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The Ohio State University, Ph.D., 1972
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COMPUTER SIMULATION AND ANALYSIS OF THE PHYSIOLOGY AND PATHOLOGY OF THE BODY FLUIDS AND COMPARISON OF RESULTS WITH PHYSIOLOGICAL DATA.

DISSERTATION

Presented in Partial Fulfillment of the Requirements for the Degree Doctor of Phylosophy in the Graduate School of The Ohio State University

By


The Ohio State University

1972

Approved by

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Adviser
Department of Electrical Engineering
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ACKNOWLEDGMENTS

The work described in this dissertation has been carried on during over one year with the help and the cooperation of my wife, Rita.

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"Instrumentation for the maintenance of an open loop condition in the body fluid volume control system of small laboratory animals and for the automatic recording of urine flow and conductivity during antidiuretic hormone bioassay".

"Steady State analysis of capillary fluid exchange".

"Analysis and modeling of the renal countercurrent mechanism"

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ABSTRACT

A digital computer model of the body fluid regulation system is presented and the results compared with physiological data in both normal and pathological states. The model includes the analysis and the simulation of three main functions: absorption of material from the gastrointestinal tract, distribution of material among the body fluid compartments, and excretion through the kidneys. A first approach to the simulation of the thirst mechanism is also presented.

The gastrointestinal tract is simulated by equations describing the handling of water and sodium chloride by the stomach and intestine. The statics and dynamics of water and solute exchange between the plasma, interstitial, and intracellular compartments are analyzed. The renal function is studied through the simulation of the nephron sections and of the countercurrent mechanism. The hormonal control of the renal function includes both the antidiuretic hormone and the aldosterone information channels.

Partial responses obtained from sections of the model are compared with physiological data available from the literature as well as the overall model responses. The simulations of water and osmotic diuresis are satisfactory as well as the simulation of more complex experiments involving different kinds of stimulations such as bleeding, infusion of protein solutions, infusion of electrolytes and urea solutions.
A number of conclusions relative to the behavior of the system, and reached through the use of the model, are listed in Chapter XI. Among the contributions offered by this work are:
a) The suggestion of a number of new experiments needed to verify certain model predictions and to further define the system.
b) The indication of improper techniques and methods used in past experiments.
c) The demonstration of the model as a powerful research tool to be used for the planning of experiments, for the interpretation of results, for the testing of hypotheses, for the estimation of parameters and in general for the investigation of the system.
d) The presentation of a background for the detailed sensitivity and stability analysis of the system and for the definition of the boundaries and reasons of pathological states.

It is felt that this model has accuracy, capability and versatility not previously available and sufficient for its extensive use by bioengineers, physiologists and pathologists for the investigation of the body fluid homeostasis and of its abnormalities.
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I.1 Introduction and Definition of a Model

Scientific knowledge is sought by physicians and engineers because it provides the ability and the tools to make decisions and to guide action. Engineering can be defined as the science of investigating and controlling the human environment and of directing its sources of energy and information to the use and convenience of man.

While engineering has mostly been concerned with the external human environment, physiology, biophysics and medicine have mostly dealt with the internal one. However, the interaction of these two scientific branches is becoming increasingly obvious, particularly in the fields of physiological and pathological investigation, that is, in the understanding of the mechanisms underlying the operation of the living systems in the normal and diseased states and their passage from one state to the other.

Animals, as well as man, use energy and information to perform two major tasks;

a) Internal self-regulation (Homeostasis), which involves the maintenance of a number of physiological variables within narrow limits or within limit cycles.
b) Interface with the outside world, which involves the operation of servo-control systems necessary to the pursuit of prey and food, escape or defense from danger, modification of the surrounding environment for a more comfortable living, etc.

Because of their multivariable and highly interconnected organization, living organisms require for their effective study some overall analytical strategy, such as systems theory.

It is the purpose of this research to apply systems theory to the analysis and modeling of the physiological mechanisms regulating the volumes and the solute concentrations of the body fluids. This analysis will account for the absorption of fluid into the organism, its distribution in various body compartments and its excretion by the kidneys under the control of hormonal agents (antidiuretic hormone and aldosterone).

The systems analysis of physiological mechanisms consists of the application of systems theory to the study, and for the explanation, of physiological phenomena.

Systems theory is mostly a theory of models of real systems. A model is a mathematical image or representation of a real system and usually involves some assumption or simplification which makes the mathematical analysis easier or possible and provides constraints to the validity of the model. The model consists of a set of mathematical relationships between the variables and the parameters of the system and should reproduce the desired aspects of the system's behavior as nearly as possible. A model is a powerful tool in the investigation of a system and can be used for either the synthesis of the system's
components or for analysis or optimization purposes.

In the case of physiological processes the system is given and the researcher's task is to understand it in order to improve it (if possible), to maintain it within the boundaries of its normal function and to bring it back into such boundaries when disease modifies its operation.

This is a problem of both analysis and synthesis. The synthesis aspect becomes prevalent whenever a section of the system cannot be studied without damage to the system itself; such a section must then be represented as a "black box" whose transfer function has to be evaluated from the available information on its input and output quantities.

I.2 Models as Tools for the Study of Physiological Systems.

The investigation of a physical system can be carried out by measuring the response of the system to specific inputs or parameter variations. If the system is very complex it is preferable to disassemble it into subsystems or components that can be studied individually. This is often impossible in the case of physiological systems because of two major reasons;

a) In many cases the measurements cannot be performed without major alterations and damage to the organism.

b) The integrity of the organism is a necessary condition for life.

The isolation of components or subsystems is rarely possible and even in such cases subsystem's response may be grossly altered by the lack of interaction with other components.
The necessity of using models is therefore apparent. The value of a model in the study of physiological systems has many aspects which depend upon the system being investigated and the purpose of the investigation.

The most important applications and use of models are listed below.

a) A model provides a general, organized and quantitative view of the system and of the interrelationships between its variables and parameters.

b) A model can be used in the design of experiments and in the prediction and interpretation of experimental data.

Since the physical laws governing the behavior of the model are either known or assumed, the response of the model can be found. The outcome of an experiment run on the model can be compared with the outcome of the same experiment run on the real system and the model can be improved until it becomes a reasonable approximation of the real system (Fig. 1 a). The model can then be used to interpret the results of other experiments, that is to evaluate what parametric variations are needed to produce a given set of results. The diagnostic importance of such setup is obvious (Fig. 1 b). However, caution must be applied in the use of models, especially if they are nonlinear. The use of a model to extrapolate results may sometimes be very misleading.

When some aspect of the system is under investigation, it is important to design the best experiment that may bring to light the desired information or clarify a controversial point. A model can be used in devising such an experiment and the results may then be used, if necessary, to improve the model itself. (Fig. 1 c).
a) Development and improvement of the model.

b) Interpretation of experimental data and diagnosis.

c) Design of experiments.

Fig. 1. Improvement and use of models of physiological systems.
c) As an extension of point b a model can be used to clarify whether controversial findings may be the result of artifacts and bad experimental technique, or of individual variations, or of unknown factors that can be hypothesized and tested with the model.

d) Since there is no difficulty in either establishing relationships or measuring quantities in the model, new information may be obtained with regard to variables or parameters that is impossible to measure in the real system but that can easily be computed or obtained from the model.

e) Finally, a model can be a very valuable teaching tool because of the easy access to its results, the flexibility and variety of the simulation, the short time and low cost of operation.

Despite the advantages, caution is necessary in the use of models. The simplifying assumptions necessary to develop a workable model will produce useful results only in limited sets of cases. A model, therefore, may have a limited range of validity and must be used within such range. The researcher, or the model user, may also be misled by the belief that since a component of the system and its analog in the model satisfy the same mathematical relationships, they are identical. This is not necessarily true, as is indicated by the obvious difference between a voltage and a concentration difference, or a dashpot and a resistor, despite their similar mathematical representation.

The information content of a model may also be different from that of the system, may vary from model to model and may often be misleading. An example for the case of an electrical system is provided by the
Thevenin equivalent circuit which, while being a very useful model of the original circuit, does not provide any indication of the original distribution and value of active and passive components.

I.3 Model Approaches and Techniques.

Two main approaches or levels of modeling may be identified. The first consists of the investigation of the physics of the organism at the molecular and cellular level and in proposing explanations and equations for the processes observed. The resulting model will describe phenomena such as membrane transport of substances, membrane excitability and cell function, and may be extended to describe the behavior of cellular organizations such as glands, nerve bundles, epithelial layers and so on.

The second approach consists of the investigation of the input-output relationship of an organ or system component or process. The parameters of the resulting model for the transfer function may not necessarily represent biological quantities and may not be clearly identifiable in the biophysics of the system being modeled. The model equations may not provide any information or representation of the real system except for yielding a more or less correct input-output relationship of the component under study in terms of an equivalent transfer function. In this way such a component can be accounted for in a larger system while being regarded as a "black box". For example, the heart pumping action may be simulated by a certain time relationship between ventricular
volume and pressure. Obviously this does not account for nor explain the mechanism of muscular excitability and contraction; however, it allows a study of cardiovascular dynamics.

While the first approach has the advantage of being closely associated with the detailed physics and biology of the system, the second allows an easier analysis of the interrelationship between various organs and processes but with the disadvantage of having, in general, a more limited range of validity. The modeling presented in this work will mostly be of the second type, although an effort will be made to associate the model's parameters to biophysical quantities and to avoid purely empirical relationships.

A model has been defined as a set of mathematical equations which provide a representation (often approximated) of a real system. Some variables represent inputs, others represent outputs, and others are internal quantities. Time may be one of the variables.

To solve a model means to find the outputs and the internal variables as functions of the inputs and/or of time. If the model and its equations are sufficiently simple, this task may be performed manually. However, even in the simplest cases, this is a complex and long procedure; in most cases it is impossible.

Analog, digital, and hybrid computers provide powerful tools for the implementation of models.

The analog computer is simpler to use, has the advantage of performing simultaneous computation of all variables, and provides easy ways of inserting numerical quantities and parameter variations, and of graphically
representing any variable as a function of others or of time. The solution of linear differential equations is particularly easy. However, the analog computer often requires complex scaling procedures and presents great difficulties in the simulation of static and dynamic nonlinearities and of time delays. The drift of the amplifiers may also be a problem.

The digital computer is harder to program but does not require scaling procedures, the simulation of nonlinearities and of time delays is easy, and there is no problem of drift. However, the solution of differential equations requires complex numerical procedures, and special programming and equipment is needed in order to obtain plots directly. With the proper programming technique, very accurate results may be obtained and very complex computations may be performed.

Hybrid computers have the advantages and disadvantages of both the analog and digital ones and their evaluation depends upon the amount of their digital and analog hardware.

I.4 Objectives of this Research

Physiological control systems can be classified as homeostatic systems and servo-control systems (see p.1).

The first group includes those regulating systems which are involved in the control of the internal environment of the organism and which, for this reason, are more directly necessary for the maintenance of life. Examples of such systems are the control of body temperature, the control of blood volume, the regulation of blood sugar, and so on. Each of these
systems is involved in keeping the variations of certain quantities within
certain bounds. These must be quantities whose value is critical for the
stability and well being of the organism but whose values can be forced into
suboptimal or intolerable ranges by environmental and parametric changes.
Other variables, however, may have a relatively large range of variation
without endangering the well being of the organism. The identification
of the controlled and non-controlled variables and the quantitative
understanding of the regulatory mechanisms may be of great help to
pathophysiology and medicine.

Among the most effective and most necessary homeostatic mechanisms
is the regulation of body fluid volumes and concentrations. Such regulation
is essential to the maintenance of life. Water represents 55 to 70% of
the body weight and it is the medium in which all the chemical reactions
of the cells occur. It is by means of the body fluid that nutrients
are transported to the cells, wastes are removed from the cells' environment,
and information (hormonal) is carried throughout the body. No less
important are the electrolytes. Ionic concentration differences are at
the origin of all electrical phenomena in the body and the nonuniform
distribution of individual electrolytes between intracellular and extra-
cellular fluids is essential for most organic functions. Minor alterations
of some electrolytes' concentrations produce major irregularities in
muscular concentration and neural transmission. The aquatic medium of
living organism is maintained in homeostasis by a complex system of
interlocking feedback loops which, at the present time, have neither been
entirely identified nor investigated.
It is the objective of this research to apply systems and model theory to the analysis and quantitative investigation of the regulatory mechanisms involved in the homeostasis of body fluids. This main, general objective can be more clearly described by the following operations:

a) Identify the physiological concepts related to water and electrolyte balance on which there is, at the present time, substantial agreement by researchers, textbooks and recent scientific papers. Analyze such concepts in terms of systems theory, identifying and describing the feedback loops, the transfer function of the component blocks and the overall principles involved in the maintenance of a constant internal environment.

b) Analyze the above physiological concepts and the relevant published data and use them to derive mathematical expressions describing quantitatively, and on the base of the underlying physical phenomena, the static and dynamic relationships between the physical quantities involved in the system. The sources of data will be both medical and engineering articles available from the Ohio State University Libraries and searched through the Science Abstracts, the Index Medicus and the MEDIAR facilities.

c) Use the above mathematical analysis to build a quantitative model of the fluid regulation system which is valid for the average normal man over a time interval ranging from a few minutes to a few days.

d) Use the above model to simulate physiological situations for the purpose of verifying its validity and the validity of the assumptions and equations used. Simulate the effect of various inputs and compare
the model's results with clinical data. Analyze the data concerning controversial points of physiology and attempt an engineering analysis of the possibilities in order to choose the most probable theory.

e) Use the above model to study the qualitative and quantitative effects of parameter variations (and abnormalities) over a short and long term. Simulate pathological situations and compare the model's results with clinical data. Investigate the possibility of using the model as a device for the interpretation of clinical data, that is for the identification of parametric changes responsible for pathological behavior.

f) Present a general background work for the stability and sensitivity analysis of the system.

Most and perhaps all of the above points have been the objectives of previous research. These objectives have been approached in various ways and to various degrees by other investigators. It is the purpose of this work to carry on the research and to develop a model having analytic details, capability, versatility and accuracy not previously available. An attempt will be made to account for all the most important control factors (such as hormonal controls, fluid exchange across membranes, renal control and so on), some of which have been neglected in most of the previous works. A more detailed comparison between the proposed objectives of this work and the objectives obtained in previous research will be made in Chapter II.
CHAPTER II

GENERAL CONCEPTS IN THE PHYSIOLOGY AND CYBERNETICS OF BODY FLUIDS.

REVIEW OF PREVIOUS MODELS.

II.1 General Considerations

A thorough knowledge and understanding of the physiology of body fluids is a necessary background not only for the therapeutics of body fluid disturbances but also for their preventive medical treatment. The degree of knowledge required for this purpose has not yet been achieved completely. However, enough is known to allow for the design of models which may help in the formulation and verification of hypotheses and in the settling of controversies in the unknown or uncertain areas of physiology. A brief review of the literature on these models will be presented later in this chapter.

Awareness of the known physiology of a homeostatic system is an obvious requirement for any attempt to model such a system. The most general physiologic and cybernetic concepts of body fluid homeostasis are given in the following two paragraphs. A more detailed analysis of the physiology of each component of the system will be given before the modeling of the component is attempted.
II.2 Fluid Input, Output and Distribution.

Water is continuously lost by living organisms because of evaporation and because of the necessity of excreting the metabolic chemical wastes which can only be excreted in the form of water solutions. Any living system therefore faces the necessity of replacing its body fluids in order to avoid death by dehydration. On the other hand, the fluid input into the system may be excessive which requires the organism's ability to remove the extra fluid by modulation of the output flow.

Water may be added to the organism by:

a) Drinking and eating
b) Intravenous injection
c) Metabolic oxidation

Water may leave the organism by:

a) Excretion of urine
b) Excretion of sweat and saliva
c) Evaporation from lungs and skin
d) Excretion of feces.

While in the organism, water is distributed and can move relatively freely throughout a few main compartments such as the blood plasma, the blood cells, the interstitial spaces, the intracellular spaces and many minor compartments such as the intraocular, the cerebrospinal and other small fluid-filled cavities.

Electrolytes and various solutes may enter and leave the organism through the same routes utilized by water with the obvious exception of
evaporation and with the addition of metabolic production; they are also distributed in the same compartments, although in different concentrations, and if not bound (as in the bones), they can move across the compartments' boundaries. Fig. 2 shows a block diagram that summarizes the above statements.

![Diagram of water and solute distribution](image)

**Fig. 2** Input and output routes and distribution of water and solutes in the organism.
A few cybernetic considerations are obvious from the diagram of Fig. 2. It is rather intuitive that the GIT may have a buffer function in limiting or filtering the amount or type of stress applied to the plasma by the input variables. This function will be discussed in Chapter III. It is also intuitive that the interstitial compartment may have a buffer function in interfacing the plasma with the cells. This function will be discussed in Chapters IV and V.

The kidney may be regarded as the power amplifier of the system because of its energy requirements and its powerful action in filtering out, often against their concentration gradients, the plasma substances to be excreted.

The fluid-filled cavities (cerebrospinal, ocular and so on) have a very minor importance in fluid balance and, therefore, will be totally neglected.

II.3 Information Channels, Control Efforts and Feedback Loops.

Fig. 3 shows the overall block diagram of the water and electrolytes balance system.

The net water and solute flow that enters the plasma compartment is the difference between the absorption from the GIT and the excretion by way of the kidneys (and by evaporation, for water). This fact provides the unity feedback path for both water and solutes (see Fig. 3).

The exchange of substance between the three main compartments includes, in Fig. 3, the metabolic solutes and water.
The interfaces between the compartments (capillary wall and cell wall) have very different characteristics which provide a great deal of autoregulation of the body fluids by means of minor internal feedback loops. However, the most effective regulatory organ is the kidney. Through various mechanisms that will be described later in more detail, water and individual solutes are separated from the blood and stored in the bladder. The flow of urine into the bladder is taken as the output of the system.

In general terms, the operation of the kidneys is as follows; a large amount of fluid is filtered from the blood and then a large percentage of this fluid is reabsorbed into the blood while the difference is excreted. The filtration and reabsorption constants are different for different substances and are dependent upon a number of time varying factors.

Among the most important factors affecting reabsorption are the plasma concentrations of two hormones, antidiuretic hormone (ADH) and aldosterone. While the first controls the reabsorption of water, the second controls the reabsorption of sodium ions which in turn affects the balance of other electrolytes and indirectly of water.

The antidiuretic hormone is secreted into the plasma by the neurohypophysis (under the control of plasma osmolality and blood volume receptors as well as by a number of emotional and pharmacological factors), and is partially excreted in the urine and partially metabolized in the liver. Its blood concentration depends, therefore, upon its distribution in the body and upon its secretion and destruction rates. The relationship between concentration and secretion rate is indicated in Fig.3 as "ADH dynamics". The same type of dependence holds for aldosterone. This
Fig. 3. General block diagram of body fluid homeostasis.
hormone is secreted by the adrenal glands under the direct or indirect control of sodium ion and potassium ion concentration sensors and of blood volume receptors.

The mechanisms briefly described above form two control loops whose inputs are the blood volume, the plasma osmolality and the plasma concentrations of sodium and potassium ions and whose output are the plasma concentrations of the two hormones, which in turn control the kidney function.

It is a physiological fact that the alteration of any of the input quantities modifies (through the hormonal loops) the kidney function in such a direction as to attempt to compensate (through the negative feedback) for the initial alteration. It appears, therefore, that the plasma volume and osmolality and the plasma concentration of the main electrolytes are controlled variables in the homeostatic sense. In turn, the stability of these quantities implies under normal conditions, the control of the interstitial and intracellular volumes.

The quantitative efficiency, priority levels and range of these regulations cannot be indicated for certain at this stage and may be evaluated partially through the use of a model.

The complexity of the system is obvious and the existence of many static and dynamic nonlinearities will be evident from the following chapters. These two factors and the criteria indicated in Chapter I suggest that a digital computer is much more suitable than an analog computer for the implementation of this model. Because of this and other reasons, such as versatility, a digital computer is the tool
chosen for the implementation of this model. The digital simulation will account for all the system blocks indicated in Fig. 3 with the exception of the blood cell compartment which will be considered as a portion of the intracellular space.

II.4 Interrelationships between Control Systems

Since, obviously, the output quantities of the system cannot be negative, the organism cannot totally compensate its own losses by regulation of the output; a control of the input is therefore required. In other words, under normal conditions, the input to the system is neither arbitrary nor random but is specified by the organism's needs. Information on the system's state is relayed to the "thirst center" in the hypothalamus, and, if input is needed, a thirst feeling is produced. However, for the purpose of developing the model the input will be considered an independent and arbitrary variable. An attempt to include the thirst mechanism will be made at the end of this study.

The water-electrolytes regulation system is not independent of other body control systems. Beside being the medium of chemical reactions, water is also the most important factor in body cooling. When internal or external factors tend to increase the body temperature, water evaporation and sweat tend to reduce it. Problems of priority may therefore come to play and the organism has to decide whether to use water for temperature control, for plasma volume control, for intracellular homeostasis, or for other purposes.
The quantitative and hierarchical interaction of water-electrolytes homeostasis and other systems (temperature regulation, cardiovascular, respiratory, and so on) may again be studied best by the iterative procedure of physiological experimentation and model analysis mentioned in Chapter I (Fig. 1). These interactions will be disregarded in this model.

II.5 Review of Previous Literature.

As previously mentioned, the compromise between model validity and mathematical complexity is a major problem in physiological modeling. The improvement of models' validity range without incurring excessive mathematical complexity has been one of the trends in physiological model research.

In 1965 De Land and Bradham presented a digital computer simulation of the statics of the exchange of water, electrolytes and other solutes among body fluid compartments. In the same year De Haven and Shapiro extended the analysis to the statics of urine formation. These models were mostly concerned with the theory of primitive chemical equilibria applied to membrane systems. Neither the hormonal control nor the kidney mechanism were accounted for and the capillary wall was considered as an ideal semipermeable membrane.

In 1966 Levine attempted a mathematical analysis of the kidney function and of the renal effects of both aldosterone and ADH. However, the body compartments were not considered and a computer simulation of the given equations was not attempted. In the same year Nagasaka
(et al.) proposed a nonlinear model of the ADH control of urine excretion which is relatively simple but based on a number of limiting approximations and simplifications. No results concerning the behavior of this model are reported.

In 1967 Reeve and Kulhanek presented another analog computer nonlinear model of the ADH control of urine flow and compared the results with physiological data. Their model is relatively simple; it considers the body fluids in a single compartment and does not account for the details of the renal physiology and for the aldosterone control.

In 1968 Corson and Weed analyzed a small-signal linear approximation of Nagasaka's model, improved the ADH control loop and included the effect of the three main body fluid compartments. The purpose of their work was mainly to show approach techniques and methods of analysis. The model response was not reported. A more complete analog model was proposed by Koshikawa and Suzuki in the same year. Their model included both hormonal loops and the renal handling of sodium and urea; however, it considered the body fluids pooled in a single compartment and it did not clearly indicate what were the transfer functions of the blocks composing the hormonal control loops.

In 1970 De Haven and Shapiro improved their previous digital model by adding the effect of ADH on renal excretion. The resulting simulation is one of the most interesting because it accounts for the individual behavior of a large number of chemical species both in the urine and in the body compartments. In the same year another very interesting and complete digital model was developed by Teates and Cathley. It was
prepared to simulate fluid balance in rats and it included the gastrointestinal and "drinking" subsystems. Some simplifying approximations were made but the results compared well with physiological data.

More recently (1972) a digital computer model was presented by Merletti and Weed which accounted for the mechanism of capillary and cellular fluid exchange and for the antidiuretic hormone control. The gastrointestinal tract and kidney transfer functions were very much simplified and the aldosterone control loop was neglected. However, good results were obtained in the simulation of water loading, dehydration, and diabetes insipidus. The present work is in part an extension of the latter research.

An interesting and quite complete model of circulation and body fluid regulation was recently presented by Guyton (1972). This model included both hormonal control loops and the thirst and drinking mechanism.

Many other models of subsystems have been presented (e.g. capillary exchange, material transfer across membrane, and so on) and will be mentioned in later chapters.

Practically all of the above models can be used for the study of pathological states and some have actually been used for it. However, only the most complete models can provide significant results. The number and types of situations and states that can be investigated vary from model to model but are still limited.

As was previously mentioned, the extension of the practical applications of a model of body fluid homeostasis is one of the major objectives of this research.
II.6 General Comments on this Model

It is probably impossible to attain a model which simulates exactly and predicts any behavior of the body fluid control systems. However, it is evident from the previous section that many of the available models lack even essential characteristics and are often based on such extensive approximations that their validity and utility are impaired. Some models are relatively accurate but simulate only a limited section of the system so that their results cannot be compared to clinical data.

An attempt will be made in this research to attain the most complete model without disregarding details but also without too cumbersome mathematics. The major topics that the model will cover are indicated below.

a) Absorption of water and electrolytes from the GIT into the body fluid compartments (sodium chloride will be considered in particular).

b) Static distribution of water and electrolytes between the three main body fluid compartments (sodium, chloride, potassium, urea, and proteins will be considered in particular).

c) Dynamics of the fluid shifts and distribution between the compartments.

d) Renal processes of filtration and reabsorption of substances (model of the nephron)

e) Control action of aldosterone and antidiuretic hormone.

The approximations relative to the analysis of each of these topics will be indicated in the proper chapters.

It is believed that the extent and detail of this simulation and
especially the range of validity, applications and practical use
of the resulting model(s) will provide a valid tool for the advancement
of knowledge in the fields of physiology and pathology.
Bibliography (Chapter II)


CHAPTER III

PHYSIOLOGY AND MODELING OF THE GASTROINTESTINAL TRACT FUNCTION

III.1 General Physiology and Approximations

The gastrointestinal tract (GIT) does not have a major regulatory function in the control of body fluids in the sense that it is not included (at least in the model) in the system feedback loop (see Fig. 3). However, as it will be seen in Chapter IX, the GIT plays a very important function in smoothing, delaying and modifying sudden stress (fluid loads) applied to the organism. In other words, the GIT has a filtering function in the electrical sense of the word.

The first organ of considerable importance in the GIT is the stomach. Its function is the storing, mixing, processing, and discharging of food into the intestine after the addition of gastric juices. Also, the state of the stomach (degree of fullness, level of acidity and so on), affects, along with other parameters (e.g. dryness of the mouth, psychological factors), the sensation of thirst.

The stomach responds differently to food of different chemical composition; however since this work is concerned only with water and electrolytes, only the response of the stomach to these substances will be considered. Furthermore, since at the present time the input flows
are independent variables, the psychological effects of the stomach state (e.g. thirst feelings) will be neglected.

The presence of food in the stomach stimulates the secretion of gastric juices which are added to the stomach content and modify its osmolality, volume and pH. The total flow of gastric juices in the stomach is in the range of 8 to 10 liters per day but in the case of water and electrolyte ingestion this secretion is quite reduced because of the absence of stimulating chemicals. A limited absorption of water and solutes takes place across the stomach walls (Scholer and Code, 1957). Peristaltic contractions of the stomach produce slow emptying of the chime into the duodenum. In turn, the chemical nature, the volume and tonicity of the duodenal content control the rate of emptying of the stomach through the enterogastric reflex. The detailed study of this reflex, which involves neural factors as well as the release and metabolism of the hormone enterogastrone, is beyond the scope of this study. The whole reflex mechanism will be considered as a black box, whose properties will be described later in this chapter.

The fluid that leaves the stomach spreads very quickly in the intestine, where it is partially absorbed and partially excreted with the feces. Large variations in diet and in the volume of water ingested have little or no effect on the volume of terminal ileal content and on the stool water content (Nasset, 1968, in "Medical Physiology", V. Mountcastle ed.).

The intestine includes various segments of different characteristics; duodenum, jejunum, ileum and colon. Since most of the water and electrolyte absorption takes place in the jejunum and ileum only these segment will be considered.
On the basis of the above physiological considerations, the following major assumptions and approximations can be made for the case of ingestion of water and electrolytes of neutral or near neutral pH.

a) The flow of gastric juices into the stomach is approximately equal to the flow of gastric juices reabsorbed from the intestine so that the extracellular fluid volume and osmolality are not significantly altered by the "recirculation" of the gastric juices.

b) The absorption of water and electrolytes across the stomach wall is assumed to be negligible during the time of stomach storage of the ingested solution. During such time, the composition of the stomach content is assumed to be constant.

c) The rate of stomach emptying is assumed to be controlled, through the enterogastric reflex, by the osmolality of the fluid leaving the stomach (which is equal to the osmolality of the fluid in the stomach).

d) The intestine is assumed to have uniform characteristics along its length.

e) The amount of water excreted daily in the stool is assumed to be constant.

f) As a first approximation the response of the GIT will be considered only for water and sodium chloride solutions.

III.2 Modeling of the Stomach Function.

Studies of the stomach emptying of various solutions were published by Hunt and Spurrel in 1951 and by Hunt in 1963. These data show the volume of the stomach content to decrease exponentially with time after a filling by ingestion. The exponential type of response is maintained when the
osmolality of the ingested fluid changes, but the time constant is modified by the enterogastric reflex. The stomach and the enterogastric reflex can then be considered as a "black box" whose dynamic response is represented by a first order differential equation with variable \( \tau \) (Eq.1).

\[
\frac{dV_s(t)}{dt} = \frac{1}{\tau} V_s(t) + F_s
\]

Hunt's data show the volume of the stomach content 20 minutes after the ingestion of 750 ml of NaCl and of urea solutions of various osmolalities. For NaCl solution such volume is minimum (minimum \( \tau \)) for an osmolality of 230 mosm/l. Calling such volume \( Y \) and the osmolality \( X \) the following two straight lines can be well fitted to the experimental data:

For \( X \leq 230 \) \[ Y = -0.677X + 210 \]

For \( X > 230 \) \[ Y = 0.702X + 101.7 \]

The value of \( \tau \) as function of \( X \) can then be found from Eq.2 and 3.

\[
\text{Eq. 2 } \quad \tau = \frac{20}{\lg \frac{750}{-0.677X + 210}} \quad \text{for } X \leq 230 \text{ mosm/l}
\]

\[
\text{Eq. 3 } \quad \tau = \frac{20}{\lg \frac{750}{0.702X - 101.7}} \quad \text{for } X \geq 230 \text{ mosm/l}
\]

Where: \( \tau \) = time constant of stomach emptying (minutes)

\( X \) = osmolality of the input solution (milliosmoles/liter).

Similar equations can be obtained for urea solutions.
Fig. 4 shows a plot of $\tau$ as a function of $X$ for NaCl solutions. Fig. 5 shows an analog model of the stomach function based on the assumptions described in the previous section.

It is interesting to observe from Fig. 4 that the emptying of the stomach is fastest for osmolalities in the range of isotonicity or slightly less while it is slower for very hypotonic solutions and very much slower for hypertonic ones. The regulatory importance of this behavior, produced by the mechanism of the enterogastric reflex is obvious. Very hypotonic and very hypertonic solutions enter the intestine more slowly than near isotonic solutions, therefore reducing, at least in time, the stress applied to the organism (low pass filtering). The buffer function of the stomach will be discussed in more details later in this chapter.

![Figure 4: Time constant of stomach emptying as function of stomach content osmolality. (Hunt, 1963).](image-url)
Fig. 5 Analog model of stomach emptying. $F_s =$ stomach input flow, $X =$ stomach input and output osmolality, $F_i =$ intestine input flow, $V_s =$ volume of stomach content.

III. 3 Absorption from the Intestine.

The absorption of water and electrolytes takes place mostly in the jejunum and ileum. The absorption rates are a function of the osmolality of the intestinal content. Interesting data were obtained by Vaughan in 1960 in jejunal-ileal sections of dog's intestine. According to these data the absorption rate of water and sodium is linearly related to the intestinal osmolality in the fashion indicated qualitatively in Fig. 6.

From the relationships of Fig. 6 it can be observed that both sodium and water can move against their concentration gradient and therefore some active transport mechanism is involved in their movement. This mechanism is still a physiological controversial point. Some researchers explain it by postulating an active transport of water (Smyth and Taylor, 1957;
Grim, 1962; Visscher, 1957, and so on), others by assuming the transport of water and solute by pinocytosis, others by means of sodium transport alone (Curran, 1960; Fordtran, 1966; Diamond, 1964, and so on). Since active transport of water has never been proven to exist, the investigation of a mechanism involving sodium transport alone is perhaps more logical at the present level of knowledge. The most presently accepted of the suggested mechanisms involving sodium transport alone is indicated in Fig. 7.

**Fig. 6** Qualitative relationship between net absorption flows of water and sodium and the intestinal osmolality.

T = Active transport flow of solute.

\[
\begin{align*}
T & = \text{Active transport flow of solute.} \\
P_{AO} & = \text{Osmotic permeability of A to water.} \\
P_{AS} & = \text{Osmotic permeability of A to solute.} \\
P_{BH} & = \text{Hydrostatic permeability of B to solution.}
\end{align*}
\]

**Fig. 7** Movement of sodium and water across a cellular layer.
Compartment 1 is the intestinal lumen, 3 is an epithelial cell layer in the intestinal wall, 2 is the blood plasma. A is a semipermeable non-porous membrane with a powerful sodium active transport while B is a passive and porous membrane. It is assumed that no hydrostatic type flow takes place across A and no osmotic type flow takes place across B. Because of the active transport and of the limited volume, the osmolality in 3 is maintained above that in 1. Water then flows passively from 1 into 3, increasing the hydrostatic pressure in 3. Since membrane B is porous, the solution in 3 leaks passively into 2 because of the hydrostatic gradient.

Since the chloride ion moves together with the sodium ion (for electrical reasons) the active transport flow can be considered a flow of sodium chloride. Equations 4 and 5 express the balance condition for water and solute flow in the system of Fig. 7.

\[ \text{Eq.} 4 \quad P_{AO'}(C_3 - C_1) = P_{BH}H \]

\[ \text{Eq.} 5 \quad T - P_{AS}(C_3 - C_1) = P_{BH}H \cdot C_3 \]

Solving Eq. 4 for H and substituting it into Eq. 5 yields a second order equation in \( C_3 \) whose physically meaningful solution is:

\[ \text{Eq.} 6 \quad C_3 = \frac{C_1}{2} - \frac{P_{AS}}{2 \cdot P_{AO}} + \sqrt{\left( \frac{C_1}{2} - \frac{P_{AS}}{2 \cdot P_{AO}} \right)^2 + \frac{T}{P_{AO}} + \frac{P_{AS} \cdot C_1}{P_{AO}}} \]

It can be observed that \( C_3 = C_1 \) for \( T = 0 \) and \( C_3 > C_1 \) for \( T > 0 \), as expected, within the range of validity of the approximations.
Substitution of C into Eqs. 4 and 5 yields the expressions for water and solute flows $W_F$ and $S_F$ in the direction 1 to 2.

$$W_F = \frac{P_{AO}}{2} - C_1 - \frac{P_{AS}}{2} + \frac{P_{AO}}{2} \sqrt{\left(\frac{C_1}{2} - \frac{P_{AS}}{2P_{AO}}\right)^2 + \frac{T}{P_{AO}}} + \frac{P_{AS}}{P_{AO}} C_1$$

$$S_F = T + \frac{P_{AS}}{2} C_1 + \frac{P_{AS}^2}{2P_{AO}} - \frac{P_{AS}}{2} \sqrt{\left(\frac{C_1}{2} - \frac{P_{AS}}{2P_{AO}}\right)^2 + \frac{T}{P_{AO}}} + \frac{P_{AS}}{P_{AO}} C_1$$

It appears that a linear relationship of the kind indicated in Fig. 6 between $W_F$ and $C_1$ and between $S_F$ and $C_1$ may be obtained if the term $T/P$ is dominant over the other two terms under the square root sign, that is, if $T$ is sufficiently large and $C_1$ and $P_{AS}$ are sufficiently small. Given the absorptive function of the intestinal membrane and the relatively limited range of concentration of the sodium chloride solutions that can be ingested, it appears reasonable to assume that the above conditions are satisfied. The mechanism just described may, therefore, be assumed as the one underlying Vaughan's results.

Although Vaughan's data were obtained from dogs, it will be arbitrarily assumed here that the flow inversion points (400 mosm/liter for water and 70 mosm/liter for sodium chloride) are the same in man and dog.

In 1964 Whalera measured the absorption of water and sodium from isotonic saline solutions placed in human jejunum and ileum and found the amounts absorbed per hour and per length of both these intestinal sections. The
average absorption coefficients of the jejunum in the case of isotonic NaCl solution were $1.67 \text{ ml/hr \cdot cm}$ for water and $0.275 \text{ mM/hr \cdot cm}$ for sodium.

Assuming:

a) The flow reversal points for water and sodium are the same in man and dog, and

b) The water and sodium flows across the intestinal wall are linearly related to the osmolality of the intestinal content, as is indicated in Fig.6,

the above values allow the transformation of the qualitative diagrams of Fig.6 into quantitative ones.

The remaining important factor to be considered is the intestinal surface through which the absorption takes place. No reliable data are available for this evaluation. However, it is known from X-ray observations that barium sulphate solutions spread very quickly along the jejunum and the ileum and are observable in the whole small intestine until the absorption is completed. This suggests a model of the intestine as a collapsed fabric sleeve whose internal surface is wetted by the input fluid along its whole length. Also, according to this interpretation, increased volume does not change the absorbing surface but only the shape of the sleeve section from flat to round.

It is also known that the intestinal content is not continuous, but is broken down in packets which are moved forward and backward by peristaltic waves. The length of the intestine which is in contact with the chime is therefore less than the total length.

In absence of better information it is arbitrarily assumed here that
the absorptive length of the small intestine is 120 cm for any volume of fluid and that the absorption coefficients are uniform along this length. If the jejunum-ileum length of 290 cm is taken, (according to Fordtran,1965) it appears that the absorbing length here assumed is a little less than half the total length.

Because of lack of information it is not known whether this is a realistic model of the intestinal function. Other models may be proposed and tested. For example, it might be assumed instead that the wet surface is proportional to the volume of the intestinal content, or that the filtration coefficients are related to the intestinal pressure. Since physiological ideas about these assumptions are still very vague, the interplay of further medical experimentation with the use of the model, as was indicated in Chapter I, may be very useful.

III.4 Modeling of Intestinal Absorption and Results.

The assumptions and the data discussed in the previous section lead to Equations 9 and 10, which are represented graphically in Fig.8. (Fig.8 does not account for $F_i$ and $S_i$).

\[
\text{Eq.9} \quad \frac{dV_i}{dt} = -13.36 \times 10^{-3} + 34.10 \times X_i + F_i
\]

\[
\text{Eq.10} \quad \frac{dO_{ci}}{dt} = 0.35 - 4.94 \times 10^{-3} \times X_i + S_i
\]
Eq. 11 $X_i = \frac{O_{ci}}{V_i}$

where:
- $F_i$ = water flow from the stomach into the intestine (liters/min.)
- $S_i$ = solute flow from the stomach into the intestine (mosm./min.)
- $V_i$ = volume of intestinal content (liters).
- $O_{ci}$ = osmotic content of intestine (mosm.)
- $X_i$ = osmolality of intestinal content (mosm/l)

The system of Equations 9 to 11 can be represented by the analog model of Fig. 9, which also includes the model of the stomach function given previously in Fig. 5. The nonlinearity of the system and the existence of feedback are apparent from both the diagram and the equations.

The absorption of a fluid load placed in the intestine can be simulated by setting $F_i = S_i = 0$ in Eqs. 9 and 10 and by fixing the proper initial conditions for $V_i$ and $O_{ci}$.

The system of Eqs. 9 to 11 describes a model of the intestinal response to sodium chloride solutions. These equations can be solved on a digital computer to provide information about the behavior of such a model. The numerical techniques used for this purpose are described in Appendix A. The results obtained by simulating the "instantaneous" placing of 400 ml of various NaCl solutions in the human small intestine are shown in Fig. 10. The times required for the complete absorption of various volumes of sodium chloride solutions of various concentrations placed in the intestine are given in Fig. 11. The comparisons of these results with physiological data may lead to a more accurate determination of the absorption characteristics of the human intestine.
Fig. 8. Relationship between water and solute (NaCl) flow across the intestinal wall and the intestinal osmolality.
Fig. 9. Analog model of the gastrointestinal tract.

ECF = Extracellular Fluid Compartment.
Fig. 10. Response of the model to the placement of 0.4 liters of fluid into the small intestine. The response to four NaCl solutions having osmolalities of 0, 200, 400, 600 mosm/l is shown.
Fig. 11. Time required for the complete absorption of a solution as a function of its amount and osmolality. The solution is assumed to be placed instantaneously into the small intestine.
III.5 Modeling of the Overall GIT Function and Results.

Fig.12 shows the results obtained from the model by simulating the placement of 0.4 liters of NaCl solutions of various osmolalities in the stomach. The osmolalities of the solutions were 0, 200, 400, 600 mosm/l. The graph shows the time course of the intestinal content volume and osmolality and the change in body fluid volume in each case. It may be observed that, as was shown in Fig.10, the osmolality of the intestinal content approaches isotonicity during the process of absorption. This is in excellent agreement with physiological findings. Another observation is that, for low osmolalities, the intestinal absorption is fast, while the stomach emptying is relatively slow; it may therefore happen that the stomach emptying rate becomes the controlling factor in fluid absorption. No physiological evidence was found which bore on this result.

The most important observation concerns the volume of fluid withdrawn from the body fluid compartments during the digestion of hypertonic solutions. By comparison of Figs.10 and 12 it is apparent that the 0.4 l, 600 mosm/l solution is absorbed into the body in about the same time whether it is placed into the stomach or into the gut. However, the fluid moving into the intestine from the blood is substantially less when the solution is placed in the stomach.

The buffer action of the stomach is better shown in Fig.13, where the maximum negative change in body fluid volume is plotted against the osmolality of 0.4 l of NaCl solutions placed in the stomach (curve 1) or in the gut (curve 2). The circulatory stress in case 1 is about one half that in
Fig. 12. Response of the model to the ingestion of 0.4 liters of NaCl solutions having osmolalities of 0, 200, 400, 600 mosm/l.

(*) The GIT content is not considered as part of the body fluid volume.
case 2. Qualitatively these results agree with physiological findings.
For example, it is a well known fact that a person whose stomach has been surgically removed may die of circulatory collapse after eating a large hypertonic meal.

As it appears from Fig. 12 as well as from Fig. 11, the higher the osmolality of the input solution, the longer the time required for absorption. This allows the organism to react and compensate better for the amount of solute which is being added to it and to reduce the applied stress. The buffer action of the GIT on the osmotic and volumetric stress of the body compartments will be ever more evident from the results presented in Chapter IX.

Fig. 13. Maximum reduction of the body fluid volume, due to exorption of water from the blood into the intestine, as function of the osmolality of the hypertonic solution (c.4 l) of NaCl placed into the stomach (curve 1) or into the intestine. (curve 2).
Bibliography (Chapter III)


CHAPTER IV

PHYSIOLOGY AND MODELING OF THE STEADY STATE DISTRIBUTION
OF WATER AND SOLUTES IN THE BODY.

IV.1 The Body Fluid Compartments. General Physiology and Approximations.

This chapter is concerned with the analysis of the steady state equilibrium of the fluids separated by the cell membrane and by the capillary membrane. The dynamics of the exchange across such membranes will be considered in Chapter V.

The three main body fluid compartments are the blood plasma, the interstitial space (IS), and the intracellular space (IC). The plasma and the interstitial spaces together form the extracellular fluid (EC). The term "compartment" is used here in a macroscopic sense, and it is assumed that each of these three compartments is uniform and homogeneous. The plasma is the only fluid for which the above assumptions hold in a satisfactory degree. Both the interstitial and intracellular fluids may vary widely, both in nature and composition, in different organs and even within the same organ. Furthermore, the intracellular compartment is not continuous, being made up by the millions of body cells, and it is not uniform even within a single cell. However, if the whole body is considered, an average composition may be defined for the intracellular and interstitial compartments. These average idealized compartments are

13
the ones considered in this study. In particular, the blood cells fluid will be considered as a part of the intracellular compartment and the lymph fluid as a part of the interstitial.

Edelman and Leibman (1959) in their review of the anatomy of the body fluids defined two more compartments, namely the connective tissue and bone fluids and the transcellular fluid. The first of these compartments will be considered here as a part of the intracellular fluid, the second is really a special section of the interstitial fluid and will be considered as such.

The boundaries between the plasma and the interstitial space (capillary membrane or more generally, any blood vessel's wall), and between the interstitial and intracellular space (cell membrane) have very different properties. The capillary membrane is very permeable to water, electrolytes and small molecules and it has pores through which large molecules (proteins) can leak in limited amounts. The cellular membrane is less permeable to water and electrolytes, it is practically impermeable to proteins, and it includes metabolic mechanisms (pumps) by which concentration gradients of individual electrolytes or solutes can be maintained.

The exchange of material between the plasma and the interstitial space takes place both across the capillary membrane and by means of the lymphatic circulation. A model of these compartments is indicated in Fig. 14. Table 1 shows the composition of the body fluids as reported by Guyton and it indicates the total osmolality of each compartment as being approximately 302 mosm/l. Other authors have indicated slightly different compositions and total normal osmolalities ranging from 270 to 315 mosm/l.
It is evident from this table that the plasma and the interstitial fluid have practically the same composition, with the exception of different protein concentrations, while the intracellular fluid has a radically different composition.

The body fluid compartments are in a state of dynamic equilibrium because fluid is continuously being subtracted from the body and periodically added to it. (See Fig. 3). A situation of static equilibrium can only be reached in a nephrectomized animal (if the metabolic solute production and the water insensible losses are negligible over the time considered). A steady state analysis of fluid distribution system is important for two reasons: first, it indicates how various substances are distributed within the body, and second, it indicates toward which new state the system moves when some fluid or substance is added or subtracted from it.

If the short term oscillations of the body fluid compartments resulting from daily input and output are averaged or neglected, a steady state analysis may also be, in some respect, an investigation of the long term regulation of the internal fluid equilibrium. (e.g. interstitial fluid regulation, edema formation, protein distribution, etc.).

Four problems can be identified in the study of static and dynamic balance of the body fluid compartments; they are listed below.

Problem 1. Given the total body water and the total amounts of each of the various body solutes, given the proteins content of the intracellular and extracellular compartments, and given the physico-chemical characteristics
heart and lungs

input

GIT

output

capillary bed

M1

plasma

interstitial fluid

M2

intracellular fluid

a) exchange of water and electrolytes and solutes of low mol. weight.
b) leakage of whole plasma into the interstitial fluid.
c) lymph flow.


Fig. 14. Schematic diagram of the body fluid compartments.

Table 1
Composition of the body fluids. (from Guyton, Textbook of Medical Physiology, 1971)

<table>
<thead>
<tr>
<th></th>
<th>Plasma (mOsmols./L of H2O)</th>
<th>Interstitial (mOsmols./L of H2O)</th>
<th>Intracellular (mOsmols./L of H2O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td>144</td>
<td>137</td>
<td>10</td>
</tr>
<tr>
<td>K⁺</td>
<td>5</td>
<td>4.7</td>
<td>141</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>2.5</td>
<td>2.4</td>
<td>0</td>
</tr>
<tr>
<td>Mg²⁺</td>
<td>1.5</td>
<td>1.4</td>
<td>31</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>107</td>
<td>112.7</td>
<td>4</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>27</td>
<td>28.3</td>
<td>10</td>
</tr>
<tr>
<td>HPO₄²⁻ - H₂PO₄⁻</td>
<td>2</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>SO₄²⁻</td>
<td>0.5</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Phosphocreatine</td>
<td></td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>Carnosine</td>
<td></td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>Amino acids</td>
<td>2</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Creatine</td>
<td>0.2</td>
<td>0.2</td>
<td>9</td>
</tr>
<tr>
<td>Lactate</td>
<td>1.2</td>
<td>1.2</td>
<td>1.5</td>
</tr>
<tr>
<td>Adenosine triphosphate</td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Hexose monophosphate</td>
<td></td>
<td></td>
<td>3.7</td>
</tr>
<tr>
<td>Glucose</td>
<td>5.6</td>
<td>5.6</td>
<td>3.7</td>
</tr>
<tr>
<td>Protein</td>
<td>1.2</td>
<td>0.2</td>
<td>4</td>
</tr>
<tr>
<td>Urea</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>TOTAL mOsmols.</strong></td>
<td><strong>303.7</strong></td>
<td><strong>302.2</strong></td>
<td><strong>302.2</strong></td>
</tr>
<tr>
<td>Corrected osmolar activity (mOsmols.)</td>
<td>282.6</td>
<td>281.3</td>
<td>281.3</td>
</tr>
<tr>
<td>Total osmotic pressure at 37° C. (mm. Hg)</td>
<td>5454</td>
<td>5430</td>
<td>5430</td>
</tr>
</tbody>
</table>
of the membranes separating the compartments, find the equilibrium
distribution of water, electrolytes and proteins in each compartment.

Problem 2. Given the equilibrium distribution found in Problem 1 and
given the amounts of water and individual solutes added to or subtracted
from the system, find the new equilibrium state.

Problem 3. Given the initial and final equilibrium states found in
Problems 1 and 2, find how the system moves from one state to another as
a function of time.

Problem 4. Given the initial values of Problem 1 and the system water
and solute inputs as functions of time, find the state of the system as
a function of time.

The solution of the first two problems will be attempted in the
other sections of this chapter. Problems 3 and 4 will be discussed in
the next chapter.

IV.2 Analysis of the Equilibrium between Interstitial and Intracellular
Compartment.

The idealized membrane which in this model separates the interstitial
space from the intracellular space is assumed to be a "black box" having
certain macroscopic properties. Such properties will determine the
equilibrium condition between the two compartments. A detailed analysis
of these properties and of the resulting equilibrium has been presented
by De Land and Bradham (1965) and by Shapiro (1968) whose results are used
in this model and whose work is briefly summarized in this section. The
following assumptions are made:
a) The cellular membrane is impermeable to proteins, and
b) The osmolar fraction for a substance A is the amount of A (in osmoles) on a side of the membrane divided by the total amount of material (in osmoles) on that side of the membrane. The membrane is assumed to have the ability of maintaining a constant ratio between the osmolar fractions of each substance in the two compartments.

Let us now consider the two regions, $R$ and $R'$, where $R$ is the interstitial compartment and $R'$ the intracellular. Let $R$ contain $q$ osmoles of proteins and $R'$ contain $q'$ osmoles of proteins; let $R$ and $R'$ contain $n$ substances each, beside the proteins, and let the boundary membrane be permeable to all the $n$ substances. Let $X_i$ be the amount, in osmoles, of substance $i$ in $R$ and $X_i'$ be the amount, in osmoles, of substance $i$ in $R'$. Let us define:

\begin{align*}
\text{Eq. 12} & \quad \bar{X} = q + \sum_{i=1}^{n} X_i \\
\text{Eq. 13} & \quad \bar{X'} = q' + \sum_{i=1}^{n} X_i' \\
\text{Eq. 14} & \quad b_i = X_i + X_i' \\
\text{Eq. 15} & \quad \bar{b} = q + q' + \sum_{i=1}^{n} b_i = \bar{X} + \bar{X}'
\end{align*}

where $\bar{X}$ and $\bar{X}'$ represent the total amount of material (osmoles) in $R$ and $R'$ and $\bar{b}$ is the total amount (osmoles) of material in the system. The $b_i$'s, $q$ and $q'$ are known and the $X_i$'s are unknown as well as $\bar{X}$ and $\bar{X}'$. The osmolar fractions are defined as:

\begin{align*}
\text{Eq. 16} & \quad \hat{X}_i = \frac{X_i}{\bar{X}}
\end{align*}
Eq. 17
\[ \hat{X}_1 = \frac{x_1'}{\bar{X}} \]

and their ratio is:

Eq. 18
\[ K_1 = \frac{\hat{X}_1}{\bar{X}_1} = \frac{x_1'}{x_1} \frac{\bar{X}}{\bar{X}'} \]

The membrane, by mean of its metabolic pumps, maintains a constant value of \( K_i \) for each substance. The \( K_i \)'s are assumed known. The system of Eq. 14 and Eq. 18 can be solved for \( X_1 \) and \( X_1' \) as functions of \( \bar{X} \) and \( \bar{X}' \) and Eq. 19 and Eq. 20 are obtained.

Eq. 19
\[ X_1 = \frac{\bar{X} b_1}{\bar{X} + K_1 \bar{X}'} \]

Eq. 20
\[ X_1' = \frac{K_1 b_1 \bar{X}'}{\bar{X} + K_1 \bar{X}'} \]

Eq. 12 and Eq. 19 may be represented graphically by the system of Fig. 15. The system is represented in term of the region R components. Using Eqs. 13 and 20 the representation can be in term of the region \( R' \) components.

It is interesting to observe that for a freely diffusible substance \( J \) not affected by metabolic pumps, \( K_J = 1 \) and \( X_J = \bar{X} b_j/b \). Eqs. 19 and 20 are not the solution of the system because \( \bar{X} \) and \( \bar{X}' \) are unknown. Substituting \( X_1 \) from Eq. 19 into Eq. 12, and replacing \( \bar{X}' \) with \( \bar{b} - \bar{X} \), Eq. 21 is obtained:

Eq. 21
\[ \frac{q}{\bar{X}} + \sum_{i=1}^{n} \frac{b_1}{X + K_1 (\bar{b} - X)} - 1 = 0 \]
Fig. 15. Graphical representation of the equations regulating the steady state balance between interstitial and intracellular compartments.

Inputs: \( b_1 \) to \( b_n \), \( b = \sum_{i=1}^{n} b_i \), \( q \). Data: \( K_i \) to \( K_n \).

Outputs: \( X_1 \) to \( X_n \). \( N = \) numerator. \( D = \) denominator.
The only unknown in Eq. 21 is \( \bar{X} \). Solution of Eq. 21 for \( \bar{X} \) and substitution of \( \bar{X} \) into Eq. 19 and Eq. 20 yield the distribution of each substance in region \( R \) and \( R^* \). It can be shown that if \( q \neq 0 \) and \( q' \neq 0 \), as in our case, Eq. 21 has only one real root in the interval 0 to \( \bar{b} \). (De Land, Bradham, 1965). Eq. 21 can be written as a polynomial of degree \( m+1 \), where \( m \) is the number of substances having \( K_1 \neq 1 \), and can be solved by numerical methods.

It is possible to observe from Table 1, as well as from Edelman's data, that sodium (Na), potassium (K), and chloride (Cl) are the most important ions in the body. Another important solute is urea; although its concentration is low in the body fluids, urea is important because it is the major metabolic product and because of its high concentration in the urine. The next two ions in order of importance are bicarbonate and phosphate (\( \text{HCO}_3, \text{H}_2\text{PO}_4 \)). All the other solutes appear to be of secondary importance. For the sake of simplicity, and as a first approximation of this analysis, only the following substances will be accounted for individually: water, (\( \text{H}_2\text{O} \)), sodium (Na), potassium (K), chloride (Cl), urea, proteins. The other ions and solutes will be pooled together and considered as a single substance referred to as "other ions" (Oi). The distribution of this fictitious substance will be to some degree representative of the bicarbonate ion, which is in the highest amount among the "other ions".

It can be observed that since one liter of solution contains about 55.6 osmoles of water and about 0.3 osmoles of solutes the numerical value of \( \hat{X}_1 \) can be well approximated by \( X_1/X_w \) where \( X_w \) is the amount of water in \( R \). \( \hat{X}_1 \) can be similarly approximated. The ratio of the osmolar fractions,
K_i can then be well approximated by the ratio of the osmolar concentrations. In other words, each K_i may be expressed in \((\text{mosm/l})/(\text{mosm/l})\) rather than in \((\text{osmoles/osmoles})/(\text{osmoles/osmoles})\), the two numerical values being very close. (the error in K_i is less than 1%). The values of the K_i's can therefore be easily determined with very good approximation from Table 1. Data from Guyton, Edelman and other authors lead to the model distribution of the body water and solutes given in Table 2.

Table 2 does not indicate specific physiological data but rather average values where a simplifying assumption is made. The simplification consists in assuming equal ionic concentrations in the plasma and interstitial compartments. Although not exactly true, this appears to be a reasonable approximation since the differences of concentrations are all below 0.2. These differences are mostly due to the electrical charge of the protein molecules and to the resulting Gibbs-Donnan equilibrium which is thereby neglected. The advantage resulting from such an assumption is a considerable simplification of the equations describing the exchange of water and electrolytes between the compartments. The elimination of this approximation as well as of others that will follow, may be attempted in a successive step in the improvement of the body water and electrolyte modeling.

Eq.21 can be rewritten for the specific system described by Table 2, as Eq.22.

\[
\frac{q}{X} + \frac{b_6 + b_5}{b} + \sum_{i=1}^{n} \frac{b_1}{j_i \cdot X + K_i b} - 1 = 0
\]

where \(j_i = 1 - k_i\) and where X is the only unknown.
### Table 2: Idealized Composition of the Body Fluid Compartments

<table>
<thead>
<tr>
<th>I</th>
<th>Substance</th>
<th>Plasma</th>
<th>Interstitial</th>
<th>Intracellular</th>
<th>IC conc.</th>
<th>J&lt;sub&gt;1&lt;/sub&gt; = 1 - K&lt;sub&gt;1&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Na</td>
<td>140 mosm/l 1441 mosm</td>
<td>140 mosm/l 1620 mosm</td>
<td>10 mosm/l 274 mosm</td>
<td>0.0714</td>
<td>0.9286</td>
</tr>
<tr>
<td>2</td>
<td>K</td>
<td>4 mosm/l 12.6 mosm</td>
<td>4 mosm/l 46.3 mosm</td>
<td>140 mosm/l 3840 mosm</td>
<td>35</td>
<td>-34</td>
</tr>
<tr>
<td>3</td>
<td>Cl</td>
<td>112 mosm/l 352.8 mosm</td>
<td>112 mosm/l 1295 mosm</td>
<td>4 mosm/l 109.6 mosm</td>
<td>0.03571</td>
<td>0.96429</td>
</tr>
<tr>
<td>4</td>
<td>Oi*</td>
<td>33.03 mosm/l 104.03 mosm</td>
<td>33.03 mosm/l 381.45 mosm</td>
<td>128.97 mosm/l 3536 mosm</td>
<td>3.9053</td>
<td>-2.9053</td>
</tr>
<tr>
<td>5</td>
<td>Urea</td>
<td>4 mosm/l 12.6 mosm</td>
<td>4 mosm/l 46.20 mosm</td>
<td>4 mosm/l 109.6 mosm</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Water</td>
<td>175 osm 3.15 l</td>
<td>641.6 osm 11.55 l</td>
<td>1522.2 osm 27.4 l</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>-</td>
<td>Proteins</td>
<td>1.2 mosm/l 3.78 mosm 70 g/l</td>
<td>0.2 mosm/l 2.31 mosm 20 g/l</td>
<td>4 mosm/l 109.6 mosm 400 g/l</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>-</td>
<td>Total osmolality</td>
<td>294.2 mosm/l</td>
<td>293 mosm/l</td>
<td>293.8 mosm/l</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Oi = "other ions". See text for explanation.
The polynomial form of Eq. 22 is:

\[ A_6 \bar{x}^5 + A_5 \bar{x}^4 + A_4 \bar{x}^3 + A_2 \bar{x}^2 + A_1 \bar{x} + A_0 = 0 \]

The numerical methods used in solving Eq. 23 are described in Appendix B.

The real root of Eq. 23 in the interval 0 to \( \bar{b} \) (limits included) is the desired value of \( \bar{x} \). Substitution of this value in Eq. 19 yields all the \( x_1 \)'s. The values of the \( x_1 \)'s can then be easily obtained from Eq. 14. The osmolar concentrations can then be obtained from Eqs. 24 and 25:

\[ C_i = \frac{x_i}{x_6} \frac{1000}{18} \quad \text{for } i = 1, 2, 3, 4, 5 \]

\[ C'_i = \frac{x'_i}{x_6} \frac{1000}{18} \quad \text{for } i = 1, 2, 3, 4, 5 \]

where \( C_i \) and \( C'_i \) are the osmolar concentrations of substance 1 in the interstitial and intracellular compartments respectively.

IV.3 Simulation of the Steady State Equilibrium Between the Interstitial-
Intracellular Compartments and Extracellular-Intracellular Compartments.

The data reported in Table 2 allow the determination of the \( b \)'s, the \( K \)'s and the \( J \)'s necessary for the solution of Eq. 22. It must be noted that the distribution of substances as indicated in Table 2 may not exactly satisfy Eqs. 22, 19, and 20, and, therefore, a slightly different distribution may be produced by the computer model. Each of the \( b \)'s is the sum of the osmoles of the \( i \)th substance in the interstitial (IS) and intracellular (IC) compartments. With these data the system of Eqs. 19, 20, 22 can be solved as indicated in Appendix B.
The results of the solution for a "normal" condition (data from Table 2) are indicated in section 1 of Table 3. As can be seen, the computed distribution of substances is very close to the one of Table 2 as would be expected.

It may be observed that since the ionic concentrations are assumed to be the same in the plasma and interstitial compartment, the latter may be extended to include the first without any alteration in the K's. In other words the cellular membrane may be considered as separating the IC compartment from the extracellular (EC) rather than from the interstitial. The EC compartment will then split into the plasma and interstitial spaces and the factors affecting the separation will be discussed in the next section. As far as its effect on the intracellular fluid, the extracellular compartment could as well be uniform and with the protein concentration of the IS. Therefore this will be assumed in this section. This temporary assumption does not affect the distribution of material on the two sides of the cellular membrane. The advantage is that the b_i's can now represent the total body amount of substance i and they are more easily determined experimentally. (The total body amount of proteins, however, will not be correct because of the neglected difference between plasma and interstitial protein concentration). The computer results will then indicate how each substance will be distributed into the EC and IC compartments when its total body amount is given. The results are indicated in Table 3 (Section 2). As expected, the concentrations in the two cases (Section 1 and Section 2) are the same within the computational and data errors.
The simulation program can now be used to find how the IC-EC distribution is altered by the addition or subtraction of material. Various experimental situations are listed below, and in Table 3; some are indicated in Figs. 16 and 17.

a) Modification of the EC (or IS) protein content.

Throughout this subsection any comment or statement concerning the EC compartment is valid as well for the IS one. The reader may consider it in the way he prefers.

Section 3 of Table 3 shows the EC-IC distribution for zero protein content of the EC fluid. In such case the EC fluid disappears because it is entirely absorbed into the IC. The existence of proteins outside the cells is, therefore, essential to the maintenance of an extracellular fluid and, in general, of life. However, the amount of extracellular protein is not at all critical to the effect of the EC-IC balance. This is apparent from Sections 4 and 5 of Table 3 in which the protein content of the EC space is taken to be respectively 20 times higher and 20 times lower than normal. Although these variations are quite outside the physiological and pathological ranges, the alterations in ion and water distribution are almost irrelevant. Similar irrelevant changes are obtained by varying the IC protein content. This observation lead to the very important conclusion that the oncotic pressure (colloid osmotic or protein osmotic pressure) gradient across the cellular membrane is not a controlling factor in the IC-EC balance and that the balance is controlled by the metabolic ion pumps.

This conclusion, which was also reached by De Land and Bradham, indicates
the error, sometime made by the physiologists, of applying Starling's laws to the exchange across active cellular membranes.

Physiological experimentation would be very useful in establishing the above point definitively.

b) Infusion of electrolyte solutions.

In 1964 Bradham et al. ran some experiments on nephrectomized dogs to verify the validity of their model. Their experimental data are reported in Fig.16 a and b and in Fig.17 a. The variations in IC and EC compartments resulting from the simulation, with this model, of Bradham's experiments are indicated in Sections 6, 7, and 10 in Table 3. The variations in compartment volumes are also indicated in Figs.16 and 17 and compared to experimental data. The agreement between experimental and predicted results appears satisfactory.

Sections 8 and 9 of Table 3 and Fig.16 c and d show the computer response to the infusion of solutions of potassium chloride identical in volume and concentration to the sodium chloride solutions used by Bradham. The very different response of the system to the potassium ion is evident. Of particular interest is the fact that both the solutions a and c in Fig.16 are almost isotonic (308 mosm/l); however, in case a there is a decrease in cellular fluid, while in case c there is an increase. Physiological experimentation would be very useful in verifying the computer predictions in this case. This verification would be of further value in validating the assumptions underlying this simulation with particular regard to the cellular membrane function.
Table 3. Computer predicted distributions of water and solutes.

EVA = extravascular amount. TBA = total body amount. ISC = interstitial concentration. ECC = extracellular concentration. ICC = intracellular concentration.

<table>
<thead>
<tr>
<th>Substance</th>
<th>K</th>
<th>Cl</th>
<th>O</th>
<th>Urea</th>
<th>Water</th>
<th>Protein</th>
<th>Total osmolality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1)</td>
<td>(2)</td>
<td>(3)</td>
<td>(4)</td>
<td>(5)</td>
<td>(6) ln 1</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EVA mosm</td>
<td>1894</td>
<td>1304.6</td>
<td>3915.45</td>
<td>155.8</td>
<td>36.95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISC mosm/l</td>
<td>139.27</td>
<td>11.26</td>
<td>33.10</td>
<td>4.00</td>
<td>11.65</td>
<td>0.2</td>
<td>291.8</td>
</tr>
<tr>
<td>ICC mosm/l</td>
<td>9.94</td>
<td>140.63</td>
<td>3.97</td>
<td>129.29</td>
<td>4.00</td>
<td>27.30</td>
<td>4.0</td>
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<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBA mosm</td>
<td>2335</td>
<td>3898.9</td>
<td>1757.4</td>
<td>4019.47</td>
<td>168.4</td>
<td>42.1</td>
<td></td>
</tr>
<tr>
<td>ECC mosm/l</td>
<td>139.31</td>
<td>4.02</td>
<td>111.32</td>
<td>33.11</td>
<td>4.00</td>
<td>14.81</td>
<td>0.2</td>
</tr>
<tr>
<td>ICC mosm/l</td>
<td>9.95</td>
<td>140.69</td>
<td>3.97</td>
<td>129.32</td>
<td>4.00</td>
<td>27.29</td>
<td>4.0</td>
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<tr>
<td>3</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBA mosm</td>
<td>2335</td>
<td>3898.9</td>
<td>1757.4</td>
<td>4019.47</td>
<td>168.4</td>
<td>42.1</td>
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<tr>
<td>ECC mosm/l</td>
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<td>0.0</td>
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<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>ICC mosm/l</td>
<td>55.46</td>
<td>92.61</td>
<td>41.74</td>
<td>95.47</td>
<td>4.0</td>
<td>42.1</td>
<td>2.60</td>
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<tr>
<td>4</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBA mosm</td>
<td>2335</td>
<td>3898.9</td>
<td>1757.4</td>
<td>4019.47</td>
<td>168.4</td>
<td>42.1</td>
<td></td>
</tr>
<tr>
<td>ECC mosm/l</td>
<td>138.25</td>
<td>4.04</td>
<td>110.38</td>
<td>33.22</td>
<td>4.0</td>
<td>14.95</td>
<td>3.1</td>
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<tr>
<td>ICC mosm/l</td>
<td>9.67</td>
<td>141.38</td>
<td>3.94</td>
<td>129.75</td>
<td>4.0</td>
<td>27.14</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBA mosm</td>
<td>2335</td>
<td>3898.9</td>
<td>1757.4</td>
<td>4019.47</td>
<td>168.4</td>
<td>42.1</td>
<td></td>
</tr>
<tr>
<td>ECC mosm/l</td>
<td>139.38</td>
<td>4.02</td>
<td>11.38</td>
<td>33.10</td>
<td>4.0</td>
<td>14.81</td>
<td>0.003</td>
</tr>
<tr>
<td>ICC mosm/l</td>
<td>9.95</td>
<td>140.65</td>
<td>3.97</td>
<td>129.29</td>
<td>4.0</td>
<td>27.29</td>
<td>4.0</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBA mosm</td>
<td>2568.6</td>
<td>3895.9</td>
<td>1973.9</td>
<td>4019.47</td>
<td>158.4</td>
<td>43.5</td>
<td></td>
</tr>
<tr>
<td>ECC mosm/l</td>
<td>139.08</td>
<td>4.06</td>
<td>112.7</td>
<td>33.27</td>
<td>3.67</td>
<td>16.54</td>
<td>0.17</td>
</tr>
<tr>
<td>ICC mosm/l</td>
<td>9.03</td>
<td>142.14</td>
<td>4.02</td>
<td>128.55</td>
<td>3.67</td>
<td>28.95</td>
<td>4.05</td>
</tr>
</tbody>
</table>
Table 3. Computer predicted distributions of water and solutes. (continuation)

EVA = extravascular amount. TBA = total body amount. ISC = interstitial concentration. ECC = extracellular concentration. ICC = intracellular concentration.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Na</th>
<th>K</th>
<th>Cl</th>
<th>O1</th>
<th>Urea</th>
<th>Water</th>
<th>Protein</th>
<th>Total osmolarity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Normal distribution between EC and IC compartments

| TBA mosm | 2335 | 3898.9 | 1177.4 | 4019.47 | 168.4 | 41.4 | - | - |
| ECC mosm/l | 179.3 | 4.02 | 111.32 | 33.11 | 0.00 | 14.81 | 0.2 | 291.9 |
| IEC mosm/l | 9.95 | 140.69 | 3.97 | 129.32 | 0.00 | 27.29 | 4.0 | 291.9 |

EC - IC distribution with 0.71 of 0.892 M NaCl added

| TBA mosm | 2359.4 | 3898.9 | 2381.8 | 4019.47 | 168.4 | 42.8 | - | - |
| ECC mosm/l | 147.85 | 4.43 | 121.67 | 35.2 | 3.93 | 18.22 | 0.16 | 316.2 |
| IEC mosm/l | 10.55 | 155.37 | 4.45 | 137.4 | 3.93 | 28.58 | 4.46 | 316.2 |

EC - IC distribution with 1.5 of 0.154 M KCl added

| TBA mosm | 2335 | 4114.4 | 1973.0 | 4019.47 | 168.4 | 43.5 | - | - |
| ECC mosm/l | 132.9 | 4.14 | 119.09 | 32.24 | 3.87 | 15.57 | 0.18 | 292.4 |
| IEC mosm/l | 9.45 | 145.00 | 4.25 | 125.93 | 3.87 | 27.93 | 3.92 | 292.4 |

EC - IC distribution with 0.7 of 0.892 M KCl added

| TBA mosm | 2335 | 4523.3 | 2381.8 | 4019.47 | 168.4 | 42.8 | - | - |
| ECC mosm/l | 132.00 | 4.70 | 142.42 | 33.11 | 3.93 | 15.75 | 0.18 | 316.3 |
| IEC mosm/l | 9.42 | 164.52 | 5.08 | 129.33 | 3.93 | 27.05 | - | 316.3 |

EC - IC distribution with 0.7 of 0.892 M NaHCO₃ added

| TBA mosm | 2335.4 | 3898.9 | 1757.4 | 4603.47 | 168.4 | 42.8 | - | - |
| ECC mosm/l | 165.73 | 4.07 | 104.00 | 33.42 | 3.93 | 15.93 | 0.16 | 316.3 |
| IEC mosm/l | 11.83 | 142.7 | 3.71 | 150.07 | 3.93 | 26.87 | 4.08 | 316.3 |

EC - IC distribution with 1 of isotonic urea solution added

| TBA mosm | 2335 | 3898.9 | 1757.4 | 4603.47 | 168.4 | 43.1 | - | - |
| ECC mosm/l | 135.7 | 3.02 | 103.7 | 32.34 | 10.6 | 15.16 | 0.1 | 291.9 |
| IEC mosm/l | 9.71 | 177.5 | 2.28 | 165.7 | 1.5 | 27.93 | 3.92 | 291.9 |
Table 3. Computer predicted distributions of water and solutes (Continuation)

EVA = extravascular amount. TBA = total body amount. ISC = interstitial concentration. ECC = extracellular concentration. ICC = intracellular concentration.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Na</th>
<th>K</th>
<th>CI</th>
<th>O1</th>
<th>Urea</th>
<th>Water</th>
<th>Protein</th>
<th>Total osmolality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substances</td>
<td>(1)</td>
<td>(2)</td>
<td>(3)</td>
<td>(4)</td>
<td>(5)</td>
<td>(6) in 1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Normal distribution between EC and IC compartments

| TBA mmol | 2335 | 3898.9 | 1757.4 | 4019.47 | 168.4 | 42.1 | - | - |
| ECC mmol/l | 136.07 | 4.11 | 114.0 | 32.88 | 3.9 | 14.66 | 0.19 | 285.1 |
| ICC mmol/l | 10.19 | 144.1 | 4.07 | 132.4 | 4.09 | 26.64 | 3.92 | 285.1 |

EC - IC distribution with 1 l of water added

| TBA mmol | 2335 | 3898.9 | 1757.4 | 4019.47 | 168.4 | 42.1 | - | - |
| ECC mmol/l | 138.10 | 4.00 | 111.07 | 33.08 | 3.9 | 14.81 | 0.19 | 291.0 |
| ICC mmol/l | 9.90 | 140.78 | 3.96 | 129.18 | 3.9 | 28.28 | 3.87 | 291.0 |

EC - IC distribution with 1 l of water subtracted

| TBA mmol | 2335 | 3898.9 | 1757.4 | 4019.47 | 168.4 | 41.1 | - | - |
| ECC mmol/l | 136.07 | 4.11 | 114.0 | 32.88 | 3.9 | 14.66 | 0.19 | 299.0 |
| ICC mmol/l | 10.19 | 144.1 | 4.07 | 132.4 | 4.09 | 26.64 | 3.92 | 299.0 |

EC - IC distribution with 1 l of 0.125 M NaCl added.

| TBA mmol | 3959.9 | 3898.9 | 1882.38 | 4019.47 | 168.4 | 43.1 | - | - |
| ECC mmol/l | 138.10 | 4.00 | 111.07 | 33.08 | 3.9 | 14.81 | 0.19 | 291.0 |
| ICC mmol/l | 9.90 | 140.78 | 3.96 | 129.18 | 3.9 | 28.28 | 3.87 | 291.0 |

EC - IC distribution with 1 liter of 0.125 M HCO₃ added

| TBA mmol | 2335 | 4023.9 | 1757.4 | 4019.47 | 168.4 | 43.1 | - | - |
| ECC mmol/l | 138.72 | 4.00 | 111.07 | 33.08 | 3.9 | 14.81 | 0.19 | 291.0 |
| ICC mmol/l | 9.90 | 140.14 | 3.96 | 129.18 | 3.9 | 28.28 | 3.87 | 291.0 |
1.4 liters 20 ml/Kg 0.154 M NaCl solut.
0.7 liters 10 ml/Kg 0.892 M KCl solut.
1.4 liters 20 ml/Kg 0.754 M NaCl solut.
0.7 liters 10 ml/Kg 0.892 M KCl solut.

Fig. 16. Steady state distribution of electrolyte solutions between the extra and intracellular compartments.

x = individual experimental result. (dog)
--- = average of experimental results (dog)
- - - = computer results (7) . . . . . . .
Experimental data from Brauner, 1964.
Fig. 17. Steady state distribution of various fluids between the extracellular and intracellular compartments.

x = individual experimental results. (dog)
Φ = experiments not included in the average because probably affected by artifact.
--- = average of experimental results.
----- = computer results (70 Kg man)

Experimental data from Bradham, 196*.
c) Infusion of water and urea solutions.

Since both water and urea can diffuse freely across the cellular membrane, it is expected that both water and urea solutions will distribute in the EC and IC compartments in proportion to the respective volumes of such compartments. So it is predicted by the model. (Sections 11, 12, and 13 of Table 3 and Fig. 17 b, c, and d). The subtraction of 1 l of water simulated in Fig. 17 d may be assumed to be produced by the insensible fluid losses. It is interesting to observe that in all cases the steady state osmolalities of the EC and IC compartments are the same. This is due to the unity value of the $k_1$ for water.

d) Use of this model in the design of experiments.

The possibility of using this model for the determination of solutions having specific properties is obvious. The volume and the ionic composition of a solution that produces the required modifications in IC and EC fluids can be found by trial and error. As an example, one can propose the problem of finding an electrolyte solution that would expand the EC compartment by 1 l without affecting the IC volume, and another solution to do the opposite. These two solutions can be found, after 3 to 5 trials, in about 10 minutes. Sections 14 and 15 indicate the response of the model to the infusion of such solutions, respectively 1 l of a 0.125 M NaCl solution and 1 l of 0.125 M KHC\textsubscript{3}O\textsubscript{3} solution (each solution has osmolality of 250 mosm/l; the HCO\textsubscript{3} ion is considered identical to the "O\textsubscript{i}" ion.) As it appears from the table, the sodium chloride solution expands the EC space while the potassium bicarbonate solution expands the IC space. The ability to expand or contract one of the body compartments without
affecting the other, or while affecting the other in a known way, or to produce fluid shifts between them, is of great value in physiological experimentation and therapeutics. This model may be a valuable tool in this regard.

IV. 4 Physiology of the Equilibrium between Plasma and Interstitial Compartment.

a) Approximations and Assumptions.

In the previous section the extracellular compartment was temporarily considered uniform. Such an assumption, as was stated, has a minimal or no effect upon the balance across the cellular membrane. In the study of the equilibrium across the capillary membrane, this assumption has, of course, to be removed.

The following assumptions are made with regard to the plasma and interstitial compartments:

a) Only a hydrostatic and an oncotic gradient are present across the capillary membrane. The slight osmotic gradient (mainly due to the Donnan effect) is neglected.

b) The capillary bed is the only area of exchange between the two compartments.

c) The exchange of gases (O₂, CO₂) is not taken into consideration.

d) The plasma composition and physical characteristics within and along the capillary are constant.

e) An average capillary vessel is considered in the model, which accounts for all the body capillaries and has an arteriolar and venular section each having constant permeabilities.
f) The venular section of the capillary is more porous than the arteriolar one. The effect of the pores present in the arteriolar section is neglected in this model.

The simulation results are expected to give some indication of the validity of such approximations.

The forces (pressures) acting on the capillary membrane were studied by Starling, last century, and are named after him. They are shown in Fig. 18. It should not be forgotten that the oncotic pressure $\Pi_p$ of a protein solution (mainly albumin and globulin) is related to the concentration $C$ of the solution in a non-linear fashion because of the interaction of the protein molecules. The relationship is given by many authors and in particular by the Handbook of Physiology (1963) as Eq. 26:

$$\Pi_p = 0.21 \cdot C + 1.6 \times 10^{-3} \cdot C^2 + 9 \times 10^{-6} \cdot C^3$$

where: $C = \text{protein concentration in g/l}$

$\Pi_p = \text{osmotic pressure in mmHg} \quad \text{(see Fig. 20)}$

The permeability coefficients and the flows are defined in Fig. 18.

The capillary hydrostatic pressure drops from the arterial end value of 30 to 40 mmHg to the venous end value of 10 to 20 mmHg, averaging about 32 mmHg on the arterial side and 12 mmHg on the venous side. This produces a filtration flow $F$ and a reabsorption flow $R$, respectively in the arterial and venous region, given by equations 27 and 28.

$$F = K_a A_a (P_a - P_t - \Pi_pp + \Pi_{pt})$$

$$R = K_v A_v (-P_v + P_t + \Pi_pp - \Pi_{pt})$$

with $K_a A_a = K_t$ and $K_v A_v = K_v$ for brevity.
The flows F and R are "ultrafiltrates", that is, they only carry water, electrolytes and small solute molecules (and do not alter the electrolyte equilibrium). They do not carry proteins.

Two more flows have to be considered (see Fig. 18). The first is the plasma leakage from the capillary into the interstitial fluid through the capillary pores. This leakage takes place mostly on the venous side and it is assumed to be caused by hydrostatic pressures. (Eq. 29) (Wiederhielm, 1968).

\[ F_p = K_1 (P_v - P_t) \]
with: \( K_1 \) = pore permeability

\( P_v \) and \( P_t \) = venous and IS fluid hydrostatic pressures.

Since \( P_v > P_t \) is true practically always, this flow is into the interstitial space. The condition \( P_v < P_t \) may only take place in small body areas (e.g. compressed tissue or fluid locally injected in the IS space). The second flow concerns the lymphatic system. Fluid is actually slowly pumped out of the interstitial space because of the rectifying characteristics of the lymphatic vessels which contain valves. The spontaneous slight contractions of such vessels together with tissue movement produce the so-called "lymphatic pump" (Kinmonth and Taylor, 1956).

When the IS fluid pressure rises above a threshold \( P_{th} \) a further contribution to this flow is provided by the IS fluid pressure effect. This mechanism will be discussed more in detail later in this chapter. Physiological measurements indicate that lymph and interstitial fluid
have the same composition and that no selective filtration is operated by
the lymphatic capillaries. The lymph flow is given by Eq. 30 where, again,
linearity is assumed between pressure and flow for $P_t > P_{th}$.

\begin{align*}
F_1 = K_3 + K_2 (P_t - P_{th}) & \quad \text{for } P_t > P_{th} \\
F_1 = K_3 & \quad \text{for } P_t < P_{th}
\end{align*}

It is very important to observe that both flows $F_p$ and $F_1$ carry proteins.
If $C_{pp}$ is the concentration of the plasma proteins and $C_{pi}$ is the IS fluid
protein concentration, the amount of protein carried by $F_p$ will be $F_p C_{pp}$
and the amount of proteins carried by $F_1$ will be $F_1 C_{pi}$. The above statement
implies the assumption that the flows $F_p$ and $F_1$ have protein concentrations
$C_{pp}$ and $C_{pi}$. This may not be exactly true. Proteins may perhaps leave
the capillary following their concentration gradient so that the protein
concentration of $F_p$ becomes higher than $C_{pp}$. Lymph fluid actually has a
protein content slightly higher than $C_{pi}$, perhaps because of merging with
the intestinal lymph loaded with nutrients. These possible differences,
however, are not considered here.

If it is assumed that the lymphatic system is neither expanding nor
contracting, that is, its content is constant, then, if a flow $F_1$ enters
the lymphatic capillaries, the same flow leaves the large lymph ducts to
enter the vena cava, thus returning to the plasma. $F_1$ is, therefore, a
special type of reabsorption flow.

b) Quantitative evaluation of the permeability coefficients.

Most data available from the literature concerning capillary permeability
Fig. 18. Schematic diagram of the model of capillary exchange.

\[ A_a = \text{area of the arterial section} \]
\[ A_v = \text{area of the venous section} \]
\[ K_a = \text{unit area permeability coefficient of arterial section to ultrafiltrate}. \]
\[ K_v = \text{unit area permeability coefficient of venous section to ultrafiltrate}. \]
\[ K_4 = K_a A_a = \text{total permeability of arterial section to ultrafiltrate}. \]
\[ K_5 = K_v A_v = \text{total permeability of venous section to ultrafiltrate}. \]
\[ K_1 = \text{pore permeability to whole plasma}. \]
\[ K_2 = \text{permeability of lymphatic capillaries}. \]
\[ K_3 = \text{lymph flow due to lymph pump}. \]
have been obtained by raising the venous pressure and therefore refer to the venous filtration coefficient. This coefficient was found by Landis et al. to be 5.7 μl/(min·100 g of tissue·mmHg) in the forearm, while Brown et al. found 6.1 μl/(min·100 g of tissue·mmHg) for the whole body (Handbook of Physiology, 1963). For the average 70 Kg man, the average of the above values, modified for the total body weight, becomes 4.27 ml/min·mmHg. (K5).

Wiederhielm (1968) gave the values of the filtration and area ratios between arterial and venous sections of capillary as:

\[
\frac{K_a}{K_v} = 0.6 \quad \frac{A_a}{A_v} = 0.25 \quad \text{therefore,} \quad \frac{K_a A_a}{A_v K_v} = 0.15
\]

so, given \( K_5 = 4.27 \), it is found \( K_4 = 0.64 \) ml/min·mmHg. The average flow of lymph in the resting man is about 2 ml/min., but it may vary widely during periods of activity or after meals. (Guyton 1968 and 1971, Handbook of Physiology, 1963). A normal value of \( F_l = 2 \) ml/min. is taken.

Considering that the lymph protein concentration (assumed equal to the IS fluid protein concentration) is 20 g/l while that of the plasma is 70 g/l, and requiring, for steady state, that the IS protein content is constant, the equation \( F_{p_{pp}} = F_{l_{pl}} \) is obtained. Such an equation can be solved for \( F_{p} \) and yields the value of \( F_{p} = 0.57 \) ml/min. Knowing \( K_4 \), \( K_5 \) and the normal value of \( F_l \) and \( F_p \), the normal steady state situation of the system can be studied.

c) The controversy over the value of the IS fluid pressure.

The four flows given in Eqs. 27, 28, 29, and 30 can be algebraically
added to provide the net flow $F_n$ leaving the vascular system.

Eq. 31 $F_n = F - R - F_p + F_l = K_4 P_a + K_5 P_Y + (K_4 + K_5) (\bar{\Pi}_{pt} - \bar{\Pi}_{pp} - P_t) + F_p - F_l$

In a steady state situation it must be $F_n = 0$ (Eq.32) and $F_p C_{pp} = F_{1} C_{pi}$.

The second condition has been used for determining $F_p$ (see previous section), and, therefore, it is verified by definition.

The only unknown in Eq.31 is $P_t$. Although experimental data on the value of $P_t$ are available, there is no general agreement upon their validity.

The value satisfying Eq.32 may therefore be of interest.

Eq.32 $K_4 P_a + K_5 P_Y + (K_4 + K_5) (\bar{\Pi}_{pt} - \bar{\Pi}_{pp} - P_t) + F_p - F_l = 0$

where: $K_4 = 0.64$ ml/min.mmHg, $K_5 = 4.27$ ml/min.mmHg.

$P_a = 32$ mmHg, $P_Y = 12$ mmHg

$F_p = 0.57$ ml/min, $F_l = 2$ ml/min

$\bar{\Pi}_{pt} = 4.91$ mmHg ($C_{pi} = 20$ g/l) (see Eq.26)

$\bar{\Pi}_{pp} = 25.6$ mmHg ($C_{pp} = 70$ g/l) (see Eq.26)

Eq.32 can be easily solved for $P_t$ and yields a value $P_t = -6.4$ mmHg.

Substitution of this value into Eq.29 provides the value for $K_1$ as $K_1 = 0.031$ ml/min.mmHg.

The prediction of a negative value of interstitial pressure is worth some discussion because of the present controversy over this subject.

Measurement of interstitial pressure by means of needles and micropipettes has given values in the range of 1 to 5 mmHg. (See, for example, Handbook of Physiology, 1963, and Wiederhielm, 1968). On the other hand, measurement
of interstitial pressure by means of implanted capsules (Guyton's capsule) has given values in the range of -13 to -3 mmHg. The data relative to the latter method have come almost entirely from a single laboratory and are still controversial. (Guyton, 1971, Wiederhielm 1968, Stromber, 1970).

An important point against the theory of negative interstitial fluid pressure may be discussed here. Such point is relative to the fact that if the IS fluid pressure is negative, and since the central venous pressure is zero or slightly positive, the lymph should flow against a hydrostatic pressure gradient. This may sound very perplexing but it may be explained by the following electrical analog. The valves present in the lymphatic vessels (capillaries included) have a flow rectifying action and may be represented by a diode \( D_1 \) with a forward resistance \( R_f \). (Fig. 19). The contractions of the large lymphatic vessels produce an impulsive movement of fluid which may be represented by the current generator \( J \) with internal resistance \( R \). Body movements, respiratory movements and arterial pulsation produce continuous fluctuations of the instantaneous IS fluid pressure; such variations are represented by a voltage generator \( E \).

Let us now consider a region of IS space where the above variations take place. Its compliance may be represented by a capacitance \( C_1 \) and the resistance to the flow of fluid between this and other regions or between the region and the vascular compartment may be represented by a resistor \( R_i \). The complete electrical analog is given in Fig. 19.

If the time constant \( R_i C_1 \) is sufficiently larger than the period of variation of \( E \) and \( J \), the voltage \( V_{AB} \) has a negative DC component, which is the analog of the average interstitial pressure.
The DC component of current $I$ is the analog of the average lymph flow and seems to flow against a potential difference. However, the instantaneous current $I$ flows along a potential gradient. This is one of the cases, so common in living systems, where the correlated variations of two quantities (IS pressure and valve resistance in this case) lead to the transformation of random signals into deterministic ones.

Guyton (1971) has observed that in totally anesthetized animals the IS pressure is less negative (about $-3 \text{ mmHg}$ instead of $-7 \text{ mmHg}$) and that if a pulseless extracorporeal circulation is provided, $P_t$ rises to practically $0 \text{ mmHg}$. This is also predicted by the electrical analog. If the variations of $E$ and $J$ decrease or disappear, $V_{AB}$ decreases or disappears.

The analog model also justifies qualitatively the relationship of Eq. 30. If $V_{AB}$ is maintained sufficiently negative, the average value of $I$ becomes equal to the average value of $J$ because the variations of $E$ are not sufficient to affect $I$. However, if $V_{AB}$ is not too negative,
the average value of $I$ is larger than the DC component of $J$ and increases for increasing $V_{AB}$. The above observations appear to support the theory of negative interstitial pressure, and, therefore, Guyton's results will be accepted.

The last two quantities that still have to be determined for the model equations are the coefficient $K_2$ for the lymph flow and the threshold pressure $P_{th}$. Physiological data about these values are very poor and vague. According to Guyton (1967), the maximum lymph flow in humans is about 30 ml/min (extrapolated from animal experiments) and it is reached in conditions of severe edema (not due to lymphatic problems). The flow does not increase above this value because the increased IS fluid pressure compresses the lymphatic vessels. Conditions of severe edema are obtained for IS pressures in the range 2 to 4 mmHg (Guyton, Textbook of Medical Physiology). Still according to Guyton (1968), the rise of lymph flow starts at $P_t = -7$ mmHg. On the base of this information it is taken here: $P_{th} = -7$ mmHg, $K_2 = 2.8$ ml/min/mmHg and $F_L \leq 30$ ml/min. for any value of $P_t$. The relationships $\Pi = f_1(C)$ and $F_L = f_2(P_t)$ are reported in Fig.20.

IV.5 Model Equations. (Plasma - IS Space Balance).

In a steady state condition neither the volume nor the protein content of the IS space change in time. Such situation is expressed mathematically by the following equations:
Eq. 33 \[ K_4 P_a + K_5 P_V + (K_4 + K_5) (\Pi_{pt} - \Pi_{pp} - P_t) + F_p - F_1 = 0 \]

Eq. 34 \[ F_p C_{pp} - F_1 C_{pi} = 0 \]

and by the additional equations:

Eq. 35 \[ F_p = K_1 (P_V - P_t) \]

Eq. 36 \[ F_1 = K_3 \quad \text{for } P_t < -7 \text{ mmHg.} \]

\[ F_1 = K_3 + K_2 (P_t - P_{th}) \quad \text{for } -7 < P_t < 3 \text{ mmHg} \quad (P_{th} = -7 \text{ mmHg}) \]

\[ F_1 = 30 \text{ ml/min} \quad \text{for } P_t > 3 \text{ mmHg} \]

Eq. 37 \[ \Pi_{pp} = 0.21 \cdot C_{pp} + 1.6 \cdot 10^{-3} C_{pp}^2 + 9 \cdot 10^{-6} C_{pp}^3 \]

Eq. 38 \[ \Pi_{pi} = 0.21 \cdot C_{pi} + 1.6 \cdot 10^{-3} C_{pi}^2 + 9 \cdot 10^{-6} C_{pi}^3 \]

In the previous set of equations all the parameters are known. It may be observed that if \( P_a, P_V \) and \( \Pi_{pp} \) (or \( C_{pp} \)) are given, the equations 33 to 38 form a system of six equations in six unknowns, the unknowns being \( \Pi_{pi}, C_{pp} \) (or \( \Pi_{pp} \)), \( P_t, F_p, F_1, C_{pi} \). The solution of this system, which is very nonlinear, for various values of the input pressures \( (P_a, P_V, \Pi_{pp}) \) yields the output pressures \( (P_t, \Pi_{pi}) \) and flows \( (F_p, F_1) \). The numerical techniques used for the solution of the above nonlinear system are described in Appendix C. These solutions represent steady state values, that is, no information is given about how these values are reached or how long it takes to reach them.

The previous system of equations is represented graphically in Fig. 21. The main purpose of this figure is to show the existence of feedback in the system and the location and nature of the nonlinearities.
Fig. 20. a) Relationship between oncotic pressure and concentration of a protein solution. (Handbook of Physiology, 1963)
\[ \pi = 0.21 \cdot C + 1.6 \cdot 10^3 C^2 + 9 \cdot 10^6 C^3 \]

b) Relationship between lymph flow and interstitial fluid pressure. (Guyton, 1967).
\[ F_1 = 2 \text{ ml/min for } P_t \leq 7 \text{ mmHg} \]
\[ F_1 = 2 + 2.8 (P_t + 7) \text{ for } -7 < P_t < 3 \text{ mmHg} \]
\[ F_1 = 30 \text{ ml/min for } P_t > 3 \text{ mmHg} \]

c) Relationship between interstitial fluid volume and pressure. (Guyton, 1971).
\[ V_{IS} = 0.571 \cdot P_t + 15.5 \text{ for } P_t < 0 \text{ mmHg} \]
\[ V_{IS} = 20 \cdot P_t + 15.5 \text{ for } 0 < P_t < 2.4 \text{ mmHg} \]
\[ V_{IS} = 6.84P_t + 48 \text{ for } P_t > 2.4 \text{ mmHg} \]
Fig. 21. Block diagram of the steady state mechanism of plasma-interstitial fluid balance.
Although the input and output quantities of this model are only pressures and protein concentrations, information about the interstitial fluid volume \((V_{IS})\), and about the formation and level of edema, can be obtained by using Guyton's data relating \(V_{IS}\) to \(P_t\) (Guyton, Textbook of Medical Physiology). The relationship \(V_{IS} = f_3(P_t)\) is reported in Fig. 20. It may also be observed that, since the IS protein concentration has practically no effect on the IS-IC fluid balance, (see section 3 of this chapter), the model for EC-IC fluid balance (see section 2) and the one for plasma-IS balance are not interacting when \(P_a\), \(P_v\), \(\|_{pp}\) or any capillary membrane or lymphatic parameters are changed.

IV.6 Simulations and Results.

The simulations attempted with this model will be divided into responses to pressure variations, responses to parameter variations and simulations of physiological or pathological states reported in the literature.

a) Response of the model to pressure variations.

Fig. 22 shows the variations of the hydrostatic and oncotic IS pressures and of interstitial fluid volume for varying \(P_a\), \(P_v\), \(\|_{pp}\). Increasing \(P_a\) from \(P_a = P_v = 12\) mmHg to \(P_a = 70\) mmHg produces a decrease of \(\|_{pi}\) but no major alteration of \(P_t\) or \(V_{IS}\). This is in agreement with physiological findings; arterial hypo or hyper-tension is not a relevant factor in capillary exchange.

Decreasing \(P_v\) from the normal 12 mmHg to 4 mmHg decreases \(P_t\) and \(V_{IS}\)
Fig. 22. Steady state response of the model to variations of capillary arterial, venous and oncotic pressures.
(fluid is absorbed into the vascular compartment to counteract the state of shock). Increasing $P_V$ above normal and up to $P_a$ increases $P_t$ and $V_{IS}$, however, $P_V$ has to raise above $\Pi_{pp}$ to produce edema. This fact has been verified many times in physiological experiments.

Increasing $\Pi_{pp}$ above normal produces a drop in IS pressure and volume and an increase in $\Pi_{pi}$ due to the increase leakage of protein from the blood. More significant is the decrease of $\Pi_{pp}$ below normal which is produced by nutritional edema. Again, the edema develops when $\Pi_{pp}$ has about the same value of $P_V$ and becomes severe for $\Pi_{pp} < P_V$. This fact also has been observed many times in both animals and humans. In particular, the control of IS volume and the "safety factor" against edema have been discussed by Guyton in most of his publications.

b) Response of the model to parameter variations

Fig.23 shows the variations of $\Pi_{pi}$, $P_t$ and $V_{IS}$ for variable $K_1$ (capillary plasma leakage coefficient) and for normal $P_a$, $P_V$ and $\Pi_{pp}$. $K_1$ may be remarkably increased, locally, by capillary damage, by inflammation and by burns. $K_4$ and $K_5$ may also be increased in such instances but in this simulation they have their normal values.

According to the model response, $K_1$ may be increased 15 times before edema develops. Edema is, of course, observed in cases of inflammation and burns, but the quantitative data available are poor and unreliable for comparison with the model's response.

Edema also occurs as a result of reduced lymph flow. The continuous curves in Fig.24 represent the variations of IS pressures and volume for variable $X = K_3$ and $K_2 = 0$. The abscissa therefore represents the lymph flow. It may be observed that edema starts to develop for lymph flow equal
Fig. 23. Response of the model for variable capillary plasma leakage.

\[ V_{IS} = V_2 \]

- \( P_A = 32 \text{ mmHg} \)
- \( P_V = 12 \text{ mmHg} \)
- \( C_{pp} = 70 \text{ g/l} \)
- \( \Pi_P = 25.6 \text{ mmHg} \)
Fig. 2b. Response of the model to variable lymph flow.
to 50% of normal and becomes severe when lymph flow is below 25% of the normal value. These results show very clearly the importance of the lymph circulation despite the fact that the lymph flow is only about 3 l per day while the cardiac output is about 8000 l per day. (Total lymphatic occlusion produces death within a few days while local lymphatic occlusion produces massive local edema.) The dotted curve in Fig. 24 is valid for \( X = K_3 = K_2 \). In other words, the lymph flow is reduced while maintaining some dependence between flow and \( P_t \). As it appears, such dependence is very important in the prevention of edema. \( K_3 \) and \( K_2 \) now have to become about 5% of their normal value before edema starts to develop. Again the importance of correlated variations between parameters appears obvious.

c) Comparison of model results with physiological and pathological data.

Partial lymphatic occlusion was obtained by Papp in 1957. The resulting increase in intracellular fluid volume ranged from 8% to 100% while the IS protein concentration ranged between 14% and 66% with an average of 42% of that of plasma. The computer simulation of lymphedema (continuous line in Fig. 24) yields an IS protein concentration ranging from 34% to 59% of that of plasma with an average of 46% for the same range of variation of \( V_{IS} \). The agreement of the averages is very satisfactory.

Weech et al. (1935) observed that malnutrition edema in dogs started to develop at plasma protein concentrations below about 51 g/l, and they measured the protein content in both plasma and edema fluid. Their results, in Fig. 25a, are compared to the model predictions. Again the agreement is satisfactory.

In 1970 Jue et al. measured the increase in lymph flow caused by increased
Fig. 25. a) Simulation of nutritional edema.
   b) Lymph flow changes in venous congestion.
venous pressure in dogs. The venous pressure is about 50% of the venous capillary pressure. Under this assumption their modified results are reported in Fig. 25 b together with the computer results for the same experiment. As it appears, doubling the capillary venous pressure (or the venous pressure) increases the lymph flow by over 500% and brings the system on the verge of edema. (Fig. 22). The importance of lymph flow in the control of interstitial fluid volume is again quite evident.

It may be observed that, inasmuch as the modifications discussed in this section are not secondary to electrolyte unbalances, the intracellular compartment is not involved in their effects. The buffer action of the interstitial compartment with respect to variations in plasma hydrostatic or oncotic pressures is therefore evident.

IV.7 Equilibrium between the three Compartments.

In the previous section the body compartments have been considered two at a time. In general, however, all three are modified by the input or output of substances. A total model of the steady state equilibrium can be obtained by joining the two models described in this chapter with some modification of the second. Given the total body amount of water, of each electrolyte and of intracellular and extracellular protein, the model for the IC-EC balance can be used to find $V_{IC}$, $V_{EC}$ and all the ionic concentrations in the EC and IC spaces. The problem of finding the plasma and interstitial fluid volume and the relative oncotic pressure remains.

Eqs. 33 to 38 are still valid but are now insufficient for the solution
of the problem because $C_{pp}$ ($\Pi_{pp}$) is not known. However, three new conditions may now be written for the system:

Eq. 39

$$V_p + V_{IS} = V_{EC}$$

Eq. 40

$$C_{pp}V_p + C_{pi}V_{IS} = ECP$$

Eq. 41

$$V_{IS} = f_3(P_t) \quad \text{(see Fig. 20)}$$

where:

- $V_{EC} = \text{extracellular fluid volume}$
- $ECP = \text{extracellular protein amount}$

Eqs. 33 to 41 form a system of nine equations in 9 unknowns, the unknowns being: $C_{pp}, \Pi_{pp}, C_{pi}, \Pi_{pi}, V_p, V_{IS}, P_t, P_a, F_1$. The solution of this system is somewhat more complicated than in the previous case (Eqs. 33 to 38) but it may be obtained and it yields the values of the 9 unknowns. If desired, the fictitious value of EC protein content $q$ may now be corrected and the value of $P_a$ and $P_Y$ may also be corrected as functions of $V_p$. The two models can then be solved again with these new data if more accuracy is required. This iteration may be repeated, if desired, however, the small effect of the value of $q$ in the IC-EC exchange and the fact that both $P_a$ and $P_Y$ are controlled by the cardiovascular reflexes suggests that one or two trials will be sufficient. The equations given in this chapter, and in particular the technique described in this section, provide a solution to Problems 1 and 2 proposed at the end of Section 1 of this chapter.

The programs used for the implementation of the model were identical to the subroutines ECIC and IVIS (Appendix D) except for minor differences concerning the input of data and the output of results.
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CHAPTER V

PHYSIOLOGY AND MODELING OF THE DYNAMIC DISTRIBUTION
OF WATER AND SOLUTES IN THE BODY

V.1 General Comments

The general characteristics of the body fluids have been discussed in Chapter IV and their arrangement has been indicated in Fig. 14. This chapter is concerned with the dynamics of the exchange of water and solutes across the capillary and cellular membranes.

The general considerations and approximations given in Section 1 of Chapter IV are still valid in this analysis. In particular, the assumption of "instantaneous" osmotic equilibration across the capillary membrane will be maintained (a detailed justification of this assumption will be given in Section 3) and the effect of the protein concentration gradient across the cell membrane will be neglected (see Chapter IV).

In Section 2 the exchange across the cell membrane will be discussed, while Section 3 will describe the model of capillary dynamics. This will complete the simulation of a nephrectomized man and the model results will be presented in Section 4.

V.2 Dynamics of Water and Electrolyte Exchange across the Cell Membrane

As previously stated in Chapter IV, the dynamics of water and electrolyte
exchange across the cellular membrane involves very complex chemical, mechanical, and electrical phenomena which take place at the microscopic level. Because of the complexity of these phenomena, because of the variability of cell behavior in different organs, and because of the lack of data concerning cell membranes, the "black box" approach to the simulation of the cell membrane will be maintained. This approach consists of writing equations which describe the "average" cell membrane at the macroscopic level as an anisotropic boundary having direction-dependent permeabilities to the various ions. This approach is not very rigorous because it implies certain constraints upon the active transport of ions and upon the membrane voltage and it is uncertain whether these constraints lead to a negligible or significant error at the macroscopic level.

The following assumptions will be made:

a) The net water flow across the cellular membrane is due only to osmotic forces. The effect of the mechanical tension of the membrane will be neglected.

b) The flow of ion i from side 1 to side 2 of the membrane is proportional to the concentration of i on side 1 and to the membrane permeability to i in the direction 1 to 2.

c) The flow of ion i from side 2 to side 1 of the membrane is proportional to the concentration of i on side 2 and to the membrane permeability to i in the direction 2 to 1.

d) The membrane presents the same unidirectional permeability for all ions when they are diffusing along their concentration gradients (This assumption is rather arbitrary and it is mainly due to the lack of information concerning average parameters for human body cells)
The equations for water and solute flows will now be considered.

a) Water flow

Water molecules move randomly in both the EC and IC fluids; at equilibrium the number of water molecules crossing the membrane in one direction is equal to the number of water molecules crossing it in the reverse direction and the net water flow is zero. If there is an osmotic gradient (that is, a water concentration gradient) this balance is upset and a net flow of water takes place. This is described by Eq. 42 and Fig. 26.

\[ O_1 = \text{osmolality of Compartment 1; } \quad O_2 = \text{osmolality of Compartment 2} \]

\[ V_1 = \text{volume of Compartment 1; } \quad V_2 = \text{volume of Compartment 2} \]

\[ N_1 = n_{w1} + n_{s1} = \text{total moles in Compt. 1; } \quad N_2 = n_{w2} + n_{s2} = \text{total moles in Compt. 2} \]

\[ n_{w1}, n_{s1} = \text{n. of water and solute moles in Compart. 1} \]

\[ n_{w2}, n_{s2} = \text{n. of water and solute moles in Compart. 2} \]

Fig. 26 Water flows across the cell membrane.
Eq. 42  \[
\frac{dV_1}{dt} = K \left[ \frac{n_w}{N_2} - \frac{n_w}{N_1} \right]
\]

where \( N_1 = n_{w1} + n_{s1}, \quad N_2 = n_{w2} + n_{s2} \) (See Fig. 26 for symbol significance.)

Eq. 42 can be rewritten as:

Eq. 43  \[
\frac{dV_1}{dt} = K \left[ \frac{1}{1 + \frac{n_{s2}}{n_{w2}}} - \frac{1}{1 + \frac{n_{s1}}{n_{w1}}} \right]
\]

It may be observed that since body fluids have osmolalities in the range 0.2 to 0.4 osm/l and since there are 55.2 osmoles of water in a liter of water, the ratios \( n_{s1}/n_{w2} \) and \( n_{s1}/n_{w2} \) are in the range 0.04 to 0.08. Taking the first two terms of the Taylor expansion of the expression \( 1/(1+x) \) for \( x = 0 \) \( (1/(1+x) = 1 - x) \) and substituting them in Eq. 43 we obtain:

Eq. 44  \[
\frac{dV_1}{dt} = K' \left[ \frac{n_{s1}}{n_{w2}} - \frac{n_{s1}}{n_{w2}} \right]
\]

observing that \( V_1 = n_{w1}/55.6, \quad V_2 = n_{w2}/55.6; \) (1 l of \( H_2O = 55.6 \) osmoles) we have:

Eq. 45  \[
\frac{dV_1}{dt} = K' \frac{55.6}{V_1 - V_2} \left[ \frac{n_{s1}}{V_1} - \frac{n_{s2}}{V_2} \right] = K' (O_1 - O_2)
\]

that is the water flow is proportional to the solute osmotic gradient.
b) Solute flow

The cellular membrane has a nonsymmetric behavior for solutes due to the presence of active transport and of the resulting electrical potential. Consequently a charged ion will encounter a different "resistance" in crossing the cellular membrane depending upon the direction of the crossing. This concept is described by assumptions b and c (previous subsection) and by Eq. 46.

$$\frac{dX_{11}}{dt} = -K_{112}C_{11} + K_{121}C_{12}$$

where $X_{11}$ = amount of ion i in compartment 1 (EC)

$C_{11}, C_{12}$ = concentration of ion i in compartment 1 and 2

$\frac{dX_{11}}{dt} =$ net flow of ion i from compartment 2 to compartment 1

$K_{112}, K_{121}$ = directional permeabilities

The coefficients $K_{112}$ and $K_{121}$ are presumably not constants. Changes of the concentrations $C_{11}$ and $C_{12}$ will modify both the voltage across the membrane and the active transport current therefore affecting the $K_{112}$ and $K_{121}$ of all the ions. However, since at steady state

$$\left(\frac{dX_{11}}{dt} = 0\right) \text{is} \quad \frac{K_{112}}{K_{121}} = \frac{C_{12}}{C_{11}} = \text{constant},$$

and since during transients in the physiological range the ratios $C_{11}/C_{12}$ are never too far from their steady state values, it will be assumed that the $K_{112}$'s and the $K_{121}$'s are constant.

Equations 47 through 50 define $C_{11}, C_{12}, O_1$ and $O_2$.
\begin{align*}
\text{Eq. 47} & \quad C_{11} = \frac{x_{11}}{v_1} \\
\text{Eq. 48} & \quad C_{12} = \frac{x_{12}}{v_2} \\
\text{Eq. 49} & \quad o_1 = \sum_{i=1}^{n} C_{i1} + \frac{q_1}{v_1} \\
\text{Eq. 50} & \quad o_2 = \sum_{i=1}^{n} C_{i2} + \frac{q_2}{v_2}
\end{align*}

where \( n \) = number of diffusible solutes

\( q_1, q_2 \) = amount of protein in compartments 1 and 2 (non diffusible) (in osmoles)

The input flow of water can be added to the right term of Eq. 45 while the input flow of each solute (except protein) can be added to the right side of Eq. 46.

Eqs. 51 and 52 are the duals of Eqs. 45 and 46 for compartment 2.

\begin{align*}
\text{Eq. 51} & \quad \frac{dV_2}{dt} = -K \cdot (o_1 - o_2) \\
\text{Eq. 52} & \quad \frac{dx_{12}}{dt} = K_{112} C_{i1} - K_{121} C_{i2}
\end{align*}

Equations 45 through 52 describe the behavior of the model and are represented graphically in the analog diagram of Fig. 27. The system is clearly nonlinear because of the variation of \( V_1 \) and \( V_2 \). It may be observed that when the input is removed from the system the steady state approached is the same described in Chapter IV because the condition
\[
\frac{K_{112}}{K_{121}} = \frac{c_{12}}{c_{11}}
\]
is, for all practical purposes, equivalent to the condition of Eq. 18:
\[
K_1 = \frac{x_1}{x_1} = \frac{c_{12}}{c_{11}}
\]

\(c\) Parameter evaluation

The value of \(K\) for Eq. 45 may be obtained from the disappearance curves of \(D_2O\). Data from Edelman (1952, 1962) and from Scholer and Code (1954) show that \(D_2O\) equilibrates very rapidly throughout the EC fluid and then diffuses into the cell. The initial diffusion flow of \(D_2O\) is unidirectional and allows the computation of the associated unidirectional water flow. The latter can be expressed as \(K n_{w2} / \bar{N}_2\) (see Eq. 42). Since \(n_{w2} / \bar{N}_2 \approx 1\), this flow is represented by \(K\).

The experimental data indicate that the unidirectional water flow is approximately 25% of the EC fluid volume per minute, that is, about 3.71 l/min. Since \(K = K' / 55.6\) (Eq. 45) the value of \(K\) appears to be
\[
K = \frac{0.0667}{\text{osm/l}}
\]

It has been observed that the value of osmotic permeability to water obtained by using isotopic tracers is smaller than the real permeability because of the presence of pores in the membranes which allow bulk flow (Koefoed, Johnsen and Hussing 1953). The ratio between the real and the tracer-evaluated permeability has been measured for many cells (Dick 1966) and in particular for human red blood cells (Villegas et al., 1958). This ratio has been found to be 2.5. Assuming that this ratio is correct, on the average, for the fictitious model boundary between EC and IC fluids, the real value of \(K\) is then:
Fig. 27. Dynamics of the equilibrium across the cellular membrane. The diagram shows only one of the blocks simulating the ion dynamics. There are as many of these blocks as there are ions and solutes.
More difficult and less accurate is the evaluation of the parameters for the electrolyte equations (Eq. 46). Data from Gellhorn et al. (1944) show that the concentration of radioactive sodium injected into the blood of dogs decays according to a double exponential curve having time constants of 1 and 10 minutes. It is assumed here that the faster exponential describes the Na diffusion throughout the extracellular space (which is taken to be in equilibrium within 1 minute, as assumed in Section 1 of this chapter). It is also assumed that the slower exponential describes the limited Na diffusion through the cellular membrane. Under these assumptions the amount of isotopic Na exchanged per minute across the cellular membrane is 10% of the EC sodium (or 76% of the IC sodium) Assuming that the same is true for man, the values of $K_{12}$ and $K_{21}$ for sodium are:

$$K_{12} = \frac{0.1 \cdot \text{EC amount of Na}}{\text{EC Na concentration}} = 1.48 \quad K_{21} = \frac{K_{12}}{0.0714} = 20.37$$

where 0.0714 is the value of $K_1$ for sodium (Chapter 4). The quantity $K_{12}$ represents, for sodium, the coefficient of passive diffusion along the concentration gradient while $K_{21}$ represent the diffusion coefficient for the direction in which facilitation is provided by active transport. The hypothesis has been made that the passive diffusion coefficient is the same for all the ions (assumption d). Some evidence supports this hypothesis for sodium, chloride and sulfate ions. It is also assumed that the amount of urea exchanged across the cellular membrane is 25%
the EC amount of urea per minute (same as water).

The above hypotheses and the equation

\[ \frac{K_{112}}{K_{121}} = K_i \]

lead to the set of values indicated in Fig. 28.

Because of the lack of specific data, these values are obtained by non-rigorous considerations and their real validity remains to be verified.

From the numerical values of Fig. 28 it can be observed that, despite the large amount of water exchanged between the compartments, (about 3 l per minute) the balance of this exchange is only little upset by changes in solute concentration. Also, it appears that changes in EC potassium concentration are equilibrated much faster than similar changes in other ionic concentrations. This fact has been experimentally verified in rabbits (Walker and Wilde, 1952). Because of the speed of the potassium equilibrium, the one minute elemental time interval for the digital model appears to be too large. An interval of 0.1 minute is therefore taken for the iterative solution of Eq. 46 and the minute input is uniformly distributed over the 10 six second intervals. Another possibility would be that of considering the overall body equilibration of potassium as "instantaneous" (that is, completed within a minute). The first approach is chosen for the programming advantages that offers.
**EXTRACELLULAR FLUID** | **INTRACELLULAR FLUID**  
---|---
**WATER**  
$H_2O$  
$V_1 = 14.81$  
$\rightarrow$  
$K_{21}C_2$  
$K_{21} = 20.37$  
$V_2 = 27.29$

**SODIUM**  
$Na$  
$C_1 = 139.31$  
$\rightarrow$  
$K_{12}C_1$  
$K_{12} = 1.48$  
$C_2 = 9.95$

**POTASSIUM**  
$K$  
$C_1 = 4.02$  
$\rightarrow$  
$K_{21}C_2$  
$K_{21} = 1.48$  
$C_2 = 3.98$

**CHLORIDE**  
$Cl$  
$C_1 = 111.32$  
$\rightarrow$  
$K_{12}C_1$  
$K_{12} = 51.8$  
$C_2 = 129.32$

**OTHER IONS**  
$O_i$  
$C_1 = 33.11$  
$\rightarrow$  
$K_{21}C_2$  
$K_{21} = 1.48$  
$C_2 = 4.0$

**UREA**  
$U$  
$C_1 = 4.0$  
$\rightarrow$  
$K_{21}C_2$  
$K_{21} = 3.7$

**PROTEINS**  
$C_1 = 0.2$  
($\approx 20 \text{ g/l}$)  
$\rightarrow$  
$C_2 = 4.0$  
($\approx 400 \text{ g/l}$)

---

Unidirectional flows:

$C_1, C_2:\text{mosm/l}$  
$V_1, V_2:\text{l}$  
$K:\frac{\text{ml/min}}{\text{mosm/l}}$  
$K_{12}, K_{21}:\frac{\text{mosm/min}}{\text{mosm/l}}$

---

Fig. 28 Parameter significance and values for extracellular-intracellular water and solutes equilibrium.
V.3 Osmotic, Hydrostatic, and Oncotic Equilibrium between Plasma and Interstitial Compartments.

a) Osmotic Equilibrium.

As it was said in Section 1 of this chapter, the electrolyte equilibrium across the capillary membrane is reached very quickly. For example, if 0.1 l of water is added "instantaneously" to the plasma of the "average normal man", the plasma osmolality will drop 9 mosm/l, producing an osmotic pressure gradient of 153 mmHg across the capillary wall (1 osm/l corresponding to an osmotic pressure of 22.4 atm; 1 mosm/l corresponds to 17 mmHg)

Considering an average capillary water permeability coefficient of 5 ml/min mmHg (see Chapter IV), the resulting initial water flow will be 765 ml/min. The time constant of the resulting volume and osmolality transients (assumed to be exponential) would be about 8 seconds. Considering that ions may also move across the capillary wall, the transients may be even faster. Although the above example is only theoretical (the intravenous injection of 0.1 l of water into a man would damage his blood cells) it serves well the purpose of showing the speed of electrolyte equilibrium across the capillary wall.

It seems reasonable to assume that a new equilibrium between plasma and interstitial space would be reached within a minute. Such an equilibrium involves only electrolyte osmotic forces. As indicated by Pappenheimer (1953), the process of osmotic equilibration across the capillary membrane consists of two related phenomena: a) molecules of each solute diffuse from the compartment having higher concentration
of that solute into the one of lower concentration, b) molecules of water diffuse from the compartment of lower osmolality into the compartment of higher osmolality. Both processes continue until the solute and solvent concentration difference across the membrane approaches zero. The volume of the two compartments at the end of the electrolyte osmotic transient depends upon the relative rapidity of the two phenomena indicated above; in other words, such volumes depend upon whether the osmotic balance is reached mostly by ion movement or by water movement.

Oncotic and hydrostatic forces take longer to equilibrate and they produce flows of ultrafiltrate and plasma leakage, rather than opposite flows of water and electrolytes. For example, 0.1 l of a nonprotein solution added "instantaneously" to the human plasma would lower the protein concentration from 70 to 67.8 g/l producing an oncotic pressure gradient of about 1 mmHg and an initial ultrafiltrate flow of only about 5 ml/min.

The predicted rapidity of the electrolyte balance across the capillary membrane is supported by experimental evidence which justifies the assumption of "instantaneous" equilibration (Heversy and Jacobson 1940; Gellhorn et al. 1944; Edelman et al. 1952).

As mentioned above, the volumetric changes of the plasma and IS spaces immediately following the injection of a solution depend upon the relative rapidity of water and solute flows across the capillary wall. Experiments performed by Wolf (1971) on nephrectonized dogs show that, after the intravenous injection of an hypertonic solution, the plasma volume increase is larger than the volume injected. This indicates that water is withdrawn from the IS space under the effect of the osmotic gradient.
Let us assume that after the injection of $\Delta V$ liters of hypertonic solution enough water is absorbed into the plasma to make it isotonic with the IS fluid before any amount of electrolyte can leave either compartment. If $\Delta W$ is this amount of water, the plasma volume increase after this water shift will be $\Delta W + \Delta V$.

It can be observed that the volume $\Delta W + \Delta V$ is in the neighborhood of the increase observed by Wolf. It is therefore concluded that water moves across the capillary membrane much faster than the electrolytes do. The amount $\Delta W$ is given by Eq. 54.

\[ \Delta W = \frac{V_2 \cdot OC_1 - V_1 \cdot OC_2}{OC_1 + OC_2} \]

which is obtained by solving Eq. 55 for $\Delta W$. Eq. 55 describes the condition of equal osmolality.

\[ \frac{OC_1}{V_1 + \Delta W} = \frac{OC_2}{V_2 - \Delta W} \]

where $OC_1$, $OC_2$ = osmotic content (electrolytes + urea) of plasma and IS space ($OC_1$ includes the injected solutes)

$V_1$, $V_2$ = volumes of plasma and interstitial space ($V_1$ accounts for the injected solution)

After the water shift, the two volumes will be $V_1 = V_1 + \Delta W$ and $V_2 = V_2 - \Delta W$. If $i$ is the type of solute injected, the solutes other than $i$ are now diluted in the plasma and start flowing into it from the IS space while the injected solute(s) flow out. The amount $\Delta S_i$ of solute $J$ that has
to be shifted between the compartments in order to reach the same
concentrations on both sides of the capillary membrane is given by Eq. 56.

$$\Delta S_j = \frac{x_{2j} \cdot v_1 - x_{1j} \cdot v_2}{v_1 + v_2}$$

Eq. 56

which is obtained by solving Eq. 57 for $\Delta S_j$. Eq. 57 describes the condition
of isoconcentration of $J$.

$$\frac{x_{1j} + S_j}{v_1} = \frac{x_{2j} - S_j}{v_2}$$

Eq. 57

where $x_{1j}$, $x_{2j}$ = amount of ion $J$ in compartment 1 and 2 (plasma and IS)
and where $\Delta S_j$ has a positive sign when entering the plasma.

If the shift of solutes proceeds with similar velocity for each
solute, the condition of isotonicity is not much upset; when the condition
of isoconcentration of each solute is reached, the condition of isotonicity
is automatically verified. (It is to be noted that the reverse is not true,
isotonicity does not imply isoconcentration of each solute). Therefore no
further water or solute shift takes place and the two compartments are
in electrolyte equilibrium.

The same procedure can be used in computing the plasma IS electrolyte
equilibrium state when the input, rather than being a solution injected in
the plasma, is a solution added to or subtracted from the IS space because
of fluid shift between that compartment and the intracellular space. This
equilibrium state is computed by a subroutine "FLIS" (Appendix D) which
performs the following operations:
a) Compute $V_1$, $V_2$, $OC_1$, $OC_2$, $X_{11}$'s, $X_{21}$'s following the application of an input to either compartment (plasma or IS)

b) Compute $\Delta W$ (Eq. 54) and correct $V_1$ and $V_2$ for such shift of water

c) Compute the $\Delta S_j$'s (Eq. 56) and correct the $X_{11}$'s and the $X_{21}$'s for such solute shifts

d) Verify that Eq. 54 and Eq. 56 provide now $\Delta W = 0$ and $\Delta S_1 = 0$. If not, repeat points 2, 3, and 4.

e) Compute the final state concentrations of each solute and the osmolality of the two compartments.

The above analysis rests on the major assumption that the process of equilibrium consists of a fast exchange of water under osmotic gradient and a subsequent exchange of electrolytes without significant further water movement. It is interesting to observe that the osmotic equilibrium process across the cellular membrane proceeds in a very different way; in this case:
the electrolyte and water flows are simultaneous and the first is faster than the second;
the condition of correct concentration ratios is reached in a few minutes while the condition of isotonicity is reached in a few hours. (see Section 4).

b) Osmotic and hydrostatic equilibrium.

The osmotic, oncotic and hydrostatic forces are acting simultaneously across the capillary membrane. Because of the different flows produced by their action they are considered in the model as acting sequentially in
each elemental time interval. This is also required by the digital nature of the simulation. The shift of material between the plasma and IS space following an injection produces volume modifications of the two compartments. In turn, these modifications produces changes in the hydrostatic and oncotic pressure of the two fluids which result in an ultrafiltrate flow change (and a plasma leakage change) across the capillary membrane. This flow carries all exchangeable solutes and does not produce any further electrolyte unbalance.

The exchange of material between plasma and IS spaces due to oncotic and hydrostatic action consists of four components:
1) a filtration flow leaving the capillaries
2) a reabsorption flow entering the capillaries
3) a plasma leak flow leaving the capillaries
4) a lymph flow entering the circulation

The expressions for these flows are given in Eqs.27, 28,29 and 30 in Section 4 of Chapter IV. A diagram of the physiological system was given in Fig.18. The net flow expression was given in Eq.31 and it is repeated in Eq.58 for convenience.

\[
E_{58} \quad F_n = K_4P_A + K_5P_V + (K_4 + K_5) (\Pi_{pt} - \Pi_{pp} - P_t) + F_p - F_l
\]

where the parameters and the normal values of the variables have been defined in Chapter IV on p.73. The protein flows carried by \( F_p \) and \( F_l \) are obtained by multiplying \( F_p \) by \( C_{pp} \) and \( F_l \) by \( C_{pi} \) (see Chapter IV). The capillary pressures are regulated by a neural mechanism by means of arteriolar and venular resistance control. It is assumed here that such
control is effective in maintaining constant $P_A$ and $P_V$ for plasma volume changes of $\pm 15\%$. For larger changes it is assumed that the pressures in the arteries and veins vary linearly with the plasma volume (Guyton 1971). The volume change in the venous tree is taken to be 70% of the total plasma volume change. It is further assumed that the change in arterial capillary pressure is $1/6$ of the change in arterial pressure, while the change in venous capillary pressure is $3/4$ of the change in venous pressure (Guyton 1971). These considerations, with Guyton's data, lead to the following equations:

Eq. 59  \[ P_A = P_{A0} \text{ for } 0.8 V_{10} < V_1 < 1.2 V_{10} \]
\[ P_A = P_{A0} + 25.2 (V_1 - 1.15 V_{10}) \text{ for } V_1 > 1.15 V_{10} \]
\[ P_A = P_{A0} + 25.2 (V_1 - 0.85 V_{10}) \text{ for } V_1 < 0.85 V_{10} \]

Eq. 60  \[ P_V = P_{V0} \text{ for } 0.85 V_{10} < V_1 < 1.15 V_{10} \]
\[ P_V = P_{V0} + 11.05 (V_1 - 1.15 V_{10}) \text{ for } V_1 > 1.15 V_{10} \]
\[ P_V = P_{V0} + 11.05 (V_1 - 0.85 V_{10}) \text{ for } V_1 < 0.85 V_{10} \]

The dependence of $P_t$ upon the interstitial fluid volume was given in Fig. 20 as a piecewise linear approximation of Guyton's data. The equations of the oncotic and hydrostatic equilibrium can now be easily written as:

Eq. 61  \[ V_1 = V_{10} - \int_0^t F_n \, dt \quad (V_1 = \text{plasma volume}) \]
Eq.62 \[ V_2 = V_{20} + \int_{0}^{t} F_n \, dt \quad (V_2 = IS \text{ volume}) \]

Eq.63 \[ Q_{pp} = Q_{ppo} \int_{0}^{t} (F_p C_{pp} - F_1 C_{p1}) \, dt \]

Eq.64 \[ Q_{pi} = Q_{pio} \int_{0}^{t} (F_p C_{pp} - F_1 C_{p1}) \, dt \]

where Eq.61 and Eq.62 imply the condition of electrolyte equilibrium and of zero input flow. The subscript o denotes initial conditions.

These equations are represented by the analog diagrams of Figs.29 and 30 which clearly show the nonlinearities of the system as well as the feedback loops. The input flow into \( V_1 \) and the fluid flows due to electrolyte forces from \( V_2 \) to \( V_1 \) and from the IC compartment into \( V_2 \) may be added under the integral sign of Eqs.61 and 62.

![Diagram](image-url)

**Fig. 29.** General arrangement of the oncotic and hydrostatic control system of plasma and interstitial volume. Subscript o means initial condition.
Fig. 30. Analog diagram of the mechanism involving oncotic and hydrostatic pressures in the control of the plasma and interstitial compartment volumes ($V_1$ and $V_2$). The subscript zero means initial value.
V.4 Simulations and Results

The model described in Chapter V allows the solution of Problems 3 and 4 indicated in Section 1 of Chapter IV. The sequential organization of the program is reported in Fig. 31 while the program and its subroutines are in Appendix D. The time increment used is 1 minute; however, points 3, 4, and 5 are included in an inner loop with a reduced time increment of 0.1 minute. This reduces the approximation errors in accounting for the electrolyte exchanges across the cellular membrane. This model allows the simulation of the response of a nephrectomized dog to the injection of water and solutes. For a simulation period in the range of a few hours the model response can be expected to differ somewhat from the animal response because the former does not account, at this stage for the insensible water losses and for the metabolic solute production. Since, at this point, the interest is in the 2 to 3 hour transient response to an intravenous injection, such factors may be neglected because of their limited effect during the transient time.

Fig. 32 shows a comparison between computer results and experimental observations following the intravenous injection of hypertonic solutions in dogs. The measurements were performed by Wolf in 1971. Model predictions and experimental results agree well in the case of rapid injection of 12 ml/Kg of body weight of a 0.833 M solution of NaHCO₃. The agreement is less satisfactory for the response to the NaCl injection although one of Wolf's experiments presented the slight undershoot in plasma volume predicted by the model.
1. Read total body quantities of water and electrolytes, oncotic and hydrostatic pressures and system parameters, observation time, and so on.

2. Compute initial steady state

3. Read input, if any, and find PL-IS electrolyte equilibrium state.

4. Compute IS-IC water and electrolyte shifts during $\Delta t$

5. Correct PL-IS equilibrium for such shifts

6. Compute ultrafiltrate and protein PL-IS shifts during $t$

7. Correct PL and IS volume for such shifts

8. Print information

9. If observation time has expired go to 1.
   If not go to 3

Fig. 31 Program organization ($\Delta t = 1$ min). The inner loop including points 3, 4, and 5 is executed 10 times with a $\Delta t = 0.1$ min for each run through the main loop. Steps 1 and 2 have been described in Chapter IV.
The reasons for the relative disagreement are of various natures:

a) For high plasma volume increases (0 to 20 minutes after the injection) some expansion of the capillaries and consequent increase in permeability coefficients is to be expected. In the model these coefficients are constant resulting in the prediction of higher plasma volumes.

b) Three hours after the injection the insensible losses begin to be significant resulting in an experimental plasma volume slightly lower than the one predicted.

c) Three experiments are not sufficient to provide a statistically significant average plasma volume transient.

d) The experimental errors and model approximations contribute to the differences.

Fig. 33 shows data from Bradham (1964) and computer results indicating the plasma volume changes of dogs (man, in the computer simulation) at different times after the injection of the solution specified in the figure. The experimental data were obtained between 2.5 and 3.5 hours after the injection.

Figures 34 and 35 show the transients in plasma and interstitial fluid volumes and in intracellular and extracellular osmolalities following the injection of hypertonic solutions of equal volume and concentration but different composition. It appears from these responses that the volume transients are the largest when the solution contains ions which are prevalently intracellular (KHCO₃) and the smallest when the solution contains typical extracellular ions (NaCl) or freely diffusible solutes.
Fig. 32. Plasma volume response to the injection of hypertonic solutions. Experimental data from Wolf, 1971.
Fig. 33. Plasma volume response to the injection of hypertonic solutions. Experimental data from Bradham et al. 1964. $x = \text{exp. data 'two to three hours after the injection'}. $

(urea). However, the steady state changes are larger for solutions of extracellular and freely diffusible ions or solutes, and smaller for the case of intracellular ions. The intracellular volume changes over a two hour period are almost negligible (all less than 5%).

It is clear that the volumetric stress is initially taken by the intravascular compartment and subsequently shared by the interstitial. The intracellular compartment undergoes slower volume changes which in the intact animal are probably almost entirely avoided by the action of the kidneys. Such action should also be expected to reduce substantially the osmotic stress. The osmolality transients appear to have a fast phase due to electrolyte flows and a much slower phase due to water movements. In two cases they appear to be far from being completed after two hours (NaCl and KHCO₃ solutions) in the other two cases the condition of approximate
Fig. 34. Simulated plasma volume and interstitial volume transients following the injection of hypertonic solutions of the same volume and concentration. (12 ml/kg of 0.833 M solution in a 70 Kg man. Volume injected = 0.840 l)
Fig. 35. Intracellular (IC) and extracellular (EC) osmolality transients in response to the injection of the solutions of Fig. 34.
isotonicy reached within two hours is mostly due to solute exchange (NaHCO$_3$ and urea).

Figure 36 shows the volume and osmolalities transients following the injection of 1 l of "isotonic" saline. It is interesting to observe that the so called "isotonic" saline solution actually produces a considerable plasma volume transient and a slight change in EC and IC osmolality. The injection of saline solution is often used to increase the plasma volume. To this end, this model may be useful in designing solutions to produce a desired transient in plasma volume.

As an example, it may be proposed to find a solution to increase rapidly the plasma volume of a nephrectomized animal with a minimum modification of the other volumes or of osmolality. Such a condition may be useful in investigating the dependance of ADH secretion and plasma ADH concentration upon the plasma volume. After a few trials it is found that 1 l of solution having concentration 0.115 M of NaCl, 0.025 M of NaHCO$_3$ and containing 95 grams of proteins, injected intravenously within 5 minutes will raise the plasma volume from 3.24 l to 4.27 liters without any appreciable transient following the injection.

The following table indicates the maximum changes that such a solution would produce in a three hours period after the injection:

<table>
<thead>
<tr>
<th></th>
<th>PL volume</th>
<th>0.01 l;</th>
<th>- 0.2%</th>
</tr>
</thead>
<tbody>
<tr>
<td>IS volume</td>
<td>- 0.04 l;</td>
<td>- 0.35%</td>
<td></td>
</tr>
<tr>
<td>IC volume</td>
<td>+ 0.01 l;</td>
<td>+ 0.03%</td>
<td></td>
</tr>
<tr>
<td>EC osmolality</td>
<td>0.25 mosm/l;</td>
<td>0.086%</td>
<td></td>
</tr>
<tr>
<td>IC osmolality</td>
<td>0.31 mosm/l;</td>
<td>0.1%</td>
<td></td>
</tr>
</tbody>
</table>

Individual ionic concentration: less than 0.3% for any ion and urea.
Fig. 36. Plasma and interstitial volume transients and intracellular and extracellular osmolality transients after the intravenous injection of one liter of water and one liter of isotonic saline.
It appears that all the quantities remain practically constant and no appreciable transient follows the injection, as desired. Similarly, a procedure may be devised, with the help of the model, to modify the plasma osmolality without changing significantly any of the compartment volumes. This can be done by withdrawal of blood and subsequent or simultaneous injection of a hypotonic solution or of water. The feasibility of these experiments and the practical problems involved should however be evaluated with the help and experience of the physiologist.
Bibliography (Chapter V) (See also Bibliography of Chapter IV)


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CHAPTER VI

PHYSIOLOGY AND MODELING OF THE RENAL SYSTEM

VI.1 General Physiology of the Kidney. Mechanism of Urine Formation.

a) Introduction.

In the mammalian body the kidney has three major functions: excretory, metabolic and endocrine. The metabolic and endocrine functions consist respectively of the metabolism of certain hormones and substances and of the production of certain other hormones. This chapter is concerned with the analysis of the excretory function.

In cybernetic terms the kidney is the power amplifier of the body fluid regulation system. The operation performed by the kidney is that of separating from the blood and excreting variable amounts of water and solute for the purpose of maintaining body homeostasis. The overall transfer function of the kidney is therefore relating the urine flow and concentrations (output variables) to the renal blood flow and concentrations (input variables) and to various renal parameters.

It is the purpose of this chapter to describe briefly the physiology of this organ and to develop a model of its transfer function by means of an analysis and simulation of the nephron. The hormonal control of this transfer function will be described and modeled in the following two chapters.
b) Outline of Renal Physiology

The external stresses applied to the body fluid regulation system may vary from water loading, to osmotic loading, to dehydration. Depending upon the stress applied, the system may face the necessity of conserving or excreting greatly variable amounts of water and/or solutes while also excreting metabolic wastes and poisons. In man, the concentration of urine may vary between 0.2 and 4 times the concentration of plasma while the urine flow may range from 0.2 or 0.3 ml/min. to 15 or 20 ml/min. The kidney is therefore faced with the problem of separating from the plasma a urine of variable concentration and amount while avoiding the formation of high concentration gradients across cellular membranes. Such gradients must be avoided not only because cell membranes or layers might be damaged by them, but also because maintaining them would require a large amount of energy which would reduce the efficiency of the organ.

Each kidney is separated into an outer layer named the cortex and an inner layer named the medulla. Each kidney consists of approximately 1,250,000 tubular structures named nephrons and by a fine net of capillary blood vessels immersed in a common interstitial fluid. The nephrons are not all identical. Their length and position in the kidney may vary as does the composition of the fluid in them. For reasons of analysis an "average equivalent nephron" will be defined as the ideal nephron performing the same function as the 2.5 million nephron in the kidneys. A nephron consists of the five major anatomical sections listed below:

1) Glomerulus (G) (in the cortex)
2) Proximal tubule (PT) (in the cortex)
3) Loop of Henle (LH) (in the cortex and in the medulla)
4) Distal tubule (DT) (in the cortex)

5) Collecting duct (CD) (in the cortex and in the medulla)

The collecting ducts converge in the center of the kidney (papillary region) into the ureters which carry the urine to the bladder.

The most general concepts of renal physiology have been described in Chapter II (glomerular filtration, tubular reabsorption and hormonal control).

Despite the progress in renal physiology in recent years, many aspects of the tubular reabsorption mechanism is still entirely unknown and many other are very controversial. In general the quantitative description of the tubular transport is very poor. Fig. 37 shows four diagrams of the nephron structure taken from four current textbooks. Some degree of disagreement and uncertainty is evident from these diagrams. A few points are, however, well established in the texbooks. The most significant of these points are:

a) A large amount of plasma ultrafiltrate is produced in the glomerulus and enters the proximal tubule.

b) Sodium is actively reabsorbed from the proximal tubule. Water and solutes are passively reabsorbed as a result of this active process. The fluid entering the loop of Henle is about 20% of the filtrate. It is approximately isotonic, with an urea concentration somewhat above twice the blood urea concentration.

c) The loop of Henle has a hairpin shape with the ascending limb wall impermeable to water and capable of active sodium extrusion. The fluid leaving such limb is always hypotonic.

d) The active sodium transport from the ascending limb of the loop of Henle associated with the movement of fluid along the loop, produces an interstitial
Fig. 37. Present views of nephron function.
sodium concentration profile which is maximum in the inner medulla (papilla)
e) Active sodium transport takes place across the distal tubule wall. This produces passive reabsorption of water so that the flow entering the collecting duct is only about 5% of the glomerular filtrate.
f) The final concentration of the urine takes place in the collecting duct where sodium is reabsorbed actively and in part exchanged with potassium and other ions; water is reabsorbed passively because of the high medullary osmotic concentration. Urea is reabsorbed passively as a consequence of water reabsorption and produces an urea concentration profile in the medulla.
In normal conditions (hydropenia) the output flow is somewhat less than 1% of the filtrate (0.7 to 1.2 ml/m).
g) The water and sodium permeabilities of the distal tubule and collecting duct depend respectively upon the concentration of ADH and aldosterone in the plasma.

Table 4 summarizes the factors controlling the formation of urine.

The modeling of the renal function will be attempted on the basis of the above points and of a few assumptions and hypotheses which will be specified and discussed in the following sections. The assumptions are made on the basis of two fundamental criteria:
a) They must lead to results in reasonable agreement with physiological evidence and experimental data,
b) they must lead to a mathematical treatment sufficiently simple to be handled by an average speed computer in a reasonable time.

The most important simplification in this model will be the consideration of only two solutes: sodium chloride and urea. These solutes account for
approximately 80% of the solutes present in the kidneys and in the urine. The other solutes will be considered as not being filtered at the glomerulus and not being present in the medulla. The main reason for such a rather significant simplification is that, since no model of the type proposed here is presently available, a first approach of reasonable complexity is a necessary background for subsequent developments and improvements. A secondary reason is the lack or uncertainty of information concerning the behavior of the other solutes. Since this assumption does not exactly fit physiological facts some disagreement between experimental and model results is to be expected.

Table 4

Schema of general factors involved in urine formation.
VI.2 Modeling of Glomerular Filtration

The glomerular filtration is a special type of plasma ultrafiltration. Assuming the filtrate flow proportional to the filtration pressure as was done for the systematic capillaries, Eq. 65 results:

\[ \text{GFR} = k_G \left( P_G - \Pi_{FG} + \Pi_B - P_B \right) \]

where \( \text{GFR} \) = glomerular filtration rate (ml/min)

\( P_G \) = blood pressure in the glomerular capillaries (mmHg)

\( P_B \) = hydrostatic pressure in the Bowman capsule surrounding the glomerulus (mmHg)

\( \Pi_{FG}, \Pi_B \) = colloid osmotic pressure in the glomerular capillaries and Bowman capsule (mmHg)

A few assumptions are made with regard to the four pressures listed above. They are:

a) Since the amount of filtered proteins is negligible it can be assumed \( \Pi_B = 0 \)

b) The value of \( P_B \) depends upon the elastic properties of the tubular wall and upon the values of the renal interstitial and ureteral pressures. Very little is known about the behavior and values of these variables and parameters. It appears, however, from animal experiments that the variation of \( P_B \) is limited in the anatomically normal kidney. On this basis \( P_B \) will be assumed constant in this model.

c) The value of \( P_G \) is controlled by a feedback system (renal autoregulation) which has not been entirely explained although models have been proposed for it. (Guyton et al, 1964).
The percent variation of $P_G$ around its normal value is related to, but much smaller than, the variation of arterial pressure. In turn, the latter is a function of blood volume. It will be assumed that the percent variation of $P_G$ is a fraction $K_7$ of the percent variation of the blood volume. This results in Eqs. 66 and 67.

$$\text{Eq. 66} \quad \frac{P_G - P_{G_0}}{P_{G_0}} = K_7 \frac{BV - BV_o}{BV_o}$$

$$\text{Eq. 67} \quad P_G = K_7 \frac{P_{G_0}}{BV_o} \left( BV - BV_o \right) + P_{G_0}$$

where the subscript 0 indicates "normal value" and $V_p$ is the plasma volume.

d) Since 20% of the renal plasma flow leaves the glomerular capillaries in the form of ultrafiltrate, the oncotic pressure in these capillaries rises accordingly from 25 to about 30 mmHg. This rise depends upon the ratio of GFR to RPF (renal plasma flow) and since such ratio is approximately constant it will be assumed that $\Pi_{FG}$ is 15% higher than $\Pi_{pp}$, the plasma oncotic pressure. This assumption implies the consideration of the glomerular capillaries as a lumped system. Its distributed nature is however quite important in the filtration process and it should be accounted for in the next iteration of this model (Riggs 1970).

e) The value of $K_G$ is given in the literature (Pitts 1968, Handbook of Physiology) as being in the range 4 to 13 ml/min mmHg. The value of $K_7$ is chosen empirically for a satisfactory fit of the available data. The value $K_G = 5$ ml/min mmHg and $K_7 = 0.1$ are used to simulate the results presented in Fig. 39.
A) Simulated GFR response to the infusion of 60 g of protein in 240 ml of isotonic saline in 60 min. (curve a).

$\star$ = experimental values of GFR in two normal men in response to the infusion of 25% salt-poor albumin (300 mosm/l of NaCl); from Peterdorff and Welt, 1953.

B) Simulated GFR response to the infusion of 25% (curve c) and 50% (curve b) of the normal extracellular fluid volume of Locke solution (124 mEq/l of Na and Cl, 5 mEq/l of K and Cl, 26 mEq/l of Na and HCO$_3^-$) in 100 minutes.

Curve a = average of the experimental results obtained from dogs by Wesson et al. (1950) during and after infusion of Locke solution in amounts "between 25 and 50%" of the extracellular fluid volume in 100 minutes. The dogs were given ADH to limit the diuresis and a replacement solution was injected to compensate for urine losses. (The model has no urine losses.) Urine was collected during 15 to 30 min. intervals. The vertical segments represent $\pm 1$ standard deviation of the experimental data.

Fig. 38. Simulated and experimental glomerular filtration rate (GFR) responses.
The agreement between experimental and predicted results appears to be satisfactory even in the case of nonphysiological stresses applied to the system (Fig. 38 b). These results have been obtained by including Eqs. 65 and 67 in the model developed in Chapters IV and V.

VI.3 Modeling of Proximal Tubule Function

a) Flow Consideration.

Approximately 80% of the glomerular filtrate is reabsorbed from the proximal tubule. Sodium is reabsorbed actively and water and other solutes are reabsorbed passively.

In 1967 Bosser and Schwartz presented a model of proximal tubular function. From their data and from their model it appear that the proximal tubule output flow, expressed as a percent of GFR, is a linear function of GFR.

More recently other factors (not considered by Bosser and Schwartz) affecting proximal tubule reabsorption have been suggested in the literature. Among these are the oncotic pressure in the peritubular capillaries and hormonal agents (Spitzer et al 1970, Lewy et al. 1968). Since the qualitative and quantitative effects of these factors is still very uncertain, they will not be considered in this analysis.

According to the above statements, the relation between the proximal tubule output flow PTO and GFR can be written as:
\begin{align*}
\text{Eq. 68} & \quad \frac{\text{PTO}}{\text{GFR}} = \frac{a}{\text{GFR}_0} + b \quad \text{that is} \\
\text{Eq. 69} & \quad \frac{\text{PTO}}{\text{GFR}_0} = \frac{a}{\text{GFR}_0} \cdot \text{GFR}^2 + b \cdot \text{GFR}
\end{align*}

where the index 0 means normal value and \( a \) and \( b \) are constant.

Assuming that the percentage values presented by Bossert for the rat kidney are valid for the human kidney, the values of \( a \) and \( b \) appear to be:

\( a = 0.189, \quad b = 0.025 \).

b) Concentration Considerations.

The active reabsorption of sodium from the lumen of the proximal tubule (PT) produces, as a consequence, reabsorption of water, chloride and urea as well as that of other solutes not considered in this model. The water permeability of the tubular wall is such that overall isotonicity is maintained between the lumen and the cortical fluid, however, the permeability to urea is insufficient for reaching the urea equilibrium. It therefore happens that the fluid leaving the PT, although isotonic, has an urea concentration between two and three times higher than the plasma urea concentration. It will then be assumed in the model that the fluid leaving the PT has the same sodium chloride concentration as the plasma and an urea concentration three times higher than that of plasma. The reason for the choice of the value three will be apparent from the next sections of this chapter.
VI.4 The Countercurrent Mechanism

a) Physiology of the Countercurrent Mechanism

The isotonic fluid leaving the proximal tubule is about 20% of the glomerular filtrate. The concentration (or dilution) and reduction of the proximal tubular output flow takes place in the distal tubule and in the collecting duct. The distal tubule (DT) is in the cortical region (whose interstitial fluid is isotonic with blood) and its wall permeability to water is hormone dependent so that the fluid transfer across the wall is also hormone dependent.

The collecting duct is mostly in the medullary region where a solute concentration profile exists from the cortico-medullary border to the papilla. The water and solute reabsorption from the collecting duct depends upon both hormonally controlled wall permeability and the interstitial concentration profile. The latter is produced by the countercurrent mechanism in the loop of Henle. Such mechanism, originally proposed by Kuhn et al. in 1942 as an hypothesis and now widely accepted, consists of the combination active sodium transport from the ascending limbs of the loop of Henle ("single effect") and the fluid movement in the loop itself ("multiplication effect"). The water and solutes reabsorbed from the loop and from the collecting duct (CD) are removed from the medulla by the capillary net consisting of the "vasa recta" which run parallel to the loop of Henle.

Many aspect of this mechanism are presently under investigation. It is not clear, for example, whether the sodium transport takes place along
the whole ascending limb or only in its upper half, whether the transport rate is constant or concentration dependent or flow dependent or hormonally controlled. It is not clear whether the hormonal control of urine formation is most effective in the distal tubule or in the collecting duct and whether osmotic diuresis is mostly a proximally or distally controlled event. It is also uncertain whether or not urea may be actively transported in some sections of the nephron. These and many other controversies are due partially to the fact that the human kidney is somewhat different from the dog, cat and rat kidney and partially to the difficulty of collecting information "in vivo" from the tiny nephron sections.

Because of this lack of knowledge it is necessary to try numerous assumptions in the process of model building and verify them by comparison of the overall model results with the physiological data. This procedure has been used in this and previous works and it is described in the next section.

b) Previous Models. Assumptions and Hypotheses.

A few models have been proposed for the countercurrent mechanism. One model proposed by Pinter and Shohet in 1963 which included the loop of Henle and the vasa recta was later criticized by Stephenson (1965) who claimed that such model was unable to concentrate.

More recently, in 1969, a model of the whole nephron was analyzed by Kien and Koushampour. Although the model included the loop of Henle, the vasa recta and the collecting duct and it accounted for sodium chloride and urea, some of its equations remain to be clarified.
In 1971, Koushampour et al. developed a new model based on some assumptions which, in the opinion of this author, are very restrictive and limiting. Another rather simplified model was recently analyzed by Merletti and Weed (1972); the collecting duct was neglected and only one solute was considered; an analytic expression for the medullary osmolality profile was presented.

The model presented in this work is based on the results of previous models and it includes refinements that extend its validity range. It accounts for the loop of Henle, the vasa recta, the collecting duct and two solutes (NaCl and urea). The distal tubule which does not take part in the countercurrent mechanism, will be considered in the next section. The following assumptions are made:

a) The flow along the loop of Henle is constant and equal to the PT output.

b) The volume of the renal interstitial fluid is constant (the kidney neither swells or shrinks)

c) Sodium chloride is actively transported from the lumen of the whole ascending loop of Henle into the renal interstitium. The transfer rate is proportional to the fluid flow in the loop and independent of the concentration for lumen NaCl concentrations higher than 250 mosm/l; it is proportional to the lumen concentration when the latter is below 250 mosm/l and it is zero for concentrations lower than 50 mosm/l. (Fig. 40).

d) Sodium chloride is actively transported from the lumen of the collecting duct into the renal interstitium. The transport rate is proportional to the lumen NaCl concentration.

ea) Osmotic equilibrium of sodium chloride takes place at each medullary
level between the renal interstitium, the two limbs of the vasa recta and the descending loop of Henle.

f) The flow of water reabsorbed from the CD is proportional to the permeability of the CD wall and to the total osmotic gradient across such wall. Because of hydrostatic and oncotic pressures this water enters the two limbs of the vasa recta so that the interstitial volume is not altered. As a consequence the vasa recta output equals the vasa recta input plus the fluid reabsorbed from the CD.

g) The flow of urea reabsorbed from the CD is proportional to the permeability of the CD wall to urea and to the urea osmotic gradient across such wall. Such reabsorbed urea enters the ascending loop of Henle (the descending one is assumed to be practically impermeable to urea, (Kokko 1972) and the vasa recta.

h) The urea concentrations at the output and input of the vasa recta are assumed equal. Urea is removed by the vasa recta because of the increased flow along these vessels due to water reabsorption.

i) For the purpose of digital simulation the renal medulla is divided in 10 layers. It is assumed that the interstitial fluid is uniform in each layer and that it does not communicate with the fluid in any other layer. So does the fluid in each layer of each duct (LH, VR, CD). Osmotic exchange takes place only within each layer between tubular and interstitial fluid.

j) The fluid volume in each layer of each duct is referred to as a "packet"; the time required from moving a fluid "packet" to the next layer is referred to as a "clock unit". All fluid packets are equal along the loop of Henle.
while their size is decreasing along the collecting duct and increasing along the vasa recta. Flow variations are accounted for by packet size changes rather than by velocity variations.

A general diagram of the model is given in Fig. 39. The diagram shows the assumed water and solute movements in each layer of the nephron and in the vasa recta. It is interesting to observe that there are paths of recirculation for the NaCl and urea; for NaCl the paths are: ALH-I-DLH, AVR-I-DVR, CD-I-DVR-AVR-I and various combinations of these paths. For urea a path is CD-I-ALH-DT. Because of these recirculation paths the medulla acts as a solute accumulating unit with a very important function in urine concentration. The model equations will describe this function quantitatively.

It should be noted that no assumptions are made concerning the medullary profile or the relationship between flow and position in any of the nephron elements. These assumptions were made in previous models (Koushampour et al. 1971). It should also be observed that the set of assumptions chosen is by no means arbitrary nor was it the first one tried. Many other assumptions were tried and discarded. Among these a few are listed below with the results obtained.

a) The assumption of constant ALH NaCl active transport rate led to very low salt concentration in the DT and to an unphysiologically high degree of dependence between urine flow and GFR (changes of $\pm 3\%$ in GFR led to heavy diuresis and to total anuria.

b) The assumption of ALH NaCl transport rate proportional to the ALH lumen NaCl concentration led to unphysiologically high papillary and urinary NaCl concentrations.
c) The assumption of osmotic urea equilibrium between I and VR led to
the absence of a medullary urea concentration profile.

These assumptions, however, should not be totally discarded. Their
analysis has been rather incomplete because of time and computer
limitations. Other hypotheses that might be interesting to test are
the following:

a) The flow variations in the tubules are due to velocity variations
rather than packet size variations and the degree of osmotic equilibrium
is velocity dependent.

b) The ALH and CD have some degree of passive permeability to salt.

c) The DLH has some degree of passive permeability to water and/or urea.

d) Since the papillary region has very little blood supply the vasa recta
may perhaps be considered shorter than the loop of Henle, or many vasa
recta of various lengths may be considered.

e) Urea is actively transported across some sections of the nephron
wall.

f) The active transfer rate of NaCl across the CD wall is proportional
to the flow of NaCl in the CD rather than to its concentration (see
discussion of assumption b in section 5).

The model has a great versatility for the testing of these and
other hypotheses and in this versatility lies its value as a research
tool.
blood

NaCl $H_2O$ urea

blood blood

NaCl $H_2O$ urea

blood blood

$\uparrow$: active transport $\uparrow$: fluid movement $\uparrow$: passive diffusion


The movement of water, sodium chloride and urea indicated in the diagram takes place in each medullary layer.
c) The Countercurrent Model Equations

Because of the digital computer simulation the model is necessarily
discrete in both time and space. The medulla is divided in ten layers
and the fluid in the tubules moves in steps of one layer at a time. The
time between steps is referred to as a "clock unit" (cu). The content
of each tubule in each layer is referred to as a "fluid packet" (as-
sumptions i and j). The state of the system is the ensemble of the
states of each layer and is computed for each clock unit. The computation
of the state requires two steps:

1) Shift down one layer the content of DLH, CD, DVR and shift up one
layer the content of ALH and AVR. At the tenth level of the LH and of
the VR the shift is from left to right (Fig. 39). The packets in level 1
of DLH, DVR and CD are replaced by input packets, those in level 10 of
CD and level 1 of AVR are expelled, that in level 1 of ALH enters the DT.

2) Transfer the proper amount of urea from CD into I (or vice versa) and
from I into ALH, DVR, AVR. Compute the new NaCl and urea concentrations
in each layer of I, LH, CD, and VR. Go to step 1.

The two steps are executed within 1 cu.

The CD flow and concentration input values are related to the ALH
flow and concentration output values and to the DT characteristics; this
relationship will be examined in the next section.

The transit time of fluid through the nephron is approximately 1.5
to 2 minutes in dogs. The model requires 20 clock units for the loop
of Henle and 10 for the collecting duct. Since the proximal and distal
tubule transit times are probably quite smaller than the LH and CD transit
times it may be assumed that each c.u. corresponds approximately to
3 seconds of real time. One minute of real time is then simulated by 20 iterations of the steps 1 and 2 described above. After the completion of step 1, the following equations describe the material movement across the CD wall; these equations represent the set of assumptions previously described and are valid for each layer.

\[ \text{Eq. 70} \quad \frac{dW_{CD}}{dt} = -K_{1CD} \left( O_I - O_{CD} \right) \]

\[ \text{Eq. 71} \quad \frac{dS_{CD}}{dt} = K_{2CD} O_{CD} \]

\[ \text{Eq. 72} \quad \frac{dU_{CD}}{dt} = -K_{3CD} \left( U_{CD} - U_I \right) \]

where: \( O_I, O_{CD} \) = total interstitial and luminal (CD) osmolalities (mosm/l)
\( O_{SCD}, O_{UCD}, O_{UI} \) = CD NaCl concentrations, CD, urea concentration,
I urea concentration (mosm/l)
\( W_{CD}, S_{CD}, U_{CD} \) = CD flows of water, NaCl and urea (these quantities also represent the water, salt and urea amounts in each packet of CD).

where \( S_{CD} = O_{SCD} \cdot W_{CD} \) and \( U_{CD} = W_{CD} \cdot O_{UCD} \)

\( K_{1CD}, K_{2CD}, K_{3CD} \) are permeability constants.

The system of equations 70 to 72 may be solved by the fourth order Runge Kutta method with one iteration for each clock unit and will yield the amounts \( W_{CD}, S_{CD}, U_{CD} \) that cross the CD wall per layer and per clock unit (1 clock unit = 3 sec.).
The following equations describe the material movement across each layer of the ascending limb of the loop of Henle

\[ \frac{dS_{ALH}}{dt} = K_{2ALH} W_{ALH} \quad \text{for } OS_{ALH} > 250 \text{ mosm/l} \]

Eq. 73

\[ \frac{dS_{ALH}}{dt} = K_{2ALH} W_{ALH} \left( \frac{OS_{ALH}}{200} - 0.25 \right) \quad \text{for } OS_{ALH} < 250 \text{ mosm/l} \]

\[ \frac{dS_{ALH}}{dt} = 0 \quad \text{for } OS_{ALH} < 50 \text{ mosm/l} \quad (\text{see Fig. 40}) \]

Eq. 74

\[ \frac{dU_{ALH}}{dt} = K_{3ALH} (U_I - U_{ALH}) \]

where the symbols are the same as for Eqs. 70, 71, 72 but applied to the ascending loop of Henle. The active transport of NaCl is described, as a function of \( W_{ALH} \) and \( OS_{ALH} \) in Fig. 40

![Diagram of active transport of NaCl in each layer of the ALH as a function of ALH fluid flow and salt concentration.](image)

Fig. 40 Active transport of NaCl in each layer of the ALH as a function of ALH fluid flow and salt concentration.
It is assumed that no water is lost or gained by the ALH and by the DLH (assumption j). Because of the ALH impermeability to water and the active salt extrusion the fluid leaving this pipe is very dilute, its concentration being around 100 to 120 mosm/l. Half of the water that leaves each layer of the collecting duct is transferred into the ascending vasa recta and half is transferred into the descending vasa recta. The sodium chloride that leaves the ALH and the CD is distributed into the interstitial space, DLH, AVR, DVR so that these elements have the same salt concentration at each medullary level. Such concentration is computed by dividing the sum of the salt amount in each layer in these elements by the sum of their volumes in each layer. The urea that leaves the CD (Eq.72) enters the interstitial space and leaks partly into the ALH (Eq.74) and partly into the vasa recta. As previously stated, it is assumed that the plasma urea concentration remains constant along the vasa recta. This is probably not a valid assumption, however, the model shows that if more urea is removed by the vasa recta the medullary urea gradient is grossly reduced. This reduction could be avoided by assuming a higher urea input into the LH but this assumption would conflict with the measured values of urea concentration along the PT. This point deserves a more accurate and complete investigation. (See section 7).

VI.5 The Distal Tubule

The distal tubule is bathed by cortical fluid isotonic with plasma (see Fig.39). Since the fluid entering the tubule is hypotonic, water absorption (controlled by ADH) and consequent flow reduction take place
in this part of the nephron. It is clear however that although this tubule plays an important role in water reabsorption, it plays no part in urine concentration because the output fluid cannot be hypertonic. The task of urine concentration is left entirely to the collecting duct and to the effect of the medullary osmotic gradient.

The following assumptions are made with regard to the distal tubule function:

a) The flow of water transferred passively across a section of length $dx$ of the DT walls is proportional to the osmolality gradient across that wall section.

b) The flow of sodium transferred actively across a section of length $dx$ of the DT wall is proportional to the amount of sodium delivered to that section from the preceding one.

c) The flow of urea transferred passively across a section of length $dx$ of the DT wall is proportional to the urea concentration gradient across that wall section.

Assumption b deserves some discussion. It might appear more logical to assume the transport rate proportional to the luminal concentration. This hypothesis (referred to as 'b1') was used initially and led to a marked dependence of osmotic clearance upon DT wall water permeability and to a minimal urine osmolality of 120 mosm/l (with a DT wall water permeability reduced to $\frac{1}{3}$; nonphysiological reduction of these permeability was needed to reduce the urine osmolality to about 90 mosm/l). Both facts do not correspond to experimental observation. The minimal urine concentration in man is about 50 mosm/l. Assumption b leads to results in agreement with experimental data.
It has been proposed in the literature, and assumed in this model, that, under certain conditions, the active transport rate of NaCl in the ALH is related to the ALH flow of NaCl rather than to its concentration (Eq.73 and Fig.40). The same may be true in the distal tubule. It is perhaps possible that the stretch of the tubular walls affects the transport mechanism which would then become flow dependent. Whatever the explanation may be, assumption b leads to better results than assumption b1.

The model equations describing the material transfer across the DT wall are the following:

\[ \frac{dW_{DT}}{dx} = -K_{1DT} (O_C - O_{DT}) \]  
\[ \frac{dS_{DT}}{dx} = -K_{2DT} SF_{DT} \]  
\[ \frac{dU_{DT}}{dx} = -K_{3DT} (OU_{DT} - OU_C) \]

where \( O_C, O_{DT} = \) total cortical and luminal (DT) osmolalities (mosm/l)  
\( OU_{DT}, OU_C = \) DT urea concentration and cortical urea concentration (mosm/l)  
\( SF = \) salt flow along DT (mosm/min)  
\( W_{DT}, S_{DT}, U_{DT} = \) water, salt and urea flows in DT  
\( K_{1DT}, K_{2DT}, K_{3DT} = \) proportionality constants  
\( x = \) distance along DT from its beginning  
\( S_{DT} = W_{DT} OS_{DT}, \quad U_{DT} = W_{DT} OU_{DT} \)
In man the average distal tubule has a length of about 12 mm. By taking a $\Delta x$ of 1 mm., the system of Eqs. 75, 76, 77 can be solved numerically with 12 iterations of the fourth order Runge Kutta method.

The output flows and concentrations can be found as functions of the input flows and concentrations so the input to CD can be related to the output of ALH. This completes the simulation of the nephron.

VI.6 Evaluation of Constants and Parameters.

The evaluation of constants and parameters necessary for the solution of the renal system cannot be entirely based on physiological evidence. In most cases the required values have either been measured with widely variable results or cannot be measured with presently available techniques. It is clear that any surgical technique or "in vivo" measurement may alter the results sufficiently to make them almost worthless. However the flows and concentrations along the nephron in various conditions are known with some degree of reliability. The model's parameters can then be evaluated by trial and error until the physiological data are sufficiently approximated by the model. This technique which is one of the major advantages of model theory (see Chapter 1) has been used in this instance to evaluate the permeabilities of the various nephron sections.

The values shown in Table 5 yield resonably good results in the simulation of the hydropenic condition (condition of very mild thirst and dehydration as produced by a few hours of water deprivation).
Table 5. Estimated values for constants and parameters for the model of renal function.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium chloride transfer coefficient of ALH ($K_{2ALH}$)</td>
<td>90</td>
<td>mosm/layer cm ml</td>
</tr>
<tr>
<td>Urea permeability of ALH wall ($K_{3ALH}$)</td>
<td>0.017</td>
<td>mosm/layer cm mosm/l</td>
</tr>
<tr>
<td>Water permeability of DT wall ($K_{1DT}$)</td>
<td>0.011</td>
<td>ml/mm mosm/l</td>
</tr>
<tr>
<td>Sodium chloride transfer coefficient of DT ($K_{2DT}$)</td>
<td>0.07</td>
<td>mosm/mm mosm/l</td>
</tr>
<tr>
<td>Urea permeability of DT wall ($K_{3DT}$)</td>
<td>0.005</td>
<td>mosm/mm mosm/l</td>
</tr>
<tr>
<td>Water permeability of CD wall ($K_{1CD}$)</td>
<td>$0.58 \cdot 10^{-4}$</td>
<td>ml/layers cm mosm/l</td>
</tr>
<tr>
<td>Sodium chloride transfer coefficient of CD wall ($K_{2CD}$)</td>
<td>0.026</td>
<td>mosm/layer cm mosm/l</td>
</tr>
<tr>
<td>Urea permeability of CD wall ($K_{3CD}$)</td>
<td>0.1</td>
<td>mosm/layer cm mosm/l</td>
</tr>
</tbody>
</table>

According to Pitts (1968), the blood flow in the outer medulla is 8 to 10% of the renal blood flow (RBF) while the papillary blood flow is reduced to 1 to 2% of RBF. The model assumes almost uniform flow into the vasa recta (the nonuniformity being due to the draining of reabsorbed water) equal to 5% of RBF leading to the value of 32 ml of plasma per minute or an input plasma "packet" size of 1.6 ml (assuming a vasa recta transit time of 1 minute).
In normal conditions the flow in the loop of Henle is 20% of GFR that is, 25 ml/min corresponding to a fluid packet size of 1.25 ml when a loop of Henle transit time of 1 minute is assumed. The interstitial fluid volume in each of the ten medullary layers is assumed to be 10 ml, approximately three times the plasma content of each layer. The normal concentrations of the fluid entering the loop of Henle are assumed to be 220 mosm/l of sodium chloride and 12 mosm/l of urea, the NaCl concentration being the normal plasma concentration and the urea being three times more concentrated than in the plasma because of PT limited urea permeability. The cortical fluid surrounding the distal tubule has the normal plasma osmolality (292 mosm/l) and urea concentration (4 mosm/l).

VI.7 Simulations and Results

a) Hydroponic Condition

The model parameters have been chosen so that the hydroponic condition would be reasonably well simulated. Figs. 41 and 42 show the state of the system in such condition.

The upper diagram of Fig. 41 shows the water flow variations along the nephron (LH, DT, CD). The flow is assumed constant in DLH and ALH and decreases from 25 to about 1 ml/min in DT and CD. The distal tubule output is about 5% of GFR as observed experimentally (Guyton 1971).

The middle diagram of Fig. 41 shows the flow and concentration of sodium chloride along the nephron. The maximum flow is reached at the
bend of the loop of Henle and it is due to the recirculation of salt between the two limbs of the loop. The minimum concentration is reached at the outlet of the loop of Henle and it is 0.4 times the plasma salt concentration, while the maximum concentration, at the loop bend is 4 times the plasma salt concentration. Both values agree with physiological observation, (Guyton 1972) and with the observed dilution ratio of about 10 between the beginning and the end of the ALH.

The urea flow and concentration plots at the bottom of Fig. 41 deserve particular attention. Physiological data concerning urea are lacking and controversy exists with regard to the urea recirculation paths. The path assumed by this model is from CD to ALH to DT to CD and it leads to the flow curve of Fig. 41 and to a never decreasing urea concentration along the nephron. The concentration curve agrees with the one presented by Guyton (Guyton 1971) but disagrees with the one proposed by other investigators (Koushampour 1971). Of course this concentration curve depends upon the recirculation path (or paths) of urea. The curve proposed by Kousampour resembles the NaCl curve because it assumes urea recirculation between the two limbs of the loop of Henle. The arguments concerning the urea recirculation paths could be settled by reliable measurements of urea concentration at the bend of the loop.

The glomerular filtrate flow of urea is normally 500 μosm/min (assuming GFR = 125 ml/min and plasma urea concentration = 4 mosm/l); it is interesting to observe that along the distal tubule the urea flow exceeds this value because of the recirculating urea. This fact has been experimentally verified.
Fig. 41. Simulated water, salt and urea flows, and salt and urea concentrations along the human nephron (from the proximal tubule output to the distal tubule output) in hydroponic conditions.
Simulated concentration profiles along the medulla and the collecting duct and in the loop of Henle. Flow profile along the collecting duct. All plots are valid in conditions of hydropenia.
In the hydropenic man the urine flow is approximately 1 ml/min with a urea concentration around 280 mosm/l (70 times the plasma urea concentration) resulting in a urea output flow of 280 μosm/min. The urea flow into the loop of Henle must be somewhat higher than this value to account for the vasa recta and DT urea losses. From this condition rises the necessity of assuming a PT output urea concentration of at least 12 mosm/l, three times the plasma concentration rather than two times as indicated by many researches (again assuming plasma urea concentration = 4 mosm/l). Even in this case the urea drained from the DT and by the vasa recta must be minimal to permit the formation of any medullary urea concentration profile. In particular the very small urea removal by the vasa recta assumed in the model does not seem very physiological especially because it is associated with a much higher salt removal.

The model suggests that either the glomerular filtrate urea concentration is higher than the one assumed or the urea concentrating power of the proximal tubule is higher than the one assumed. If this were true, a more "physiological" assumption could be made concerning the vasa recta urea concentration and a higher urea papillary concentration might result. This point should be more carefully investigated.

Fig. 42 shows the concentration profile in the medulla (I) and in the collecting duct (CD). Initial conditions of isotonicy with plasma were set throughout the medulla and the repetitive solution of the model was started and continued until a steady state was reached for all the variables about 2 hours later (approximately 20 minutes of computer time).
According to the model the medullary salt concentration profile rises from 220 mosm/l to 900 mosm/l while the urea concentration profile rises from 70 mosm/l to 140 mosm/l. In hydropenic dogs the NaCl papillary concentration was observed to be in the range of 600 to 900 mosm/l while the urea papillary concentration ranged from 400 to 800 (Selkurt, Handbook of Physiology 1963). Somewhat lower values are expected in man because of the smaller number of medullary nephrons and smaller concentrating power of the human kidney but no data are available with regard to the human medullary profiles. The reasons for the limited rise in urea concentration shown by the model have been given above.

Since the cortical fluid urea concentration is close or equal to the plasma concentration (4 mosm/l) it appears unlikely that a sharp change in urea concentration would take place at the corticomedullary border (from ~ 4 mosm/l to ~ 70 mosm/l). The model suggests that a smooth rise (rather than a sharp change) in the urea permeability from the end of the DT to the end of the CD would reduce or eliminate the step in concentration while increasing the papillary urea concentration. This possibility should also be investigated in more detail.

From Fig. 42 it can also be observed that the concentration of urine takes place in the second half of the collecting duct and that in such half the concentrations vary rather rapidly. This suggests that the discretization error might be significant and that better results might be obtained by dividing the medulla in more than 10 layers. In this case, however, either a better computing algorithm or a faster computer would be needed to keep the computing time within reasonable limits.
Fig. 42 also shows the total osmolality of the fluid inside the ascending and descending loop of Henle. The average concentration difference between the two limbs is 155 mosm/l. Jamison et al. (1967) observed an average concentration difference of 117 mosm/l in normal rat kidney.

In Fig. 43 A the sodium concentration in the two limbs of the loop is compared with the data obtained from normal rats by Jamison et al.

Fig. 43 shows the flow variation along DT expressed as a percentage of GFR. The experimental data are from Malnic's (1966) experiments on rats.

It should be kept in mind that the comparison of model results with physiological data may be less significant that it may at first appear because of the usual considerable spread of measurements, because the data are coming from different species such as dogs, rats, guinea pigs and desert rodents, and because of their dependance upon the variable hydration and diet condition of the animals. Perhaps, a better way of evaluating the model, at least until more standardized data will be available, it is to include it into the overall body fluid model and examine the overall results to different inputs and conditions.

b) Parametric Variations and Input-Output Relationships.

The two most important renal output variables are the urine flow and the urine osmolality \( (U_f, U_{\text{osm}}) \). Two other variables frequently used and containing the same amount of information as \( U_f \) and \( U_{\text{osm}} \) are the osmotic clearance and the salt-free water clearance \( (C_{\text{osm}}, C_w) \). These two variables are defined in Eqs. 78 a and b.
a) Comparison of simulated and experimental sodium concentration along the loop of Henle. Data from Jamison et al. (1967) as reported by Koushampour (1971).

b) Comparison of simulated and experimental flow profile along the distal tubule. Data from Halnic et al. (1966)

Fig. 43. Comparison of the renal model results with experimental data.
\[ \text{Eq. 78} \quad \begin{align*} 
&\text{a) } C_{\text{osm}} = \frac{U_f \cdot U_{\text{osm}}}{P_{\text{osm}}} \\
&\text{b) } C_w = U_f - C_{\text{osm}} = U_f \left(1 - \frac{U_{\text{osm}}}{P_{\text{osm}}} \right) 
\end{align*} \]

where: \( P_{\text{osm}} \) = plasma osmolality, \( U_f \) = urine flow, \( U_{\text{osm}} \) = urine osmolality, \( C_{\text{osm}} \) = osmotic clearance, \( C_w \) = free water clearance.

From these equations it appears that a) \( U_f = C_{\text{osm}} + C_w \), b) \( C_{\text{osm}} \) is always positive, \( C_w \) is negative when the urine is hypertonic and positive when the urine is hypotonic. \( C_{\text{osm}} \) represents the volume of the isotonic solution containing the urine solutes while \( C_w \) represents the water that must be added or subtracted from this isotonic solution to obtain the urine concentration. The importance of these two quantities will be more apparent later (Chapters 7 and 8).

Figs. 44 and 45 indicate that the effect of individual parameters and input variable changes upon urine flow and concentrations and upon osmotic and water clearances. These results also cannot be compared with physiological data because it is practically impossible to obtain experimentally the variation of one parameter at a time. In the physiological response of the system all of these parameters would change more or less simultaneously. In diuresis, for example, the proximal tubular output would probably change first, following GFR variations, therefore altering the LH flow and the solute transport rate for ALH. The DT and CD water permeabilities would then change because of modified ADH plasma concentration; The DT and CD salt permeability would probably change last under the action of modified
aldosterone plasma concentration. The glomerular filtrate and the cortical fluid concentrations also would be altered. Despite these facts, it is still useful, from a control theory standpoint, to evaluate the effect of individual parameters upon the urine formation in order to establish their degree of control.

In both Figs. 44 and 45 all the parameters or variables other than the one varied are held constant at their "normal" value (Table 4) corresponding to the hydropenic condition. In the simulation sufficient time was allowed after the change to permit the termination of all transients; Figs. 44 and 45, therefore represent static relationships. Of course the modification of any of the non-varied parameters will somewhat modify the curves presented. As it appears from Fig. 44A the PT output (PTO) (closely related to GFR by Eq. 69) strongly affects the urine flow. Decreasing the PTO by 10% (equivalent to a GFR change of ~ -6%) almost stops the formation of urine, while increasing it by 10% increases the urine flow rate by over two times. This is in agreement with Guyton's view that although GFR is regulated, its small variations strongly affect urine secretion. This may indeed be the reason for the GFR regulation. If GFR were not regulated, variations of blood flow in exercise, digestion or heat conditions, or small blood pressure changes would greatly upset the body water balance and the process of metabolic waste excretion. It is also interesting to observe that $C_{osm}$, and therefore the solute output, is linearly related to PTO, a very significant fact in osmotic diuresis.

The NaCl active transport rate from ALH also strongly affects
Fig. 44. Simulated effect of individual parameter variation and input variable changes upon urine flow and osmolality and upon osmotic and water clearances.
Fig. 45. Simulated effects of individual parameter variations upon urine flow and osmolality and upon osmotic and water clearances.

Fig. 46. Simulated total osmotic profile along the nephron in conditions of a) antidiuresis (---), b) hydropenia (——), c) water diuresis (----).
urine flow and concentration (Fig. 44 B) by controlling $C_{osm}$ and $C_w$ in similar fashion. This is indeed the mechanism of action of some diuretic drugs, such as furosemide, which poison the active transport mechanism. The DT and CD water permeabilities (which are ADH dependent) also affect the urine output (Fig. 44 C and D). It can be observed that because of the medullary osmotic gradient, an increase in CD permeability coefficient has a greater effect than the same increase (in %) of the DT one. As observed experimentally, a decrease in water permeability, especially of the DT wall, has a much greater effect upon the water clearance than it has upon the osmotic clearance.

The effect of varying the DT NaCl active transport rate (which is aldosterone dependent) is shown in Fig. 45 B while the effect of medullary plasma flow variations is indicated in Fig. 45 A. The latter effect is rather controversial and deserves some discussion. An increase in medullary plasma flow ($M_{PF}$) has two consequences; first some medullary solutes are washed out therefore reducing the medullary osmotic profile and producing a diuresis; second, because of the solute washout the fluid entering the ALH and the DT is somewhat more diluted so that (for constant DT permeability) more water will be reabsorbed, therefore producing an antidiuresis. The first effect is commonly believed to be prevalent. In the model the second one is prevalent although by not a great amount. Attempts to modify parameters and hypotheses in order to obtain the expected results have been, for the time being, fruitless. It is interesting to observe that, according to the model, changes in $M_{PF}$ do not affect the water clearance but only the osmotic clearance.
It is possible that the vasodilator (and the vasoconstrictors) agents used in animal experiments also affect the total renal blood flow and pressure therefore modifying the GFR and so hiding and apparently reversing the effect of the varied KFF. According to the model, if GFR were affected, in percent terms, only 1/10 as much as KFF, the above effect would take place. On the other hand, according to Lever (1965) only small amount of vasodilator agents have a diuretic effect while larger doses have some antidiuretic effect as predicted by the model. This point deserves a deeper analysis of the literature and a more extensive model simulation with the testing of various hypotheses and parameter sets as well as more careful experimental verification.

c) Other results and Conclusions

a) Fig. 46 show the total osmotic profile along the nephron in three different conditions: a) antidiuresis, b) hydropenia, c) water diuresis. Condition a is simulated by an increase of 50% of DT wall water permeability and of 25% of the CD wall water permeability. An increased medullary osmotic profile results from this condition and the urine osmolality becomes equal to the papillary osmolality while the urine flow is reduced to 0.24 ml/min. Since the water reabsorption is passive it is evident that the increase in papillary osmolality is a necessary condition to the formation of a highly concentrated urine.

Condition b has been described in the previous section; it may be observed that the urine concentration is about 1/2 the concentration at the bend in the loop of Henle.
Condition c is simulated by a decrease of 75% of the DT wall water permeability and of 50% of the CD wall water permeability. The result is a heavy diuresis (a urine flow of 15 ml/min.) of very diluted urine (70 mosm/l) and a reduction of the medullary osmotic profile.

These results are in general agreement with the available data from animals and humans with the exception of the medullary osmotic profile in case c which has been observed in rats and dogs to decrease more than it is predicted by this model.

b) A characteristic phenomenon of a diuresis is the so called "enhancement" and "abatement" of urea clearance respectively at the onset and termination of the diuresis (Lever, 1965). This phenomenon consists of two phases; first a rapid increase of urinary urea flow, which then returns to values somewhat higher than normal during the diuresis and, second, a rapid decrease of urea flow which then rises again to normal values after the diuresis. The reason for these changes is the washout and the reconstitution of the amount of urea recirculating in the medulla. The model simulates this behavior as indicated in Fig. 47. The results were obtained by a speplike drop and subsequent rise of the DT and CD water permeabilities to mimic the water diuresis followed by recovery. The entity of the permeability changes is not particularly critical. Urine flow and osmolality are plotted together with urea flow in Fig. 47.

c) In 1957 Berliner and Davidson observed that if GFR is reduced by renal artery constriction during an intense water diuresis (therefore in the absence of ADH) the urine may become hypertonic while the
diuresis is reduced. Similar results are obtained with the model especially if the DT water permeability is affected by ADH more than the CD permeability. A simulated decrease of DT water permeability to 40% of its value in hydropenia (with constant CD permeability) results in a urine flow of about 8 ml/min with an osmolality of 107 mosm/l. The subsequent reduction of PT output to 2/3 of its normal value reduces the urine flow to 0.4 ml/min and rises the osmolality to 380 mosm/l. The effect is somewhat less marked if the CD permeability is also changed.

![Urea Flow and Osmolality Graph](image)

Fig. 47. Simulation of urea clearance "enhancement" and "abatement" at the onset and termination of diuresis. (see text.)
This shows that the urine concentration is really due to the presence of the medullary gradient whose effect is altered by ADH and by the CD input flow and concentration. Isotonic and slightly hypertonic urine may be produced in the absence of ADH as is observed in dehydrated diabetic patients.

d) In 1971 Jamison observed that, in rats, the amount of water reabsorbed from the collecting duct is larger during water diuresis than during antidiuresis. He estimated the difference as 1% of GFR. This fact appears at first inconsistent with the mechanism of water diuresis. However this finding may be simulated by the model if it is assumed that ADH has a such higher effect on the DT permeability than it has on the CD permeability. Whether this is generally true in animals or in man is not known. This result, together with the observations of the previous point seems to suggest that ADH has indeed more effect on DT than on CD perhaps because of the higher vascularization of the cortex with respect to the medulla.

Another interesting experimental observation is the fact that in water diuresis the CD may become the site of further urine dilution rather than concentration. According to the model this requires some more marked CD permeability control by ADH than is required in the two cases above. If the CD wall becomes at least half as permeable to water as it is in hydropenia, the effect of salt active transport will be prevalent over that of water reabsorption thus inverting the concentration profile along the collecting duct.

e) It has been experimentally verified that in diuresis the medullary urea concentration profile is abolished while the salt profile is
markedly reduced. The model mimics very well the disappearance and reformation of the urea profile, however, the salt profile is only a little affected by diuresis (Fig. 46). This suggests the existence of a passive sodium permeability of the CD wall, so that in diuresis the sodium chloride could be drained from the medulla into the CD thus reducing the medullary storage of salt more than the model presently does. This hypothesis has been tested with this model and led to substantial increase in osmotic clearance during water diuresis. Since this does not seem to be the case in the real system this hypothesis has been abandoned. However, this particular point deserves a more careful investigation since a better choice of tubular parameters might lead to more physiological results in support of this hypothesis.

f) The response to an increase in the input NaCl and urea concentrations has been simulated. In both cases an increase in urine flow, a decrease in urine osmolality and an increase in the output flow of the solute whose input concentration had been increased, were observed as expected. These results are significant in the simulation and study of osmotic diuresis. However the quantitative significance of these data cannot be evaluated at this stage because osmotic diuresis produces changes in GFR and in plasma antidiuretic hormone and aldosterone concentration as well as changes in the glomerular filtrate concentrations.

The overall model is a necessary tool for the study of phenomena of this complexity.

g) In conclusion, it is felt that the real value of this model is presently in its versatility to test hypotheses, hundreds of which can be tried if time is available for their proper study, parameter
estimation and computer testing. The present set of hypotheses and parameters provided some good results but certainly there are better choices of assumptions and values of constants. The identification of such assumptions and values requires a deeper study of the medical literature and the close cooperation with medical specialists of the field as well as the availability of experimental facilities.

It is believed that this model of renal function represents progress with respect to the previous ones because it avoids very limiting assumptions and it permits a wider range of simulation while maintaining the mathematics at a rather simple level. It has to be kept in mind, however that only the overall model will permit the simulation of complex responses such as water diuresis, osmotic diuresis and so on, and that only these simulations will give the final indication about the validity of each model block.
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CHAPTER VII

PHYSIOLOGY AND MODELING OF THE ANTIDIURETIC HORMONE (ADH) CONTROL LOOP

VII.1 Physiological and Cybernetic Concepts in the ADH Control Loop.

a) General Concepts

A general block diagram of the body fluid homeostatic system has been presented in Fig. 3 of Chapter II. In that diagram, as well as in Chapter II, the ADH control mechanism was presented as an information channel establishing a dependence between the renal transfer function and the state of the plasma compartment for the purpose of controlling that state.

It is the purpose of this chapter to study the ADH control channel and to model it by the following 3 blocks:

a) Relationship between ADH secretion rate and input variables (mainly plasma state variables).

b) Relationship between ADH plasma concentration and ADH secretion rate.

c) Relationship between distal tubule and collecting duct water permeability and ADH plasma concentration.

In turn the modified reabsorptive properties of the renal tubules will affect the plasma state therefore closing the ADH control loop and providing a negative feedback path.

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It should be noted that the ADH loop, although very useful and important for the organism, is not essential to its survival in a normal environment. The opening of the ADH information channel results in high water excretion (polyuria) with consequent dehydration, thirst and high water input (polydipsia) characteristic of a diseased state known as diabetes insipidus. As it often happens, loss of homeostasis results in a greater dependence of the organism upon the environment, that is in a reduced capability of survival. However, even in the case of limited availability of water, survival may be insured, within a limited range, by other mechanisms such as reduction of GFR and shift of control efforts from the impaired hormonal control loop to the other (see Fig. 3 and Chapters VI, VIII, IX). On the other hand excessive ADH secretion results in a urine flow insufficient for the excretion of metabolic wastes, in water intoxication, in nervous disturbances due to improper electrolyte balance and in self poisoning of the organism. (Schwartz-Barther syndrome). Partial compensation is provided in this case by diarrhea and vomiting.

b) Input Variables and Receptors. ADH Dynamics and ADH Feedback Paths

The most important quantities affecting ADH secretion rate are listed below:
1) Plasma osmolality (see Section 3)
2) Blood volume (see Section 3)
3) Blood $P_{O2}$ and $P_{CO2}$
4) Plasma concentration of other hormones (mainly glucocorticoids and renin)
5) Drugs (alcohol, nicotine etc.)
6) Emotional states (fear, anger, pain etc.)

If stimuli 5 and 6 are disregarded (as "nonphysiological" states), stimuli 1 and 2 become the most important ones and will be the only ones considered in the model. The plasma osmolality (or perhaps only the concentration of certain solutes) is sensed by osmoreceptors in the hypothalamus while the blood volume changes affect the arterial and central venous pressures which are in turn sensed by arterial baroreceptors in the aorta and by low pressure receptors in the cardiac atria. Both receptor systems have outputs which are integrated into the hypothalamus and the resulting signal controls the release of ADH by the neurohypophysis. The ADH is secreted into the plasma from which it is removed mostly by the kidneys and by the liver.

The plasma ADH concentration therefore depends upon three factors: a) the rate of release, b) the rate of removal, c) the volume of distribution, that is the volume of fluid into which ADH may diffuse. Finally the plasma ADH concentration controls the water reabsorption from the renal tubules. The overall control loop is presented in Fig. 48. The "other stimuli" (Fig. 48) for ADH release have been mentioned before. The "other effects" of ADH are mainly vasocostrictor effects (from which the name "vasopressin" is also assigned to ADH) which take place at very high plasma ADH levels. These effects will not be considered in the model. The two blood volume sensing paths will be considered as a single path in the model.
VII.2 Analysis and Critique of Physiological Evidence

The physiological evidence and the quantitative data regarding the ADH control loop are very controversial and confused. This situation is due to three main reasons: a) the present impossibility of direct measurements of ADH secretion and removal rates, b) the
difficulty and unreliability of the measurements of ADH concentration by bioassay, c) the improper planning and organization of experiments. These reasons will now be examined.

ADH is an octapeptide compound of molecular weight of 1050 (arginine vasopressin) whose amount is measured in mU (milliunits), 1 mU corresponding to about 2.5 ng of hormone. The small amount of ADH secreted and the position of the secretory gland (lower central part of the brain) rule out the possibility of measuring the secretion rate directly. The low ADH plasma concentration (normally only a few mU per liter of plasma and the nature of the molecule rule out chemical methods of evaluation leaving only the less reliable biological assay (Kerletti et al. 1972). This method requires sampling of the plasma and its subsequent testing for ADH activity in rats or similar small laboratory animals. The ADH plasma concentration will be known only approximately (errors of 20 to 50% may be frequent and undetected) and only at the sampling instants and much after the completion of the experiment.

The purpose of much of the available experimental work is to establish a relationship between the ADH secretion and its stimuli (blood volume, plasma osmolality) by taking the plasma ADH concentration ($P_{ADH}$) as an estimate or index of the secretion rate. If $P_{ADH}$ is the plasma concentration of ADH, $S$ is the ADH secretion rate and $D$ its removal rate and if $V$ is its distribution volume (assumed constant) the following differential equation holds:

$$\text{Eq. 79} \quad \frac{dP_{ADH}}{dt} = S - D$$
It has been observed that $D$ is related to $P_{ADH}$ by the equation

$$D = C \cdot P_{ADH}$$

where $C$ represents the volume of plasma cleared of ADH per unit time ($C$ is assumed constant). Eq. 79 then become:

$$\frac{dP_{ADH}}{dt} = V \cdot (S - C \cdot P_{ADH})$$

whose solution is:

$$P_{ADH} = P_{ADH_0} - \frac{S}{C} e^{-t/T} + \frac{S}{C} ; \quad T = \frac{V}{C}$$

where $P_{ADH_0}$ = initial value of $P_{ADH}$

It is apparent from Eq. 81 that $P_{ADH}$ will be constant only when 1) $S$ and $C$ are both constant and, 2) $t \gg T$. Only in this case will $P_{ADH}$ be proportional to $S$ and could be taken as an indirect estimate of $S$. In most experimental works the two conditions given above were not satisfied and in the opinion of this author, this has greatly contributed to the confusion. It should be observed that condition 1 implies the open loop operation of the system while condition 2 implies a steady state operation. If the loop is closed the system will compensate for the stimuli applied, $S$ may change substantially at the application of the stress but will then return to the control values after a transient. $P_{ADH}$ will follow $S$ with a first order time lag. The measurement of $P_{ADH}$ will then depend upon the entity and the duration of the stress, upon the sampling times, and upon all the time constants of the system (due to gastrointestinal absorption
intercompartmental exchange, renal dynamics etc.). If the unreliability of the bioassay is considered as an additional source of error it is clear how different researchers may have obtained widely different results in the estimates of $P_{\text{ADH}}$ or $S$.

This is a case where a good engineering analysis may bring a substantial contribution toward the improvement of experimental methods and the meaningful evaluation of the data in the physiological field. Methods may be devised for opening either the plasma osmolality feedback loop or the blood volume feedback loop or both and for controlling these two quantities independently. These methods may involve the continuous reinfusion of the urine or the cancellation of a feedback by an equal and opposite one artificially produced (Merletti et al. 1972), or, more drastically, the removal of organs such as the kidneys or the neurohypophysis, the resection of the nervous pathways or other techniques possibly applicable to man.

VII.3 Approximations or Assumptions Relative to ADH Secretion.

a) General Assumptions.

The transfer function of the osmolality and volume receptors has never been thoroughly investigated. Verney in 1947 observed that only changes in the concentration of typically extracellular electrolytes (mostly NaCl) induced changes in urine output. In 1956 and 1957 however, Zuidema et al. found that solutions of urea induced the same response as solutions of NaCl and that the response did not change over long periods
of infusion indicating that the plasma osmolality and not its rate of change is the stimulus for ADH secretion.

It was recently suggested by Guyton (personal communication) that the rate of blood volume change may affect ADH secretion, however Share (1969) observed the same antidiuretic response in dogs bled at different rates.

It will be assumed in the model that:

a) the ADH secretion rate depends upon the total plasma osmolality and not upon its derivative,

b) the ADH secretion rate depends upon the total blood volume and not upon its derivative.

On the basis of the results presented by Brooks et al. (1966) it will be assumed that:

c) the time constant of the volume and osmolality receptors is negligible (that is on the order of less than 1 min).,

Despite the unreliability of most data it will also be assumed that: 

d) the variations of $P_{ADH}$ observed in the literature are representative of variations of $S$, in other words, it is assumed that the data are good enough to satisfy the steady state case of Eq.81, $P_{ADH} = S/C$.

b) Dependence of ADH Secretion upon Plasma Osmolality.

The relationship between ADH secretion rate ($S$) and plasma osmolality ($P_{osm}$) has been considered in previous model as being represented by a parabola, when the osmolality is above a given threshold value (Nagasaka et al.1966, Corson and Weed 1968, Merlotti and Weed 1972). This assumption was based on the data obtained by
Buchborn (1956, 1957) in humans, data which suggested such a relationship. However, in Buchborn experiments the blood volume was varied as well as the plasma osmolality, and the results have been later criticized by Walker (1961). Much better experiments were recently performed by Johnson et al. (1970) who separated the osmotic stimulation from the volumetric one in sheep. It is very unfortunate that their experiments were not run in a steady state condition nor in an open loop configuration of the system.

Despite the qualitative and quantitative insufficiencies of the data, the parabolic relationship between $S$ and $P_{osm}$ will still be assumed in this model. Eq.82 describes it:

$$\text{Eq.82} \quad S = K \cdot (P_{osm} - P_{osmt})^2 \quad \text{for } P_{osm} > P_{osmt}$$
$$\quad S = 0 \quad \text{for } P_{osm} < P_{osmt}$$

where $P_{osmt}$ is a threshold value of the plasma osmolality $P_{osm}$.

c) Dependence of ADH Secretion upon Blood Volume and Stimuli Integration.

Data concerning the ADH control by blood volume are available from various authors (Johnson et al. 1969 and 1970, Lydtin and Hamilton 1964, Share 1969). Little information, however, is available about the integration of the osmotic and volumetric stimuli in determining the resulting ADH secretion (Gauer 1968, Arndt 1965). The two stimuli may be concurrent such as in water loading) or opposed (such as after ingestion of a hypertonic
solution) or only one may be present (such as after a rapid hemorrhage). While an increase in $P_{\text{osm}}$ will increase $S$, an increase in blood volume (BV) will decrease $S$ (see Fig. 48). It is a known fact that a sufficient decrease of BV will increase $S$ in the face of a lowered $P_{\text{osm}}$. Teleologically the plasma dilution is a lesser evil than circulatory collapse so the control of BV, in certain conditions, is prevalent over the control of $P_{\text{osm}}$.

A number of hypotheses can be made concerning the interaction of the two receptors. Three possible ones are:

a) Independent equations relate $S$ to $P_{\text{osm}}$ and to BV and the resulting effect are added algebraically (Korletti and Weed 1972)

b) Blood volume changes control the sensitivity of the osmoreceptors, that is, control the coefficient $K$ of Eq. 82.

c) Blood volume changes control the threshold $P_{\text{osmt}}$ of the osmoreceptors. In a way, BV changes are gating the response to $P_{\text{osm}}$ changes. This type of interaction has been observed in other physiological receptors.

The threshold of the osmoreceptors $P_{\text{osmt}}$ was determined, for human subjects, by Koses and Miller in 1971 and its variation with BV was observed by the same authors in 1967. Unfortunately, despite the very interesting and simple experimental technique only one "non-normal" value of the threshold was determined (500 ml increase in BV). Indirect threshold changes, resulting from BV alteration, may also appear under hypotheses a and b.

In the absence of better data, and rather arbitrarily, it will be assumed in this model that hypothesis c is valid and described by Eq. 83.
I.83 \[ P_{\text{osmt}} = a \Delta BV^2 + b \Delta BV + c \]

where \( \Delta BV = \% \) change of BV with respect to normal.

Substitution of Eq. I.83 into Eq. I.82 indicates that \( S \) will be a function of \( P_{\text{osm}}^2 \) and \( BV^4 \) and that the BV effect may be marked even at low \( P_{\text{osm}} \). Extrapolation of the available animal data and use of the few human data leads to the following choice of values:

\[
a = 0.005, \ b = 0.8, \ c = 280, \ K = C \cdot 0.0287
\]

where \( C \) is the ADH clearance (l/min)

Since in steady state, \( P_{\text{ADH}} \cdot C = S \) and since the literature data (which are all relative to \( P_{\text{ADH}} \) and not to \( S \)) have been assumed to be steady state data, Eq. I.82 also represents \( P_{\text{ADH}} = f(P_{\text{osm}}, BV) \) if \( K \) is replaced by \( K/C \) (\( K/C = 0.0287 \)). The chosen values for \( a, b, c, K/C \) produce a reasonable fit of the available data. The "normal" \( P_{\text{ADH}} \) results to be 4 mU/l of plasma; most data from the literature indicate a range of "normal" concentrations between 2 and 6 mU/l. Both tridimensional and bidimensional representations of \( P_{\text{ADH}} = f(P_{\text{osm}}, BV) \) are given in Fig. 49. Multiplication of the ordinates by \( C \) will yield \( S \). The evaluation of \( C \) will be discussed in the next section.

VII.4 ADH Dynamics

a) Protein Binding and Volume of Distribution of ADH

In all previous models of water regulation ADH has been considered...
Fig. 49. A) Tridimensional representation of $P_{ADH} = f(P_{osm}, \Delta BV)$. B) $P_{ADH} = g(ABV)$ for various values of $P_{osm}$. C) $P_{ADH} = h(P_{osm})$ for various values of $\Delta BV$. 
as a free solute limited to the plasma volume which was then assumed to be its volume of distribution. Indeed there is no evidence that ADH might enter the blood cells or any other cell. However, other solutes of similar molecular size freely enter the IS space and no reason was given about why free ADH should not do the same. On the other hand, ADH must enter the renal interstitial space to perform its action on the renal tubules; ADH is also found in urine and it is presumably filtered at the glomerulus. Although interstitial fluid cannot be easily sampled (ADH assay of the IS fluid collected into Guyton's capsules would be very interesting in this regard), lymph can, and this fluid is usually considered representative of the IS space. Czaczkes (1964) observed a lymph ADH concentration of only 0.5% that of plasma in dehydrated dogs but Brooks and Share (1966) observed average thoracic fluid and lymph ADH concentrations of the order 25% that of plasma (dogs). The latter fact suggests the possibility of ADH being partially and rather loosely bound to plasma proteins (limited to the plasma space) and partially free (therefore leaking into the IS space).

Estimates of the ADH protein binding range from no binding (Czaczkes et al.1964, Brook and Share 1966), to "some" binding (Heller and Lederis 1957), to 30% binding (Fabian et al.1969), to 25% binding (Bocanegra and Lauson 1961), to total binding (Ahmed et al.1967). The observed volume of distribution ranges from less than the plasma volume (Czaczkes 1964), to 58% of the EC volume (Fabian et al.1969) to a large range of values between the plasma and the EC volumes observed by others in both man and dogs.
Some mathematical analysis may help to clarify (possibly not to contribute to) the general confusion.

Let us define $H_t$, $H_b$, $H_f$ as the total, bound, and free amount of ADH in the body fluids and $b$ and $f$ as the fractions of bound and free ADH respectively. Let $V_p$ be the plasma volume, $V_{EC}$ the extracellular volume, $P_{ADH}$ the total plasma ADH concentration, $I_{ADH}$ the IS ADH concentration, $V$ the apparent volume of distribution.

Let us assume that $H_f$ diffuses into $V_{EC}$ while $H_b$ diffuses only in $V_p$. The following equation will hold:

\[ V = \frac{H_t}{I_{ADH}} = \frac{1}{b/V_p + f/V_{EC}} = \frac{V_{EC}}{f + bV_{EC}/V_p} \]

From Eq. 86 it appears that:

1) for $b = 1$ \( V = V_p \;
2) for $b = 0$ \( V = V_{EC} \n3) for $b = 0.25$ and $V_{EC}/V_p = 4.56$ (as in man and in dog) it results \( V = 0.53 V_{EC} \) which is very close to the value observed by Fabian $(V = 0.58 V_{EC})$ while $b$ is close to the values observed by both Fabian
and Bocanegra (0.3 and 0.25 respectively). Dividing Eq.85b by Eq.85a the ratio \( \frac{I_{\text{ADH}}}{P_{\text{ADH}}} \) is obtained. For \( b = 0.25 \) and \( \frac{V_{\text{EC}}}{V_p} = 4.56 \) this ratio is 0.39 which does not compare very satisfactorily with the value of 0.25 observed by Share but neither is grossly different from it.

On the basis of the above results it will be assumed in the model that:

a) 25% of the available ADH is bound to plasma proteins and that the remaining 75% diffuses freely into the EC volume

b) Since there is convincing evidence that the protein-ADH bound (if any) is a very loose one, it will further be assumed that the percentage of bound ADH is constant in time; in other words the dissociation or the binding processes have negligible time constants.

c) The capillary membrane presents some finite permeability to ADH. In the absence of any data concerning such permeability it will be arbitrarily assumed that ADH moves freely enough so that the duration of the transients involved in ADH-Plasma - IS equilibrium is so short so as to allow the assumption of "Instantaneous" equilibration. Some support for this assumption will be presented in the next subsection.

d) The ADH acting upon the kidney tubules is only the one present in the IS space

e) Mixing of the secreted ADH in \( V_p \) and \( V_{\text{EC}} \) is "instantaneous"
b) ADH Clearance

As previously mentioned, the ADH clearance is the volume of plasma cleared of ADH per unit time. The clearance process takes place mostly in the liver and the kidneys. For $S = 0$, $P_{ADH}$ decays exponentially to zero (Eq. 81). Most researchers have found a single exponential decay, a fact which is in support of assumptions b and c of the previous subsection. However, cases of double exponential decay have been reported (Lauson 1970); this suggests that it may be worth while to investigate the two compartment dynamics of ADH neglected in this model. Czaczkes et al. (1964) found the decay rate to be to some degree related to the state of hydration in human subjects.

The experimental estimates of the decay constant $T$ in man (Eq. 81) range from 8 minutes (Fabian et al. 1969) to 1 hour (Czaczkes et al. 1964, overhydrated man) with most observations being in the range of 15 to 30 minutes. The reported values for the clearance $C$ range from 0.15 l/min (Lauson 1967) to 1.1 l/min (Fabian et al. 1969) with intermediate values found by others.

Since $T$ and $C$ are closely related and cannot both be chosen arbitrarily, some mathematical analysis is necessary. In the following analysis the volume of plasma $C$ is assumed to be cleared of both bound and free ADH every minute. The ADH dynamics described by Eqs. 80 and 81 is somewhat complicated by the assumed partial ADH binding to proteins. The symbols used in Eqs. 84, 85, 86 are maintained. The fundamental equation of ADH is the following.
Eq. 87 \[ \frac{dH_t}{dt} = S - C \cdot P_{ADH} \]

which can be written as (see Eq. 84, 85)

Eq. 88 \[ \frac{1}{f} \frac{d}{dt} (I_{ADH} V_{EC}) = S - C \cdot \left[ \frac{b}{f} \frac{V_{EC}}{V_p} + 1 \right] \cdot I_{ADH} \]

or as

Eq. 89 \[ \frac{d}{dt} \left[ \frac{P_{ADH}}{b + \frac{f}{V_{EC}}} \right] = S - C \cdot P_{ADH} \]

If it is assumed that \( \frac{dV_p}{dt} = \frac{dV_{EC}}{dt} = 0 \), Eq. 88 and 89 can be solved for \( I_{ADH} \) and \( P_{ADH} \) yielding Eqs. 90 and 91

Eq. 90 \[ I_{ADH} = I_{ADH0} - \frac{S}{c} - \frac{1}{c \cdot \frac{b V_{EC}}{f V_p} + 1} \cdot e^{-\frac{(t - t_0)}{\tau}} + \frac{S}{c} \cdot \frac{1}{\frac{b V_{EC}}{f V_p} + 1} \]

Eq. 91 \[ P_{ADH} = P_{ADH0} - \frac{S}{c} \cdot e^{-\frac{(t - t_0)}{\tau}} + \frac{S}{c} \]

where \( \tau \) is the same in both equations and it is given by:

Eq. 92 \[ \tau = \frac{1}{\left[ \frac{b}{V_p} + \frac{f}{V_{EC}} \right] \cdot c} \]
Eqs. 90 to 92 are only approximated because $V_p$ and $V_{EC}$ are not constant although they normally neither vary very much nor very fast.

From Eq. 92 it may be observed that $\tau$ depends upon four factors: 1) the amount of ADH binding, 2) the value of $V_p$, 3) the value of $V_{EC}$, 4) the value of $C$. As observed by Czaczkes the value of $\tau$ would be higher in an overhydrated man than in a dehydrated one because of the higher $V_p$ and $V_{EC}$; however, a quantitative analysis shows that the percent change of $\tau$ is of the same order of magnitude as the percent change of $V_p$ and $V_{EC}$ and therefore not sufficient to explain the rather large range of variation observed by Czaczkes (1964). No explanation is available as to why and how $C$ should decrease in overhydration. Perhaps the two compartments analysis of ADH distribution may shed some light on this problem which certainly needs more experimental work before a solution is reached.

As previously stated $C$ will be assumed constant in this model; its variations will be considered only as a pathological state involving impaired hepatic or renal function. Assuming the normal values of $V_p = 3.24$ l and $V_{EC} = 14.81$ l and $b = 0.25$, $f = 0.75$, Eq. 92 becomes: $\tau = 7.84/C$. Assuming $C = 0.4$ l/min yields $\tau = 19.6$ min, both values being within the range observed experimentally. As it will be seen in Chapter IX this choice leads to good overall results. The correct Eqs. 88 and 89 are used in the digital simulation instead of the approximated Eqs. 90 and 91.
VII.5 Membrane Effects of ADH

The antidiuretic hormone not only affects the water permeability of the renal distal tubules and collecting ducts, but also, although to a lesser extent, the urea permeability and the sodium active transport mechanism. These secondary effects will not be considered in this model.

Most of the experiments directed to establish a relationship between membrane water permeability and ADH concentration have been performed on toad skin or toad bladder and the results are not necessarily representative of the mammalian or human tubular behavior. A few experiments have been performed "in vitro" on rat and rabbit collecting ducts and distal tubules and the results are mostly qualitative rather than quantitative. Grantham and Burg (1966) observed a threefold increase in rabbit CD water permeability where the bathing fluid ADH concentration was raised from 0 to 25 μU/ml. Further increase of ADH did not increase the response; 60% of the response was obtained with 5 μU/ml indicating a non-linear relationship between ADH concentration and water permeability of the membrane. Data from the above authors and from Morgan et al. (1968) show a two to five fold increase in rabbit and rat CD permeability between the "no ADH" and the "ADH" conditions. Ullrich et al. (1966) observed also a threefold increase in DT water permeability in rats between the conditions of "absence" and "presence" of ADH. Clapp and Robinson (1966), however claimed that ADH has no effect on DT of dogs. The data also show that there may be a rather slow time lag between a change in ADH concentration and the resulting
change in membrane water permeability but do not permit its estimate.
Better experiments should be designed for the purpose of evaluating such
a time lag. Again it appears that the conceptual difference between steady
state and transient state of a system is not clear to many physiologists
and that the data obtained during a transient are often presented as re-
representative of a functional steady state relationship between two
variables.

Despite these inaccuracies two facts seem to appear from the data:
a) The membrane permeability may rise only to a maximum finite value.
Further increase of ADH concentration will have no effect.
b) The ratio between the maximal permeability and the minimal (no ADH)
is approximately 3 or 4 for both DT and CD (in rats and rabbits).

These experimental observations, the examination of Fig. 44 C and D
(Chapter VI) and the results presented by Raisz et al. (1953), by Hollander
et al. (1957) and by Czaczkes (1964) lead to assuming the relationship of
Fig. 50 between free ADH concentration and DT and CT water permeabilities
in man. Such relationships are piecewise linear approximations of the
curvilinear function relating DT and CD water permeabilities to the \( P_{ADH} \)
or \( I_{ADH} \) (\( P_{ADH} \) and \( I_{ADH} \) are proportional to each other if \( V_p \) and \( V_{EC} \) are
constant.) More experimental work is needed to determine these relationships
more accurately. Because of the insufficient data concerning the dynamic
response of the kidney tubule permeability to ADH, it will be assumed that
the relationships of Fig. 50 hold at all times, that is the membrane
response to ADH concentration changes is assumed "instantaneous".
Eqs. 93 and 94 describe the relationships between the tubular permeabilities
and the ADH concentration.
Fig. 51 shows a diagram of the model of the ADH information channel as described in these last three sections.

VII.6 Comparison of Results with Physiological Data.

It is at this point possible to simulate the steady state effect of ADH on renal function. This effect was experimentally observed by Raisz et al. (1953), Hollander et al. (1957) and by Lauson (1960) who presented data and empirical equations relating the water clearance $C_W$ to the rate of ADH infusion into hydrated human subjects. Under the assumptions that: a) GFR remained constant, b) the measurements were made in steady state conditions, c) the secretion rate of endogenous ADH was zero, d) the infused ADH (of synthetic or animal origin) had the same effect as the human endogenous ADH, and e) $V_p$ and $V_{EC}$ remained approximately constant, the results of these authors may be used to relate $C_W$ to $P_{ADH}$. Since, according to Lauson, the ADH clearance $C$ is 0.15 l/m in man, this value of $C$ was used
Fig. 50. Assumed relationships between DT, CD water permeabilities and $P_{_{\text{ADH}}}$ or $I_{_{\text{ADH}}}$.

Fig. 51. Analog diagram of the modeled ADH information channel.
to relate the experimental $P_{ADH}$ to the ADH infusion rates used by the above authors.

Hollander's and Raisz's results are reported in Fig.52 with scales for the ADH infusion rate, the plasma and the interstitial ADH concentration. The two dotted curves represent the empirical equation presented by Lauson for $C_w$ and used in a previous model (Merletti and Weed, 1972) and the $C_{osm}$ (osmotic clearance) curve used in the same model. The continuous curves represent this model results. It is apparent that a smoother curve relating the DT and the CT water permeabilities to ADH would bring the model's $C_w$ curve closer to the Lauson's curve. It is also clear that, at low concentrations, ADH affects $C_{osm}$ slightly more than it was previously assumed (Merletti and Weed 1972).

It is important to observe that the $C_w$ and $C_{osm}$ curves that were assumed as data into the Meletti and Weed model are now results of the present model and involve a detailed simulation of the renal function which had been previously entirely bypassed by the assumption of such curves. It should also be observed that the continuous curves of Fig 52 may now be altered by the changes of renal parameters other than those controlled by ADH, such as sodium chloride active transport from the loop of Henle (as resulting from some diuretic drugs) or from the distal tubule (as controlled by aldosterone), or such as proximal tubular changes (as in osmotic diuresis). Such versatility and capability were not previously available.
Fig. 52 Comparison of results with physiological data. Relationship between free water and osmotic clearances and ADH concentration (or secretion rate) in steady state conditions.
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CHAPTER VIII

PHYSIOLOGY AND MODELING OF THE ALDOSTERONE CONTROL LOOP

VIII.1 Cybernetic Concepts and Physiological Evidence Concerning the Aldosterone Control Loop.

a) General Concepts.

While the antidiuretic hormone affects directly the renal reabsorption of water and indirectly that of solutes, aldosterone affects directly the reabsorption of sodium and potassium and indirectly that of water and other solutes. The block diagram in Fig. 3 (Chapter II) outlines the aldosterone control loop and its interaction with the ADH loop in the control of the volume of the body fluids and of their electrolyte content. The aldosterone information channel establishes a relationship between the sodium active transport rate across the renal tubular wall and the channel input variables (mainly plasma state variables). The blocks which make up the channel have transfer functions and dynamic behavior far more complex and less known than those in the ADH channel.

It is the purpose of this chapter to describe briefly the known physiology of the aldosterone loop and to attempt, with a primitive model, a first approximation of its behavior. It should be kept in mind that because of the lack of knowledge on the subject, any statement regarding the aldosterone information channel is open to criticism in the present
and to verification or rejection in the future. For the same reason, a considerable degree of arbitrariness will be necessary in the model.

In very general terms one can say that the secretion rate of aldosterone is a function of blood volume and pressure, of extracellular sodium and potassium concentration and of other hormone concentrations (mostly adrenocorticotropic hormone, ACTH). This dependence is established through a number of intermediate steps (e.g. renin-angiotensin system) which may be affected by quite a number of input or disturbance-like factors. The aldosterone concentration in the body fluids depends upon the secretion rate (by the adrenal glands), the destruction rate (by the liver) and the volume of distribution of the hormone. Through a further number of steps, also affected by a number of excitatory and inhibitory factors, the aldosterone concentration controls the active reabsorption of sodium and the exchange of sodium with potassium and ammonium ions in the distal tubules and collecting ducts. The aldosterone loop produces a negative feedback having a stabilizing effect on body fluids (see Fig. 52); however the time response of the aldosterone channel is much longer than that of the ADH channel, indicating a long term regulating action of the former and a relatively short term regulating action of the latter.

Insufficient or zero production of aldosterone produces sodium depletion, loss of fluid and weight, electrolyte and nervous disturbances (Addison disease). Excessive aldosterone secretion may be either the cause or the result of a disease. If it is due to adrenal gland malfunction (primary aldosteronism) it produces sodium retention, increase in blood volume and blood pressure. Secondary aldosteronism (not due to adrenal
malfuction) may be due to various reasons some of which are of particular interest. As an example, leakage of plasma protein into the IS compartment or into the urine will produce edema and blood volume reduction thus stimulating aldosterone secretion, increasing sodium and water retention and blood pressure. If the original damage to the capillary membrane is not repaired, in a few days the edema condition is worsened by the very action of the aldosterone feedback.

b) Input variables and Receptors. Aldosterone Dynamics and Feedback Path.

The qualitative physiological evidence concerning the aldosterone loop is very shaky and unreliable. The quantitative evidence is very controversial and totally insufficient for a description of the system. Under these conditions sources of information available from the literature are often only representative of the author's opinion and not of generally accepted facts. Although most physiologists would agree with the presentation of the aldosterone loop given in Fig. 53, very little agreement would be found with regard to the importance of different factors and to the transfer function of the various blocks.

In some unknown way, blood volume, renal arterial pressure, plasma concentrations of sodium and potassium are sensed by specialized renal cells (juxtaglomerular cells) which secrete a compound called renin. The static and dynamic behavior of these cells is unknown; however, the secretion of renin has been observed to rapidly follow the variation of the input variables. In the plasma, renin is modified into angiotensin II. These steps are enzyme mediated and their static and dynamic characteristics
are unknown. Angiotensin II has many effects. The most important ones are the control of the arterioles, which results in increased blood pressure and the stimulation of aldosterone secretion by the adrenal glands. The plasma ionic concentrations also affect aldosterone secretion directly. The plasma aldosterone concentration is related to the aldosterone rate by a mechanism somewhat more complicated but basically similar to the one described for ADH in the previous chapter (see Section 2).

Fig. 53. Proposed block diagram of the aldosterone feedback loop. Each block represents a transfer function, each line a variable. A + sign at the input of a block indicates concurrent variations of input and output of the block, a - sign indicates the opposite. Since only one - sign is encountered along each loop, the feedback of each loop is negative.
The aldosterone concentration affects the active mechanism which provide the active transport of sodium across the tubular walls. Many biochemical steps are involved in this control so that a delay results between the change in aldosterone concentration and the change in sodium reabsorption and potassium excretion. Experimental findings indicate that this delay is of the order of magnitude of 1 hour (Ross 1964).

No reliable quantitative information is available concerning either the statics or the dynamics of the control of sodium reabsorption by aldosterone (except for the time delay estimates). The modified rates of electrolyte output also result in modified water excretion; both effects modify the plasma volume and composition therefore closing the feedback loop. As it appears from Fig. 53 the feedback is of the negative type.

c) Comments on Physiological Evidence

The remarks and comments presented in in Section 2 of the previous chapter with regard to ADH are even more valid for aldosterone and will not be repeated. A few comments will however be added.

While some of the evidence available may be useful to the medical doctor, very little of it is useful to the physiologist and bioengineer. As an example, the observation presented by many investigators that a low sodium diet will increase aldosterone secretion in a certain observable way may be helpful to the doctor but it is of almost no use to the bioengineer unless the time course of blood volume, plasma sodium and potassium concentrations is given along with that of aldosterone secretion.
Only in the second case can the bioengineer use the information in a process of synthesis to investigate the transfer function existing between related variables of the system. In other cases the data presented concern variables either unrelated or very indirectly related. As an example, a plot of the urinary aldosterone concentration as a function of urinary sodium concentration is of no use in identifying the transfer function of any system block. The evidence found by this author relating the aldosterone secretion rate to the plasma electrolytes is almost entirely of the above types.

The evidence found relating aldosterone secretion to blood volume is slightly better but still very criticizable. In 1969 Fabre et al. bled dogs from one of the adrenal veins and measured the aldosterone content of the blood obtained. They plotted the secretion rate and the blood loss against time. A source of error was the aldosterone present before the bleeding and that produced by the other adrenal gland during the bleeding, but an even greater source of error was certainly due to the rapidity and amount of bleeding. The particular $N$ type curve obtained in plotting the aldosterone secretion rate against time is very probably due to the transients of the renin-angiotensin-aldosterone system in response to the fast and large variations of blood volume and pressure and it is not representative of any steady state relationship. Similar considerations hold for the experiments run by others (e.g. Farrel et al. 1956).
V.2 Approximations and Assumptions

a) Control of Aldosterone Secretion.

Because of the lack of data this section of the model relies heavily on simplifying assumptions and it is therefore open to criticism. The following assumptions will be made:

a) The aldosterone secretion rate is linearly related to the plasma sodium concentration.
b) The aldosterone secretion rate is linearly related to the blood volume and not directly related to the blood pressure.
c) The aldosterone secretion is not controlled by the plasma potassium concentration and aldosterone does not affect the body output of potassium.
d) The effects mentioned in a and b are independent and algebraically added.
e) The dynamics involved in the relationships assumed in a, b, and c is negligible; in other words, the aldosterone secretion follows its controlling variables "instantaneously" (time constant less than 1 minute).
f) The cardiovascular effects of angiotensin and aldosterone, which indirectly affect the water regulation system, through the blood pressure control, are neglected.

Assumption c is mainly due to the fact that the model of renal function does not account for the renal handling of potassium.

It is of some interest to observe that in the model, as well as in the physiological system, the input variables to the ADH and aldosterone channels may have either concurrent or opposite effects in different situations. As an example, water loading induces concurrent stimulation
of ADH secretion by increased BV and decreased $P_{osm}$ but opposite stimulation of aldosterone secretion by decreased plasma sodium concentration and increased BV. The opposite happens in sodium chloride osmotic loading. The quantitative importance of each of the input stimuli and the condition of balance of opposite inputs are unfortunately still unknown.

b) Aldosterone Dynamics

The distribution and metabolism of aldosterone has been studied, among others, by Tait et al. (1961,1962) and by Vecsei et al. (1969). Their results indicate that the disappearance of exogenous aldosterone from the plasma of human subjects follows a double exponential decay of the type indicated in Eq. 95.

$$P_{AL} = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t}$$

where $P_{AL} = \text{plasma aldosterone concentration}$

$A, B, \alpha, \beta = \text{coefficients that may be obtained from the experimental results.}$

Such behavior may be explained in a number of possible ways;

a) The diffusion of aldosterone into two fluid compartments.

b) The diffusion of aldosterone into many (more than 2) fluid compartments (represented by different organs) in which case more than two exponential curves would result, but only two may be identified because of the scattering of the data and approximations of the graphical methods involved.

c) The partial binding of aldosterone to plasma proteins.

d) The dependence of aldosterone clearance upon aldosterone plasma concentration.
No convincing experimental evidence exists to permit a logical choice among the above possibilities. There is however evidence that aldosterone enters the body cells (Bojesen 1964), a fact that would lend some support to the two (or multi) compartment hypothesis. Rather arbitrarily it will be assumed in this model that aldosterone is not bound to proteins and that it diffuses into two fluids compartments, one of which includes the intracellular fluid of the kidney tubular walls.

c) Membrane Effect of Aldosterone

As it was previously mentioned, a number of biochemical steps are involved in the action of aldosterone upon sodium active transport rate across a membrane. These steps produce a delay and a time lag between the changes in aldosterone concentration and the resulting changes of transport rate. Experimental data in this subject were obtained by Edelman (1968) on the toad bladder membranes "in vitro" and show that the dynamics involved in these steps is indeed complex. The sodium transport rate may increase for hours even after aldosterone has been removed from the membrane environment.

In order to give some approximate representation of this dynamics behavior it will be assumed in the model that the changes in Na transport rate follow the changes in tubular intracellular aldosterone concentration with 1 hour delay and a first order time lag.

For the sake of simplicity and because of the total lack of information, it will also be arbitrarily assumed that only the distal tubule active transport of sodium is affected by aldosterone. An attempt
to considering the control of sodium transport in the CD as well as in
the DT may be made with this model as soon as some more information
becomes available on the membrane effects of aldosterone in these two
sections of the nephron.

VIII.3 Model Equations and Parameter Evaluation.

In the previous section the basic qualitative assumptions of this
model have been outlined. Equations are now necessary to describe the
assumed relationships and the numerical estimates of parameters is
necessary to implement the model. As in the previous section, the
quantitative analysis will be separately applied to the study of
secretion, dynamics and membrane effects of aldosterone.

a) Control of Aldosterone Secretion.

Although the evidence concerning the aldosterone is quite controver-
sial there is general agreement about the "normal" aldosterone secretion
rate being in the range of 100 to 200 μg/day, while there is no agreement
about how such secretion is controlled. According to Guyton (1971) a
decrease of only 5% of plasma sodium concentration (P\text{Na}) can double the
aldosterone secretion rate (S\text{AL}); according to Muller (1971) a decrease
of 50% of P\text{Na} is required to increase S\text{AL} by 40%; Davis et al. (1963)
observed that S\text{AL} was not altered when the decrease in P\text{Na} was less
than 10%. Similar substantial disagreement exists with regard to the
blood volume dependance of S\text{AL}. It is evident how in such conditions
any choice of the functional relationship $S_{AL} = f(\Delta BV, P_{Na})$ is essentially arbitrary. Such a choice may be improved in the future by a trial and error procedure as indicated in Fig.1 (Chapter I).

The relationship $S_{AL} = f(\Delta BV, P_{Na})$ chosen in this model is linear and describes a plane in the upper hemispace $S_{AL}, \Delta BV, P_{Na}$ as indicated by Eq.96 and Fig. 54. The "normal" $S_{AL}$ is chosen to be 144 $\mu$g/day, that is, 100 ng/min.

Eq.96  

$$S_{AL} = 200 - 6.66 \cdot BV - 0.715 \cdot P_{Na} \quad \text{with} \quad S_{AL} \geq 0$$

Fig. 54. Relationship between aldosterone secretion rate ($S_{AL}$) and change of blood volume ($\Delta BV$) and of plasma sodium concentration ($P_{Na}$).
b) Aldosterone Dynamics.

The assumptions concerning aldosterone dynamics have been stated in section 2.b of this chapter. The disappearance of injected aldosterone from the plasma of human subjects is described by Eq.95 which is repeated below for convenience.

\[ P_{AL} = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t} \]

where \( P_{AL} \) is the plasma concentration of aldosterone.

If a two compartment model of aldosterone distribution is assumed, the experimental values of \( A, B, \alpha, \beta \) will allow the estimate of the model's parameters.

![Two compartment model of aldosterone distribution](image)

**Fig. 55.** Two compartment model of aldosterone distribution. Arrows indicate aldosterone flows.
Let us assume the model of Fig. 55 where compartment 1 includes the plasma and the aldosterone metabolizing organs. $K_1$ represents the permeability coefficient of the boundary between the two compartments and $K_2$ is the aldosterone clearance. The volumes of the two compartments are assumed to be constant in time so that an easier analysis of the model is possible.

The following linear differential equations can be written for this model.

$$\frac{dC_1}{dt} = \frac{K_1}{V_1}(C_2 - C_1) - K_2C_1 + S_{AL}$$

$$\frac{dC_2}{dt} = \frac{K_1}{V_2}(C_1 - C_2)$$

The characteristic equation of the system is:

$$s^2 V_1 V_2 + s(K_1 V_1 + K_2 V_2) + K_1 K_2 = 0$$

with the real and distinct solution $s_1 = -\alpha$, $s_2 = -\beta$.

The transfer functions $C_1(s)/S_{AL}(s)$ and $C_2(s)/S_{AL}(s)$ are given by:

$$\frac{C_1(s)}{S_{AL}(s)} = \frac{1}{V_1} \cdot \frac{s + K_1/V_2}{(s + \alpha)(s + \beta)}$$

$$\frac{C_2(s)}{S_{AL}(s)} = \frac{K_1}{V_1 V_2} \cdot \frac{1}{(s + \alpha)(s + \beta)}$$
The time response of $C_1$ and $C_2$ to an aldosterone injection is the impulse response of the transfer functions $C_1(s)/S_{AL}(s)$ and $C_2(s)/S_{AL}(s)$ and it is given by:

\[
\text{Eq.103} \quad C_1(t) = \frac{1}{V_1(\beta - \alpha)} \left[ \left( \frac{K_1}{V_2} - \alpha \right) e^{-\alpha t} - \left( \frac{K_1}{V_2} - \beta \right) e^{-\beta t} \right]
\]

\[
\text{Eq.104} \quad C_2(t) = \frac{K_1}{V_1V_2(\beta - \alpha)} \left( e^{-\alpha t} - e^{-\beta t} \right)
\]

The unknown coefficients of Eq.103 can now be forced equal to the known coefficient of Eq.97 while $\alpha$ and $\beta$ can be forced equal to the roots of the characteristic equation. The following system of equations is then obtained:

\[
\text{a) } A = \frac{K_1 - \alpha V_2}{V_1V_2(\beta - \alpha)}
\]

\[
\text{Eq.105} \quad \text{b) } B = -\frac{K_1 - \beta V_2}{V_1V_2(\beta - \alpha)}
\]

\[
\text{c) } \alpha + \beta = \frac{(K_1V_1 + K_1V_2 + K_2V_2)}{V_1V_2}
\]

\[
\text{d) } \alpha \beta = \frac{K_1K_2}{V_1V_2}
\]

Inversion of the system 105 yields system 106 which permits determination of the unknown $V_1$, $V_2$, $K_1$, $K_2$ as functions of the known $A$, $B$, $\alpha$, $\beta$. 
Using the experimental values of $A$, $B$, $\alpha$, $\beta$ obtained by Tait (1961) (6 normal women) the following average values are obtained for $K_1$, $K_2$, $V_1$, $V_2$.

$$K_1 = 0.579 \text{ l/min} \quad K_2 = 1.113 \text{ l/min}$$
$$V_1 = 27 \text{ l} = 0.67 V \quad V_2 = 13.29 \text{ l} = 0.33 V$$
$$V = V_1 + V_2 = 40.31 \text{ l}$$

Some interesting conclusions can be reached on the basis of these values. First, the volume $V = V_1 + V_2$ is in the range of the normal total body volume of water (~42 l) indicating that aldosterone diffuses into practically all the body cells. Second, the volume $V_1$ (27 l) is larger than the extracellular volume (15 l) indicating that aldosterone rapidly diffuses into the extracellular volume and into part of the intracellular one, probably into some specific organs not yet identified.

Third, the volume $V_2$ represents the water volume of the organs into which aldosterone diffuses more slowly and which is $1/3$ of the total body water (according to this model). Fourth, the aldosterone clearance
(1.1 l/m) appears to be close to the normal liver blood flow (1.4 l/m) which indicates that about 80% of the aldosterone entering the liver is picked up by this organ and metabolized. This fact also justifies the assumption that the liver belongs to compartment 1 rather than compartment 2 and it is in agreement with the experimental finding that the liver clearance.

According to the above conclusions it will be assumed in the model that:

a) \( V_1 = \frac{2}{3} V \); \( V_2 = \frac{1}{3} V \) \( (V = \text{total body water}) \)

b) \( K_1 = 0.579 \text{ l/min} \); \( K_2 = 1.113 \text{ l/min} \)

It will also be arbitrarily assumed that the renal tubules belong to compartment 2.

This model of aldosterone dynamics suggests other experiments that may be run to verify or gain information. For example, the application of the final value theorem to Eqs. 101 and 102 for \( S_{AI}(s) = \frac{R}{s} \) indicates that, in steady state, in an adrenalectomized animal (no endogenous aldosterone) the concentrations \( C_1 \) and \( C_2 \) obtained in response to a constant aldosterone infusion of \( R \text{ ng/min} \) would be \( C_1 = C_2 = \frac{R}{K_2} \).

It should be noted that because of the double exponential decay of \( C_1 \) and because of the values of \( A \) and \( B \), and of \( \alpha \) and \( \beta \) being of the same order of magnitude, it is quite incorrect to talk about the "half life" or about the "rate of disappearance" of aldosterone as is commonly done in physiological papers. Such "half life" and "rate of disappearance" are functions of time and not representative of either \( \alpha \) or \( \beta \).
Although the discussion presented in this subsection concerns a linear model, the digital simulation of Eqs. 98 and 99 accounts for the variations of \( V_1 \) and \( V_2 \) therefore including nonlinear effects.

c) Membrane Effects of Aldosterone.

Two experimental facts concerning the membrane effects of aldosterone are well known; first, there is a delay of about one hour between the injection of aldosterone and the change of sodium excretion in animal and humans; second, the effect of the injection is very gradual and long lasting as is also indicated by the toad bladder experiments (see section 2c in this Chapter.). These two facts, attributed to the intracellular biochemical steps involved in the alteration of Na transport are simulated by a one hour delay and a first order time lag with a half hour time constant (arbitrarily chosen).

The input to this block is the aldosterone concentration \( C_2 \) in compartment 2, the output is the concentration \( C_3 \) of some nonidentified substance that directly controls Na active transport. In steady state the condition \( C_3 = C_2 \) is arbitrarily assumed. In turn, the distal tubule Na active transport coefficient \( K_{2DT} \) is assumed to depend upon \( C_3 = C_2 \) (steady state) as indicated in Fig. 56 and by Eq. 107.

\[
K_{2DT} = K_{2DTo} \cdot 0.4 + 6.66 \cdot 10^{-3} C_3 \quad \text{for } C_3 \leq 120 \text{ ng/l}
\]

Eq. 107

\[
K_{2DT} = 1.2 \cdot K_{2DTo} \quad \text{for } C_2 > 120 \text{ ng/l}
\]

where \( K_{2DTo} \) is the normal active transport rate (see Table 5 pag. 151).
Because of the lack of information Eq. 107 is quite arbitrary and purely based on a reasonable fitting of the overall model results to physiological data (see Chapter IX).

![Graph](image)

**Fig. 56.** Assumed relationship between sodium chloride active transport rate in the distal tubule and the aldosterone concentration (or secretion rate) in steady state conditions.

The analog diagram of the overall model of the aldosterone information channel is given in Fig. 57. Except for the last block, the model is approximately linear since in either fluid loading or dehydration the variation of $V$ are limited to about $\pm 5\%$.

**VIII.4 Simulations and Results.**

The lack of experimental data makes it very hard to check the validity of the aldosterone channel model. In particular, useful data
Fig. 57. Analog diagram of the model of the aldosterone information channel.
such as those of Fig. 52 for ADH have not been found by this author. Such data would be useful in verifying the steady state relationship between the aldosterone secretion rate and the sodium reabsorption (or excretion) rates obtained from the model. The experiments necessary for the data acquisition should be very carefully planned to insure open loop and steady state operation of the system.

The model results are reported in Fig. 58 and relate the sodium excretion rate to the aldosterone secretion (or infusion) rate and concentration in steady state (in which case $C_1 = C_2 = S_{AL}/K_2$). The results are obtained with the renal function model described in Chapter VI where all the renal variables and parameters were kept constant except for the aldosterone controlled DT sodium chloride transport coefficient $K_{2DT}$. The values of the variables and parameters other than $K_{2DT}$ are given in Table 5 (Chapter VI).
Fig. 58. Steady state relationship between urine flow of NaCl and aldosterone secretion (or infusion) rates and concentrations.
Bibliography (Chapter VIII)

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IX.1 The Complete Model

In Chapters III through VIII the various sections of the body fluid regulation system have been described and modeled. The organization of these sections into a single model will allow the complete simulation of the system. To this end a few more details need to be considered; the evaluation of the insensible water losses, of the water oxidation and of the metabolic solute production.

The estimates of insensible water losses are in the range 0.8 to 1 l/day while the estimates of metabolic water production are in the range 0.1 to 0.3 l/day (Wesson 1969, Ruch and Patton 1965). Both phenomena are accounted for in the model by a net water loss of 0.6 ml/min (0.864 l/day). Cellular metabolism produces a number of byproducts such as urea, uric acid, creatin and other compounds which are excreted in the urine. Urea is the main metabolite. In "normal" conditions the rate of urea excretion equal the rate of production. The normal average rate of urea excretion is 0.28 mosm/min and this value is assumed to be the rate of metabolic production. Both the rate of insensible water loss and of urea production are assumed to be constant. This assumption is a reasonable one under conditions of rest and of normal diet.
The insensible water losses are subtracted every minute from the plasma volume. It is debatable as to whether or not it would be more proper to subtract them from the interstitial space; however, due to the rapid IS equilibration and to the small value of the insensible flow, the difference is irrelevant. The same consideration hold for the metabolic urea which, in the model, is added to the plasma every minute. The urinary losses of water, sodium chloride and urea are subtracted every minute from the plasma amount of these substances, therefore closing the system loop. (Fig. 3)

As will be seen later in this chapter, the intracellular volume is very well controlled even in rather unphysiological or diseased conditions. Since in this model the blood cells are considered part of the intracellular space their volume is assumed to be constant.

Other details necessary for the completion of the model are programming facilities for the ingestion of water or sodium chloride solutions during various periods of time and for the intravenous injection or infusion of various solutions.

The number of situations and responses which can be simulated with this model is indeed very large; only a limited set of representative results will be reported here. A sample of responses to fluid ingestion or infusion, to dehydration, and to bleeding and transfusion will be reported in the next section. The comparison between some of the model responses and physiological data will be discussed in Section 3. The onset of certain pathological or drug induced states will be described in Section 4. All these results will be limited to a time
interval of six hours or less (except for the simulation of dehydration which is extended to 24 hours). The consideration of longer time intervals requires the simulation of the drinking control mechanism. An attempt toward the simulation of such mechanism will be made in the next chapter.

IX.2 Response to the Oral Ingestion and to the Intravenous Infusion of Various Solutions

A number of model responses to various stimuli are reported in this section and in the following one. The simulations are chosen among the most significant and the easiest to reproduce and verify experimentally. The purpose of these two sections is both the qualitative verification of the model's behavior and the suggestion of experiments to verify quantitatively the model's predictions.

a) Response to Oral Ingestions

Fig. 59a shows the response of the model to the ingestion in 10 minutes of 1 l of water, 1 l of isotonic sodium chloride solution (292 mosm/l) and 1 l of twice isotonic sodium chloride solution (584 mosm/l).

A number of observations can be made concerning the response to water ingestion as it appear from the model. First the change in aldosterone concentration appears to be irrelevant, therefore justifying the disregard for the aldosterone loop in previous models concerned only with the response to water ingestion. Second, the diuresis that follows the water load also increases the output of solutes, leaving the organism in a state of slight solute depletion. As a consequence,
once the water load is excreted the body fluids are more diluted than
before the water loading and, therefore, the diuresis continues until
the initial plasma osmolality is reached again. This results in a
slight volume depletion which induces a mild antidiuresis. Of particular
interest is the pattern of urea excretion which shows a a biphasis
response. This response was explained in Chapter VI and will be further
discussed in the next section.

Table 6 indicates the maximal percent variations with respect to
normal of the volumes and osmolalities of the three body compartments
following the ingestion of the solutions of Fig. 52a (during the 5 hours
of simulation). It is evident from the table that in the case of water
ingestion (1 liter) the intracellular compartment ($V_{IC}$) is practically
unaffected while most of the stress is taken by the interstitial space
($V_{IS}$) and part of it by the plasma ($V_p$).

The isotonic saline load produces a much smaller diuresis and
larger changes in plasma volume which takes most of the stress. The
changes of the intracellular variables are still negligible. No biphasic
response in urea flow is observable. An appreciable decrease in aldo-
sterone concentration takes place in this case and it is partially
responsible for the increase in sodium chloride output. Changes in
glomerular filtration rates are slightly more marked and longer lasting
than in water diuresis.
Urine flow (ml/min)

Urine osmolality (mosm/l)

NaCl output flow (mosm/min)

Urea output flow (mosm/min)
Urine osmolality (mosm/l)

NaCl output flow (mosm/min)

Urea output flow (mosm/min)

0 60 120 180 240 300 (min)

---

1 liter of water
1 liter of 292 mosm/l NaCl solution
1 liter of 584 mosm/l NaCl solution
1 liter of 292 mosm/l urea solution
1 liter of 292 mosm/l NaCl solution
1 liter of water with 70 g of protein
1/2 liter of 292 mosm/l NaCl solution with 70 g of protein.

Fig. 59. Response of the model to the ingestion of 1 liter of various solutions in 10 minutes (a) and to the intravenous infusion of various solutions in 50 minutes (b).
Table 6

Maximal percent variations of body fluid volumes and osmolalities
in response to oral ingestion of 1 l of various solutions

<table>
<thead>
<tr>
<th>Solution</th>
<th>( V_p )</th>
<th>( V_{IS} )</th>
<th>( V_{IC} )</th>
<th>( \theta_{EC} )</th>
<th>( \theta_{IC} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 l of water</td>
<td>+2.16</td>
<td>+3.37</td>
<td>+0.513</td>
<td>-3.34</td>
<td>-0.64</td>
</tr>
<tr>
<td></td>
<td>-1.54</td>
<td>-2.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 l of isotonic saline</td>
<td>+4.32</td>
<td>+2.33</td>
<td>-0.43</td>
<td>+1.45</td>
<td>+0.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 l of twice isotonic saline</td>
<td>+4.01</td>
<td>-1.55</td>
<td>-1.64</td>
<td>+4.78</td>
<td>+1.42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+3.19</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The ingestion of hypertonic saline induces at first an antidiuresis
(water is withdrawn from the plasma into the gut) followed by a limited
diuresis (the gut fluid is absorbed very slowly). This is the strongest
of the three stimuli and it induces the largest changes of the intra-
cellular variables. However, even in this case such changes are extre-
mely limited. Again, most of the stress is taken by the plasma and
interstitial fluids and the application of such stress is very limited
and delayed by the gastrointestinal tract.

An interesting observation is that (according to the model) the
changes of GFp are on the order of \( \sim 3\% \) while the inulin-clearance
method for the estimation of GFR yields errors of \( \sim 5\% \) to \( \sim 10\% \) or more.
It was shown in Chapter VI that a 3% change in GFR has a considerable
effect upon water and solute excretion. Therefore the statement so
often found in the literature that "GFR was constant during the experiment" does not really mean that the results were not partially due to GFR variations.

b) Response to Continuous Ingestion

Fig. 60 (A and B) shows the plasma osmolality and urine flow response to the continuous oral ingestion of water at rates of 0.4, 8, 12, 16, and 20 ml/min. Fig. 60 C shows the ratio between output flow and input flow. It appears that at rates below 9 to 10 ml/min the steady state urine flow is slightly higher than the input flow so that a reasonably constant "steady state" value of plasma osmolality is reached. At input flows between ~9 and ~12 ml/min the urine flow is lower than the input flow. This fact, together with the urinary removal of solutes (not being replaced) induces a continuous decrease in plasma osmolality. At input flows above ~12 ml the characteristics of the gut to plasma transfer function (see Chapter III Fig. 8) come into play, limiting the amount of water entering the plasma. Water then accumulates in the stomach and intestine, inducing vomiting and diarrhea. Again, the important buffer function of the GIT is evident from these results.

c) Response to Intravenous Infusions

Fig. 59 b shows the response of the model to the intravenous infusion of 1 l of isotonic saline (292 mosm/l), 1 l of isotonic urea solution (292 mosm/l), 1 l isoosmotic protein solution (70g/l) and \( \frac{1}{2} \) l of isotonic saline (292 mos/l) containing 70 g of protein (twice isoosmotic).
Plasma osmolality (mosm/l)

Input flow (ml/min)

Urine flow (ml/min)
Fig. 60. Simulated response to continuous water ingestion.
The response to the infusion of 1 l of twice isotonic saline (584 mosm/l) is reported, for clarity, in Fig.61 together with the responses to plasma infusion and removal. All infusions take 50 minutes (infusion rate of 20 ml/min.)

It is evident, in the case of isotonic and hypertonic saline infusion that the variations of body fluid volumes and osmolalities are larger than in the case of oral ingestion, despite the much lower rate of input flow (20 ml/min for infusion, 100 ml/min for ingestion.) Table 7 shows the maximal percent variation of body fluid volumes and osmolalities during the first 5 hours following the infusion.

The buffer action of the GIT is obvious from the comparison between the responses to ingestion and infusion of the same solutions. It is also obvious from such comparison that the model response is very much dependent upon the rate of infusion. This indicates that it is improper to compare or pool experimental data obtained by infusing the same solution at different rates. Unfortunately, this is often done in the literature.

The intravenous infusion of isotonic saline results in diuresis, in an increased salt excretion, and in a limited increase in urea excretion. These variations are mostly limited to the infusion period (50 min). Qualitatively similar but quantitatively more marked variations take place during and after the infusion of hypertonic saline (osmotic diuresis). The infusion of isotonic urea solution (292 mosm/l) has a diuretic effect much more marked than that of isotonic saline.
Table 7

Maximal percent variations of the body fluid volumes and osmolalities in response to the intravenous infusion of various solutions (see text and Fig. 59 b)

<table>
<thead>
<tr>
<th>Solution (infusion rate 20 ml/min)</th>
<th>Variable (% variation)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$V_p$</td>
</tr>
<tr>
<td>1 l of isotonic saline</td>
<td>+7.40</td>
</tr>
<tr>
<td>1 l of isotonic urea solution</td>
<td>+8.33</td>
</tr>
<tr>
<td></td>
<td>-2.46</td>
</tr>
<tr>
<td>1 l of isoosmotic protein solution</td>
<td>+25.92</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 l of twice isoosmotic protein solution in isotonic saline</td>
<td>+25.0</td>
</tr>
<tr>
<td>1 l of twice isotonic saline</td>
<td>+15.12</td>
</tr>
</tbody>
</table>

The excretion of urea increases considerably (by 4 times, at the peak of the diuresis) while NaCl excretion also rises as a consequence of the increase in GFR. These facts are in agreement with the common use of urea solutions as diuretics previous to the discovery of mercurial diuretics and of more effective drugs.
Of particular interest is the response to the infusion of protein solutions. As it appears in Fig. 59, the infusion of 1 liter of water containing 70 g of protein (isonicotic) induces a step-like increase of 18.5% in plasma volume. A slight antidiuresis takes place at the beginning of the infusion and it is followed by a marked diuresis which subtracts fluid from the interstitial space. The infusion of the same amount of protein in half a liter of isotonic saline produces the same change in plasma volume but more prolonged antidiuresis followed by a more limited diuresis. One half liter of protein solution 4 times isonicotic (240 g/l) in isotonic saline induces only an antidiuresis. It is evident that (according to the model) the urinary response to protein infusion depends upon the amount and concentration of the infused protein as well as upon the salt content of the solution and the rate of infusion. It appears that the controversy over the diuretic or antidiuretic effect of protein infusion often mentioned in the literature may be solved simply by a better description of the experimental conditions and of the results; according to the model, it is improper to discuss the effect of infusing x grams of proteins since parameters and quantities other than x contribute to the determination of the response.

IX.3 Response to Plasma Infusion, Plasma Removal and Dehydration

The model response to infusion and removal of 0.5 l (10% of the blood volume) of plasma in 10 minutes is shown in Fig. 61. It appears
that the removal of plasma is not compensated by fluid transfer from other compartments (unless the hemorrhage is so large as to induce significant changes in blood pressure). Compensation would take place by means of drinking and eating. The plasma removal results in an increase in ADH and aldosterone concentrations, a slight decrease of GFR and a marked reduction of urine flow. The antidiuresis is so intense that the algorithms used in the computation of the renal state become appreciably affected by the quantization error of the renal medulla, yielding unreliable values of urine concentration. This error might be reduced by dividing the renal medulla in more than 10 layers and using a faster computer for the model implementation. The unreliability of the urine concentration values is indicated by question marks in Figs. 61 and 62. Despite this fact, the decrease of urine concentration at very low urine flows is in agreement with the observation of Roscoe (1956) and it is observed also in the simulated dehydration before the results become unreliable.

The plasma transfusion induces a very mild diuresis and a decrease in both aldosterone and ADH concentrations.

Fig. 62 shows the results of a simulated period of 24 hours of dehydration. Both ADH and aldosterone concentrations increase and a situation of antidiuresis settles in about 6 hours. It should be kept in mind that the initial conditions used in the simulation describe a state of hydropenia, that is a state of mild dehydration. The broken lines in Fig. 62 represent extrapolated values. At urine flows in the range 0 to 0.2 ml/min the model results are somewhat unreliable for the
Urine osmolality (mosm/l)

NaCl output flow (mosm/min)

Urea output flow (mosm/min)

Fig. 61. Response to plasma infusion and withdrawal.

Fig. 62. Response to 24 hours of dehydration.
Fig. 61. Response to plasma infusion and withdrawal and to the infusion of hypertonic saline:
- 0.5 liters of plasma withdrawn in 10 minutes.
- 0.5 liters of plasma infused in 10 minutes.
- 1 liter of 584 mosm/l NaCl solution infused in 50 minutes.

Fig. 62. Response to 24 hours of dehydration.

X = data from Czackzes et al. (1964)
reason given above, so extrapolation of the previous (first 12 hours) values is preferred to the actual results.

The comparison of the results presented in Fig. 62 with those of Fig. 59 shows that the urine osmolality \( U_{\text{osm}} \) five hour after the ingestion of a water load may be higher that after 12 or more hours of dehydration. This very interesting observation may explain the controversy described by Hendry et al. (1964) concerning the concentration of urine in dehydrated subjects. Hendry described the duration of the dehydration required to attain maximal \( U_{\text{osm}} \) as "something of a mystery". This model shows that dehydration does not lead to a monotonic increase in \( U_{\text{osm}} \) and that the "morning urine" can be even less concentrated than the urine produced without any dehydration at all, as observed by Hendry. This observation is substantiated, teleologically by the organism's need to save solutes (and therefore maintain fluid volume) beside water in dehydration, and physically by the reduction of GFR and by the decreased effectiveness of the countercurrent mechanism (see Fig. 40 in Chapter VI).

**IX.4 Comparison of the Model Results with Physiological Data.**

a) General Comments

Some general comments are necessary before the model's results are compared with physiological data. These comments are listed below.

a) The urine output of the model corresponds to the renal output and not to the bladder output of the system. Since in the large majority
of experiments the bladder output is measured by natural voiding, a time delay should be expected between experimental and simulated results.

b) At low urine flows the permanence of urine in the bladder is longer and because of the non-zero permeability of the bladder wall some water and solutes are reabsorbed. The experimental output flows of water and solutes may therefore be lower and delayed with respect to the simulation results.

c) A number of experiments consisting of the description of the response to fluid ingestion or infusion or to dehydration were performed over 10 years ago when the osmolality determinations were affected by errors ranging from 5 to 10%.

d) No complete and statistically significant set of experimental data was found in the literature. All the data found and presented here were obtained in experiments relative to particular aspects of the water regulation system, performed on different persons in different initial conditions and only one or two variables were usually measured. This makes the experimental data very scattered and unreliable. A more detailed criticism of the evidence will be given at the end of this section.

b) Comparison of Experimental and Simulated Results

The simulation results presented in the previous section indicate that urine osmolality varies in the range 70 to 1400 mosm/l. These values are in excellent agreement with those reported in any textbook of physiology (range from 60 to 1400 mosm/l).
In Fig. 62 the ADH concentration during hydration is reported together with experimental values observed by various authors (Czaczkes et al. 1964, Walker 1961). The agreement is satisfactory.

Fig. 63 shows the model's urinary response to the ingestion of 1 l of water in 10 minutes compared to experimental data (humans) from Smith (1951), Koshikawa and Suzuki (1968), Nagasaka et al. (1966), Findley and White (1937). The data clearly show the unreliability of single experiments and the good fitting of the simulated response to the average experimental response.

The data of Fig. 64 show the time course at the percentage of water load excreted by three dogs following ingestion of a 35 ml/Kg of body weight of water. The continuous curve shows the model's response to the same load in man (2.5 l). It is unfortunate that the experimenter did not continue the measurement until the 100% excretion was reached and passed.

Fig. 65 shows the hysteresis loop relating urea output flow to urine flow. The reason for this hysteresis (enhancement and abatement of urea clearance) have been explained in Chapter VI. Both experimental and computer results describe the response to the ingestion of a liter of water (in 10 minutes, in the simulation). The number on the computed curve indicate time in minutes from the ingestion. No time scale was given in the data (Koshikawa and Suzuki 1968). It is also unfortunate that data from a single experiment were reported by the experimenters. Despite these facts the agreement between real and predicted results is satisfactory.

The simulated urinary response to the ingestion of 1 l of isotonic
Fig. 63. Simulated and experimental urinary response to the ingestion of one liter of water.

- simulated response
- data from Smith (1951)
- data from Koshikawa et al. (1968)
- data from Nagasaka et al. (1966)
- data from Findley and White (1937)
Fig. 64. Cumulative fluid excretion following the ingestion of 35 ml/(Kg of body weight) of water.

- simulated results (2.45 l of water ingested by a 70 Kg man)
- experimental results obtained by Chan (1971) from dogs.
Fig. 65. Hysteresis loop of urea flow versus urine flow following ingestion of one liter of water. 
= data from Koshikawa et al. (1968)

Fig. 66. Urine flow following ingestion of one liter of isotonic NaCl solution (292 mosm/l). 
= data from Smith (1951)
saline solution (0.96 NaCl in 10 min) is reported in Fig 66. The two curves are relative to the two initial states of hydropenia ("normal" state) and of dehydration (6 hours of water deprivation starting from the hydropenic state). The importance of the initial state in the determination of the response is evident; the dehydrated "subject" tends to withhold fluid. Again it is unfortunate that the experimental observations (Smith, 1951) were not continued until the end of the limited diuresis, that no information was given about the initial state of the subject and that a single experiment was reported.

Fig. 67 shows simulated variations of the plasma osmolality, urine osmolality and urine flow following the ingestion of 1, 1.5, and 2 l of water at the rate of 0.1 l/min. The experimental data are from Smirk (1933) and Koshikawa et al. (1968) for the plasma osmolality and from Schoan (1957) for the urine osmolality. The latter author reported only one experiment for each of the three water loads, Koshikawa et al. also reported data from a single experiment.

Fig. 68 shows the simulated and experimental response to repeated ingestion of water. The experimental data, again relative to a single experiment, are from Koshikawa (1968). The initial state of the subject was not given. The computer results assume an initial state of hydropenia. It is clear that more experimental work is needed to either validate or reject the simulated response.

Fig. 69 reports the observed and predicted values of plasma ADH concentration following a water load in persons being in different states of dehydration. The water load given to the subject was
Fig. 67 Simulated and experimental responses to the ingestion of 1, 1.5, and 2 l of water.

a) $\times$ = data from Smirk (1933) (water ingested "between 1 and 1.5 l").

b) $\ldots$ = data from Fildes et al. (1968) (water ingested 1 l).
Fig. 67 Simulated and experimental responses to the ingestion of 1, 1.5, and 2 l of water.

a) $\times$ = data from Smirk (1933) (water ingested "between 1 and 1.5 l).  
$\bullet$ = data from Koshikawa et al. (1968) (water ingested 1 l)

- - - - = computer results

b) $\times$ = data from Shoen (1957)

- - - - = computer results

c) - - - - = computer results
Fig. 68 Simulated and experimental response to repeated water ingestion. Data from Koshikawa et al. (1968)
hours of dehydration
10
6
0
hours of dehydration

plasma ADH conc.
mU/l

ingestion of 1.7 l of water
Fig. 69 Simulated and experimental plasma ADH decay following ingestion of 1.7 l of water by subjects in different states of hydration. 

x = data from Czaczkes (1964). The experimental subject drank "between 1.5 and 2 l of water".
"between 1.5 and 2 l of water" ingested in an unknown time (Czaczkes et al. 1964). The model "ingested" 1.7 l of water in 17 minutes. The three simulated curves correspond to dehydration periods of 0, 6, and 10 hours starting from the hydropenic state. Czaczkes observed the different rate of initial decrease of ADH concentration at higher levels of dehydration and suggested that this rate might be a function of the ADH concentration. This model indicates that this rate might be more simply a function of a) the rate of fluid ingestion, b) the rate of fluid absorption from the GIT. Again, more experimentation is needed to establish these points.

In 1945 Wolf reported data describing the urinary concentration and flow of chloride in man during steady state ingestion of 7 ml/min of water. Assuming the sodium concentration equal to that of chloride in the urine (in mEq/l) the results of Fig. 70 are obtained. The simulated curves are for continued ingestion of 6 and 8 ml/min of water. Although the agreement between simulated and experimental results is excellent after the second hour, the different initial conditions between model and subject do not allow a significant comparison of the initial transient. Again, the initial condition of the subject were not specified. In the same year Wolf measured the ratio between oral water input and urine input in man during continuous ingestion of water at rates between 6 and 10 ml/min. His experimental results were averages of 12 to 26 experiments and are reported in Fig. 71 together with a simulated response to input flows of 6 and 10 ml/min. The agreement between simulated and experimental results is excellent. In particular it is
Fig. 70 Urine NaCl concentration and flow during continuous ingestion of 6 and 8 ml/min of water = data from Wolf 1947) for continuous ingestion of 7 ml/min.
Fig. 7.1 Ratio of urine flow to input flow during continuous ingestion of 6 and 10 ml/min of water.

x = data from Wolf 1945 for 6 to 10 ml/min of water ingestion.
interesting to observe that the steady state output flow is larger than
the input flow (volume depletion due to water ingestion, see also
Fig.60 C). It is unfortunate that Wolf did not report either the range
or the standard deviation of its results.

Fig.72 shows the sodium chloride excretion pattern by two subjects
before, during, and after intravenous infusion of 2.2 liters of
isotonic saline in 90 minutes (Papper et al.1956). Considering the
delay in urine collection, the simulated results are in reasonable
agreement with the experimental observations. Similar experiments
have been performed by Strauss et al.(1951) who infused 3 l of isotonic
saline into three recumbent subjects in two hours. The resulting output
rates of urine, sodium chloride and urea are reported in Fig.73 together
with the simulation results. Fig.73 A shows two simulated curves; curve
1 relative to the case of hydropenic subject, curve 2 relative to the
case of a somewhat dehydrated subject (8 hours without water). Consider­
ing the delay due to natural urine collection, curve 2 gives a good
fitting of the data. Only curves 2 (dehydrated model) are reported
in Fig.73 B and C. The initial conditions of the experimental subject
were not described by Strauss et al. The importance of such condition
in the determination of the response has already been mentioned and
has been pointed out by Birchard et al. as well in 1953.

The model has been shown to be reasonably valid even in cases of
large and unphysiological infusions such as 2 to 3 l of isotonic saline.
The response is not as satisfactory in the case of massive hypertonic
salt infusions indicating that further work is necessary for a better
simulation of NaCl osmotic diuresis.
Fig. 72 Sodium chloride excretion by two subjects before, during and after the intravenous infusion of 2.2 l of 0.9% NaCl solution (Isotonic) in 90 minutes.

— Experimental data from Papper et al. (1956)

—— Computer simulation
Fig. 73  Urinary water, NaCl and urea response to the intravenous infusion of 3 l of isotonic saline (0.9% NaCl) in 2 hours.

--- experimental data from Strauss et al (1951)

--- Computer results. Curve 1: hydropenic subject;
  curve 2: dehydrated subject (8 hours without water)
Fig. 74 shows computed urinary response to the intravenous infusion of 73 g of sodium chloride in 730 g of water. The solution is 11 times more concentrated than the plasma. The experimental data are from Dean et al. (1949) who infused between 0.91 and 1.21 g of NaCl/Kg of body weight in 4 subjects during periods between 65 and 187 minutes. The results they presented were the averages of 4 experiments. Clearly, the averaging of so different experiments is rather improper and partially justifies the disagreement between computed and experimental results. No information was given by the experimenters concerning the spread of the results obtained.

The results in Fig. 74 seem to suggest that in the model the glomerular filtration rate should be more affected by the changes of arterial and plasma oncotic pressures. Another, and probably better, explanation for the relative disagreement between these experimental and model results is the simplified model of the proximal tubular function.

Fig. 75 compares simulated results to the experimental results obtained by Lombardo et al. (1951). Four subjects ingested 0.2 l of 0.14% NaCl solution every hour for 10 hours and were bled of 9 cc/Kg of body weight (540 cc for a 70 Kg. man) after 4.5 hours. The data refer to subjects in a horizontal position and at a 20° angle with the horizontal plane and are average changes observed in the 4 experiments following the bleeding. The data previous to the bleeding are not clearly presented (e.g., the urine flow was "of convenient size") by the experimenters and are assumed to coincide with the similar results immediately preceding the bleeding. The simulated change of GFR appears
to be smaller than the experimentally observed change, however, it should be remembered that GFR measurements are affected by a 5 to 10% error. The agreement between simulated and experimental changes of urine and sodium flows is reasonable, considering the high experimental errors due to the low flow of urinary water and solutes. It is unfortunate that the time separation of the experimental measurements does not show if the predicted oscillations indeed exist.

Fig. 75 shows the versatility of the model in the simulation of complex experiments involving repeated and different inputs such as injections, ingestions, infusions, and bleeding of various amount and at different times.

Fig. 74 Urinary response to the intravenous infusion of 73 g of NaCl in a 10% solution (11 times more concentrated than plasma) $x =$ average of 4 experiments (Dean and Eccles, 1949). See text for critique of the experimental data.
Fig. 75 Simulation of Lombardo et al. experiments

↑ = ingestion of 0.2 l of 0.14% NaCl solution. ↓ = bleeding of

0.5 l. x = experimental data from subject in horizontal
position. o = experimental data from subject at 20° angle with
horizontal plane. Data from Lombardo et al. (1951)
c) Critique of the Physiological Evidence

The unsatisfactory characteristics of the physiological evidence are apparent from the previous subsection. It is also evident that the experiments performed in the past are not very suitable for the verification of models because of the following main reasons:

a) The initial state of hydration of the subjects was often unverified or not given.

b) In many cases only a single experiment was run; therefore, the results have little statistical validity.

c) Very often when more than one experiment was run the results were not presented properly (e.g. only average given and not range of individual data).

d) The stimuli were often described inaccurately.

e) The experiments were often interrupted before a significant part of the results could be obtained.

f) Only certain variables were measured when it would have taken little effort to measure other significant variables as well.

g) Results from different experiment types were averaged.

These observations indicate once more the necessity of using a model in the planning and in the organization of experiments in order to determine what should be measured, for how long, how often, with what accuracy and how should the results be presented and interpreted. Only from this interaction of physiologists and bioengineers may enough good quality data be collected for the verification and improvement of the model and for the investigation of the system. It might be added that
most of the experiments required to verify this model are neither
difficult nor dangerous and in many cases are very simple (see Figs. 58
to 62) and can be performed on human subjects.

IX.5 The Onset of Drug Induced and Pathological States

Fig. 76 shows the behavior of the model at three different conditions:
a) For the ADH secretion rate equal to zero for t > 0 (onset of diabetes
insipidus)
b) For the aldosterone secretion rate equal to zero for t > 0 (onset
of Addison's disease)
c) For the active transport rate in the ascending loop of Henle reduced
to 50% of normal for t > 0. (as under the action of a mercurial diuretic).
This latter set of results has only qualitative value since mercurial
diuretics may reduce in various degrees transport processes in other
parts of the nephron as well.

The interruption of ADH secretion induces a diuresis and an increasing
degree of dehydration which, through renal and hormonal factors (aldo-
sterone), progressively reduce the diuresis that do not eliminate it.
However, salt and urea output are brought back to values close to the
normal ones, a fact which helps in controlling volumes at the expense
of osmolality. It is evident how, in the model, most of the volume
loss is taken by the interstitial space and only some by the plasma; the
intracellular volume decrease is irrelvant. The aldosterone control
loop partially compensates for the opening of the ADH loop.
The interruption of aldosterone secretion produces only a limited diuresis but a substantial delayed output of salt with little change in urea output. The degree of dehydration is much smaller than in the previous case. An increase in ADH secretion partially compensates for the lack of aldosterone as it has been often observed in patients with Addison's disease. As it is observed clinically, a few days are required for the lack of aldosterone to become critical and induce symptoms. The opening of the aldosterone loop is therefore much less critical to the system than the opening of the ADH loop.

The reduction of salt transport out of the ascending loop of Henle induces a sudden diuresis and natriuresis (increase in salt output) which are almost entirely corrected by the action of other factors (renal and hormonal) elicited by the resulting dehydration. These results indicate the possibility of using this model for the study of drug action. No reliable experimental data have been found to verify these results.

It is obvious that the situations and states that the model can simulate are in much larger numbers than can be reported here. In particular, the pathological states range from alterations of the GIT behavior to changes of capillary and lymphatic characteristics to variations of cell membrane properties, from alteration of glomerular filtration or renal tubular processes to malfunction of the hormonal control loops to changes of metabolic solutes production or insensible water losses. Also, the initial state can be varied widely since this state is computed by the model as a function of the total body amounts
Plasma aldosterone concentration (ng/l)

Glomerular filtration rate (ml/min)

Urine flow (ml/min)

Urine osmolality (mosm/l)

NaCl output flow (mosm/min)
Fig. 76 Onset of pathological and drug induced situations.
- ADH secretion rate = 0 for t > 0
- Aldosterone secretion rate = 0 for t > 0
- Na transport across ALH wall reduced to 50% of normal
of water and solutes and as a function of capillary and cell membrane properties.

It is felt that the data presented are a good sample of the model's possibilities and that a further investigation of such possibilities would be significant only when more data will be obtained, or found in the literature. It is also felt that the full evaluation and use of the model will be possible only with the cooperation of the physiologists and medical doctors.
Bibliography (Chapter IX)


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CHAPTER X

THE COMPLETE MODEL. LONG TERM SIMULATIONS AND CONTROL ASPECTS

X.1 General Comments

As was mentioned in Chapter II, the input to the body fluid regulation system is not arbitrary but is a function of the organism needs. The consideration of these needs is necessary if the model is used in the simulation of time intervals in the range of days. This chapter presents a first approach to the study of the thirst mechanism and to the study of long term responses of the model (12 to 48 hours).

The long term simulations can be used for various purposes including: a) the study of the limit cycles of the controlled variables and of their dependence upon the drinking criteria chosen, b) the study of the effect of drinking various fluids upon such variables, c) the study of the onset and development of pathological states, d) the investigation of the possibilities of correcting pathological states by drugs, fluid infusions or withdrawals.

X.2 The thirst Mechanism

The thirst mechanism has been studied and simulated by previous researchers among which are Reeve and Kulhanek (1968) and Oatley (1967, 1970, 1971).
The previous research indicates that the factors eliciting thirst and those relieving it are of different nature. These factors are of both physiological and psychological origin. Only the physiological factors will be considered here; the effect of habit, emotion or conditioning will be neglected.

On the basis of the data available from the literature it will be assumed that thirst is elicited by either a sufficient increase in plasma osmolality or a sufficient decrease in blood volume or both, and that thirst is relieved by a sufficient filling of the stomach or intestine or both. (Reeve and Kulhanek, 1968, Oatley 1967). It will also be assumed that, when thirsty, the organism drinks continuously at the rate of 0.1 l per minute and does not drink when not thirsty.

The above assumptions indicate that thresholds are necessary to identify the state of thirst and that such state may be represented by a logic variable having value 1 (TRUE) to indicate thirst, and value 0 (FALSE) to indicate absence of thirst.

The plasma osmolality value above which thirst is felt, is chosen as 294 mosm/l while the blood volume decrease (ΔBV) necessary to induce thirst is chosen as 10% of the normal blood volume (5.24 l). These values are in part arbitrary and in part justified by the following facts:

a) It takes approximately 6 hours of dehydration from the hydropenic state for the plasma osmolality to reach 294 mosm/l. The choice of this value would therefore produce drinking 3 to 4 times per day which appears reasonable.
b) It has been observed in many instances that it takes a hemorrhage of at least 10% the blood volume to induce thirst in a blood donor. Although this evidence is rather weak and approximate, these threshold values are considered satisfactory for a first approach to the problem. It is further assumed that the presence of 250 ml of fluid (or more) in either the intestine or the stomach is sufficient to relieve the sensation of thirst and interrupt drinking. This value of fluid volume is chosen arbitrarily. The following logic variables are defined:

\[
\begin{align*}
OEX &= 1 \text{ if } P_{\text{osm}} > 294 \text{ mosm/l} & \text{OEX} &= 0 \text{ otherwise} \quad \text{(osmotic excitation)} \\
VEX &= 1 \text{ if } \Delta BV < -10^\circ & \text{VEX} &= 0 \text{ otherwise} \quad \text{(volume excitation)} \\
SIN &= 1 \text{ if } S_Y > 0.25 \text{ l} & \text{SIN} &= 0 \text{ otherwise} \quad \text{(stomach inhibition)} \\
IIN &= 1 \text{ if } I_Y > 0.25 \text{ l} & \text{IIN} &= 0 \text{ otherwise} \quad \text{(intestine inhibition)} \\
\end{align*}
\]

Where \( P_{\text{osm}} = \text{plasma osmolality}, \quad \Delta BV = \text{change of blood volume} \)

\( S_Y = \text{stomach content volume}, \quad I_Y = \text{intestinal content volume} \).

The logic variable \( D \) is used to indicate the thirst state. (\( D = 1 \) means thirst, \( D = 0 \) means no thirst.). \( D \) is initialized as \( D = 0 \) and computed during each time iteration according to the logic equation:

\[
\text{Eq.108} \quad D = (VEX + OEX) \cdot \overline{\text{GIN}} + D \cdot \overline{\text{GIN}}
\]

where \( GIN = SIN + IIN \), the bar means logic negation and where, as evident from the equation, once \( D \) becomes 1 it maintains that values until \( GIN \) becomes 1. Eq.108 describes the logic of the "to drink or not to drink" decision.

Fig.77 represents a simplified block diagram of the water regulation system with the inclusion of the drinking control. Fig.77 differs from
Fig. 77. Block diagram of the model of the water regulation system including the drinking mechanism. The diagram is basically the same as Fig. 3.
Fig. 3 only because the plasma osmolality and the blood volume are considered as output variables. The system is, of course, the same. Many other graphical representations of this system can be found depending upon which variables are considered as the output ones.

X.3 Long Term Response of the "Normal" Model Drinking Water or Isotonic Saline Solution.

Fig. 75 shows the response of the model during a period of 48 hours. The available input is distilled water. The vertical marks indicate the time of drinking. The model drank 0.3 l of water in 3 minutes each time. A number of very important observations can be made from the results obtained:

a) The plasma osmolality oscillates in a limit cycle which slowly expands because of the progressive loss of solutes. The amplitude of oscillation is approximately ± 0.7 % the average value.

b) The intracellular osmolality is even better controlled and oscillates in a smaller limit cycle between ± 0.14 % of the average value. The average value slowly decreases because of loss of solutes.

c) The plasma volume decreases at the average rate of 0.22 l/day. Despite the drinking, the system becomes volume depleted because of the loss of solutes. This phenomenon has been already discussed in the previous chapter and also by Wolf in 1945.

d) In an attempt to maintain the proper plasma volume, the diuresis following drinking becomes progressively smaller until the urine flow
drinks of 0.3 l in 3 minutes

osmolality (mosm/l)

extrac.

intrac.

Plasma volume (l)
Fig. 78 Response to spontaneous drinking of water by a normal subject. Each mark indicates the drinking of 0.3 l of water in 3 minutes.
oscillates between 0.2 and 0.28 ml/min.
e) In an attempt to conserve salt the average NaCl output flow is reduced to 1/3 of the normal value.
f) The output flow of urea is particularly interesting. The urine output between diureses decreases to 0.22 ml/min with an osmolality of about 1300 mosm/l corresponding to a total solute output of 0.29 mosm/min, 0.07 of which is NaCl. Therefore urea is excreted at the approximate rate of 0.22 mosm/min while it is produced at the rate of 0.28 mosm/min. As a consequence urea is accumulated in the body and particularly in the renal medulla, and its output increases greatly during the limited periodical diureses inducing some increase in urine osmolality and permitting an average excretion rate close to 0.28 mosm/min. No evidence has been found in the literature to verify this interesting result.

It is apparent from Fig. 78 that drinking becomes more frequent in time as the volume depletion proceeds and that a very satisfactory control of osmolality is obtained. However, if the simulations were continued for a longer time on a faster computer (this simulation required 9 hours on a DEC-FDP9 computer) the blood volume would become the factor controlling drinking. As a consequence, the blood and plasma volumes would be maintained at a level close to 10% below normal and the control of the osmolalities would be lost. This behavior will be evident in the simulation of diabetes insipidus in the next section. During the 48 hours simulated period, the intracellular volume increased of only 0.19 l (0.14%) indicating the excellent control of this variable,
while the interstitial space lost 0.6 l (5.2%) and the plasma lost 0.36 l (11% of the plasma volume, 7% of the blood volume). The total amount of water drunk was 0.9 l in the first day and 1.2 l in the second (total of 2.1 in two days).

It is evident from these results that the initial "steady state" computed by the model is somewhat arbitrary; in fact the system has no real steady state and the state variables are continuously changing (see Chapter IV). It also appears that the intracellular osmolality is normally different from the extracellular osmolality although the difference is quite below the sensitivity of the presently available osmometers. The model's behavior presented in Fig.78 is of course dependent upon the drinking criteria chosen. It would be of interest to study how the limit cycles are affected by different choices of drinking behavior. This analysis can be performed very easily with this model.

Fig.79 describes the behavior of the model when isotonic saline rather than water is available for drinking. The response is entirely different from the previous case and shows no limit cycle but rather a drift toward a new steady state. In about six hours (from the initial hydropenic state) the plasma osmolality reaches 294 mosm/l and the model drinks 0.3 l of fluid in 3 minutes. The fluid, however, produces a further increase in osmolality so that as soon as some of the fluid drunk is absorbed, thirst is reestablished. This fact produces the drinking of 0.1 of fluid every ~30 minutes and a considerable increase in urine and salt output flows.
0.5 l

- 0.1 l / 25 min.

Osmolality (mosm/l)

extracel.

intracel.

plasma volume (l)
Fig. 79 Response to spontaneous drinking of isotonic NaCl solution by normal subject.
It appears however, that in about 40 hours the output of water and salt equals the input indicating that the model may barely cope with the situation and that the volumes and osmolalities will eventually reach a new steady state in some 50 or 60 hours.

The simulation of sea water drinking (not reported) shows the inability of the kidneys to excrete the large amount of salt drunk (sea water is approximately three times more concentrated than plasma) and shows the large increase of salt content of the body fluids which rapidly leads the organism to death.

X.4 Long Term Simulation of Disease States

Fig.80 shows the response of the model during a period of 30 hours and for zero ADH secretion rate for $t > 0$. This condition simulates the state of diabetes insipidus. The initial state is that of hydropenia. The interruption of ADH secretion induces a-diuresis and the rapid dehydration process already described in Fig.76. In about 50 minutes thirst is produced and the model starts "drinking". The fluid drunk is pure water. Because of the high urine output, thirst is produced again in about 30 minutes. The model drinks 0.2 l of water in 2 minutes every half an hour.

Because of the frequent drinking of small amounts of water, the extracellular osmolality is indeed well controlled and varies according to a very narrow, very fast and slowly expanding limit cycle. For clarity only the envelope of the oscillations is reported in Fig.80. However, despite the
The diagram shows the changes in osmolality, plasma volume, and urine flow over time. The x-axis represents time in 22-minute intervals, while the y-axis for osmolality is labeled in mosm/L.

- **Osmolality (mosm/L)**: The osmolality changes are plotted with lines indicating intracellular and extracellular osmolality.
- **Plasma volume (l)**: The plasma volume decreases over time, as shown by the downward trend.
- **Urine flow (ml/min)**: The urine flow is depicted with a peak at the beginning, followed by a decrease over time.

The data points include:
- **Plasma volume**: 2.8, 2.6
- **Urine flow**: 12, 10
Urine flow (ml/min)

NaCl output flow (mosm/min)
Fig. 80 Simulated spontaneous drinking of water by a patient in the first 32 hours of diabetes insipidus.
control of extracellular osmolality, cellular dehydration is produced. The volume and salt depletion produce a decrease in output of urine and salt. After only 27 hours the blood volume has decreased by 10% therefore becoming the thirst control factor. After this time the plasma volume is conserved while the plasma osmolality decreases dramatically.

These results show that the diabetic is not only in constant need of water but in need of salt as well and that while water is important for the conservation of osmolality, salt is very important for the conservation of fluid volume. This observation suggests that a salt solution, rather than water, should be drunk by the diabetic in order to maintain body volume and osmolality within physiological limits. Fig. 81 shows the same variables as Fig. 60 but the fluid available for drinking is either isotonic saline (292 mosm/l) or a diluted salt solution (75 mosm/l). In neither case does any oscillatory behavior develop. It is apparent that a diabetic subject drinking isotonic saline is unable to excrete the ingested salt in the proper proportion to water and so he cannot control the osmolality of his body fluids which keeps raising. If a very diluted salt solution is drunk (broken line) however, both osmolality and plasma volume can be controlled. Drinking takes place at the rate of approximately 0.2 l/36 min.

Another important pathological state of the body fluid is the edematous state. Edema may be produced by various causes such as urinary loss of protein, reduced lymph flow, high capillary permeability or increased venous pressure.

All this states can be simulated with this model and the effect of
Plasma osmolality (mosm/l)

Plasma volume (l)

Urine flow (ml/min)

NaCl flow (mosm/min)
Fig. 81 Response to spontaneous drinking of 292 mosm/l NaCl solution (---) and 74.5 mosm/l NaCl solution (----) during the first 20 hours of simulated diabetes.
drinking or infusing various solutions can be analyzed as well as the effect of some diuretics. As an example the onset of lymphedema is considered. Fig. 82 shows results obtained by setting the lymph flow equal to zero for \( t > 0 \). When thirsty, the model drinks isotonic sodium chloride solution. It appears that after the first five hours, before drinking occurs, the fluid losses only affect the plasma volume and not the interstitial volume which remains constant.

Drinking saline reduces the rate of decrease of the plasma volume and produces fluid accumulation in the interstitial space.

The drinking of water produces a somewhat different situation indicated in Fig. 83. Fig. 83 also shows the effect of infusing intravenously 0.1 l of 584 mosm/l NaCl solution containing 10 g of proteins. The infusion lasts 1 minute at the 25th hour of simulation and has the main purpose of showing the versatility of the model for the simulation of therapeutic treatment. As obvious from Fig. 83 the infusion does not significantly improve the situation being simulated. It is interesting to observe that when the blood volume is decreased by 10% and becomes the drinking controlling factor, the plasma osmolality decreases so drastically as to induce a very marked diuresis. The rate of urine loss becomes higher than the rate of fluid absorption from the gut so that the control of plasma volume is not effective. However, fluid starts being withdrawn from the interstitial space rather than being accumulated into it.

The model therefore predicts that an animal with complete lymph blockade and with only water available would die before any significant edema develops. No experimental evidence has been found which could
Fig. 62 Response to spontaneous drinking of isotonic NaCl solution in case of complete lymph blockade for t > 0
Osmolality (mosm/l)

Plasma volume (l)
Plasma volume (1)

Interstitial volume (1)
Fig. 83 Response of patient with complete lymph blockade for $t > 0$ to spontaneous drinking of water. Injection of 0.1 l of 584 mosm/l NaCl solution containing 10 g of proteins at $t = 25$ h
bear on these results.

X.5 Control Aspects of the Model.

Many of the control characteristics of the model have been evident from the data already presented. The results presented in Figs. 59 and 61 may be considered as responses to rectangular impulses applied to the input variables (water, solutes and protein inputs). The results of Fig. 62 describe the response to the initial conditions.

Fig. 60 shows the response to step inputs of water flow while Fig. 76 shows the response of the system when either one of the hormonal loops is opened. The model presented in Chapter V has no feedback at all (nephrectomized animal) and can be used to study open loop responses while the model presented in Chapter IX has no thirst control loop and can be used to study specific inputs. Open loop studies are possible by avoiding the subtraction of output flows from the body water and solute amounts minute by minute.

A detailed analysis of the system modeled would be very interesting particularly after a more extensive verification of the model's results. Because of time and space limitation only the most general control aspects of the model will be discussed here, to outline the possibility of further detailed research (see Chapter XI).

It is obvious from the results presented, that the purpose of the modeled regulatory mechanism is that of controlling the volumes and osmolalities of the body fluid compartments (see Chapter II). It is also evident from the results presented in Chapter IX and parti-
cularly from Table 6 and Table 7, that the intracellular volume and osmolality are indeed very well controlled in the closed loop system. The results indicate a very important characteristic of the system; a fluid load (especially a water load) is excreted before it can significantly affect the intracellular variables. Although this behavior is suggested by teleological considerations, there is no substantial experimental evidence to either support it or deny it. Obviously, if this is indeed the real behavior of the system, all the previous models which assumed the body fluids pooled into a single compartment, are incorrect.

It would be very interesting to evaluate the effectiveness of the system's control capabilities and the range and nature of the inputs and disturbances for which an acceptable compensation may be provided. To this end, various solutions may be infused in the system (or into the model) at different rates and the difference between input and output flows and concentrations may be observed during either transient states or steady states. The bigger the difference, the lower the control ability of the organism. Clearly, any research in this direction may lead to the identification of tests of renal function that might have considerable diagnostic importance.

A simulated experiment was run for the purpose of showing a possible method of further investigation. Sodium chloride solutions of variable concentration where infused intravenously at the constant rate of 7 ml/min. The urine flow and NaCl concentration are reported in Fig. 84 as function of the input concentration. These results, of
course, have been obtained with the drinking mechanism disabled.

Perfect compensation for both water and solutes would be indicated by results coincident with line A for the output flow and with line B for the output NaCl concentration. Model's results at three and seven hours after the beginning of the infusion are shown. It appears that the transient in output flow is practically completed after seven hours, at which time input and output flows are very close.

The transient in the output osmolality is much slower and it is not yet completed after seven hours. According to the model input sodium chloride solutions in the range of 70 to 200 mosm/l may be reasonably well compensated while solutions of lower or higher osmolality will induce a continuous decrease or increase in body salt content. Almost exact compensation is attained for input concentrations in the range of 100 to 125 mosm/l. (The plasma NaCl concentration is normally 150 mosm/l).

These results seem to indicate that volume control is prevalent over osmolality control, that is, the model can excrete a urine flow sufficient to maintain a stable body fluid volume but not always sufficiently diluted or concentrated as required to maintain body osmolality constant despite the input disturbance. The implications of this type of simulation in the study of the diluting and concentrating power of the kidney are obvious.

The open circles in Fig. 84 indicate experimental results obtained by Wolf in 1947 after 3 hours of infusion in man (7 ml/min). The agreement with the model's results is not satisfactory, however
Fig. 84 Urine, flow and NaCl concentration as functions of input (oral) NaCl concentrations 3 and 7 hours after the beginning of continuous oral ingestion of 7 ml/min of solution.

○ = concentration data from Wolf (1947)
more experiments should be made before a conclusion is reached regarding the validity or the necessary modifications of the model. These experiments and the relative simulations should be repeated with different solutes (e.g., urea) and at different flows to obtain the maximal information concerning the system's control capabilities as functions of the solute used, of the input flow and concentration.

Another approach to the analysis of the system is the identification of describing function relating two or more variables.

A third approach is the identification of small signal linear models, valid in the neighborhood of a working point, and the description of control characteristics (e.g., open loop and closed loop gain, Bode plots, stability limits, etc.) as functions of the working point.

For the purpose of describing this approach a continuous sinusoidal oral input flow has been applied to the model in initial hydropenic state. The amplitude of the flow variations was ±0.5 ml/min around the average value of 5 ml/min; the frequencies were 0.5 and 1 cycle per hour. The results are shown in Figs. 85 and 86 and in Table 8 and of course have been obtained with the drinking mechanism disabled. The response describes the closed loop behavior of the system at the chosen frequencies. Because of solute losses the average value of plasma and intracellular osmolalities and of the urine flow are slowly decreasing. The first four hours of the simulation are not presented because they include transients due to the onset of the sinusoidal stress. Although it may be debatable whether or not an input flow oscillating between 0 and 10 ml/min can be considered sufficiently small for
Intracellular osmolality (mosm/l)

Urine flow (ml/min)

Fig. 85 Response to sinusoidal water input flow of frequency 0.5 cycles/hour
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma osmolality (mosm/l)</td>
<td>286</td>
</tr>
<tr>
<td>Intracellular osmolality (mosm/l)</td>
<td>289</td>
</tr>
<tr>
<td>Input flow (ml/min)</td>
<td>2.5</td>
</tr>
<tr>
<td>Urine flow (ml/min)</td>
<td>5.0</td>
</tr>
</tbody>
</table>
Intracellular osmolality (mosm/l)

Urine flow (ml/min)

Fig. 86 Response to sinusoidal water input flow of frequency
1 cycles/hour
linearization it is clear that the frequency analysis of the system for various types of input solutions may be very interesting from both the control point of view and the physiological point of view.

Table 8

Magnitude and Phase Response to Sinusoidal Oral Water Input Flow

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Plasma Osmolality (mosm/l)</th>
<th>Urine flow (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amplitude</td>
<td>Phase</td>
</tr>
<tr>
<td>0.5 c/h</td>
<td>1.25</td>
<td>90°</td>
</tr>
<tr>
<td>1.0 c/h</td>
<td>0.5</td>
<td>135°</td>
</tr>
</tbody>
</table>

A fourth approach to the analysis of the system through this model is the sensitivity analysis of the response to variations of various quantities and coefficients. This analysis may also have considerable diagnostic importance. As an example Fig. 87 shows the response of the model to the injection of one liter of water in the following conditions:

a) normal
b) constant GFR = 125 ml/min
c) constant ADH concentration in the plasma = 4 mU/l
d) ADH clearance rate twice the normal value. (normal clearance= 0.35 l/min)

These results describe the closed loop behavior of the system without the thirst control mechanism. It is evident from Fig. 87 that the variation of ADH is the most important factor in controlling plasma osmolality in the presence of a water load. It is also evident however
Fig. 87 Response to the ingestion of 1 l of water in 10 minutes in various simulated situations

- normal
- Plasma ADH concentration = 4 mU/l = constant
- Glomerular filtration rate = 125 ml/min = constant
- ADH clearance = 0.7 l/min
that some degree of control is maintained in absence of ADH variations. A larger clearance of ADH appears to result in a better control of plasma osmolality, in a slightly smaller loss of salt during the diuresis and in a faster excretion of the water load. However, in this case the body should synthesize twice the normal amount of ADH in order to maintain the normal ADH plasma concentration. It is possible that an optimal compromise between osmolality control and ADH synthesis energy requirements has developed during the evolutionary process. This model can be used to investigate the degree of optimization that the system has reached.

Fig. 88 shows the open loop response of the model to the oral injection of 0.5 l of water in 5 min. The open loop condition is obtained by assuming that all the output flows (urinary, respiratory and skin losses) of water and solutes are reinfused into the organism (or not subtracted from it) and that only the excretion of metabolic solutes is allowed (0.28 mosm/min).

It is evident from the results that an open loop condition and a waiting period of at least two hours are necessary for the experimental estimate of the effect of fluid injection upon the plasma ADH concentration while a longer waiting period is needed in the case of aldosterone. The results show that a maintained water load of only 0.5 l (1.2 % of the total body water) increases the urine flow by over 12 times, an observation which indicates the high low frequency sensitivity of the open loop system to variations of the controlled variables.
**Osmolality (mosm/l)**

**Plasma volume (l)**

**Interstitial volume (l)**

**Intracellular volume (l)**

**Plasma ADH concentration (mU/l)**
Interstitial volume (l)

Intracellular volume (l)

Plasma ADH concentration (mU/l)

Plasma aldosterone concentration (ng/l)

Glomerular filtration rate (ml/min)

Urine flow (ml/min)
Fig. 88 Open loop response to the ingestion of 0.5 l of water in 5 minutes.
It is felt that a more detailed analysis of the properties of the model is not proper at this time. Many of the chosen relationships between variables and parameter values are arbitrary, some of the predictions of the model do not agree quantitatively with experimental findings, the data for the verification of the model are insufficient and it is practically impossible to establish the exact range of validity of the model until further and better experiments are performed. In such conditions the deeper investigation of the system with the help of this model and the concurrent development and improvement of the model itself are necessary so that a subsequent detailed analysis of the model will indeed reflect and indicate the properties of the system.
Bibliography (Chapter X)


SUMMARY, CONCLUSIONS, DIRECTIONS FOR FURTHER RESEARCH AND APPLICATIONS

XI.1 Summary

A model of the body fluid regulation system has been developed. The model simulates the three main body functions related to fluid handling: absorption, distribution, excretion. A first attempt of the simulation of a fourth function, the control of fluid intake, is also presented. The simulation of these functions will now be summarized.

The stomach function is simulated by a single pole low pass filter whose time constant depends upon the osmolality of the fluid drunk. The small intestine function is simulated by two nonlinear differential equations which describe the movement of water and sodium chloride across the intestinal wall. These two substances are the only ones acceptable for ingestion; a larger range of substances is acceptable for intravenous infusion.

Three body fluid compartments are considered: the plasma, the interstitial space and the intracellular space. The latter includes the blood cells. The conditions for equilibrium of the three compartments are identified and the equations describing them are used to compute the initial state of the system as a function of the total
body amount of each substance. The substances considered are water, sodium, chloride, potassium, urea, proteins and all the other substances pooled together. Input or output of fluid alters the initial state. The changing state of the three fluid compartments is described by over 30 variables which are computed in time increments of 1 minute.

The renal function is studied by means of the simulation of the nephron which includes the analysis of glomerular filtration, the approximate description of proximal tubular function and the rather detailed description of the loop of Henle, distal tubule and collecting duct. The renal simulation is limited to the handling of sodium chloride and urea and it describes the behavior of these substances in the renal medullary interstitial space as well as in the nephron. The time increment for the calculation of the renal state is 3 seconds while the length increment for the calculation of flows and concentrations along the nephron is 10% the length of the collecting duct and of the folded loop of Henle.

The control of renal function exercised by the ADH and aldosterone hormonal loops is simulated. Plasma osmolality and blood volume are taken as the stimuli for ADH secretion while plasma sodium concentration and blood volume are assumed to be the stimuli for aldosterone secretion. The model simulates the dynamics of these hormones as well as their effect upon the renal tubules.

The overall simulation is completed by the consideration of the insensible water losses and of the metabolic production of water and urea and by the subtraction of all the losses from the plasma compartment after each time increment.
A number of simulations is reported as a sample of the model's behavior; they include the response to ingestion of water and sodium chloride solutions, to the infusion of sodium chloride, urea and protein solutions, to dehydration, to plasma infusion and withdrawal.

The onset of certain pathological states is also simulated. Some of the model's results are compared with physiological data available from the literature and experiments for a more extensive verification of the model are suggested. A critique of certain experimental methods and data is presented.

In an attempt to extend the simulation period from the range of horus to the range of days, the thirst control mechanism is simulated by means of a switching system sensing plasma osmolality and blood volume. The response of both a normal and diseased organism to the spontaneous drinking of various solutions is simulated. The physiological and control aspects of the model's results are discussed and the guidelines for further work in the application and development of the model are outlined.

XI.2 Contributions and Conclusions

a) Main Contributions

The main objective of this research was the development of a model to be used as a tool for the investigation of the body fluid regulation system and for the interpretation of experimental results. It is felt that this objective has been reached and that this model
has simulation capabilities and versatility that were not previously available. The model can be used to test hypotheses and to estimate parameter values as indicated in Chapter I. It can also be used as a teaching tool and as a tool for the investigation of the control properties of the system as well as for the planning of experiments. This is the first and most important contribution of this study.

A second contribution is that of having collected and analyzed both qualitatively and quantitatively a large amount of experimental evidence and data (often controversial) concerned with the system in question. From this analysis it appears that in many instances very criticizable or even invalid experimental methods have been used, and that often the experimental results are presented in a very unsatisfactory way. (See Section 2, Chapter VII and Section 4 of Chapter IX). It has been found that the experimenter often lacks awareness of basic control concepts such as those of transient and steady state, of open and closed loop and so on, and that the decisions about what experiment should be run, what to measure, how often and for how long, to measure it and how to present the data have often been non-optimal.

A third contribution is that of having indicated a number of simple experiments that can be used to verify the validity of the model and to investigate the system. The experimental data necessary to the physiologist and pathologist are often quite different from the data necessary for the testing of a model. In general the latter data should describe in detail both the transient and steady state response of a large number of variables to specific inputs while the former may
just provide indications describing the qualitative behavior of a few
variables in a given range of cases. The lack of good experimental data
suitable for model testing has been indicated in many instances in this
work. It is hoped that this research can be continued with the
cooperation of medical scientists so that a more extensive analysis of
the literature and the proper experiments can be performed and the
correct information obtained.

A fourth contribution is the development and presentation of the
model in a form that allows a relatively easy control system analysis.
The background of this analysis has been presented in Chapter X and it
allows the determination of small signal linear models and of characteri-
stics and transfer functions between two or more variables. Further
investigation will permit the discussion of the stability boundaries
of the system and of its control capabilities.

Although these are the major contributions of this work they are
not the only ones. In the process of developing the model, through the
use of the model and through the examinations of the results a number of
observations have been made and conclusion have been reached. These
observations and conclusions may be of significant value in settling
controversies and in clarifying uncertain physiological aspects of the
system. Again their value can only be established with the cooperation
of physiologists and pathologists. These "secondary" contributions and
conclusions will be described in the next subsection.

b) Secondary Contributions and Conclusions

The most important observations and conclusions are summarized
in this subsection in the order in which they have been reached.

The results presented in Figs. 10 and 12 of Chapter III allow one to observe that during the process of absorption of sodium chloride solutions from the intestine the osmolality of the luminal fluid approaches isotonicy. Although this has been a known physiological fact no quantitative description and modeling of this phenomenon has been available previous to this work, to the knowledge of this writer. Similarly, the buffer function of the stomach, especially with regard to hypertonic solutions, has been long known to physiologists only on a qualitative basis. Fig.13 in Chapter III provides a quantitative description of this function.

A steady state and dynamic model of the exchange among the body fluid compartments has been presented in Chapter IV and V. Although sections of this model were previously available, no overall model had been developed yet. The conclusions of De Land and Bradham concerning the irrelevancy of Starling forces (specifically oncotic forces) in the equilibrium across the cellular membrane have been verified. A simple analog model for the study of interstitial pressure has been presented, (Fig.19, Chapter IV) to explain the possibility of negative interstitial pressure and to contribute to the solution of the controversy on this subject. The validity of a simplified approach to the dynamics of exchange across capillary and cell membranes has been verified by satisfactory comparison of simulated and experimental results (Figs. 32 and 33, Chapter V). This approach allowed the determination of overall body average parameters of these membranes (Fig.28, Chapter V).
It is believed that the model of nephron function, and especially the model of the countercurrent mechanism (Chapter VI) represents a contribution to the investigation of the renal function and a very powerful tool for the testing of hypotheses, some of which have been discussed in Section 4b of Chapter VI. This particular section of the model does not rely on limiting assumptions used in previous models and permits the examination and description of the development and of the changes of renal medullary concentration profiles. The nephron model, together with the model of aldosterone and antidiuretic hormone dynamics allows a detailed investigation of practically all the factors involved in urine formation such as changes in glomerular filtrate rate and concentrations, changes of tubular active transport rates, changes of medullary concentrations, changes of hormonal control factors, changes of medullary blood flow.

This model has also permitted the quantitative estimate of average nephron parameters (Table 5 Chapter VI), the quantitative evaluation of certain hypotheses and the analysis of the effect and importance of variations of certain variables upon the process of urine formation (Figs. 44 and 45 Chapter VI). No other model with the same capability is known to this author. In particular it has been observed that variations of glomerular filtration rates within the range of experimental error have considerable effect upon the water and solutes output flows.

The data and the discussion as well as the model results presented in section 4 of Chapter VII may contribute to the solution of the controversy concerning the ADH binding to proteins and the ADH clearance.
and "half life". Also, the analysis of experimental data presented in Chapter VIII may be helpful in the study of aldosterone dynamics.

The results presented in Chapter IX show that the model's accuracy is satisfactory in the simulation of the response to hypotonic and hypertonic input solutions. Some improvement is needed to better the response to highly hypertonic conditions (in the range of ten times the plasma concentration) Further physiological experimentation is necessary to permit a more exact definition of the validity range of the model. The responses to water ingestion and to dehydration may help to solve the controversy concerning the variability of urine osmolality (Chapter IX Section 3).

The simulation of diseased states (Chapter IX and X) may help in the understanding of such states. As an example, the results presented in Figs. 79 and 80 allow one to conclude that, in the absence of food either water or isotonic saline drinking leads the diabetic into very abnormal states while a hypotonic saline solution (70 mosm/l) permits a much better control of body volumes and osmolalities.

The model of the drinking system and the results presented in Chapter X allow an interesting investigation of the effect of varying the drinking decision criteria upon the control of the body fluids in various healthy and diseased states. The results presented in Chapter X also allow one to conclude that, according to the model, the infusion of sodium chloride solutions having concentration in the neighborhood of 100 to 125 mosm/l can be compensated by the renal system while more diluted or concentrated solutions infused for long time result in salt depletion or accumulation.
It can also be concluded from the results of Chapter X that a better osmolality control is achieved by means of a higher ADH clearance at the expense of a higher rate of ADH synthesis.

As previously mentioned, the main purpose of this research was the development of a model rather than its use. It is obvious that a more extensive use of this model in cooperation with the medical scientists will permit to reach a much larger number of conclusions concerning the water regulation system. It is also probable that such use of the model will allow the identification of significant diagnostic tests and will permit the quantitative interpretation of symptoms and laboratory data therefore bringing substantial contributions to the medical field as well as to the field of physiological and pathological investigation.

XI.3 Directions for Further Research

Further research can be conducted in three major directions:

a) Further improvement of the model
b) Physiological experimentation, verification and application of the model.
c) Investigation of the model from a control theory point of view.

These three directions will now be analyzed individually

a) Further improvement of the model

Some improvements of this model do not present major difficulties but only require some extension of the mathematical techniques already developed. Among these improvements are:
a) The consideration of the blood cells as a fourth body fluid compartment.
b) The consideration of the bicarbonate ion as an individual substance in the body fluids. This would also be a preliminary work for the investigation of acid-base balance.
c) The more detailed analysis of renal tubular function with particular regard to the function of the peritubular protein concentration.
d) The more accurate digital approximation of the renal medulla equation.
e) The consideration of potassium and bicarbonate ions in the simulation of renal function.
f) The consideration of the effect of potassium concentration in controlling tubular potassium secretion.

These improvements, which may require 3 to 5 months of further work, will also require the use of a computer faster than the DEC-PDP9. The requirement for computational speed may be reduced, however, if one algorithm used during fast renal medullary changes while another is used during very slow transients. Over 90% of the computational time is now due to the simulation of renal function.

b) Physiological experimentation, verification and application of the model.

As it was pointed out in Chapter IX, the physiological evidence found in the literature is totally insufficient for a thorough verification of the model's validity. The proper physiological data can be obtained partially through a more extensive analysis of the literature but mostly through well planned and well performed experiments on either human subjects or animals. The model can be a very important tool in the
organization of such experiments. The interaction of model prediction and of experimental results will lead to the improvement of the model and to further knowledge. As an example, facts that need verification are the velocity of fluid absorption from the gut, the velocity of osmotic equilibration between extracellular and intracellular compartments, the presence of ADH in interstitial fluid collected with Guyton's capsules, the sharp peaks of urea excretion by a normal man drinking water, etc.

c) Control aspects of the model

The complexity and nonlinearity of the model, as well as its multivariable nature provide material for a very challenging research of the control and stability characteristics of the model. Various approaches are available for such research.

Optimal linear models may be found for small signal variations around fixed working points. The phase plane analysis of certain variables may lead to interesting conclusions. The study of the model as a self optimizing system may also be very rewarding. Other aspects that may be investigated are the control of the amplitude and frequency of the limit cycles which are generated by the drinking control mechanism, the conditions for such limit cycles to exist, start or decay, the effect of infused solutions upon such cycles and so on.

The identification of a "normal" and an "abnormal" region of the parameter space may also be possible and diagnostically very important. A very general background for such analysis has been presented in Chapter X
It is the conviction of this writer that the control aspects of the model should be investigated only after a sufficient development and verification of the model itself. At the present time the degree of arbitrariness of the model is such that a detailed control system analysis is unwarranted and may lead to incorrect conclusions.

In conclusion, it is believed that this study is a good basis for more extensive physiological and engineering research and that both these sciences can benefit from the development and application of this model for a deeper understanding of the control of the human body internal environment.
APPENDIXES
Appendix A. Solution of the equations describing water and salt transfer across the intestinal wall.

Equations 9, 10, and 11 can be rewritten as Eqs. A1 and A2.

\[
\text{Eq. A1} \quad y' = C_1 + C_2 \frac{z(t)}{y(t)} = f(t, y, z)
\]

\[
\text{Eq. A2} \quad z' = C_3 + C_4 \frac{z(t)}{y(t)} = g(t, y, z)
\]

where \( y = V_1 \) and \( z = C_{01} \). Eqs. A1 and A2 form a system of nonlinear differential equations. Given a set of initial conditions for \( y \) and \( z \), the system can be solved with the following iterative algorithm (Runge-Kutta method);

\[
\text{Eq. A3} \quad y_{n+1} = y_n + \frac{1}{6} (k_1 + 2k_2 + 2k_3 + k_4) \Delta t
\]

\[
\text{Eq. A4} \quad z_{n+1} = z_n + \frac{1}{6} (l_1 + 2l_2 + 2l_3 + l_4) \Delta t
\]

where:

\[
k_1 = \Delta t \cdot f(t_n, y_n, z_n)
\]

\[
k_2 = \Delta t \cdot f(t_n + \frac{\Delta t}{2}, y_n + \frac{k_1}{2}, z_n + \frac{l_1}{2})
\]

\[
k_3 = \Delta t \cdot f(t_n + \frac{\Delta t}{2}, y_n + \frac{k_1}{2}, z_n + \frac{l_1}{2})
\]

\[
k_4 = \Delta t \cdot f(t_n + \Delta t, y_n + k_3, z_n + l_3)
\]

\[
l_1 = \Delta t \cdot g(t_n, y_n, z_n)
\]

\[
l_2 = \Delta t \cdot g(t_n + \frac{\Delta t}{2}, y_n + \frac{k_1}{2}, z_n + \frac{l_1}{2})
\]

\[
l_3 = \Delta t \cdot g(t_n + \frac{\Delta t}{2}, y_n + \frac{k_1}{2}, z_n + \frac{l_1}{2})
\]

\[
l_4 = \Delta t \cdot g(t_n + \Delta t, y_n + k_3, z_n + l_3)
\]
A time interval $\Delta t = 1$ min. provides a sufficient accuracy for this iteration. The process is halted when the volumes of fluid left in the stomach and in the intestine are both less than 1 ml. This method of solution, which is easily extended to systems of more than two equations will be often used in other sections of this study.

The first order nonlinear differential equation representing the stomach function is solved according to the Euler's iteration with a 1 min. incremental time.

$$\text{Eq. A5} \quad x_{n+1} = x_n + \Delta t \frac{x_n}{r}$$

where $r$ is previously computed according to Eqs. 2 and 3 and $x$ is the volume of the stomach content. Either the initial value of $x$ or the input flow (to be added to the right side of Eq. A5) must be given. The program used for the simulation of the stomach and intestine function was identical to the subroutine SIS (Stomach and Intestine Simulation) listed in Appendix D except for the input variables which were read from a teletype instead of being obtained from the main program.
Appendix B (Determination of IC-EC steady state).

Solution of Eq.23.

Eq.23 is reported below for convenience as Eq.B1. The values of the coefficients, for the $K_i$'s and $J_i$'s given in Table 2, are also given below ($\bar{X}$ is replaced by $X$).

**Eq.B1** \[ f(X) = A_6 X^6 + A_5 X^4 + A_4 X^3 + A_3 X^2 + A_2 X + A_1 = 0 \]

where:

- $A_6 = 88.4497 \cdot h$
- $A_5 = 88.4497 \cdot q + 95.2438 \cdot b_1 - 2.6012 \cdot b_2 + 91.7253 \cdot b_3 - 30.4414 \cdot b_4 - 199.86 \cdot h \cdot b$
- $A_4 = \bar{b} \cdot (-199.8669 \cdot q - 222.5667 \cdot b_4 + 3.2 \cdot b_2 - 210.6651 \cdot b_3 + 27.8707 \cdot b_4 + 98.72 \cdot h \cdot b)$
- $A_3 = \bar{b}^2 \cdot (98.7210 \cdot q + 123.4320 \cdot b_4 + 0.3909 \cdot b_2 + 110.1778 \cdot b_3 + 3.4834 \cdot b_4 + 13.3 \cdot h \cdot b)$
- $A_2 = \bar{b}^3 \cdot (13.3476 \cdot q + 4.8810 \cdot b_4 + 0.00995 \cdot b_2 + 9.7620 \cdot b_3 + 0.08926 \cdot b_4 + 0.3485 \cdot h \cdot b)$
- $A_1 = 0.3485 \cdot q \cdot \bar{b}^4$
- $h = \frac{b_5 + b_6}{b} - 1$
- $\bar{b} = \sum_{i=1}^{c} b_1 + q + q'$

where all the $b_1$'s are given as well as $q$ and $q'$.

It has been shown that the polynomial of Eq.B1 has a single real root in the interval 0 to $\bar{b}$. Since $\bar{b}$ is a large number, a procedure to identify approximately the location of the root may speed up the convergence of the successive iteration processes. The interval 0 to $\bar{b}$ is therefore divided in 20 sub intervals and the one containing the root is located.

The lower boundary of such sub interval is then used as initial approximation for the Newton method of solution. The iteration process
is described in Eq. B2.

\[ X_{i+1} = X_i - \frac{f(X_i)}{f'(X_i)} = X_i - \Delta X \]

Since Eq. B1 is a polynomial, the nested multiplication algorithm may be used to find \( f'(X_i) \) (Conte, 1965).

The iteration of Eq. B2 is interrupted when \( \Delta X \) is sufficiently small (0.1 mosm). The simultaneous condition \( f(X) < \epsilon \) often required, is not applied here because of the high values of \( f(X) \) and \( f'(X) \) in the neighborhood of the root and because the condition \( \Delta X < 0.1 \) provides sufficient accuracy in this case.
Appendix C  (Determination of IV-IS steady state).

Solution of the system of Eqs.33 to 38.

The system of Eqs.33 to 38 is repeated below for convenience.

\[
\begin{align*}
\text{Eq. C1} & : K_4 P_a + K_5 P_y + (K_4 + K_5)(\Pi_{pt} - \Pi_{pp} - P_t) + F_p - F_1 = 0 \\
\text{Eq. C2} & : F_p C_{pp} - F_1 C_{pi} = 0 \\
\text{Eq. C3} & : F_p = K_1 (P_y - P_t) \\
\text{Eq. C4} & : \Pi_{pp} = f_1(C_{pp}) \quad \text{(see Fig.20)} \\
\text{Eq. C5} & : \Pi_{pi} = f_1(C_{pi}) \quad \text{(see Fig.20)} \\
\text{Eq. C6} & : F_1 = f_2(P_t) \quad \text{(see Fig.20)}
\end{align*}
\]

Substitution of Eqs. C3, C4, C5, and C6 into Eqs. C1 and C2 yields a system in two equations and two unknowns, the unknowns being $P_t$ and $C_{pi}$, the system may be rewritten as:

\[
\begin{align*}
\text{Eq. C7} & : F(X,Y) = 0 \\
\text{Eq. C8} & : G(X,Y) = 0
\end{align*}
\]

where $X = P_t$, $Y = C_{pi}$

This system may be solved with the iteration algorithm of Eqs C9 and C10.
\[ X_{i+1} = X_i - \frac{F \cdot G'_y - G \cdot F'_y}{F'_x \cdot G'_y - G'_x \cdot F'_y} = X_i - \Delta X \]

\[ Y_{i+1} = Y_i - \frac{G \cdot F'_x - F \cdot G'_x}{F'_x \cdot G'_y - G'_x \cdot F'_y} = Y_i - \Delta Y \]

where the right term of each equation is computed for \( X = X_i, Y = Y_i \) and where the superscript means first partial derivative with respect to the variable in the subscript.

The iteration of Eqs. C9 and C10 is halted when \( \Delta X, \Delta Y, F(X,Y) \) and \( G(X,Y) < 0.01 \).

Other quantities such as \( \Pi_{p1} \) and \( V_{IS} \) are then computed from the solution of the system. The initial values \( X \) and \( Y \) for the iteration of Eqs. C9 and C10 are chosen in the neighborhood of the normal values of \( P_t \) and \( C_{pi} \).

It may be observed that the functions \( F(X,Y), G(X,Y) \) and their derivatives may be modified during the iteration process because of the piecewise linear dependence of \( F_1 \) upon \( P_t \).
Appendix D. Program listing.

Main Program.

BFSP: Body Fluid Simulation Program.
It includes section relative to the input and output of data, to the dynamics of intercompartmental exchange, to the hormonal control of renal function and to the drinking mechanism.

Subroutines.

SIS: Stomach and Intestine Simulation.
It solves the model of the gastrointestinal tract. (see Chapter III)

ECIC: Extracellular-Intracellular equilibrium simulation.
It computes the initial equilibrium state between intracellular and extracellular compartments. *(see Chapter IV)*

IVIS: Intravascular-Interstitial equilibrium simulation.
It computes the initial equilibrium state between plasma and interstitial compartments.

PLIS: Plasma - interstitial compartment dynamics.
It computes the the PL-IS flow of material due to osmotic unbalance.

RENS: Renal System Simulation.
It computes the nephron state as a function of time.

The complete listing of the above program and subroutines, in FORTRAN IV, follows.
C BODY FLUID SIMULATION PROGRAM, BFSP4, TEST WITH ECIC, IVIS AND PLIS,
C ADH AND ALLOSTERICAL INCLUDED, REN S AND SIS INCLUDED,
C CONTINUOUS DYNAMICS, JULY 4, R. HERLETI.
C
C SWITCH OPTIONS.
C 0 = UPI: PREG NEFL STATE AT END OF OBS. TIME.
C 1 = UPI: BOX WHITE RENAL STATE IN PRINTOUT.
C 2 = UPI: STOP AT THE END OF THE TIME LOOP, (PAUSE 4)
C 3 = UPI: USE PREVIOUS STATE AS INITIAL STATE.
C 4 = UPI: DIAL INPUT, WATER ON NAFL SOLUTIONS ONLY,)
C 5 = UPI: OPEN LOOP OFF, (IEMMA, NO URINE OUT,)
C 6 = UPI: GU TO P:\J AT THE END OF THE LOOP
C 7 = UPI: AUTOMATIC DRINKING
C LOGICAL INH, LIM, L, LX
REAL K007S, KUVG, LDC, NUL, IL
REAL K1, K2, K3, K4, K5, K6, K7, K8, K9, K10, K11
INTEGER T0, T1, T2, T3, T4, N, N0
DIMENSION K(T), X(T), CP(T), IT (3), HI (4), HN (24)
PARAMETER (X0=0.0, X1=0.0161, X2=0.219, X3=0.5259, DOB(6), ALC (16))
C COMMON L15, L6, L1: ECIC, L5 TO L6: IVIS
C L7 TO L16: FLUSH L1 TO L14: REDS; L15: SIS,
COMMON /L1, K, IF, P, H, L1/4, L1/1, US9, US10, SOUT
COMMON /L1/4, K1, K2, K3, K4, K5, K6, K7, K8, K9, K10, K11
COMMON /L1/4, K1, K2, K3, K4, K5, K6, K7, K8, K9, K10, K11
COMMON /L1/4, K1, K2, K3, K4, K5, K6, K7, K8, K9, K10, K11
COMMON /L1/4, K1, K2, K3, K4, K5, K6, K7, K8, K9, K10, K11
C EQUATIONS (L1, L2, L3, L4, L5, L6, L7, L8, L9, L10, L11, L12, L13, L14, L15, L16)
C DATA RELATIVE TO IS-I C BOUNDARY AND TO G.I., PRESS., - CONC. RELATION,
C DATA A=1.4, B1=2.0, B2=1.1, C1=4.0, C2=1.0, D1=1.0, D2=1.0, D3=1.0,
C DATA C1=1.0, C2=3.0, C3=1.0, C4=1.0, C5=1.0, C6=1.0,
C DATA 1/3=1.0, 1/4=1.0, 1/5=1.0, 1/6=1.0,
C DATA 1/7=1.0, 1/8=1.0, 1/9=1.0, 1/10=1.0,
C DATA C1=1.0, C2=3.0, C3=1.0, C4=1.0, C5=1.0, C6=1.0,
C DATA 1/3=1.0, 1/4=1.0, 1/5=1.0,
C DATA 1/7=1.0, 1/8=1.0, 1/9=1.0, 1/10=1.0,
C DATA C1=1.0, C2=3.0, C3=1.0, C4=1.0, C5=1.0, C6=1.0,
C DATA 1/3=1.0, 1/4=1.0, 1/5=1.0,
C DATA 1/7=1.0, 1/8=1.0, 1/9=1.0, 1/10=1.0,
C DATA C1=1.0, C2=3.0, C3=1.0, C4=1.0, C5=1.0, C6=1.0,
C DATA 1/3=1.0, 1/4=1.0, 1/5=1.0,
C DATA 1/7=1.0, 1/8=1.0, 1/9=1.0, 1/10=1.0,
C DATA C1=1.0, C2=3.0, C3=1.0, C4=1.0, C5=1.0, C6=1.0,
C DATA 1/3=1.0, 1/4=1.0, 1/5=1.0,
C DATA 1/7=1.0, 1/8=1.0, 1/9=1.0, 1/10=1.0,
C DATA C1=1.0, C2=3.0, C3=1.0, C4=1.0, C5=1.0, C6=1.0,
C DATA 1/3=1.0, 1/4=1.0, 1/5=1.0,
C DATA 1/7=1.0, 1/8=1.0, 1/9=1.0, 1/10=1.0,
C DATA C1=1.0, C2=3.0, C3=1.0, C4=1.0, C5=1.0, C6=1.0,
C DATA 1/3=1.0, 1/4=1.0, 1/5=1.0,
C DATA 1/7=1.0, 1/8=1.0, 1/9=1.0, 1/10=1.0,
C DATA C1=1.0, C2=3.0, C3=1.0, C4=1.0, C5=1.0, C6=1.0,
C DATA 1/3=1.0, 1/4=1.0, 1/5=1.0,
C DATA 1/7=1.0, 1/8=1.0, 1/9=1.0, 1/10=1.0,
C DATA C1=1.0, C2=3.0, C3=1.0, C4=1.0, C5=1.0, C6=1.0,
C DATA 1/3=1.0, 1/4=1.0, 1/5=1.0,
C DATA 1/7=1.0, 1/8=1.0, 1/9=1.0, 1/10=1.0,
C DATA C1=1.0, C2=3.0, C3=1.0, C4=1.0, C5=1.0, C6=1.0,
C DATA 1/3=1.0, 1/4=1.0, 1/5=1.0,
C DATA 1/7=1.0, 1/8=1.0, 1/9=1.0, 1/10=1.0,
C DATA C1=1.0, C2=3.0, C3=1.0, C4=1.0, C5=1.0, C6=1.0,
C DATA 1/3=1.0, 1/4=1.0, 1/5=1.0,
C DATA 1/7=1.0, 1/8=1.0, 1/9=1.0, 1/10=1.0,
C DATA C1=1.0, C2=3.0, C3=1.0, C4=1.0, C5=1.0, C6=1.0,
C DATA 1/3=1.0, 1/4=1.0, 1/5=1.0,
C DATA 1/7=1.0, 1/8=1.0, 1/9=1.0, 1/10=1.0,
C DATA C1=1.0, C2=3.0, C3=1.0, C4=1.0, C5=1.0, C6=1.0,
DATA INPUT SECTION,

WHITE(4,114)

FORMAT(2:13:MEND, SET SHITCHES.)
READ(4,111) (NM(I), I=1,24)

WHITE(4,114)

FORMAT(2:13:MEND, PRINT INT. N. OF INPUTS AND INPUT TYPE)
CALL FFI (1,111,FTY,ITYPE)

C ITYPE = 1 FOR SELECTION, = 2 FOR INFUSION.

C 0T=25, TIME, />PRINT INT. N. OF INPUTS, IP=INDEX FOR PRINT. 

IF (1SENS(3)) GO TO 45

WHITE(4,114)

FORMAT(2:13:MEND, PRINT INT. N. OF INPUTS, IP=INDEX FOR PRINT. 

IF (ISENS(3)) GO TO 45

WHITE(4,114)

FORMAT(2:13:MEND, PRINT INT. N. OF INPUTS, IP=INDEX FOR PRINT. 

C CONTINUE

GO TO 2

WHITE(4,114)

FORMAT(2:13:MEND, PRINT INT. N. OF INPUTS, IP=INDEX FOR PRINT. 

C 34

WHITE(4,114)

FORMAT(2:13:MEND, PRINT INT. N. OF INPUTS, IP=INDEX FOR PRINT. 

C 123

WHITE(4,114)

FORMAT(2:13:MEND, PRINT INT. N. OF INPUTS, IP=INDEX FOR PRINT. 

C 17

WHITE(4,114)

FORMAT(2:13:MEND, PRINT INT. N. OF INPUTS, IP=INDEX FOR PRINT. 

C 100
COMPUTE INITIAL EQUILIBRIUM STATE.

ROUTINE TO OUTPUT TOTAL AMOUNTS OF WATER AND SOLUTES.

SUBROUTINE EC: OUTPUT AMOUNTS OF WATER AND SOLUTES IN STEADY STATE.

OUTLINES:
1. INPUT: PA/PV/CP, OUTPUT: CPI/PT.

COMM: INITIAL STATE.

C SUBROUTINE EC: OUTPUT AMOUNTS OF WATER AND SOLUTES.

C OUTLINES:
1. INPUT: PA/PV/CP, OUTPUT: CPI/PT.

C COMPUTE INITIAL EQUILIBRIUM STATE.

C SUBROUTINE EC: OUTPUT AMOUNTS OF WATER AND SOLUTES.
C WRITE OUT INITIAL STATE.
WRITE(6,1) (Cd,1,15),1c,pc
WRITE(6,1) ((p(1),1=1,5),tcp,pcp
WRITE(6,17) pa,ps,cpp,pt,cp,v1,v2
WRITE(6,1) Gf,ah,aci
CALL Ffi5
MINE=1
WHITE(6,2)
WRITE(6,2)
105 FORMAT(2x,4HGH=,F7.2,2X,5HPADH=,F7.2,2X,5HPADL=,F7.2,2/
106 FORMAT(4X,12H IC HSM/LT=,A8,F7.2/
52 PAUSE 2
C MAIN LOOP STARTS HERE
C
DO 5 I=1,7
IF(ISEQ(7)) GO TO 65
GO TO 51
C TO DRIVE OR DT IC OR IC. I=TS IS THE QUESTION.
60 IF(TC,GT,154,CF,CM,LT,125) GO TO 62
EX=.FALSE.
GO TO 63
62 EX=.TRUE.
63 IF(SY,GT,2,GH,LY,GT,2) GO TO 64
GIN=.FALSE.
GO TO 65
64 GIN=.TRUE.
65 IF(E=CM,GT,47,GT,11) GO TO 66
DO=EX.
IF(TC,LT,154,GM,CM,LT,125) GO=.TRUE.
IF(CE) GO TO 66
GO TO 26
66 WRITE(6,126) 1
126 FORMAT(1HMAIN AT 14/)
GO TO 32
61 IF(1,EQ,11,LT,11(1)) GO TO 26
C FROM here TO 47 \INPUT SECTION.
6D 1=1,1
IF(I,EQ,11(1)) GO TO 15
6 CONTINUE
25 DO 10 I=1,6
16 DO=EX
DO=EX
IF(I,EQ,5) GO TO 47
GO TO 51
15 IF(I,EQ,5) GO TO 32
WRITE(4,17)
107 FORMAT(2H U1 TO U6,DO,DDP *)
CALL FFI(1,48(1),48(2),04(3),GH(4),DB(5),DB(6),DO,DDP)
GO TO 10
32 CALL PH(111,V1(1),V2(1),GR(1),DB(4),DB(5),DB(6),DO,DDP)
C ORAL INPUT SECTION FOR WATER AND NACL ONLY.
10 IF ISENS.(4) GO TO 46
   GO TO 47
C THE DI(1) ARE NOW THE INPUTS IN THE STOMACH.
46 FI=DB(0)
   FI=2,0.91/0,34,16)
   GO TO 58
   FI=3,1,
51 CALL S(1)
   UR(6)=SF
   DR(1)=SF/2,
   O4(3)=SF/2.
C THE DI(1) ARE NOA INPUTS INTO PLASMA.
C SUB LOOP FOR ELECTROLYTE BALANCE.
C 47 IF (ISENS.(5)) GO TO 48
   OB(1)=OB(1) - SU0/2,
   OB(3)=OB(3) - SU0/2,
   OB(5)=OB(5) - U0T + MU
   OB(6)=OB(6) - LF - II
   GO / J=1,12
   GO 27 J=1,6
   27 OOU(1)=O0U(1)/HLB
   S23=V(1)
   O0 22 J=1,6
   S23(1)=.15,
22 SUBROUTINE PLASM INPUT V1, V2, C(1), W(1) ON S23(1) AND W23,
C OUTPUT V1, V2, C(1).
   CALL PLAS,
C EC - IC ELECTROLYTE FORCES.
C 23 TC=CPI*V.42E+I/2
   O0 23 I=1,5
   TC=TC*C(1)
   W233=TC-TCP)
   XP(1)=XP(1)-I/23
   TCP=(DP+CP)/XP(6)
   O0 9 I=1,5
   S23(1)=-2(1)*C(1)*621(1)*CP(1)
   XP(1)=XP(1)-S23(1)
   CP(1)=XP(1)/XP(6)
   TCP=TCP+CP(1)
   O0 26 J=1,6
   O0(1)=.1,
   CALL PLAS
   CONTINUE
C PLASMA - IS CDOTIC - HYDROSTATIC FORCES.
C 7 OTERMINE CPP, CPI, PT, FL, PV, PA, OPP, OPI.
      CPP=OPP+AC
      CPP=OPP/11
      CPI=OPP/V1
    IF(V2>CT>3.5) PT=(V2-48.6)/6.64
    IF(V2>LE>32.5) PT=(V2-15.3)/22.6
AC3*AC3 = (AC3:AC3) - AC3 / 3.

C

OUTPUT SECTION, (4FSP)

C

IP=IP+1
IF(IP,4E,5) GO TO 46
WRITE(4,112) T,CP(1), [I=1,5],TC,V1,V2,XP(6),GFR,AMS,ALS
WRITE(4,113) T,CP(1), [I=1,5],TCP,CPP,OP1,PT,PTO,AHT,AC1
112 FORMAT(15,5H EC,12F8.2)
113 FORMAT(15,5H IC,12F8.2/)  
40 IF(ISN,5(1)) GO TO 42
GO TO 41
42 IF(T,=,.CT) HP=1
C RENAL SYSTF 3.
41 GUCG(5)
D=IP+2,AC(3)
CALL RR,5
IF(IP,=,.T) WJ T) 55
"FF #1A...85
WRITE(4,125) JFF,OS4,SJUT,JOUT
125 FORMAT(15,4F5.2,1X,5HU0SH=F7,1,1X,5MSOUT=F6,3,1X,5HU0UT=.
"SF5,3//")
55 IF(IP,=,.T) IP=1
IF(ISN,5(6)) GO TO 56
IF(ISN,5(2)) GO TO 43
GO TO 5
43 PAUSE 4  
5 CONTINUE
GO TO 5F:
STOP  
END
SUBROUTINE SIS
C SIMULATION OF WATER AND NACl SOLUTION ABSORPTION
C FROM STOMACH AND INTESTINE.
REAL LG,LOC,LV
COMMON /L15/FL,FIO,SV,LY,WF,SEF,LOC
DATA C1/32.36E-03/,C2/-34.2E-06/,C3/-3.35/,C4/4.94E-03/
C FL = STOMACH INPUT FLOW WITH OSMOL, F10.
C SV,LV= STOMACH AND INTESTINAL LUMINAL VOLUMES, LO = LUM, OSMOLAL.
C COMPUTE STOMACH TAUS.
11 TAU = 20,6/ALOG(750.0/(0.702*F10 - 101.7))
GO TO 2
1 TAU = 20,6/ALOG(750.0/(0.677*F10 + 210.0))
2 SV = SV + FI
SEF = SV / TAU
SV = SV - SEF
LV = LY + SEF
LV = LOC + SEF*F10
C RUNGE-KUTTA METHOD
RK1 = C1*C2*LOC/LV
RKL = C3*C4*(LOC+RKL2)/2.0/(LV+RKL2/2.0)
RKL2 = C3*C4*(LOC+RKL2)/2.0/(LV+RKL2/2.0)
RK3 = C3*C4*(LOC+RKL2)/2.0/(LV+RKL2/2.0)
RK4 = C1*C2*(LOC+RKL2)/2.0/(LV+RKL2/2.0)
WF = (1.1/6.0)*(RK1+2.0*RL2+2.0*RL3+RL4)
SF = (1.0/6.0)*((HLT1+2.0*RL2+2.0*RL3+RL4)
IF (SF,GE,LOC) SF = LOC
IF (WF,GE,LY) WF = LV
LOC = LOC - SF
LV = LV - WF
IF (FLV,EQ.2.0,OR,LOC,EQ.0.0) GO TO 6
L0 = LOC/LV
6 IF (FLV,LE.1.0E-05,AND,SV,LE.1.0E-05) GO TO 15
RETURN
WRITE(6,51)
51 FORMAT(//21H ABSORPTION COMPLETE)
END
SUBROUTINE ECIC
C COMPUTES THE IC AND EC AMOUNTS OF EACH.
C FEB. 25, 1972 K. MERLETI
C GIVES THE TOTAL BODY AMOUNTS OF H2O AND ELECTROLYTES
C COMPUTES VOLUMES AND CONCENTRATIONS OF IC AND EC COMPARTMENTS,
C TAL H
DIMENSION X(1),A(1),B(1),CN(1),DX(1),PK(1),DXX(1)
COMMON /X1/,/X3/,UP/L3/UX/L4/XP
DATA RK(1),0.071422/RK(2)/35.5/RK(3)/.03571/RK(4)/3.9053/, 1NK(1)/.1/,
F(6)=.01, 2=0.1/6/19.7
C$K(0)=0
1
(*A=1.6
4*x+n*m + 1.1)
C COMPUTE POLY-EQUAL COEFFICIENTS,
A(6)=88.1477
A(5)=95.2436*B(1) - 2.0412*B(2) + 91.7253*B(3)
A(4)=195.4426*B(4) - 179.3629*B(3)
A(3)=242.5657*B(5) - 3.2*B(3) - 216.8651*B(3)
A(2)=137.2134*B(6) + 76.7212*B(3)
A(1)=63.4124*B(7) + 7.3939*B(2) + 113.1778*B(3)
A(0)=3.4231*B(8) + 14.3475*B(9)
A(1)=8.3313*B(10) + 2.02995*B(2) + 9.7628*B(3)
A(0)=6.2692*B(4) + 6.3495*B(5)
A(1)=5.2454*B(6)
C START SEARCH FOR ROOT BETWEEN A. J AND B. J
C LOCATE ROOT INTERVAL, EACH INTERVAL = BR/20, B
D=BR/20
X=A
D=1
POLY2=A(1)
POLY1=A(1)
C 2 I=2,6
C POLY1=POLY1 + A(1)*XB**(I-1)
C GO 3 J=1,6
XB=XB/2
D=1
C POLY2=POLY2 + A(1)*XB**(I-1)
C IF(POLY1<.LE.7.732J..POLY2.GE.-7.78J) GO TO 6
C POLY1=POLY2
POLY2=A(1)
C CONTINUE
WRITE(6,1,4)
100 FNUAT((1.-XG REAL ROOT FOUND)
RETURN
C NEWTON ALGORITHM, 25 ITERATIONS MAX.
C 6 X(6)=A(+)
C(6)=A(+)
GO 7 J=1,25
UO = I=1,4
K=1
C XH(A(+)*XH=EN(XA(+))
C2(X(K)=U(1)+XK=C(XA(+))
C(1)+XH=EN(X2)
C DX=XH/(1+0.2)
IF(ABS(DX),LT,0,1) GO TO 8

XC*XB = L*X

WRITE(6,111)

111 FORMAT('2. N FAILED TO CONVERGE.

C COMPUTE THE X(I)S.

GO TO 9

DX(I)=X(I)*XB/(xb + RK(I)*BB - XB))

9 EXP(I)=X(I) - DX(I)

DX(6)=DX(I)*1.0E-05

EXP(6)=EXP(6)+1.0E-05

RETURN

END
SUBROUTINE IVIS
C MARCH 16 1972. PROGRAM IVIS , ROBERTO HERMITTI.
C INTERVASCULAR + INTERSTITIAL EXCHANGE, STEADY STATE.
C GIVEN K1 TO K5, PA, PV, CPP, SOLVE FOR PT, CPI, OPI, V2.
C REQUIRING NEITHER FLUID NOR PROTEIN EXCHANGE BETWEEN IV - IS.
REAL K1,K2,K3,K4,K5,K2P,K3P
COMMON /L5/K1,K2,K3,K4,K5/L6/PA,PV,CPP,PT,CPI
DATA C1,C2,C3,C4,C5/C6/0.1,6E+23/C7/9.9,E+26/
D=0
K2P*K2
K3P*K3
K4*K5
CPP=C1*CPP + C2*CPP**2 + C3*CPP**3
A=K4*PA - K5*PV + K1*PV - K3P = 7,B*K2P
B=CPP*K1*PV
X=-6,
Y=23.0
C NEWTON SOLUTION FOR N,L. SYSTEM: F(X,Y)=0,0, G(X,Y)=0,0.
C X=PT, Y=CPI.
DO 1C 1=1,52
FXY= A*K*dummyY + C2*K3*dummyY**2 + K3*K4*dummyY**3 - X*(K*K1*K2P)
GXY= B - CPP*K1*dummyX - Y(KK3P+7,0*K2P) - K2P*dummyX
FX = -(K*K1*K2P)
FY = K*C1 + C2*K*K3*dummyY + J*K*dummyC3*dummyY**2
CX = -CPP*K1 - K2P*dummyY
CY = -(K*K1)/(K*K2P) - K2P*dummyY
C X = (FX*dummyCXY - GXY*dummyFX)/(FX*dummyCXY - GXY*dummyFY)
D Y = (GXY*dummyFX - FX*dummyGY)/(GXY*dummyFX - FX*dummyFY)
IF(ABS(DX), LE, 2.1,ABS(DY), LE, 2.1) GO TO 12
X=Y-DX
Y=Y-DY
10 CONTINUE
WHITE(16,121)
101 FORMAT(2H FAILED TO CONVERGE 2.)
121 FORMAT(2H FAILED TO CONVERGE 2.)
12 PT=X
CPI=Y
IF(X,LT,-7.0,AND,J,NE,11) GO TO 13
IF(X,GT,3.0,AND,J,NE,2) GO TO 16
GO TO 2
13 K2P=K2
=1
GO TO 15
16 K2P=0.0
K3P=30.0
J=2
GO TO 15
2 RETURN
STOP
END
SUBROUTINE PLIS
C       PROGAM PLIS, PLASHA INTERSTITIAL FLUID ELECTR. BALANCE.
DIMENSION X1(5),X2(5),C(5),DX1(6),DX2(5),SS(5)
C       INITIAL VALUES.
COMMON /L7/C/L6/VI,V2,H,SZ,V/LV/DX1/L10/DX2
DC1=0.3
DC2=0.0
DO 1 I=1,5
   X1(I)=V1*C(I)
   X2(I)=V2*C(I)
   DV1=DX1(6)
   DV2=DSZ
   V1=V1+DV1
   V2=V2+DV2
1   DO 5 I=1,5
   X1(I)=X1(I)+DC1
   X2(I)=X2(I)+DC2
   DC1=DC1+X1(I)
   DC2=DC2+X2(I)
5   DO 10 J=1,1,5
   HS=V2*DC1-V1*DC2/(DC1+DC2)
   DC1=0.3
   DC2=0.0
   V1=V1*HS
   V2=V2*HS
   DO 7 I=1,5
      V1=V1+X1(I)*V1-X1(I)*V2/(V1+V2)
      X1(I)=X1(I)+SS(I)
      X2(I)=X2(I)-SS(I)
      DC1=DC1+X1(I)
    7   DC2=DC2+X2(I)
   DO 8 I=1,5
8   IF(ABS(HS).LT.0.01.AND.ABS(SS(I)).LT.1.) GO TO 9
    CONTINUE
10   CONTINUE
WRITE(6,11)
11   FORMAT(22,FAILC TO CONVERGE 4.)
DO 11 I=1,5
11   C(I)=X1(I)/V1
RETURN
STOP
END
SUBROUTINE RENS
C INPUT TO RENS; ADH AND ALDOST, CONC., PTO FLOW AND CONC.
C CORTICAL CONC.
REAL INC., KS, KU, KM3, KS3
LOGICAL ISENS
INTEGER MIN, P1, HP
DIMENSION A(4), B(4), C(4)
DIMENSION: 0(6,1), U(6,1), UU(6,10), VM(10), UU(4)
DIMENSION S(4), V(10), XA(4), VM(10)
COMMON /L11/RIN, IP, PI, RP/L4/U, UGSM, UOUT, SOUT
COMMON /L12/PTO, RIN, RIN1, RK2, RK3, RK4, KM7, KM9, KU
COMMON /L13/UG, UGDM, UG, AHF, AC3, UGDM
UOUK=1, *UC
OUOK=1, UG
IF(IRIN.EQ.1) GO TO 50
WRITE(4,1,5)
FORMAT(12* RENAL TAPE,)
C READ INITIAL RENAL STATE FROM TAPE.
PAUSE 5
READ(5,21) VI, VCI, CNC, OUC
DO 25 I=1,10
READ(5,21) OU(I), OU(I), OI(I), OI(I), OI(I), OI(I), OI(I), OI(I), OI(I), OI(I)
1, VCI(I), VM(I), VOU(I)
25 CONTINUE
C 50 COMPUTE PERMEABILITY VALUES.
VO=PTO/2.
C ADH CONTROLLED PERMEABILITIES.
IF(AHF.GT.6.32) GO TO 52
IF(AHF.LT.6.12) GO TO 53
RK1=(1,294,71+2,4)*KS
=1,24+2.25*KM
GO TO 55
52 RK1=1,294,71+2,4*KS
K=1,24+2.25*KM
GO TO 55
53 RK1=(1,294,71+2,4)*KS
K=1,24+2.25*KM
GO TO 55
54 RK1=(1,294,71+2,4)*KS
K=1,24+2.25*KM
GO TO 55
C ALDOSTENONE CONTROLLED PERMEABILITY.
55 IF(AC3.GT.12) GO TO 56
KS=0,624*AC3+2,4*KS
GO TO 57
56 KS=0,624*AC3+2,4*KS
GO TO 57
C COUNTERCURRENT MECHANISM.
C 1=ASH 2=AR 3=D0 4=D2 5=CD 6=INTERST.
C 1,2 = ASCEND. PIPES. 3,4,5 = DESCEND. PIPES. 6 = INT.
57 DO 6 K=1,2
C SHIFT ASCENDING PIPES.
DO 12 I=1,9
OU(I,I)=OU(I,I)
OU(I,1)=OU(I,1)
C
12 \text{OV}(2, 1) = \text{ON}(2, 1+1) \\
13 \text{ON}(1, 1) = \text{ON}(0, 10) \\
14 \text{OV}(1, 1) = \text{ON}(0, 10) \\
15 \text{ON}(2, 1) = \text{ON}(4, 10) \\
16 \text{DO} 13 \text{I} = 1, 9 \\
17 \text{VX}(1) = \text{VX}(1+1) \\
18 \text{VX}(10) = \text{VX}(10) \\
\text{C} \text{SHIFT DESCENDING PIPES}, \\
\text{VGR}(1, 1) = \text{VGR}(V) \\
\text{VCR}(1, 2) = \text{VCR}(9) \\
\text{DO} 14 \text{J} = 3, 5 \\
\text{ON}(J, 2) = \text{ON}(J, 9) \\
\text{DO} 15 \text{J} = 1, 6 \\
\text{N} = \text{N} - 1 \\
\text{C} \text{CONTINUE} \\
\text{N} = 16 \text{I} = 1, 9 \\
\text{M} = \text{M} - 1 \\
\text{VB}(V, 10) = \text{VB}(5, 10) \\
\text{C} \text{V}(1) = \text{V}(1-1) \\
\text{V}(1) = \text{V}(1) \\
\text{VON}(1) = \text{VON}(1-1) \\
\text{VON}(1) = \text{VON}(1) \\
\text{DO} 27 \text{J} = 3, 6 \\
\text{DO} 17 \text{I} = 1, 4 \\
\text{C} \text{OVR(1)} = \text{OVR}(1+1) \\
\text{C} \text{CONTINUE} \\
\text{C} \text{EQUILIBRATE} \\
\text{SA} = \text{SA} + 1 / 2 \\
\text{SA} = \text{SA} + 1 / 2 \\
\text{DO} 3 \text{I} = 1, 15 \\
\text{C} \text{OVE ITERATION} \text{ OF } \text{SUBK} \text{KUTTA METHOD}, \\
\text{UC} = \text{UC}(5, 1) + \text{VC}(1) \\
\text{SG} = \text{SG}(5, 1) + \text{SG}(1) \\
\text{A}(1) = \text{A}(1) + \text{A}(6, 1) \\
\text{S} = \text{S} + \text{A}(5, 1) \\
\text{VX} = \text{VX} + \text{A}(6, 1) \\
\text{NO} 3 \text{M} \text{J} = 3, 5 \\
\text{VP} = \text{VP}(1) + 4 \text{J} - 2 / 2, \\
\text{R} = \text{R} + \text{I} / 17 / 2, \text{J} / \text{VP} \\
\text{M} = \text{M} + \text{J} / 16 / 2, \text{I} / \text{VP} \\
\text{A}(J) = \text{A}(J) + 6 \text{J} - 1 \text{I} - \text{R} - \text{R} \\
\text{M}(J) = \text{M}(J) + \text{R} - \text{R} \\
\text{NO} 3 \text{M} \text{J} = 3, 5 \\
\text{C} \text{COMPUTE WATER SELF AREA SHIFTS}, \\
\text{NV} = (A(1) * 2 + A(2) * 2 + A(3) * A(4)) / 6.
DO N = (B(1)*2*B(2)+B(3)*B(4))/6,
DO UC = (C(1)*2+C(2)+C(3)+C(4))/6,
IF(DV,GT,7*VC(1)) DV = VC(1) * B, 66
IF(DV,GT,SC) DV = SC
IF(DUC,GT,UC) DUC = UC
DV = DV/2,
VC(1) = VC(1) - DV
DV = RK4((DV(1), DV) - U(1,1))
IF(ON(1), LT, 253, ) SAT * ORN(1,1) * SAC = SAP
IF(SAT, LT, 25, ) SAT = 0
DV = DO(1) + VD + VDR(1) + VAR1
ON(1,1) = (INC + ON(1,1) * VD + ON(4,1) * VDR(1) + ON(2,1) * VAR1) / VN(1)
OU(5,1) = UC - DUC / VC(1)
OU(6,1) = 2U(6,1) + (DUC + DUH - DUH) / VI
OU(1,1) = DU(1,1) + DUH / VD V(6,1) = V(6,1) + DU(6,1)
ON(1,1) = 0(1,1) - SAT * VD
VDR(1) = V(1,1) + DV
VAR1 = VAR1 / DO(1)
ON(5,1) = (SC - DO) / VC(1)
OU(5,1) = (0(5,1) + DU(5,1))
CONTINUE
DO 18 J = 2, 4
DO 19 K = 1, 10
ON(1,1) = J = 1
CONTINUE
OU(1,1) = 0(1,1) + OU(1,1)
OU(2,1) = 0(2,1) + OU(2,1)
CONTINUE

DISTAL TUBE SIMULATION

FH, CS, CU ARE VSAT AT THE DT INPUT.

FH = PTO
CS = ON(1,1)
CU = OU(1,1)
FS = FH * CS
FU = FH * CU

RUNG KUTTA ETQDO FOR DISTAL TUBE.

DO 23 J = 1, 12
R(1) = X * (-OC + (FS + FU) * FH)
S(1) = X * FS
T(1) = X * (FU - FH + UC)
DO 29 J = 2, 3
R(1) = X * (-OC + (FS + FU) * T(1-1) * T(1-1) / 2) / (FH + R(1-1) / 2)
S(1) = X * (FS + S(1-1) / 2)
T(1) = X * (FU - FH + T(1-1) * T(1-1) / 2) / (FH + R(1-1) / 2) + UC
R(4) = X * (-OC + (FS + FH + S(1) + S(3)) * (FH + R(1)))
S(4) = X * (FS + S(3))
T(4) = X * (FU + T(3)) / (FH + R(1)) + UC

IF(UF = T(1) + 2 * R(2) + 2 * R(3) + 2 * R(4) / 6)
FH = FS + (S(1) * 2 + S(3) * S(4)) / 6
FU = FU + T(1) + 2 * R(2) + 2 * R(3) + T(4) / 6
CS = FH / FS
CU = FU + FH

CONTINUE

}

These instructions refer to the use of the programs listed in Appendix D with the DEC-PDP9 digital computer.

Following loading of the program, the computer will type:

MEMO. SET SWITCHES.

The user may then type a memo or title statement of up to 72 characters which will be printed as headline at the beginning of the output sheets. There are 17 switches in the right half of the console. The first seven may be used for controlling the program as indicated in the comment statements at the beginning of BFSP. The switch setting may be changed during the execution of the program.

Following the MEMO input, the computer will type:

OBS. TIME. PRINT INT. N. OF INPUTS AND INPUT TYPE.

The user will type the observation time in minutes (duration of simulation), the desired interval between outputs of data, the number of minutes of input application and the type of input (1 for injections or ingestions, 2 for infusions). In case of injection the computer will require the times of input $T_1, T_2$ etc. which the user will input by teletype; in case of infusion the computer will require the infusion initial time.

The input device number will then be requested by:

$ICD= IFD=$

requiring the user to type the number of the devices to be used for entering constants and input flows (teletype = 4, paper tape reader=5).
Being ready to read the input constants, the computer will either type:

PAUSE 1

and wait for the user to place the constant's tape in the reader and press CTRL-P, or wait for the user to input the constants manually from the teletype. The computer will then compute and print out the initial state of the system and then type:

PAUSE 3

The user will then place the renal state tape in the reader and press CTRL-P therefore avoiding the delay due to the long and cumbersome computation of the nephron's initial steady state.

The computer will then type:

PAUSE 2

The input flow tape, if any, should then be placed in the reader and the pressing of CTRL-P will start the computation of the response. The inputs to be provided for each minute are the changes of the $b_i$'s and of the protein amounts (see Chapter IV). Such inputs are either automatically read by the paper tape reader or requested by the teletype when needed.

At the end of the observation time the computer will request a new memo and will be ready for a new simulation which may use either new initial conditions or the last computed state as initial state.

An example of printout follows.