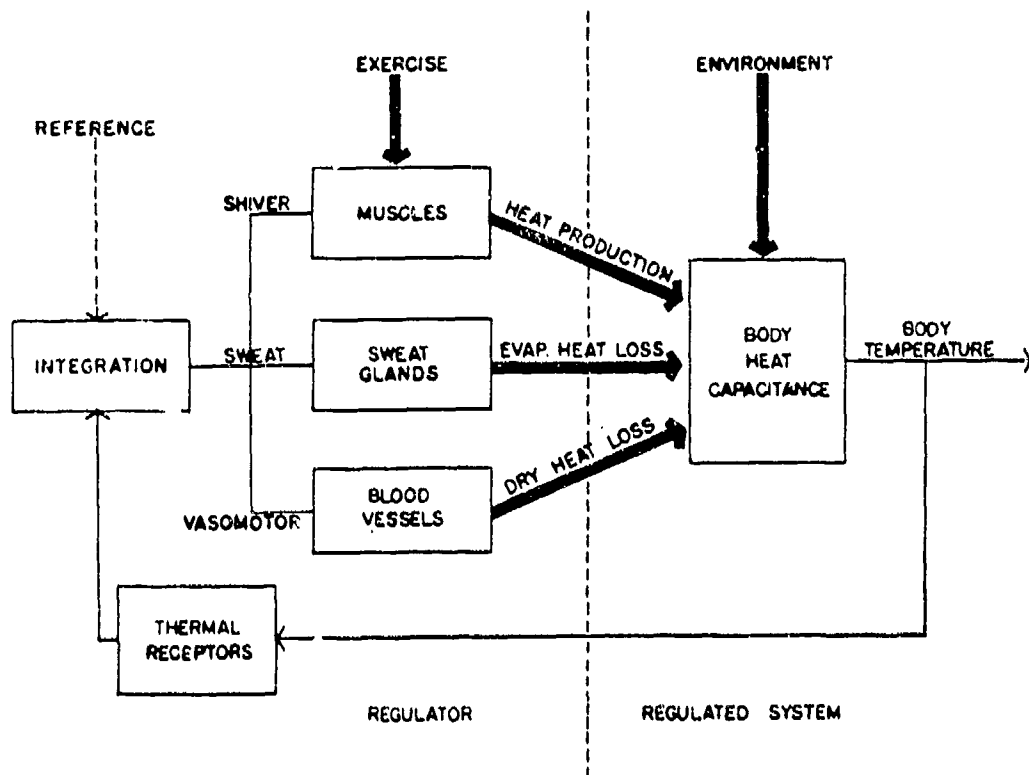


Figure 6. Block diagram of human temperature regulation (68)  
(Reprinted with permission).

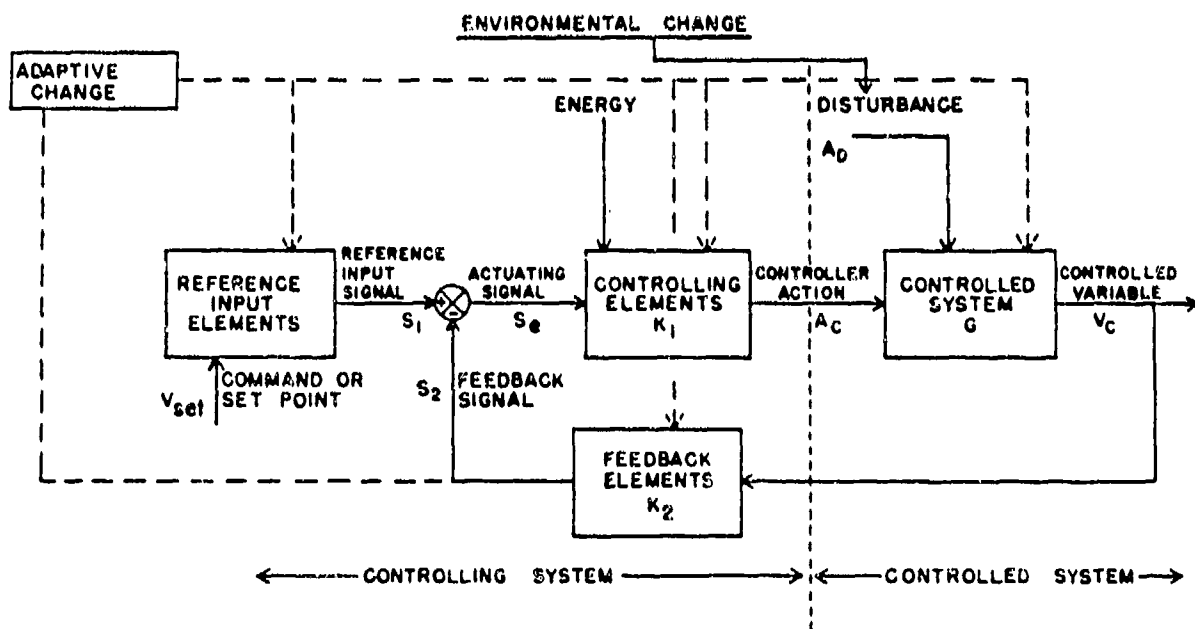
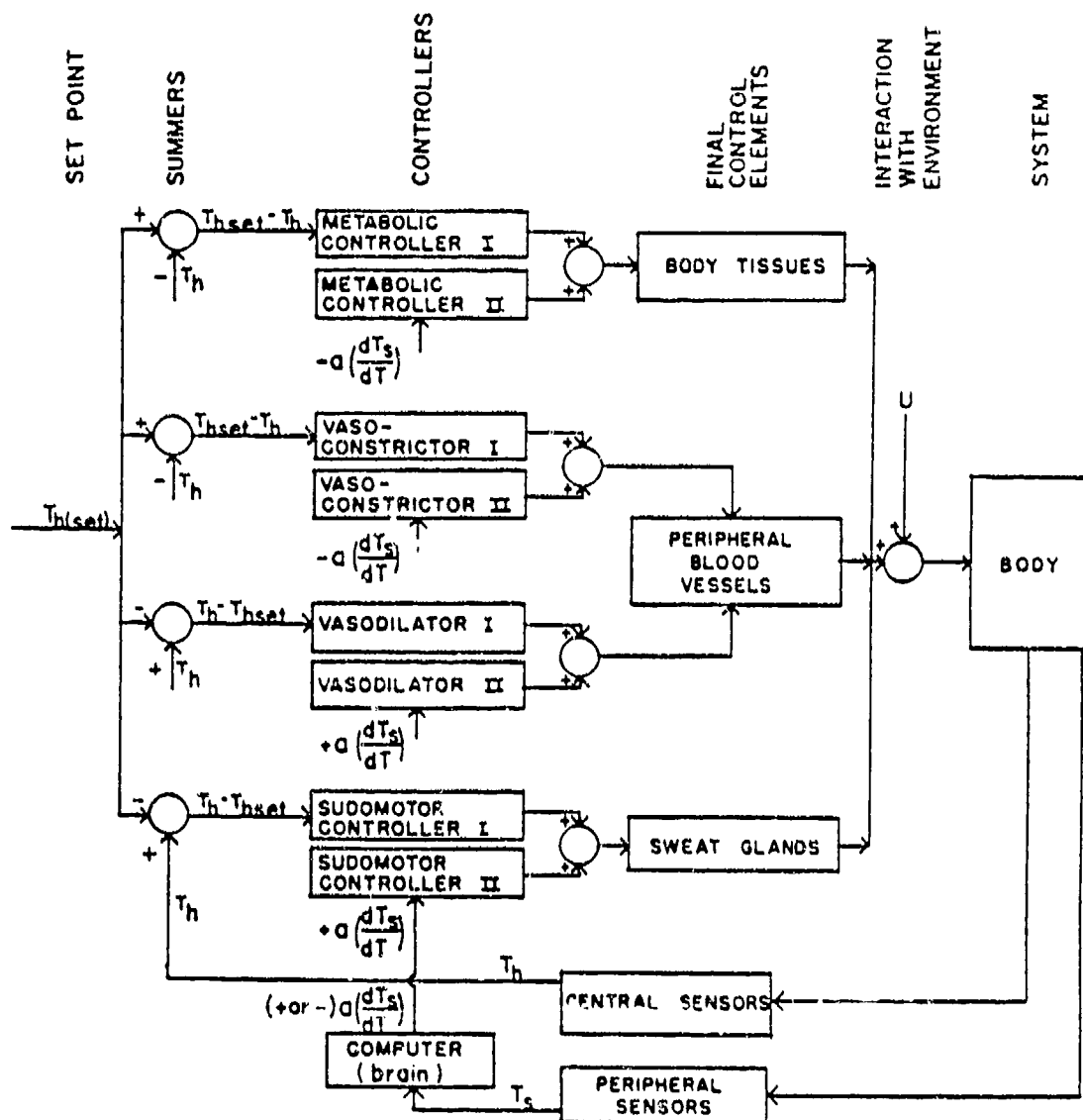
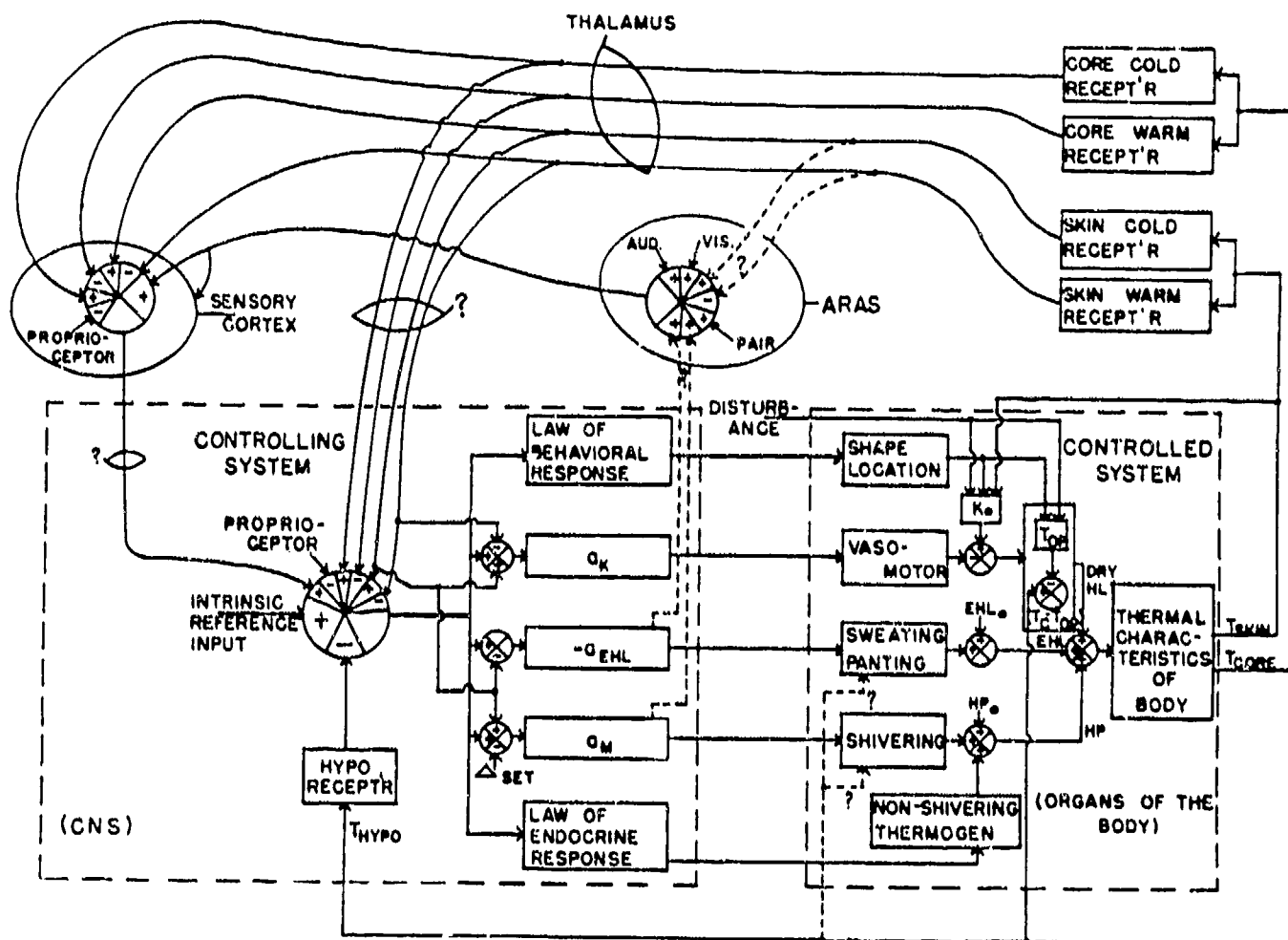


Figure 7. Model of a long term temperature regulating system (69)  
(Reprinted with permission).



$T_{hset}$  = set point temperature;  $T_s$  = skin temperature;  $T_h$  = hypothalamic temperature;  $a$  = exposed surface area of skin;  $U$  = environmental affect

Figure 8. Model of temperature regulation system with central and peripheral sensors (70) (Reprinted with permission).



ARAS = ascending reticular activating system; HP = heat production;  
 HL = heat loss; K = blood flow; EHL = evaporative heat loss; M =  
 metabolism

Figure 9. Diagram for controlling and controlled system for body temperature regulation (13) (Reprinted with permission).

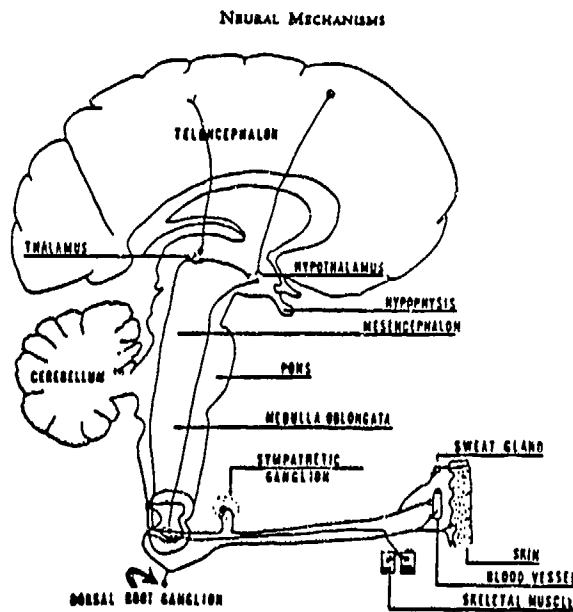


Figure 10. Model of neurophysical components of the temperature regulating system (86) (Reprinted with permission).

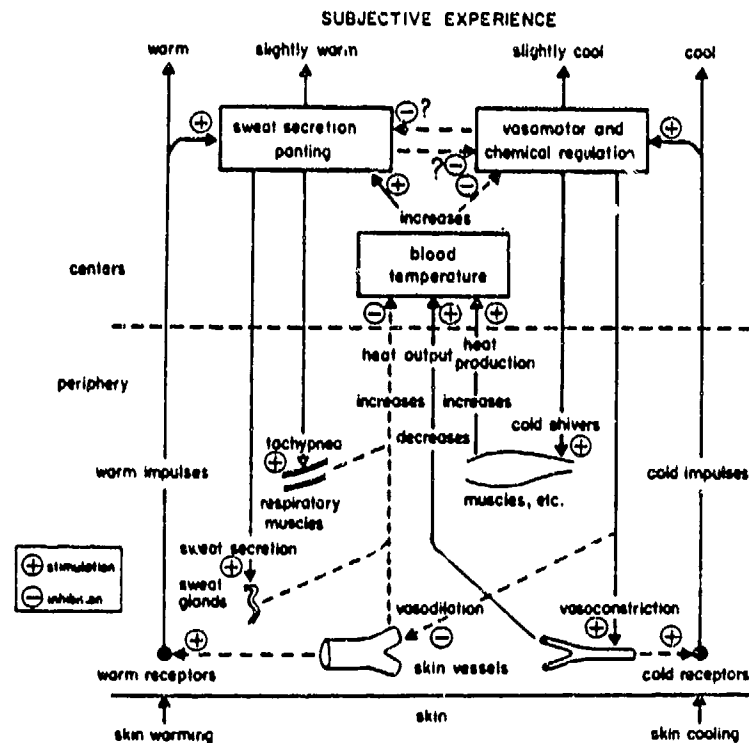
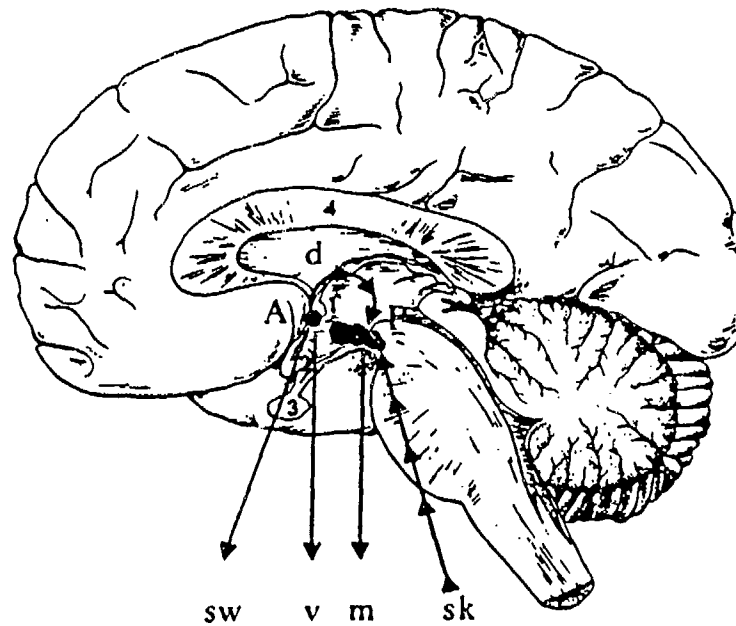


Figure 11. Model of physiological functions of temperature regulation (87) (Reprinted with permission).



A = central efferent site (heat loss center); P = central synaptic site (heat maintenance center); d = A-P pathway; sw = sweat glands; v = cutaneous vessels; m = metabolic tissues; sk = skin thermoreceptors

Figure 12. Model of neural control of temperature regulation (85)  
(Reprinted with permission).

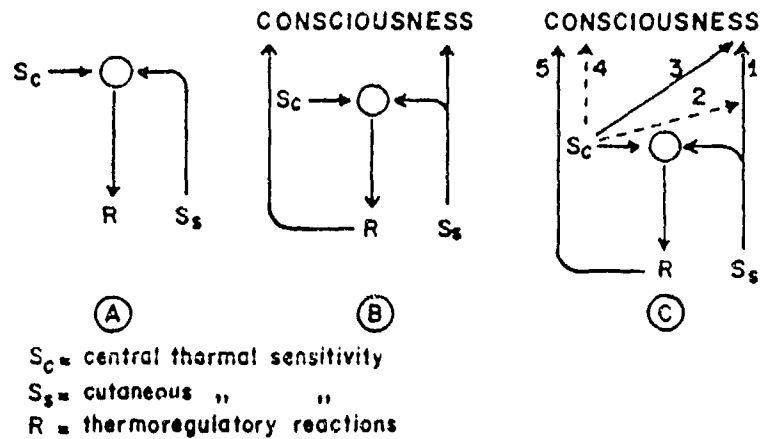


Figure 13. Model of behavioral temperature regulation (89)  
(Reprinted with permission).

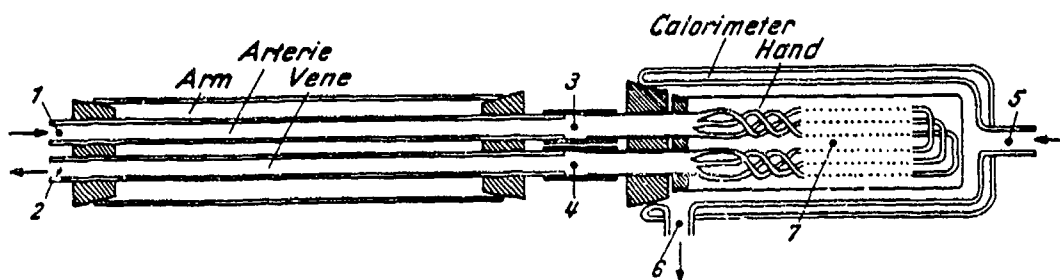
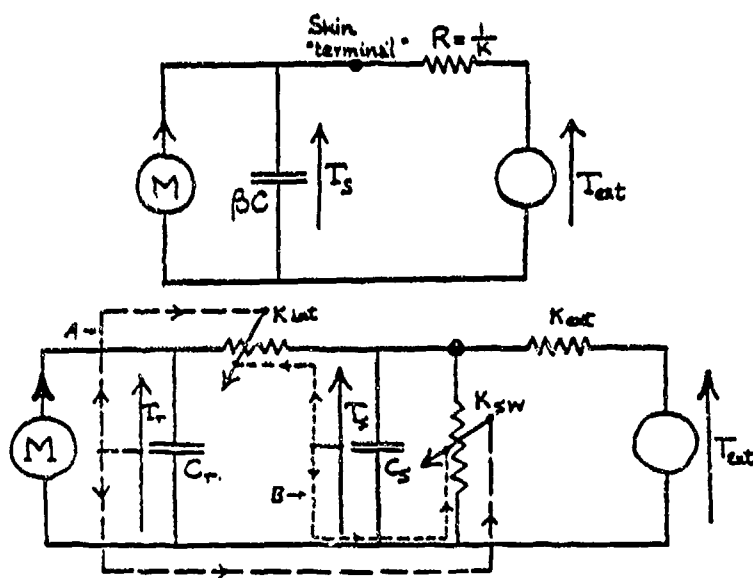


Figure 14. Physical hydrodynamic model of countercurrent heat exchange (3)  
(Reprinted with permission).



A = rectal temperature feedback; B = peripheral temperature feedback; K = thermal conductance;  $T_s$  = mean skin temperature;  $T_{ext}$  = external heat;  $T_r$  = rectal temperature; C = heat capacitance; M = metabolic heat generator; Z = thermal resistance

Figure 15. (Upper) Model of the body as a single unit. (Lower) Developed model with active control channels (92) (Reprinted with permission).



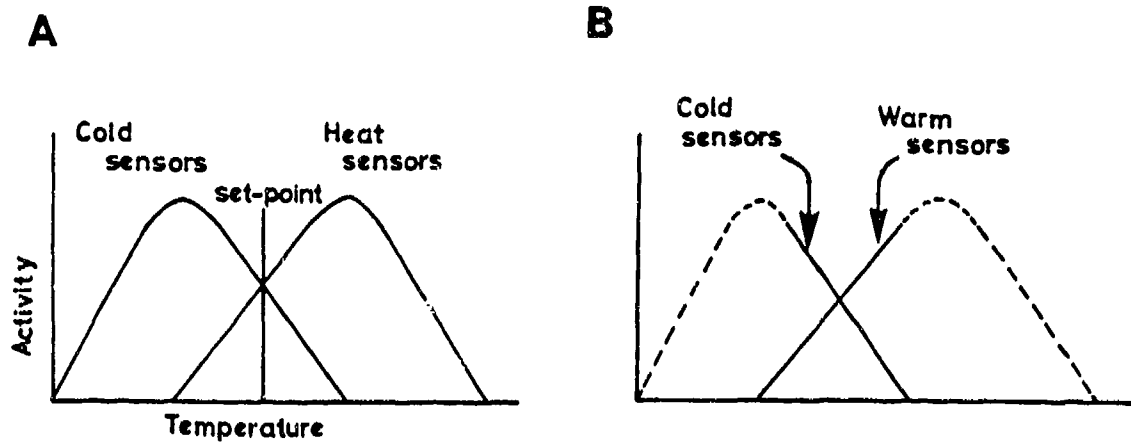
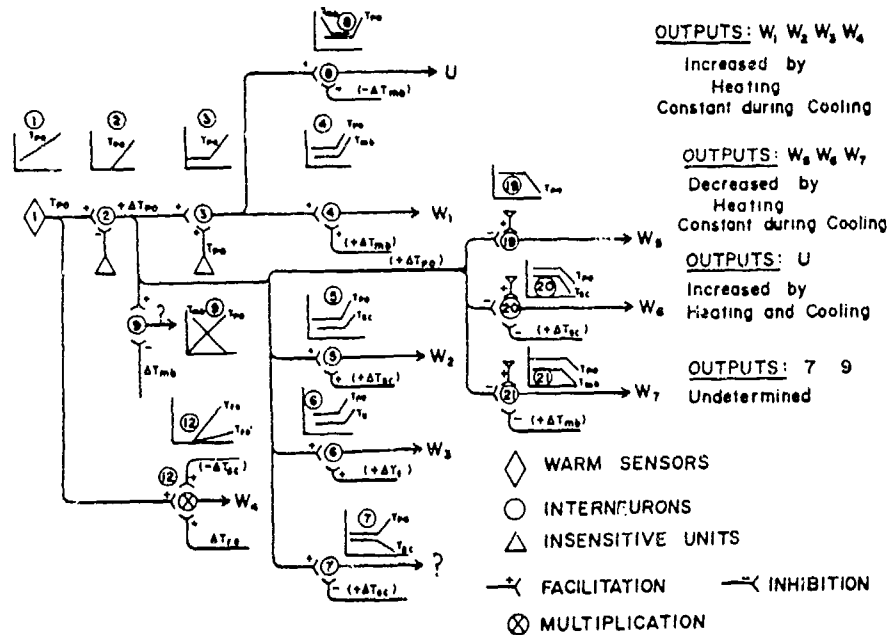


Figure 17. Model of neuronal control of body temperature (94)  
(Reprinted with permission).

PRE-OPTIC-ANTERIOR HYPOTHALAMIC INTERNEURONAL NETWORK  
(WARM)



PRE-OPTIC - ANTERIOR HYPOTHALAMIC INTERNEURONAL NETWORK  
(COLD)

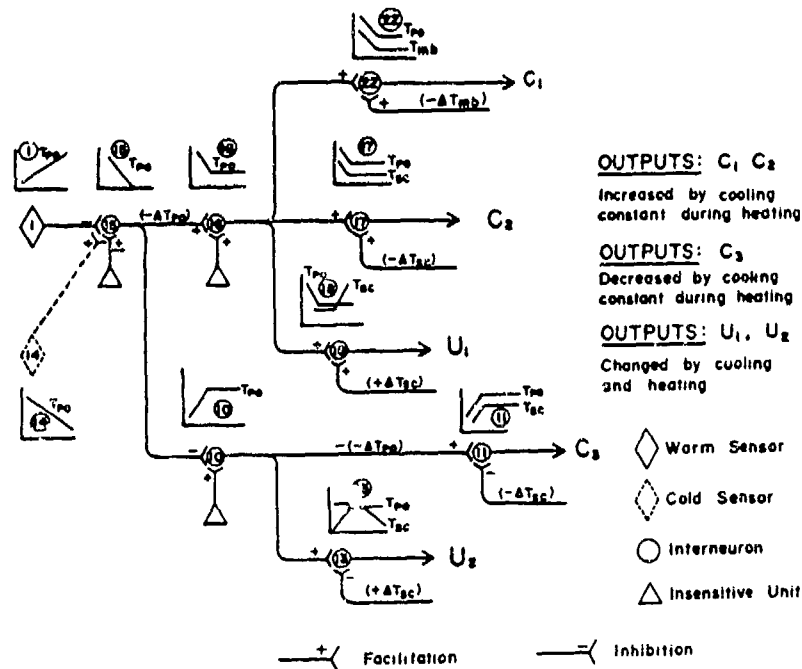
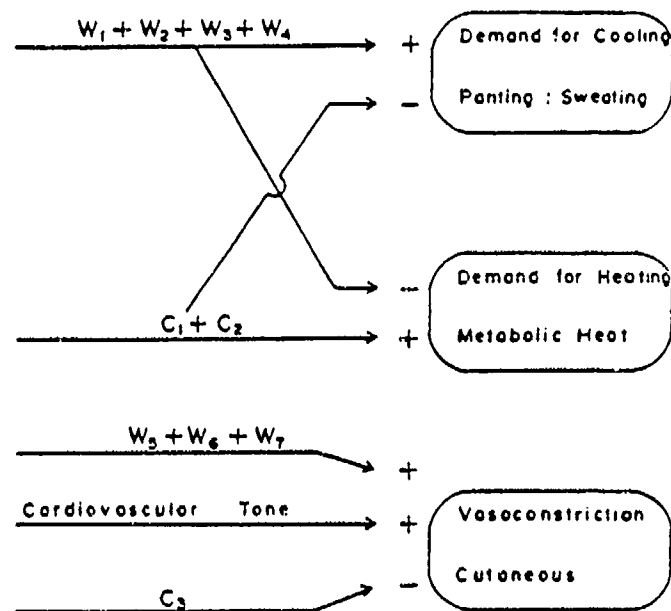


Figure 18. Neuronal model of local and peripheral temperature regulation (103) (Reprinted with permission).



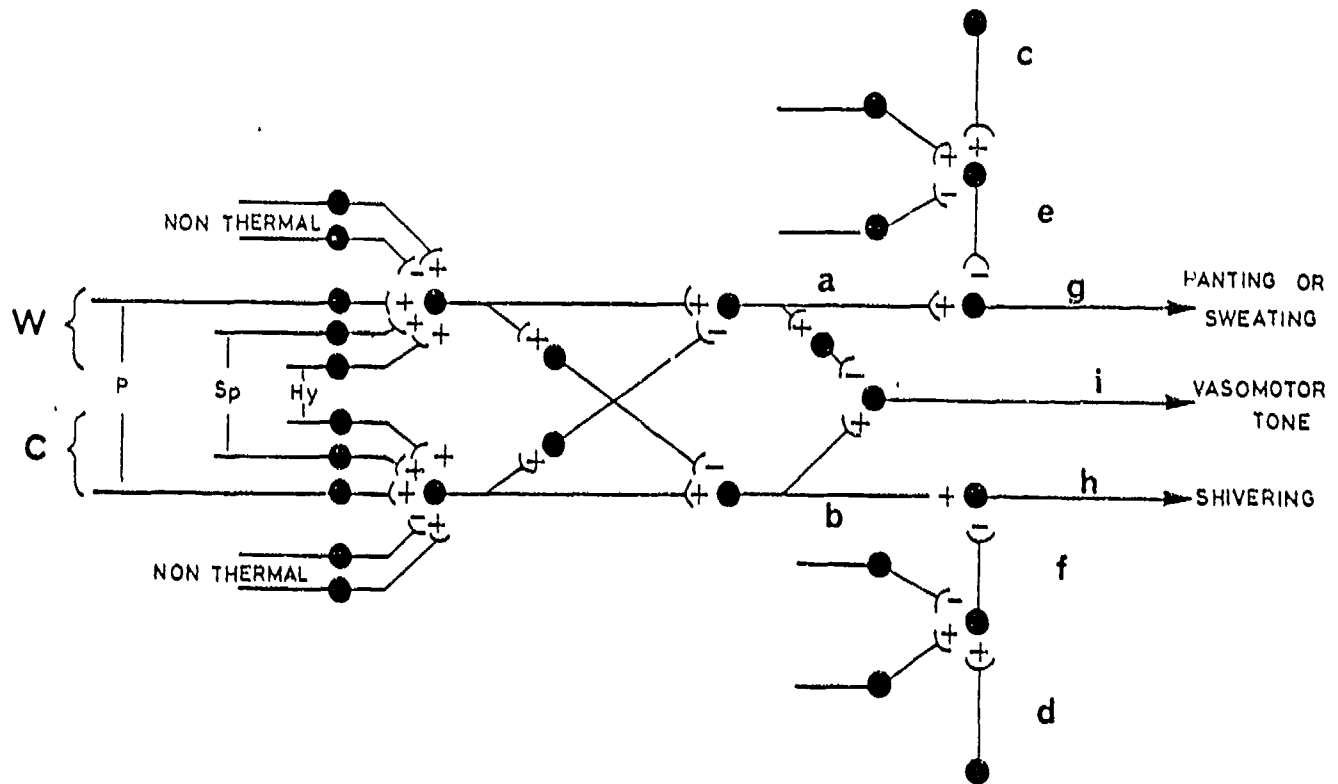
Outputs:  $W_1, W_2, W_3, W_4$  increased by heating, constant during cooling

Outputs:  $W_5, W_6, W_7$  decreased by heating, constant during cooling

Outputs:  $C_1, C_2$  increased by cooling, constant during heating

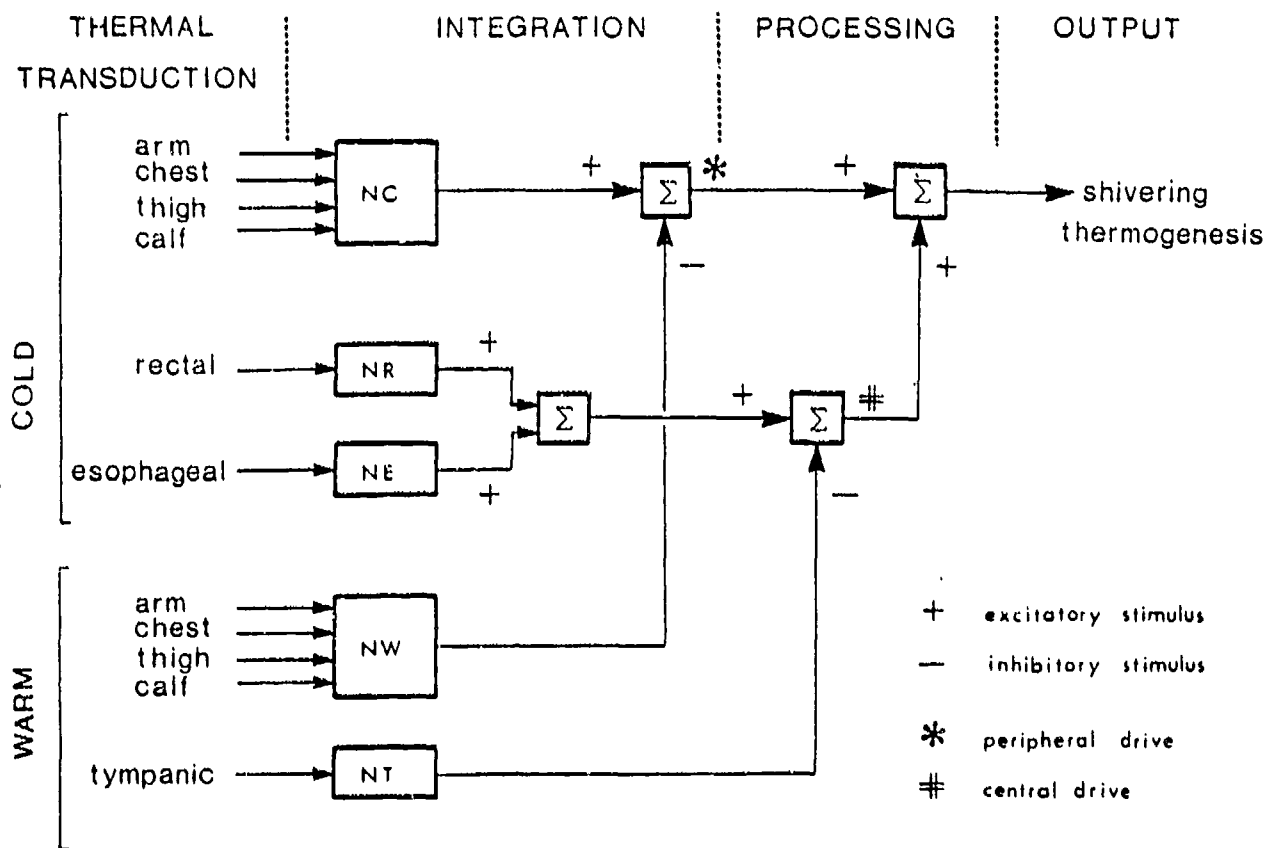
Outputs:  $C_3$  decreased by cooling, constant during heating

Figure 19. Model of the physiological functions of temperature regulation (3)  
(Reprinted with permission).



W = warmth sensors; C = cold sensors; P = peripheral; Sp = spinal cord; Hy = hypothalamus. The letters a to i represent afferent and efferent pathways.

Figure 20. Neuronal model of mammalian temperature regulation with pathways between sensors and effectors (4) (Reprinted with permission).



N = receptors for cold or warmth in a region of the body

Figure 21. Model of shivering thermogenesis based on neural temperature regulation (108) (Reprinted with permission).

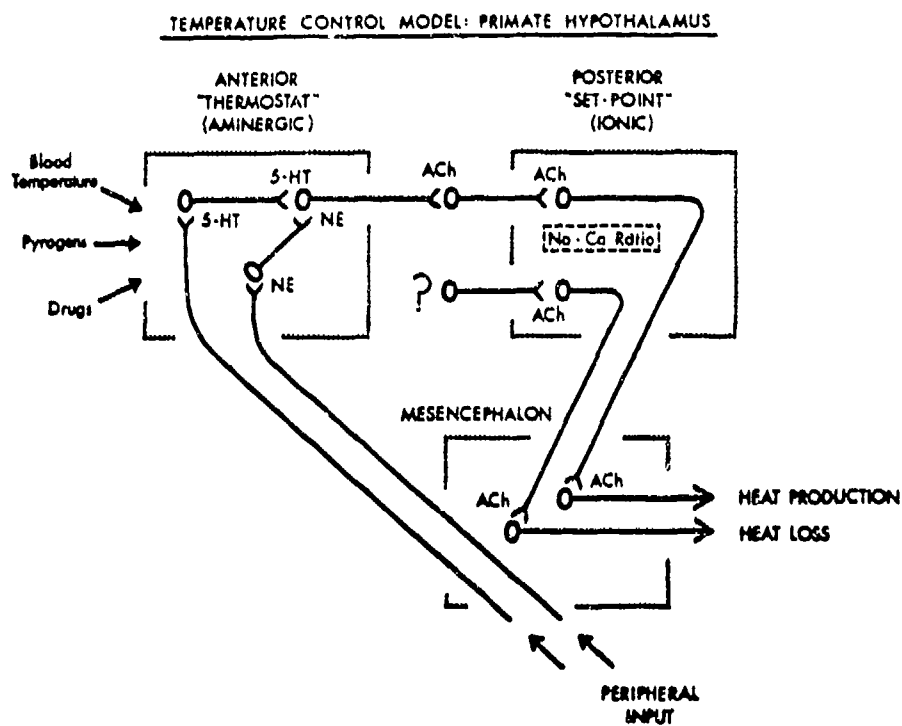
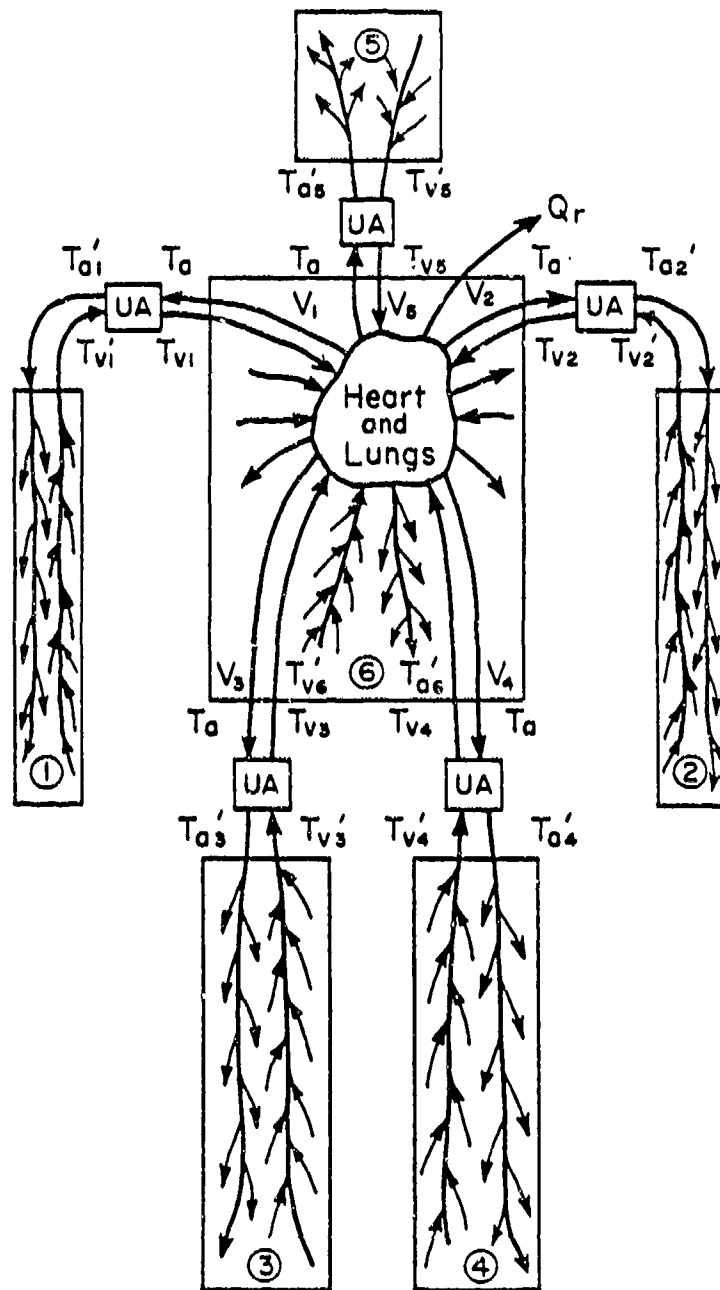
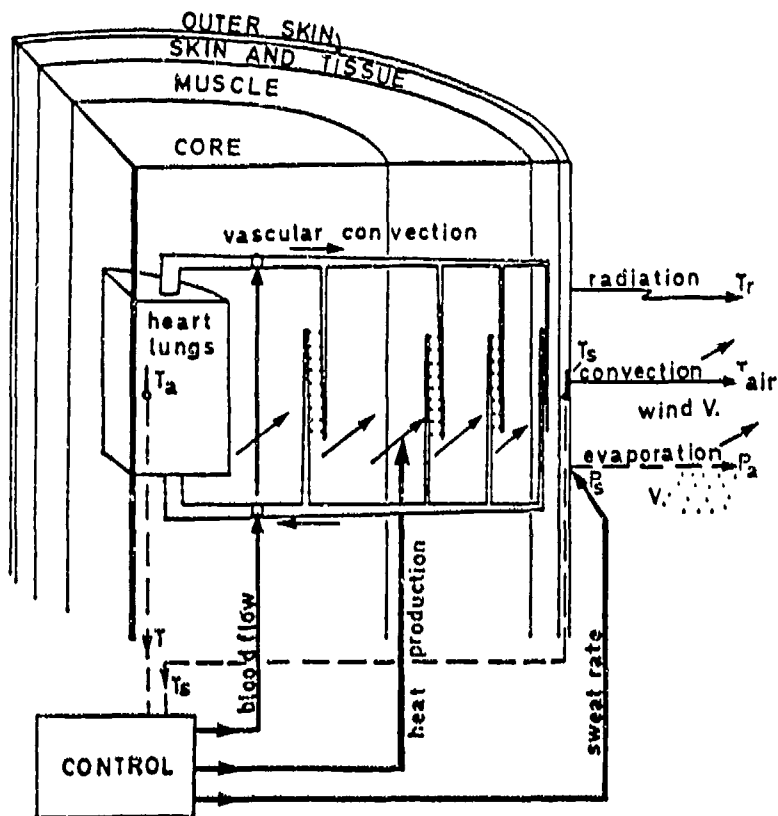


Figure 22. Neurochemical model of temperature control (112) (Reprinted with permission).



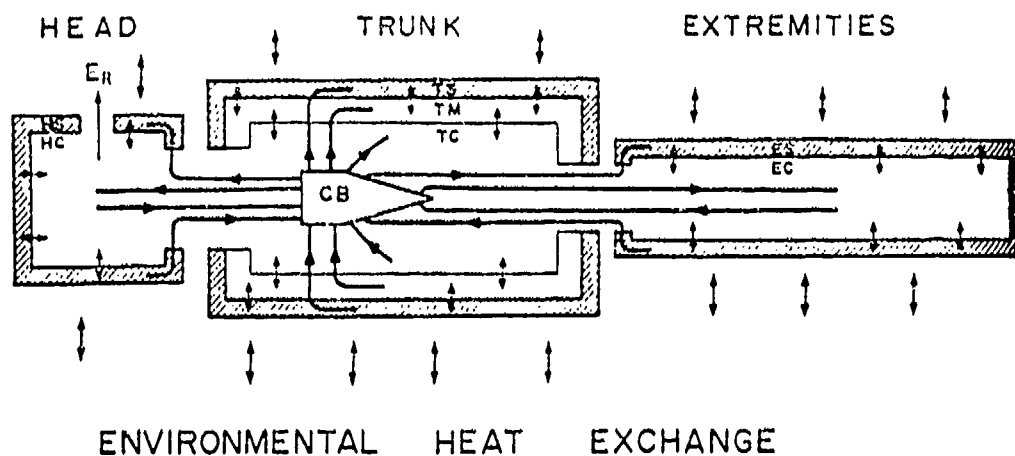
$T_a$  = arterial blood temperature;  $T_v$  = venous blood temperature;  $V$  = volumetric flow rate of blood in the capillary bed;  $Q_r$  = rate of heat loss;  $U$  = heat transfer coefficient;  $A$  = effective area of the heat exchanger

Figure 23. Six-element model of the thermal system (14) (Reprinted with permission).



$T_s$  = skin temperature;  $T_a$  = arterial blood temperature;  $P_s$  = sweat production on skin;  $P_a$  = water vapor content of the air

Figure 24. Thermal model of the human body (125) (Reprinted with permission).



$E_R$  = respiratory heat loss; HC = head core; HS = head skin; TS = trunk skin;  
 TM = skeletal muscle; TC = viscera; ES = extremity skin; EC = extremity core;  
 CB = core blood volume

Figure 25. Model of thermal regulation in the human body (69) (Reprinted with permission).

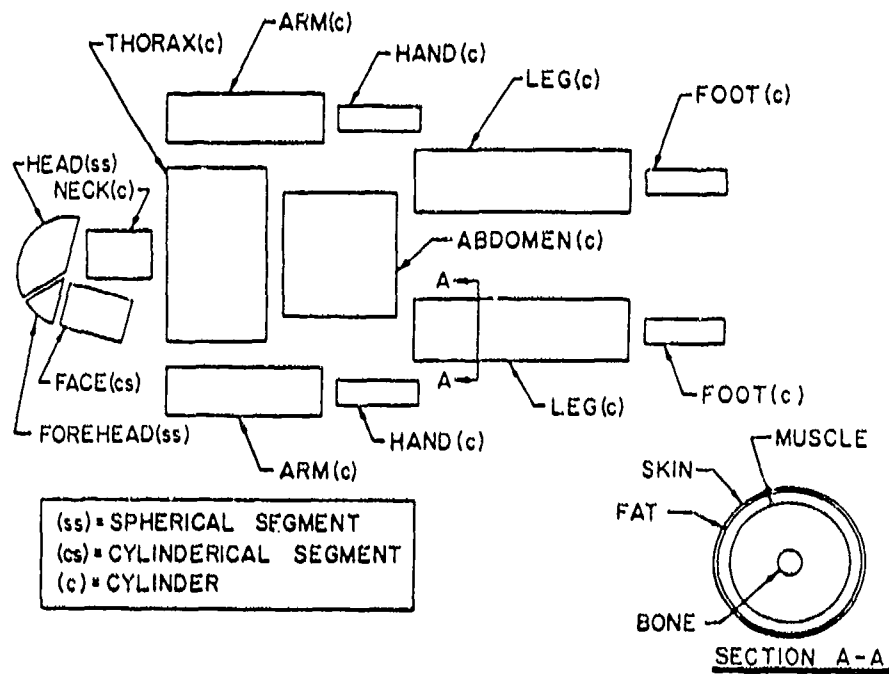
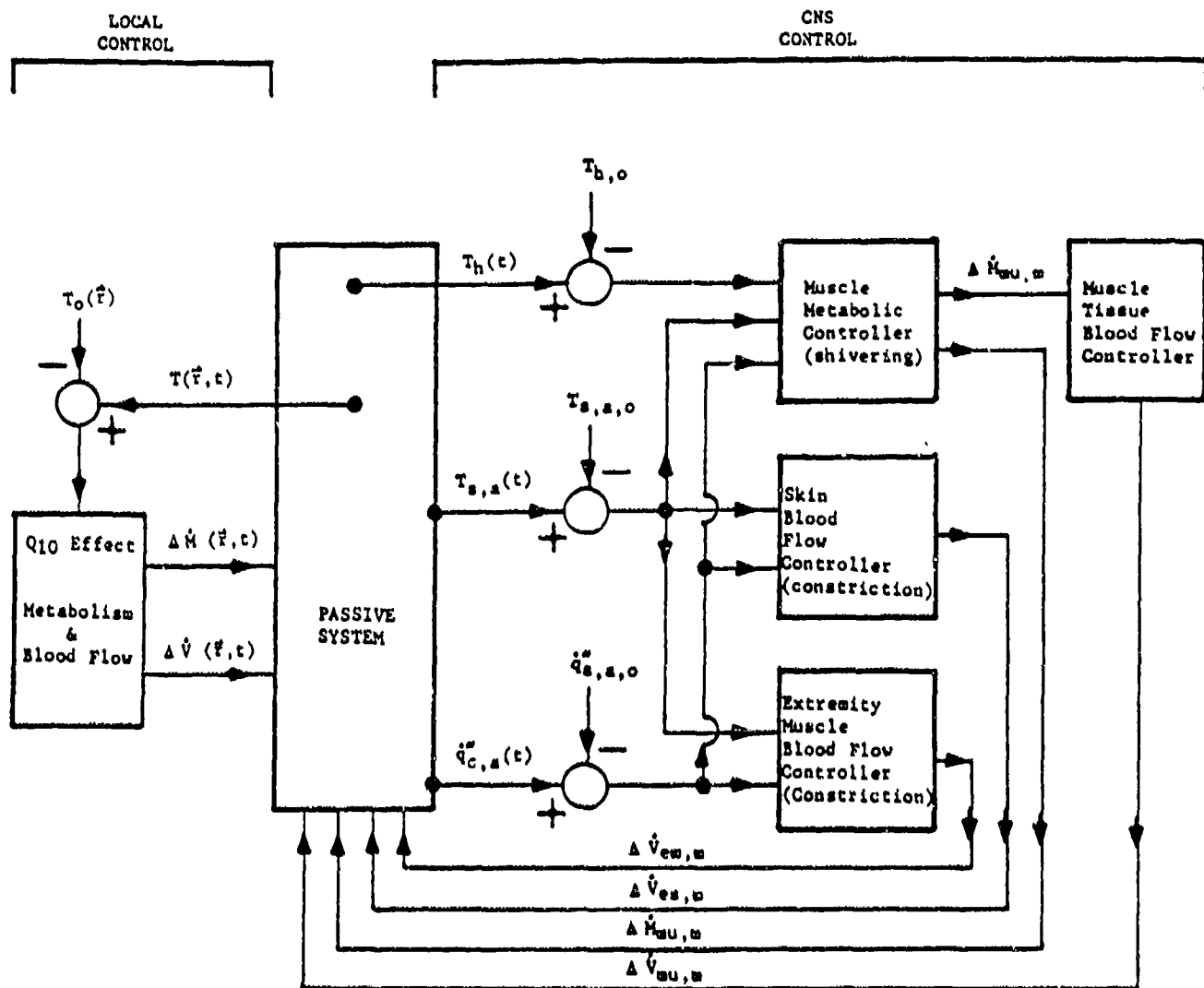


Figure 26. Body elements of thermoregulatory model of a controlled system (135) (Reprinted with permission).



M = metabolic rate; V = blood flow rate;  $T_h$  = hypothalamic temperature;  $T_s$  = skin temperature;  $q''$  = heat flux; em = efferent muscle; es = efferent skin; mu = muscle; m = mean skin temperature; a = air;  $T_o$  = set temperature; t = time

Figure 27. Model of the control and passive systems for temperature regulation with local and central nervous control elements (135)  
(Reprinted with permission).

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