Metabolic Disorders of

Domestic Animals

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Preface

This book is based on a course of lectures given by one of the authors (A. A. Wilson) to veterinary students in the Department of Animal Pathology at Cambridge. The lectures formed part of a course in pathology in which metabolic aspects were co-ordinated with those on the structural changes occurring in disease, and were concerned with the aetiology of metabolic disorders rather than their treatment. It has been customary in most veterinary schools for instruction in metabolic disorders to form part of the course of medicine, but it is hoped that the approach adopted in this book may pave the way for their inclusion in courses of pathology.

The metabolic disorders of domestic animals have been regarded as hypocalcaemia, hypomagnesaemia and ketosis. For this reason and because of the authors' interest, these disorders have been treated extensively. The approach to these conditions and also to other metabolic disorders has been to review the physiological mechanisms and to emphasize the principles involved in the consideration of metabolic disorders rather than to tabulate information.

The topics discussed do not cover all aspects of metabolic disorders of domestic animals. For instance, little reference has been made to diseases arising from dietary deficiencies or genetic factors. There are numerous books on methods of biochemical analysis. Details of analytical methods have therefore been omitted except where an understanding of the principles of the method is essential to an understanding of the topic concerned.

As this book was written primarily for veterinary students, references have not been given to every statement. However, to facilitate further study, references are given to reviews and to some original papers which may be important in considering controversial subjects or in obtaining further information.

We are grateful to the American Institute of Biological Sciences for permission to use Figure 10 from *Liver Function*, edited by Ralph W. Brauer, and to W. B. Saunders Company Limited for

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permission to reproduce Figure 12 from Sodeman's *Pathologic Physiology*. Mrs P. F. Hollott has given valuable assistance in the preparation of the text and index. Mr R. Kimberley kindly prepared the Figures used in the text. It is a pleasure to acknowledge the patience and help of the staff of Blackwell Scientific Publications Limited, particularly Mr Per Saugman while this book was in preparation.

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Introduction to Water and Electrolyte Metabolism

Introduction

All the biochemical reactions which together constitute life, take place in an aqueous medium, hence the fundamental importance of water in the general economy of the body, and its importance in both physiology and pathology. Although it has been realized for many years that water is essential for life, it is only relatively recently that the metabolism of water in pathological states has received serious attention. Any consideration of water metabolism must of necessity include the metabolism of electrolytes as the two are inextricably linked together; movements of water being very largely determined by movements of the electrolytes.

Terminology

It is as well to make clear the terminology used when expressing concentrations and amounts of the various components of the body before proceeding to any consideration of the metabolism of electrolytes and water. Unfortunately there is no generally accepted usage, particularly in the case of blood, plasma, or serum. Some concentrations are expressed in milligrams per 100 ml (very frequently, but inaccurately, abbreviated to mg %), others in milliequivalents per litre or millimoles per litre. In medical circles there is an increasing tendency to give concentrations in milliequivalents per litre whenever possible. This is very much to be desired, as the expression of amounts in milliequivalents is a measure of the chemical activity of the elements in question, and makes comparison between different components much simpler. In this book concentrations will be given in milliequivalents per litre whenever possible. In certain special cases other measures of concentration are desirable in that they clarify certain concepts, or are hallowed by long usage.

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Definitions

A *milliequivalent* (meq) of a simple or complex ion is its equivalent weight expressed in milligrams. Although not the true chemical definition, the equivalent weight can be taken as the molecular or atomic weight of an ion divided by its valency. Thus the atomic weight of sodium is 23 and its valency is 1, therefore its equivalent weight is 23; the atomic weight of calcium is 40, its valency is 2 and its equivalent weight is 20. As acetic acid is monovalent its equivalent weight is the same as its molecular weight, 60; the sulphate ion has a 'molecular' weight of 96, so that its equivalent weight is 48. Concentrations of a number of different ions can be summed algabraically so that balances can be struck between ions of different charges.

In some cases it is more convenient to express amounts in millimoles or concentrations in millimoles per litre. A *millimole* (mMole) of substance is the molecular weight of the substance expressed in milligrams. A solution containing 1 millimole per ml, is a molar (M) solution; one containing 1 millimole per litre is a millimolar solution (mM). Sometimes the concentrations are expressed in molalities, a *molal* solution being one in which there is one mole of the solute per 1000 g of water. One other measure of concentration is used in certain circumstances, viz. the osmolarity (osM) or milliosmolarity (mosM). The *osmolarity* of a solution is a measure of its osmotic activity. Osmotic activity is a function of the total number of dissolved 'particles' in given volume whether these are molecules or ions, and is thus a function of the molecular weight of the solute; all molar solutions should have the same osmolarity. This is not the case with ionizable salts. In solutions of substances such as glucose, a molar solution is also osmolar, but a solution of a salt such as sodium chloride, which can be considered to be completely dissociated in dilute solution, has an osmolarity which is twice its molarity. Magnesium chloride forms ions when dissociated, one of magnesium and two of chloride, hence a molar solution is actually 3 osmolar. In considering certain aspects of water metabolism, total osmotic activity is important and in these cases it is possible to measure the total osmotic activity directly by determining some colligative property of the solution, e.g. the depression of the freezing point, which is directly related to the total osmolar concentration.

The following relations hold between the different means of expressing concentration.

$$\text{mMole/litre} = \frac{(\text{mg}/100 \text{ ml}) \times 10}{\text{molecular weight}}$$

$$\text{meq/litre} = \frac{(\text{mg}/100 \text{ ml}) \times 10}{\text{equivalent weight}}$$

$$\text{mosMole/litre} = \frac{(\text{mMoles/litre}) \times (\text{Number of particles}}{\text{formed when 1 molecule is dissolved})}$$

$$= \frac{\text{Depression of F.P. in } {}^{\circ}\text{C}}{1 \cdot 86}$$

The Forces Influencing Movement of Water and Electrolytes

When the movements of solutes and water between the different tissue phases are considered, four types of transfer are usually recognized. These are diffusion, osmosis, 'active' transport and mass movement due to hydrostatic pressure. The Gibbs–Donnan equilibrium is also important when one of the phases contains protein.

Diffusion

This is the simplest type of movement and is the result of the thermal agitation of the solutes and solvent. If two aqueous phases in contact differ only in their concentration of solute, the molecules will move from one phase to the other in such a direction that, at equilibrium, the concentration will be the same throughout both phases. That is to say, molecules will move from the phase with the higher concentration to that with the lower. This applies to both solute and water. Thus if two phases, A and B have concentrations 1 osmolar and 0·1 osmolar, respectively, solute will move from phase A to phase B, while water moves from phase B to phase A, until the final concentration is the same in both phases. Thus diffusion is said to occur in the direction of the concentration gradient.

Osmosis

If a solute is restrained from moving between two phases while the solvent can move freely by diffusion, then solvent will move from the phase with the lower concentration of solute to that with the higher concentration. If the volume of the latter phase is fixed, then a hydrostatic pressure will build up which will eventually prevent any further

movement of solvent. This pressure is the osmotic pressure and is a function of the difference in molar concentration between the two phases.

'Active' Transport

In a biological system, a solute or solvent sometimes moves against the concentration gradient. This process is called 'active' transport, as it requires the expenditure of energy by the system; the energy being obtained from some oxidative process. This definition is not strictly accurate for charged solutes, in which cases electrical forces may be important. As a result of electrical forces an ion may move against a concentration gradient without the intervention of any active biological process. Hence, in the case of charged particles, e.g. ions, transport from one phase to another can be considered 'active' only if the ion is moved against the electrochemical concentration gradient. The electrochemical concentration gradient is determined by the electrical forces and the chemical concentration of the ion concerned.

Mass Movement due to Hydrostatic Pressure

If two phases are distinguishable only by a difference of hydrostatic pressure, then both solute and solvent will move together from the phase with the higher hydrostatic pressure until the pressure in both phases is equal. There will be no change in concentration of the solute.

The Gibbs–Donnan Equilibrium

If two phases, each containing ionisable solutes, are separated by a membrane which is impermeable to one of the ions in one of the phases, then, when equilibrium is reached, the concentrations of the permeating ions in the two phases will be influenced by the non-permeating ion in such a way that osmotic and electrical equilibria are attained. For example, if there are two aqueous phases, A and B, separated by a membrane impermeable to protein, of which phase A contains sodium chloride and protein while phase B contains sodium chloride only, then sodium and chloride ions will move between the two phases in such a way that at equilibrium the products of the sodium and chloride ion concentrations in the two phases are equal. The chloride ion concentration in phase A will be less than that in phase B, and

$$\frac{\text{(Conc. sodium ion in A)}}{\text{(Conc. sodium ion in B)}} = \frac{\text{(Conc. chloride ion in B)}}{\text{(Conc. chloride ion in A)}}$$

Flux and Turnover

As a result of any of the factors discussed above, a solute or solvent molecule can be moved between different phases, and the amount moved is called the flux of the molecule. If a molecule can move in both directions, between two phases, but the movement is greater in one direction, then the difference between the two fluxes is the net flux; in some cases the net flux is zero. Turnover is the term which is frequently employed to describe the absolute sum of the flux in both directions.

The Fluid Compartments
of the Body

Introduction

The largest single component of the body is water, which constitutes about 70% of the fat free-body weight. The total fluid of the body is considered to be divided into different compartments, though the exact anatomical location of these compartments is not certain. The primary division is into the Intracellular Fluid (ICF) and Extracellular Fluid (ECF). The extracellular fluid is further divided into Blood and Interstitial, or Intercellular Fluid (InterCF). The measured volume of the different compartments depends, to some extent, on the method used (*v. infra*), but as first approximations the following figures are usually accepted. The Intracellular Fluid is taken to be 50% of the fat free-body weight, the extracellular fluid as 20% of the body weight, and the blood plasma as 5% of the body weight.

Although the different compartments of the body differ in their compositions, as a result of their differing functions, they are delicately balanced in respect to volume, osmotic activity, hydrostatic pressure and electrical charge on ions. These balances are not the equilibria of closed physical systems but rather, steady states of open systems which, although subject to physical laws, depend on the metabolic activity of the body for their maintenance. Before considering the composition and functions of the different compartments, the question of determining their volume must be considered.

Measuring the Volume of the Body Compartments

Numerous methods have been described for determining the volumes of the different compartments but they are all based on the same principle, viz. that of determining the volume of distribution or dilution of some substance which is assumed, or has been shown, to be confined to the compartment in question. If a known weight of a substance is

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added to an unknown volume of solvent and the concentration (equilibrium) in the unknown volume determined, the volume of dilution or distribution is related to the weight of substance added, and the concentration determined, as follows:

$$\text{Volume of dilution} = \frac{\text{Weight of substance added}}{\text{Concentration determined}}$$

This principle can be applied to the determination of any of the body compartments depending on the substance used. It is, of course essential to determine the concentration after adequate time has been allowed for mixing of the substance in the compartment and for this reason it is necessary to determine the concentration several times at suitable intervals, and extrapolate to find the concentration at zero time. In some methods, however, when the substance used is excreted in such a way that it can be collected quantitatively, it is possible to relate the concentration to the amount remaining in the body, at a given instant. However, the principle of dilution still holds except that the amount of the substance remaining in the body is substituted for the amount added, in the calculation.

Measurement of Total Body Water

When dealing with the tissues of dead animals, it is possible to determine the water content by drying to constant weight. This is obviously impossible with live animals and recourse must be made to indirect methods involving determination of the volume of dilution of some substance. In the case of animals it has been possible to compare the results of using indirect methods with desiccation of separate tissues or even whole carcases.

In order to determine the total body water (TBW) by dilution techniques, the substance chosen must be one that mixes completely with all the water in the body. The rate of mixing must of necessity exceed the rate of metabolism or excretion by a considerable factor. The ideal substance for this purpose is obviously some form of labelled water, deuterium oxide or tritium hydrogen oxide. Both these have been used experimentally, but they are not convenient for routine use. The most widely used substance for determining the volume of TBW is antipyrine (Phenazone). As antipyrine is metabolized to some extent by the tissues, an extrapolation technique must be used. The technique for determining the antipyrine space is described by Brodie (1951). A dose