UNIVERSITY OF EDINBURGH

"Studies in Electrolyte and Water Metabolism in Normal and Abnormal Pregnancy"

By

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Thesis submitted for the Degree of Doctor of Philosophy in the Faculty of Medicine

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M a y 1961

I N D E X

EXPERIMENTAL PART

(A) WATER METABOLISM :

(B) ELECTROLYTE METABOLISM :

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INTRODUCTION

" Claude Bernard me disait un jour ' Nous saurons la physiologie lorsque nous pourrons suivre pas a pas une molecule du carbone ou d'azote, faire son histoire, raconter son voyage dans le corps d'un chien, depuis son entrée jusqu'a sa sortie ' "

HISTOIRE DE IA FRANCE

(Taine, 1891)

It is interesting to note that what appear to be the modern problems of research were tackled a long time ago. Such early experimental experimental explorations did not sound of great significance, as they do now, after proper understanding of our intricate problems.

T he stimulus to study water and electrolyte physiology came after a clinical observation in the eighteenth century. It was 1831 when O'Shaughnessy published his observations in the "Lancet". He mentioned that the blood of cholera patients in Newcastle-upon-Tyne had lost a large proportion of its water and also a great proportion of its saline ingredients. His observations were put into immediate practice by Dr. Latta of Leith, who treated Cholera by saline infusions with very satisfying results (Latta, 1831).

At the same time in France Claude Bernard was putting the foundation of the modern physiology of body fluids and electrolytes. It is difficult to resist the temptation to speak about Claude Bernard. T hat great man who revolutionised biological knowledge and medical thou ght started his life helping in a pharmacy. His life was a series of wonderful discoveries and multiple simultaneous scientific activities. This lead him to be Senator of the Académie Francaise, the highest scientific appointment in France. He was more than a profound and encyclopedic lecturer and writer. He was an inspiring and beloved teacher. His work in the field of electrolytes and homeostasis is just one of the many fields which were explored by him. (Mayer, 1951).

CLAUDE BERNARD

Fig. 1.

Hecoined the term milieu intérieur, giving extracellular fluid a physiological terminology based on proper understanding. He defined it as follows : " C'est le sang, non pas a la verité le tout entier, mais la partie fluide de sang, le plasma sanguin, ensemble de tous liquides interstituel, source et confluent de tous les échanges élémentaires." Realising the importance of the constant composition of the extracellular fluid he wrote : La fixité du milieu intérieur est la condition de la vie libre. The work of Claude Bernard and his writings will always be remembered as the mile stone and a starting point for proper realisation of human physiology (Bernard, 1878; Olmsted, 1939).

Berzelius was one of the early biochemists who became interested in electrolytes. In 1840

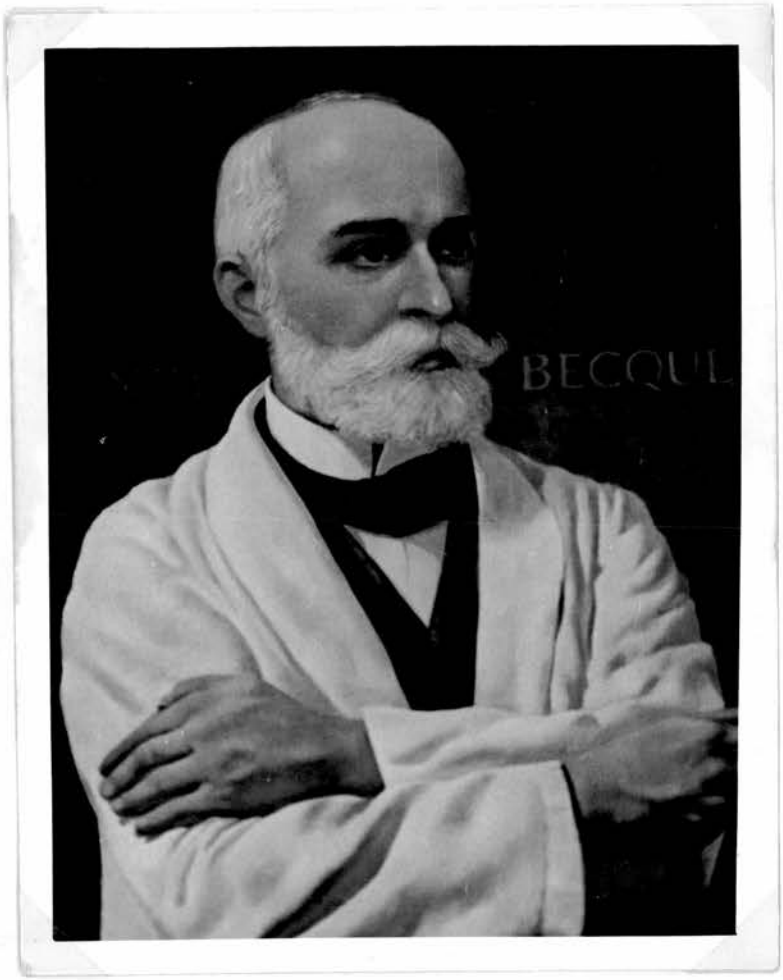
he reported that muscle contains Na Cl, K Cl and Ca PO_4 (Berzelius, 1840) Probably the earliest mention of the difference in electrolyte concentration between intracellular and extracellular compartments was mentioned indirectly when Leibig in 1847 noted that muscle ash was rich in potassium and poor in sodium, while the blood contained more sodium than potassium (Leibig, 1847). In 1891 Halliburton came to the conclusion that organised tissues have a high potassium concentration while all fluids have high sodium content. (Halliburton, 1891). It was in 1896 when Katz produced his monumental work on accurate determination of Na, K, Fe, Ca, Mg, Cl, S and P in the muscles of thirteen different animals (Manery, 1947).

With the beginning of the twentieth century the pendulum swung and interest in muscle electrolyte study waned. Instead, all the activity was directed to blood and urine instead of tissues. Analytical Chemistry and the study of the problems of starvation took the lead. During this period very valuable work was done. The distribution of electrolytes between red blood corpuscles and plasma was finally clarified by Van Slyke in 1923, (Van Slyke et al., 1923).

It was in the early thirties that the significance of what Claude Bernard mentioned, nearly a century before, was realised; the milieu interieur and its constancy. To clarify the relation between the cell and its environments the stage was set for intensive investigations of tissue electrolytes which began in many centres si-

multaneously, (Mond & Netter, 1930; Cullen et al., 1933; Eggleton, 1933; Fen & Cobb, 1934). While all this work was going on in the field of biology, there was another discovery which paved the way to a new era of radioactive isotopes.

The discovery of natural radioactivity by Bequerel in 1896 began a revolution, and triggered a chain reaction of magnificent discoveries in quick succession. In 1898, Pierre and Marie Curie discovered radium and summarized the knowledge gained in this early phase of new science. They concluded that Uranium rays discovered by Bequerel were an atomic phenomenon characteristic of the element and not related to its physical or chemical state. One year later in 1899, Rutherford and his associates identified the types of radia-



ANTOINE HENRI BEQUEREL

Fig. 2.

tion alpha and beta, and immediately afterwards the more penetrating gumma rays were discovered by Villard, (Friedlander & Kennedy, 1956).

Three Noble Prizes are linked with these great discoveries. The first was shared by the Curies and Bequerel for the discovery of natural radioactivity. Marie's daughter Irene together with Frederic Joliot Curie were to share a similar award for their discovery of artificial radioactive isotopes, (Browning, 1959). The third Noble Prize was awarded to Georg von Hevesey for his pioneer work which clearly established the value of the new material as tracers in biological research. The first clinical application of isotope tracer was reported by him in 1934 when he estimated total body water using Deuterium, (Hevesey & Hofer 1934).

The value of radioactive isotopes is now well established. As tracer elements they are unique in their honest and accurate information. So at last, and nearly a century later, we can follow a molecule of carbon or nitrogen, making her own history, telling her own story in a living body.

It was expected after all these discoveries and scientific achievements to admit new words in our daily writings and medical parlance. The Curies introduced the word radioactivity in 1898. The word isotope was suggested by Dr. Margaret Todd, a lady doctor and writer, to Professor Soddy during a dinner party, (Lenihan, 1959). Every day we talk about exchangeable electrolytes Na, K and chlorides. Moore coined the word chemical anatomy to deal with the estimation of different metabolic pools .... again a new word, (Moore, 1946).

It was natural evolution to reinvestigate our unsolved problems in the new light. A combined clinical and laboratory work is continuous in every speciality to evaluate the role of water and electrolyte metabolism in relation to various problems.

In obstetrics we had always in mind the problems of haemorrhage, infection and toxaemias of pregnancy. Blood transfusion and antibiotics were the answer to the first two problems, and we are left with pre eclampsia. Now, it is the main cause of maternal and foetal mortality.

Pre eclampsia, is still a disease of theories. The exact cause is unknown. There is no doubt that the proper understanding of the living

pathology whether of physiological or biochemical nature will pave the way to the discovery of its cause.

The relation between water and electrolytes and pre eclampsia was always stressed a long time ago. The aim of this work is to investigate this problem by studying water and electrolyte metabolism in pregnant women, normal and toxaemic.

ANTOINE HENRI BEQUEREL

B O D Y W A T E R

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Water is essential to life. A human being may stand up to six weeks without food, but water deprivation for a period from one to seven days - depending on surrounding temperature and humidity is certainly fatal.

T he fluid which is essential to life possesses unique characters among others. It has a high specific heat. It has a solvent power unequalled by any other liquid. Alone among all other liquids it expands when it freezes. All these characteristics are essential for water to be intimate ly connected with any form of life and to fulfil all the physiological requirements of a living system whether human, plant or animal, living in air or underwater, (Theobald, 1955).

Water preserves the functional integrety and allows the proper functioning of the living cell. Cellular protoplasm is a solution or suspention in water of complex, mostly colloid, compounds. Cellular energy is the outcome of two main parts, the osmotic pressure of dissolved substances, and the energy released when they undergo complete oxidation, a process for which water is required.

TOTAL BODY WATER

The only fluid space which cannot be regarded as a part of body water is that defined by the renal pelvis, ureter and bladder. Fluid contained in this place has been separated by the kidneys from the body's functioning water pool and no longer takes part in the physiological processes associated directly with water metabolism.

What is the Amount of Total Body Water ?

It has been the habit to mention total body water as 70% of body weight, (Wright, 1953). This figure has been copied from one reference to another. Reviewing the literature I found different figures by different workers covering a range from 50 - 70 % of body weight, (Schloerb et al., 1950; Prentice et al., 1952; Soberman et al., 1949 & Edelman et al., 1952).

The variation of these figures can be due to one of two factors. The first is the relation of water to body weight. The most common variant in body composition is fat, and unfortunately its water content is less than the contents of other body tissues. The second factor is the use of different tracers in the dilution techniques used

in body water measurement.

It is interesting to note that early papers gave a high percentage while recent ones give lower figures. Recent techniques are more accurate, so lower figures are more likely to represent the truth than higher ones. With full realisation of the inaccurancies inherent in the estimation of body water as a percentage of body weight it is still reasonable to use such values clinically.

Total Body Water and Age:

Edelman et al., (1952) estimated total body water in 120 normal human subjects covering an age range from 2 days to 86 years and a weight range from 2.3 kg. to 100.3 kg. In newly born infants the mean total body water was 77% of body

weight. Between 1 and 9 years the mean was 59%. Water content of the body decreased gradually with the progress of age.

Total Body Water and Sex :

In the same series Edelman et al., (1952) found that a sex difference became apparent only at the age of 16 and persisted for the remaining adult life. A clear cut, statistically significant difference exists, the body of the male contains approximately 17% of water more than that of the female. This sex difference starts to appear at puberty, and can be explained by the fact that women start to put more weight in fat than men.

What is the Total Body Water of Women ?

I can conclude that recent workers agree that the figure 55% of body weight can be used as a

standard one for non pregnant adult women, (Esselier & Jeanneret, 1956; Edelman et al., 1952; Black, 1957). Thomson & Billewicz (1957) in Britain, analysing 412 cases suggest that the average standard weight is 55 kg. Accordingly the average weight British woman's body contains 30 litres of water.

DISTRIBUTION OF BODY WATER

Water Content of Different Organs :

Water content varies in different organs. It is highest in the plasma 92%. It is lowest in fat which contains 10-30% (Siri, 1956). This is a wide range. Some workers keep it at 30%. I do not think one should be dogmatic about this figure. In fact the exact proportion is not known, nor is it certain that the proportion is the same

in different types of obesity. Both muscle and nervous tissue have the same content, 75 %. The liver contains 70 %, connective tissue 60 %. Bone water content is remarkably low, only 25 %.

Water in Different Compartments :

T he fact that most cells are rich in potassium while sodium accounts for the greater part of solutes in the extracellular fluid suggests a primary subdivision of the body into intracellular and extracellular compartments, distinct chemically and topographically, (Hastings, 1940).

Intracellular Fluid :

The intracellular fluid is in osmotic equilibrium with the extracellular fluid. Its main cation is potassium. The proportion of Na is

small except in the skeleton, while Cl is practically non existent. According to Wilkinson the intracellular fluid accounts for 70 % of total body water. It can only be measured indirectly as the difference between total body water and extracellular water.

Extracellular Fluid :

This is the milieu interieur of Claude Bernard. It is the medium in which the living cell exists. Its composition varies within a narrow limit. Any change beyond this limit could be fatal. The body is keen to keep its constancy at the expence of any other factor in cases of gross disturbance. There are three subdivision of the extracellular fluid:-

1) Intravascular Plasma.

This fluid is maintained inside the vascu-

lar tree by the osmotic pressure of the plasma proteins on the venous side of the capillary pool. Although the osmotic pressure is only 25 mm./hg. yet it is the effective factor because the osmotic pressure exerted by the crystalloids is equal on either side of the capillary membrane.

2) Interstitual Fluid.

This is the fluid which occupies the spaces in between the cells. This is the milieu intérieur of Claude Bernard which contains sodium as its main cation.

3) Transcellular Fluid.

This is a term including fluid which although in equilibrium with plasma and intra-

cellular fluid yet have been formed by diffusion through a cellular membrane other than the capillary membrane of the vascular tree. It includes the cerebrospinal fluid, aquous humour and the liquor amnii.

WATER BALANCE

A normal individual is in a state of water balance i.e. an equal intake and output, both of which vary within wide limits but always maintain the body water content.

Water Intake :

The daily consumption of water varies widely. The average daily drink is about 1000 ml. It may be as small as a pint and it may reach 4-5 litres per day in hot countries where a huge amount of water is lost as sweat to maintain a constant body temperature.

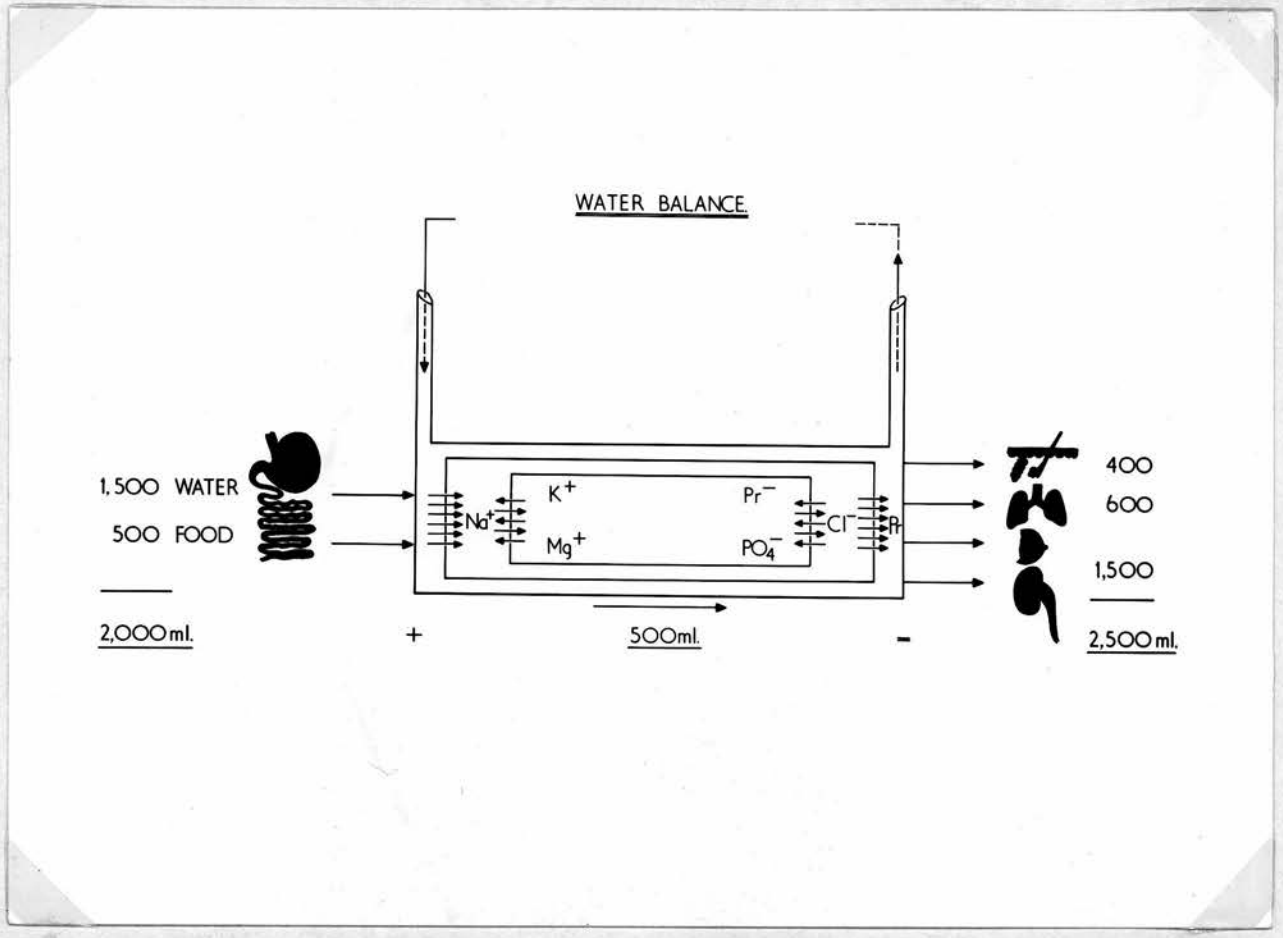
WATER BALANCE.
1,500 WATER
500 FOOD
2,000ml.
+
500ml.
-
400
600
1,500
2,500 ml.
Na+
K+
Mg+
Pr−
PO4−
Cl−
Pr

Fig. 3.

Ordinary daily food contains 60-95% of its content as water. This amounts to about 1000 ml. daily. Between 200 and 400 ml. of water are formed in the body daily as a result of its metabolic activity, at a rate of 12 ml. for each 100 calories produced.

Water can gain access to the body from a surrounding humid atmosphere through the lungs and the skin. Using tritiated water it was demonstrated recently that up to 400 ml. could be absorbed daily by this route, (Roberts et al., 1958).

Water Loss :

The main route of water loss is the kidney. The kidneys secrete any amount of body water in excess of the body requirements. It is important

to remember that water is essential for the excretion of other metabolic products. The minimum amount required by the kidneys for urine formation varies with the total quantity and with the nature of the solutes to be excreted, the osmotic load, and on the ability of the kidney to excrete a concentrated urine, (Wilkinson, 1960).

The minimum amount of water required to excrete the metabolic end products is known as the 'volume obligatoire', 400 - 800 ml. every day. For a given solute load the amount of urine secreted varies according to the concentrating capacity of the kidneys from about 500 ml. at a urine specific gravity of 1032 to 750 ml. at a specific gravity of 1020 and 1300 ml. at a specific gravity 1016, (Gamble 1954). Although the volume

obligatoire for a healthy adult is 500 - 800 ml. yet the average amount of urine excreted is about 1500 ml. daily.

Insensible Water Loss :

Another vital function of water is the role it plays in the regulation of body temperature. Water vapour is lost through expired air and through the skin. The amount lost by this route depends on many factors such as the surrounding temperature and humidity. The average insensible loss was estimated by Du Bois as .5 g. of water/ Kg. body weight / hour in adults i.e. 840 g. of water / day in 70 kg. man, (Du Bois, E.F., 1936).

In hot climates where water lost by invisible perspiration is not enough to keep a constant body temperature, the sweat glands are stimulated

and up to 10 litres of water could be lost by this route every day, (Wilkinson, 1960).

ELECTROLYTE PATTERN OF BODY COMPARTMENTS

The main feature of electrolyte pattern of the body is the intracellular position of potassium and the extracellular position of sodium. Although this feature was known in the 19th century, yet how it is maintained has been demonstrated only recently.

This was attributed in the past to some mechanism operating during the development of the cell. This pattern is then maintained throughout life by the cell membrane being impermeable to all cations. This view proved to be wrong as both Na, and K can pass through the cell membrane, (Wilkinson, 1960). The beleif now is that this electrolyte pattern is an active process explained by the existence of a pump system, (Dean, 1941). Potassium is pumped in the cell while sodium is

forced out of it. The presence of high potassium in the cells is dependent on the presence of oxygen, glucose and l glutamate in the medium, all required for an active metabolic process, (Terner et al., 1950).

Another important feature of the electrolyte pattern of the body is the higher cation cencentration in the cells than the surrounding medium. At first it was attributed to the existence of elements in an osmotically inactive form, (Peters, 1941). The accepted view now is that the hypertonic state of the intracellular fluid can be only maintained by expultion of the water from the cell actively, an energy spending procedure, which can be called secretion of the water from the cells, (Robinson, 1950; Robinson, 1953).

SODIUM METABOLISM

Sodium is the main cation in the extracellular fluid. It plays a very important role in the constancy of the milieu interieur. Its concentration within physiological limits is essential for the activity of the nervous and the muscular tissue. Sodium is the cation that keeps the body water and determines the size of the extracellular space. The kidneys use Na^+ to regulate the pH of the body. The different aspects of the physiology of sodium have only recently been discovered and explored.

Proper Understanding of Modern Experimental Techniques :

The study of Sodium metabolism in recent years was mainly done by the use of radioactive tracers.

They proved to be the ideal tools for the study of the problem. I would like to make it clear that many unjustified comments and conclusions are being made through misunderstanding of some scientific words. This certainly leads to confusion in quick, shallow or casual reading.

1 - Exchangeable Sodium, Na_{Ex} :

Before the use of radio-isotopes, our information was obtained from balance studies. Balance studies can tell what is going in, what is coming out, but never what is present in the body. The latter aspect could be revealed by chemical analysis done in a few post mortem cases.

The use of radio-isotopes enabled us to determine the physiologically active part. It is the part which exchanges quickly with the radioactive

tracer dose. Isotopes do not measure the rest of body sodium which potentially active and stored in bone.

Some workers compare figures of Na_{Ex} with figures of balance studies. It is clear that such comparison is not valid and should not be made.

2 - $2^{\prime\prime}_{4}$- Exchangeable Sodium, $2^{\prime\prime}_{4}$-Na_{Ex} :

The symbol Na_{Ex} must always be qualified. The values of 8-hour and 36-hour are different. The $2^{\prime\prime}_{4}$-Na_{Ex} is used because most of the exchangeable sodium in the body mixes with the tracer dose after $2^{\prime\prime}_{4}$ hours and because of its convenience in clinical work.

3 - Total $2^{\prime\prime}_{4}$-Na_{Ex} and $2^{\prime\prime}_{4}$-Na_{Ex} / Kg. :

In any scientific discussion the expression

Na_{Ex} must be either proceded by " Total " or followed by " / Kg. ". More than one example can be found in the literature where the whole discussion is mixed up, as well as the reader, due to unspecified words. The following is an example : A person starts to put on weight in the form of muscle. The exchangeable sodium is measured before and after. Comparing the total exchangeable sodium there will be a difference comparable to the amount of sodium retained in the new muscle. Comparing the Na_{Ex}/Kg. no difference should be expected because he retained sodium and put on weight at the same time. Accordingly somebody will comment : there is an increase in Na_{Ex}, while another may say there is no increase. So, it is always advisable to specify the word exchangeable.

4- Sodium Space :

Sodium space has nothing to do with sodium metabolism. Sodium space is supposed to mean or to give an approximate figure of the size of the extracellular space. An increase in the sodium space may very well be associated with normal or even less than Na_{Ex}/Kg.

5 - Sodium Retention :

It seems that the word retention always casts a pathological shadow on its meaning. A pregnant woman retains sodium for the development of the foetus. This is a physiological process and there is no mystery about it. If a pregnant woman retains more than what is required, then this should be called abnormal retention.

Sodium Balance :

In a temperate climate the average daily intake of Na is 100 milliequivalent / day. About 90 mEq. are excreted in urine, and the rest, 10 mEq. in feces and sweat. An internal turnover of huge amount occurs in the kidneys, where 24000 mEq. are filtered daily in the glomerular filtrate and reabsorbed back, and in the gastro intestinal tract where 685 mEq. of Na are excreted daily, (Wilkinson, 1960).

Bone and Sodium Metabolism :

Bone which has always been considered a supporting structure turned out to be an active participent in physiologic processes concerned with electrolyte metabolism.

Kaltreider and his colleagues calculated that

one third of total body sodium is present in bone, (Kaltreider, 1941). Kaltreider also discovered that only 35% of total body sodium is exchangeable with ^{24}-Na after 24 hours.

The precise chemical association of Na in bone is not known. There is good evidence to support the hypothesis that this cation is present at the crystal surface as a double salt of carbonate: Ca - O - CO_2 - Na.

The skeleton comprises a large mineral mass deposited in or on a collagenous ground substance. These electrolytes are in dynamic equilibrium with ions in the surrounding extracellular fluid. The bone bank, as Owen calls it, stabilises serum Ca & Mg concentrations and contributes substantial amounts of Ca, K, Na, and CO_3 to the base economy of the body during periods of stress, (Owen, 1952).

The mechanism which governs this blood-bone equilibrium has been revealed by Albright to be endocrinal in the case of calcium. This may prove to be the case with other cations, (Albright, 1948).

So the skeletal system is not only the supporting frame of the body and the shelter of the haemopoietic system but also a great mineral reservoir.

Distribution of Sodium in the Body :

A human body weighing 70 Kg. contains 5000 mEq. of sodium. The bones contain 3000 mEq., of which only 1000 mEq. is exchangeable. Apart from skeletal sodium, the remaining 2000 mEq. are all exchangeable and are distributed as follows:-

1500	mEq.	Extracellular
200	mEq.	Intracellular
300	mEq.	Gut contents
2000	mEq.	

Total

These figures are easy to remember but they belong to a person weighing 70 Kg. while the weight of the non pregnant British female is 55 Kg. according to Thomson and Billewicz (1957) analysing 412 cases. Thus the average total Na content of non pregnant woman is 3930 mEq.

Relation of Age to Na_{Ex} :

Edelman et al. (1954) revewing the available figures and adding their own, classified the data according to age groups. They found that whether in men or in women Na_{Ex}/Kg. is the same in different age groups. Macgillivray et al., con-

firmed these results, (1960).

Sex and Na_{Ex} :

Edelman et al. compared male and female figures. They found a difference of 2.9 mEq. /Kg., but that difference was statistically non significant.

What is the Normal Average Na_{Ex} / Kg. ?

41 ± 5 mEq. / Kg. body weight is the figure which was put by Edelman et al. to represent a normal standard reference for human adults. The figure is quite satisfactory and agrees with results of other workers, (Forbes & Perley, 1951; Warner et al., 1952; Miller & Wilson, 1953; Klein & Carey, 1957; Macgillivray et al., 1960).

Equation to Predict the Total Na_{Ex} :

As the Na_{Ex} content / Kg. is the same in

adults of same age men or women, and as a working figure is agreed upon, Macgillivray et al., introduced the following equation : (Macgillivray et al., 1960).

$$\text{Total } Na_{Ex} = 67\,W - 7398\,R + 1233$$

W = weight in Kg.

$R = W/H$ = Kg. / cm.

It is important to remember at the same time that there is no close relationship between height, weight, fatness, muscle mass or bone weight; therefore estimation of body content of Na, K, water or any other constituent which are not based on direct measurement in the individual must be subject to large error, (Wilkinson, 1960). In spite of this fact, tables and equations are of value in judging the effect of disease and in designing suitable treatment.

P O T A S S I U M .

Potassium is the main intracellular cation. Its concentration in the extracellular fluid must be kept constant. Any sudden change an increase or a decrease, leads to serious and drastic effects. A sudden rise in serum K concentration will cause sudden death due to its cardioplaegic effect.

Potassium Balance :

The daily intake of potassium is 50 - 150 mEq. It excreted mainly in urine, about 80%, the remaining 20% are excreted in the feces. After absorption from the intestines potassium is carried to the cells by the extracellular fluid. The rapid uptake of potassium by the cells prevents any increase in its serum concentration.

Body Content of Potassium :

Macgillivray and Buchanan (1958) reported

that the total K_{Ex} in non pregnant women was 43.6 mEq./Kg. Comparing these figures with those obtained by previous chemical analysis, Rhodes (1960) believes they match fairly well.

As in case of sodium, potassium is stored in a relatively inactive form in the muscular system. Skeletal muscle contains 360 mgm./100 g. compared to bone which contains 61 mgm./100 g. (Macgillivray et al., 1960).

Equation to Predict Total K_{Ex} :

Macgillivray et al. (1960) estimated K_{Ex} in 52 non pregnant females. They found that the K_{Ex}/Kg. tends to decrease with increasing age. The following formula was put to estimate the total K_{Ex} :-

$K_{Ex} = 53\,W - 5053\,R - 13\,A + 1603$

W = weight in Kg.

A = Age in years

R = Weight/ Height ratio Kg./cm.

The main fall in body potassium content with age occurs after 40 years suggesting it may be associated with menopause.

DYNAMIC ASPECT OF WATER

AND

ELECTROLYTE METABOLISM

The classification of the body into compartments and the constancy of the composition of the fluid on either side of the cellular membrane give a static picture which is far from the truth. Indeed body fluids and electrolytes are in continuous vigorous activity. This dynamic activity is essential for normal physiological and biological processes.

Water Turnover :

The turnover time of water in the body is the average length of time of a molecule of water to remain in the body. The turnover rate is the percentage of total body water changed every day. This was estimated to be 7.7% of total body water with no significant difference between males and females, (Schloerbe et al., 1950).

Apart from the total turnover of water in the body which refers to changes between the body and the external environment, there is a huge internal turnover which is summarised as follows:

1 - Eight or nine litres are secreted daily by the digestive glands (saliva, gastric juice, succus entericus, bile and pancreatic secretion) into the lumen of the bowel. They are completely absorbed except a very small loss in the faeces.

2 - A constant vast scale to and fro interchange is always taking place between the plasma and the interstitual fluid.

3 - In the kidneys 170 litres of water are filtered every day. Only 1.5 litres are secreted in urine and the remaining 168.5 litres are reabsorbed.

4 - Another small pool is in the brain where cerebrospinal fluid is filtered through the choroid plexus and is reabsorbed back through the arachnoid villi in the cerebral venous sinuses.

Movement of Water and Electrolytes :

It is rather difficult to discuss the movement of water and the movement of electrolytes separately. In the past osmosis was supposed to be the controlling factor in the movement of water between intracellular and extracellular compartments to keep the osmolarity the same on either side of the cellular membrane. In our present stage of knowledge although it is possible for water to traverse the cell boundary, yet it seems likely that on the whole there is a close association between water and ionic shift which

is normally accompanied by movement of water, (Wilkinson, 1960).

Transfer Between Intravascular and Interstitual Compartments :

The control of passage of fluids across the capillary wall in both directions depends upon :

1 - Hydrostatic pressure of plasma within the vessels.

2 - Plasma proteins osmotic pressure.

3 - Hydrostatic pressure of the interstitual fluid.

T his mechanism, which is the outflow o f fluid at the arterial ends of the capillaries and the its inflow at the venous end, is by no means the same allover the body.

Under certain circumstances there is an out-

flow of fluid throughout the length of the capillary, while the fluid returns to the venous side via the lymphatics, (Chambers, 1948).

Another example is the portal system where the hydrostatic pressure is so low that fluid exchange would be impossible if the vessels were not unusually permeable to albumen and thus allows the fluid to cross their wall, (Wilkinson, 1960).

Movement Across the Cellular Membrane :

The nature of the membrane varies widely. It may be one layer of molecules interferring with otherwise free diffusion. Sometimes it is multiple molecular layers with specific activities controlling or promoting the movements of substances in or out of the cell.

It was thought in the past that the cell mem-

brane completely segregates potassium from sodium. Now we believe the cell membrane is permeable to both. There are two ways by which transfer across cell membrane can take place.

The first is by permeation which is passive transfer through the pores which some believe to be actual openings in the membrane. The second is active transport by one of the following methods :-

(a) A complex molecule which is soluble in the cell membrane may be formed with the substance to be transported.

(b) A complex is formed with a carrier molecule which is itself part of the membrane. Later breakdown of the primary complex and the formation of another complex which works in the reserve direction takes place.

(c) The movement of a charged particle leaves unoccupied an oppositely charged particle which may be balanced by the movement of another particle of suitable charge.

The rate of movement depends upon the number of molecules bombarding the cell membrane, the shape and diameter of molecules in comparison to those of the cell membrane. Potassium molecules penetrate more rapidly as its diameter is 3 Å while that of sodium is 4.5 Å.

WATER, ELECTROLYTES AND MENSTRUATION

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Normally what is lost of water and electrolytes in the menstrual flow is very little. It is usually 50 - 150 ml. spread over a period of 3-4 days. It is estimated that 50 ml. loss contain 4-5 mEq. of Na^+ and 2-5 mEq. of K^+, (Thorn et al., 1938).

Changes During the Menstrual Cycle :

Morton (1950) found variable changes in serum Na^+ and K^+ during the menstrual cycle with a tendency to lower Na^+ level before menstruation which he attributed to water retention.

Using ^{22}Na Ansell and Clark (1956) compared men and women. The biological half life of ^{22}Na in men was 9-10 days, while in women it was spread over a range from 9-21 days showing Na^+ retention during the menstrual cycle, at least,

in some of them.

In 1957 Klein & Carey using ^{22}Na and by repeated estimations of total Na_{Ex}, came to the conclusion that there was no significant relation between Na_{Ex} and the menstrual cycle.

Chesley & Hellman (1957) found that Na^+ retention was not maintained at the premenstrual period even when a woman was put on a high sodium intake.

Sodium Retention in Premenstrual Tention :

The difficulty in studying such a problem is that there is no agreement about the range of normality. Some consider a certain degree of pain or discomfort and other associating symptoms as normal, while others consider them symptoms of dysmenorrhea or premenstrual tention.

Nevertheless, there has been recently gathering evidence supporting the suggestion that abnormal sodium retention is an important factor in causing premenstrual tention:

1 - The symptoms are mainly nervous : headache, irritability, depression, insomnia, nausea and vomiting. In a recent paper by Gibbons (1960) a direct relation between Na_{Ex} retention and symptoms of depressive psychosis was found, (Gibbons, 1960). The same relation was found in cases of recurrent schizophrenia, (Schottstaedt, 1959).

2 - A marked increase in aldosterone was reported recently by Prunty (1959).

3 - Good results are obtained by treating premenstrual tention with progesterone, (Rees, 1953;

Greene & Dalton, 1953). Progesterone has been described by Prunty as having a marked natriuretic effect, (Prunty, 1959).

RENAL HANDLING

OF

BODY WATER AND ELECTROLYTES.

The renal tissue is responsible mainly for regulating body water and electrolytes, being able to modify the amount excreted of each. Messages are carried by the endocrine system, which react according to the information obtained from chemo, mechano and osmoreceptors.

I - GLOMERULAR FILTRATION :

This is a simple physical process of filtration of plasma through a semipermeable membrane which is Bowman's capsule. The glomerular filtrate which reaches the proximal part of the convoluted tubule is chemically identical with plasma without its proteins, having the same pH and the same osmolarity.

Filtration is controlled mainly by physical factors. The effective filtration pressure = 75-

25 = 50 mm./Hg. (Bayliss, 1925). The effective filtration pressure depends upon the efficiency of the cardiovascular system. In cases of shock when the blood pressure drops to 80 or 75 mm. / Hg. the process of glomerular filtration stops. The same result will take place if there is a back pressure following distal obstruction. The normal rate of glomerular filtration is 120 ml. per minute, that is 170 litres every 24 hours.

It is presumed recently that some plasma proteins leak through Bowman's capsule with the glomerular filtrate, but it is promptly reabsorbed in the proximal tubules and a balance is maintained. Accordingly proteinuria is either due to :

1 - Excessive leakage through Bowman's capsule e.g. acute nephritis i.e. a glomerular defect.

2 - Failure of reabsorption of normal leakage i.e. a tubular defect.

TUBULAR REABSORPTION :

This is selective reabsorption of water and chemicals including electrolytes from the glomerular filtrate as a result of an active vital function of tubular cells. The process of tubular reabsorption is largely but not entirely responsible for converting the glomerular filtrate to urine. Of the 170 litres filtered every day 168.5 litres are reabsorbed. Of an average of 560 g. of Na filtered daily, 555 g. are reabsorbed.

(1) Reabsorbtion of Water and Electrolytes Through the Proximal Convoluted Tubules :

While all the amount of K^+ in the glomerular filtrate is reabsorbed in the proximal tubule, only

80% of Na^+, Cl^- and water are reabsorbed. This process is largely controlled by suprarenal cortical hormones, cortisone and aldosterone. In Addison's disease the patient is unable to absorb Na, Cl and water so he becomes hyponatraemic, hypochloraemic and dehydrated. Such a disturbance can be corrected by the administration of steroids, (Bayliss 1955, Berliner 1950).

(2) Reabsorbtion Through the Distal Convoluted Tubules :

A - Water

The remaining amount of water which has to be reabsorbed, that is 20% of the total amount, is absorbed through the distal tibules by two distinct mechanisms :

A.D.H. Dependent Mechanism :

Under the influence of A.D.H., isosmotic re-

absorption of water takes place. The presence of A.D.H. is essential. In its absence the solutes will not promote water reabsorption.

A.D.H. Independent Mechanism :

At a more distal site water is reabsorbed without solutes and this is called T^cH_2O (Smith 1951, Wesson & Anslow 1952). This process is independent of the presence of A.D.H. The amount which is reabsorbed depends upon the solute concentration, with a maximum rate of 5 - 7 ml./min. Normally about 15 ml. are delivered at the distal tubules. Of this amount 90 % is reabsorbed with solutes under the effect of A.D.H. leaving 1.5 ml. of isomotic fluid to reach the T^cH_2O zone. According to osmolarity .5 ml. is reabsorbed and the remaining 1 ml. is excreted as urine.

In the absence of A.D.H., of the 15 ml. reaching the distal tubules 90% of the solutes will be reabsorbed but non of the water. Accordingly the whole 15 ml. will reach the $T^{c}H_{2}O$ zone but in a dilute form; thus readjustment up, to the extent of 6 ml. will take place leaving 9 ml. to pass as urine containing the same amount of solutes which urine contains in one ml. in normal cases.

Smith, Wesson and Anslow's Hypothesis is highly significant because it establishes a mechanism for concentrating urine in the absence of A.D.H. It also provides a sound basis for understanding the circumstances under which hypertonic urine may be found in experimental and clinical diabetes insipidus without having to invoke the hypothesis of incomplete lesion, (Welt, 1956).

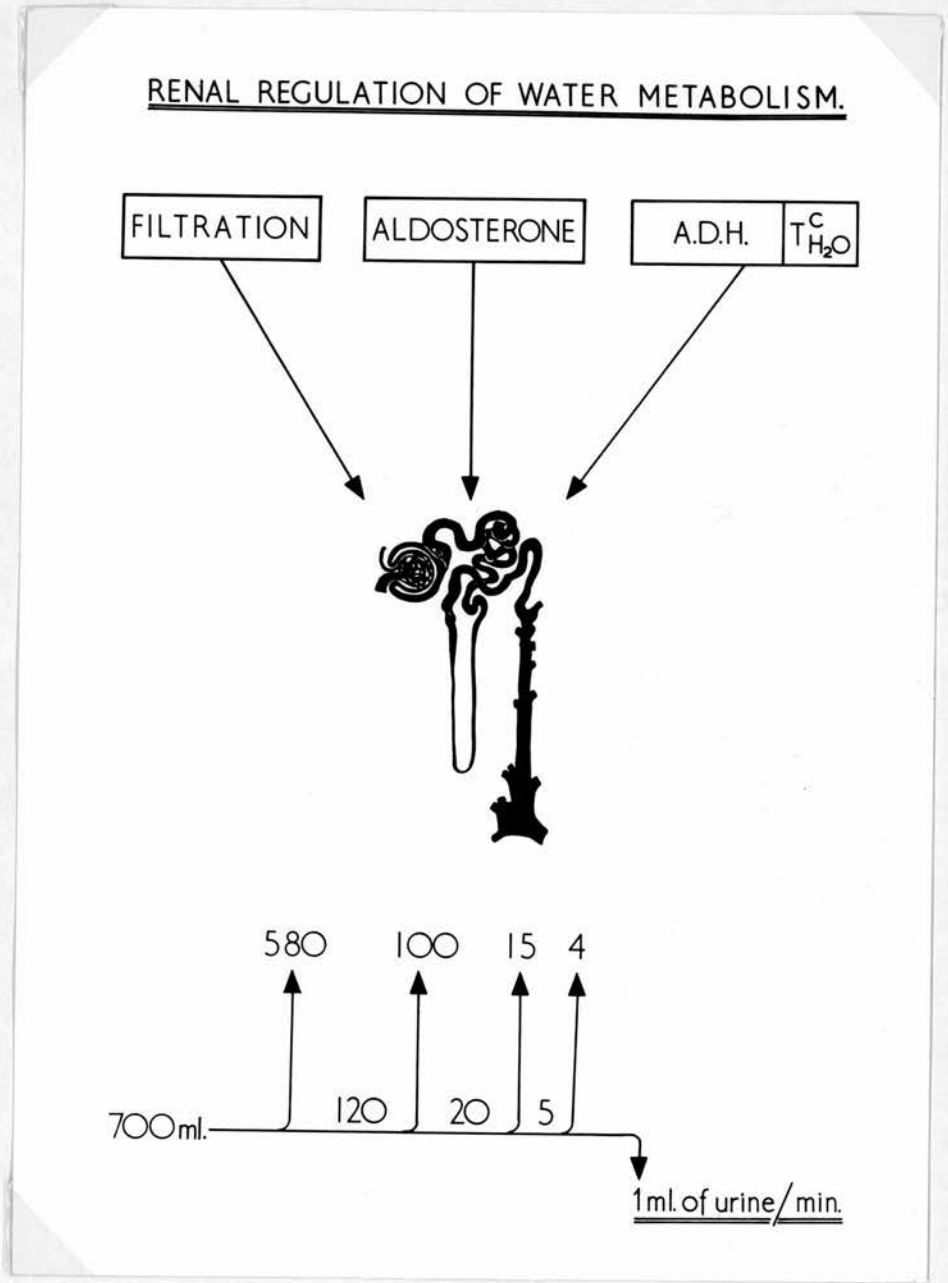
RENAL REGULATION OF WATER METABOLISM.
FILTRATION
ALDOSTERONE
A.D.H.
$T^{c}_{H_2O}$
580
100
15
4
700ml.
120
20
5
1ml. of urine/min.

Fig. 4.

B - Sodium

Twenty per cent of sodium is absorbed through the distal tubules. The amount of sodium reabsorbed is engaged in a very important mechanism of homeostasis, to keep a constant pH of body fluids.

The tubular fluid reaching the distal tubules is a mixture of acid sodium phosphate and alkaline sodium phosphate in the ratio 1 : 4. The tubular cells have the ability to manufacture H^+ by virtue of their carbonic anhydrase. Simple exchange occurs between H^+ and Na^+.

$$Na_2HPO_4 + H^+ \longrightarrow NaH_2PO_4 + Na^+$$

This mechanism which conserve the body Na^+ reserve, leads to the formation of acid urine with of a proportion of acid to alkaline phosphate 9 : 1.

The liberated Na^+ is reabsorbed.

The more acidic the body fluids are, the more H^+ will be available and more sodium will be conserved. In some circumstances there is a tendency to acidosis, the kidney will then bring another mechanism into action. Ammonia will be produced by the tubules. Ammonia will replace Na^+ which is conserved to combat acidosis.

Na Lactate + Ammonia ----- Ammonium Lactate + Na^+

(Frank & Mayer 1947, Ladd 1952; Ussing 1954).

III - TUBULAR EXCRETION :

This is the main mechanism by which K^+ is excreted from the body. It has been observed that in cases of hyperkalaemia there is more excretion of K^+. It is believed that H^+ liberated by the action of carbonic anhydrase and K^+ occupy the

same pathway. This pathway allows only one element at a time. In cases of hyperkalaemia H^+ will be retained leading to hyperkalaemic acidosis. While in cases of K^+ deficiency this pathway will be engaged in excretion of H^+ leading to hypokalaemic alkalosis.

Another mechanism of K^+ excretion is controlled by the amount of Na^+ reabsorbed in the distal tubules. The more Na^+ is reabsorbed the more K^+ is excreted. That is why patients receiving hydrochlorothiazide are liable to loose K^+. The main action of this drug is to stop Na^+ reabsorption in the proximal tubules. The fluid reaching the distal tubules will be rich in Na^+, accordingly more Na^+ will be reabsorbed in the distal tubules and more K^+ is excreted in the urine leading to hypokalaemia, (Robertson, 1960).

The way the kidneys deal with body water and electrolytes represents an intricate biological activity responsible for the constancy of the milieu intérieur.

HORMONAL CONTROL

OF

BODY WATER AND ELECTROLYTES

I. PITUITARY GLAND :

1 - Anterior Lobe ------- Growth Hormone

2 - Posterior Lobe ------- A D H .

II. SUPRARANAL CORTEX :

1 - Mineralo Corticoids ----- Aldosterone
Sodium Losing
Hormone

2 - Gluco Corticoids -------- Cortisone &
Corticosterone

III. SEX HORMONES :

1 - Androgen.

2 - Oestrogen.

3 - Progesterone.

IV. CHROMAFFIN SYSTEM :

Serotonin.

V. THYROID GLAND :

Thyroxin.

A N T I D I U R E T I C H O R M O N E

The Discovery of ADH :

Back in 1916, the phenomenon of water diure-

sis attracted the attention of Haldane & Priestley (Haldane & Priestley 1916, Priestley 1916, Priestley 1921). They studied the blood changes accompanying this remarkable renal response. They found that there was a small increase in the ratio of water molecules in plasma. They drew an analogy between such sensitiveness of the kidney to the response of water molecules in the plasma and that of the respiratory centre to CO_2 concentration in the blood.

As long ago as 1913, it was proved by Von Den Velden and by Farini that water diuresis is checked by injection of posterior pituitary extract, (Verney, 1958). In 1938 Ranson, Fisher & Ingram produced experimentally diabetes insipidus by destroying the neuro hypothesis, (Verney, 1958).

The experiments of Verney & Starling were quite interesting. They found that similar diuresis occurred when a dog's kidney was perfused in an isolated state, (Verney & Starling, 1922). This diuresis was inhibited when posterior pituitary extract was added to the perfusing blood (Starling & Verney, 1925), or by the passage of this blood into pituitary containing blood, (Verney 1926). All this work lead to the conclusion that the profuse water diuresis exhibited by the perfused isolated kidney is due to divorce of the kidney from the inhibitory influence of the posterior pituitary antidiuretic substance. Water diuresis was accordingly described as a condition of physiological diabetes insipidus.

Chemistry of A D H :

The chemistry of ADH was investigated by Du

Vigneaud (1953) and his co workers. The hormone contains 8 aminom acids : aspartic acid, cystein, glutamic acid, glycine, proline, tyrosine, phenylalanine and arginine. The synthesis of an octapeptide amide with biological activity has been accomplished, and a structure formula has been proposed.

How Does A D H Promote Water Absorbtion ?

The definite answer is not known, but there are several possibilities :

1. It might operate to fulfil some of the requirements of the osmotic diffusion pump described by Frank & Mayer, 1947.

2. Wirz, 1954 suggested that it might reduce the calibre of the distal extremity of the loop of Henle.

   Koefoed et al., 1953 proposed increase in the

number or the size of the pores in the cellular membrane.

Factors which Affect the Release of A D H :

1. Some suggest that a decrease in the volume of body fluids, irrespective of osmolarity, can release ADH, (Welt 1955, Welt & Orloff 1951).
2. Disagreable and painful stimuli increase ADH secretion.
3. Morphia and anaesthetic agents increase ADH concentration in the blood (Pickford, 1952).
4. Ethyl alcohol appears to be unique in its ability to supress the secretion of A D H, (Kleeman et al.).
5. Relman and Schwattz (1955) have reported on the impaired ability to produce concen-

trated urine in response to administration of ADH in patients with K depletion. Potassium depletion interferes with the energy yielding reaction that is related to water transport. Another explanation is that the cells allow one way traffic; if they are engaged in K excretion water reabsorption will be interferred with.

A D H and Electrolytes :

At one time it was suggested that ADH controls the osmolarity of the extracellular fluid, not only by retaining water but also by a natriuretic effect. Black & Thomson found no supportive evidence of such effect, (Black & Thomson, 1951).

However, there is no doubt that the sustained action of administered ADH in overhydrated sub-

jects is associated with increased Na excretion, (Leaf et al., 1953). This is a secondary effect of the expanded fluid volume which probably supresses aldosterone excretion, (Wrong, 1956).

GROWTH HORMONE

Luft et al., 1954 proved that Na retention and expansion of the extracellular space occurs in acromegaly. It has been proved recently that the growth hormone in sufficient dosages causes sodium retention exceeding its anabolic effect.

SUPRARENAL CORTEX

ALDOSTERONE.

The natural hormone aldosterone was discovered in the course of search for new compounds in adrenal extract of a potent biological activity.

With the aid of new methods of chromatography the new hormone was isolated in 1952 (Simpson et al., 1954, Simpson et al., 1954). The hormone is produced by the zona glomerulosa which is not under the direct control of ACTH.

BIOCHEMISTRY :

Aldosterone is unique among adrenal steroids in possessing an aldehyde group at position 18 . The method of assay is by no means finalised. Recent developments are aiming at methods with more strict criteria of physical and chemical purity of extracts for the use for chromatography, (Neher and Wettstein, 1956; Ayers et al., 1957).

The normal secretion rate of aldosterone was estimated by different workers : 170 - 190 µ g./ day (Ayers et al., 1957) 150 - 300 µ g. /day (Ulick et al., 1958) and 330 - 400 µ g. (Paterson,

1959). It was estimated that 250 μ g. /day was the maintenance dose in Addison's disease, (March et al., 1954).

The concentration of aldosterone in peripheral blood in normal subject is .04 - .08 μg. / 100 ml. (Paterson, 1959). The average amount of aldosterone in urine varies from 0 - 19μg. per day, (Avandann et al., 1956).

Biological Action :

The main action of aldosterone is to keep the constancy of the milieu intérieur. Aldosterone regulates the total amount of body sodium and its distribution between the extracellular and intracellular compartments. As sodium is the main extracellular cation, aldosterone is responsible

for the regulation of the extracellular water space.

Administration of aldosterone causes considerable retention of Na and rapid loss of K. Sodium retention is always associated with water retention for several days. Acting on renal tubules aldosterone causes Na retention and more excretion of K, (Mach et al., 1954; Speirs et al., 1954; Gross & Gysel, 1954). There is as well a fall in Na/K ratio in saliva and faeces, (August et al., 1958).

Energy from glucose metabolism probably maintains the differential concentration of Na and K on both sides of the cell membrane, (Dean 1941; Conway, 1947). Equilibrium is controlled by aldosterone which moves sodium out and potassium in the cells, (Prunty et al., 1955).

Thus, aldosterone maintains the extracellular concentration of Na by controlling renal loss, loss in sweat and by maintaining the equilibrium between intracellular and extracellular concentration by acting on the cell membrane, (Zilva, 1959).

Relative Electrolyte-Regulating Activity of Aldosterone Compared to Other Steroids :

Many naturally occuring steroids e.g. cortisol, cortisone, corticosterone, testosterone, progesterone, if given in large doses cause Na retention. That aldosterone is 2000 times as active as corticosterone was demonstrated by Desaulles , (Desaulles, 1958).

What Stimulates the Liberation of Aldosterone ?

(1) Plasma Electrolyte Level :

As aldosterone causes Na retention, it

was logic to expect that the Na level in extra-cellular fluid will control the liberation of aldosterone. It was found that a decreased sodium intake in diet and to a lesser extent an increased potassium intake has a stimulating effect on aldosterone excretion. It is important whenever assessing the urinary aldosterone excretion to take into consideration the Na content of the diet.

Which is More Important, Na Lack or K Excess ?

Na depletion causes increased aldosterone excretion. It was proved that such increased production is only possible if potassium is provided in the diet. There are other evidence that potassium may influence aldosterone irrespective of the presence of sodium, i.e. in an independent way. Subjects on Na free diet who cannot accumulate

more sodium show a reduction in aldosterone when potassium is also deprived, (Bartter, 1956). It is interesting to note that the yield of aldosterone from a perfused beef adrenal is enhansed by a perfusion fluid which is rich in potassium, (Rosenfeld et al., 1956).

So, it is concluded that both Na & K affect the liberation of aldosterone. Potassium can affect its production in the absence of sodium in diet, but the presence of potassium is important for sodium to act.

(2) Extracellular Fluid Volume :

The interesting observation that increased body fluid volume by injecting pitressin causes decreased production of aldosterone , despite the reduced Na concentration of plas-

ma, lead to the conclusion that there must be another important stimulus for its control, (Liddle et al., 1955; Beek et al., 1955; Muller et al., 1956).

It was demonstrated experimentally that a fall in blood volume in the head region is a stimulus to increased aldosterone production, (Bartter, 1956; Liddle et al., 1956). An increased aldosterone production takes place even when slight pressure is applied to the carotid arteries. This response is abolished if the vessels are denervated, (Bartter et al., 1959; Mills et al., 1958).

The accepted view now is that the greatest stimulus for the liberation of aldosterone is a fall in the intravascular volume, (Bartter et al., 1957). This is mediated in part at least by me-

chanoreceptors on carotid nerve endings, (Bartter et al., 1959).

Clinical Conditions which Causes Increased Aldosterone Excretion :

(Coghlan et al., 1960) :

1 - Na depletion and K loading.

2 - Diminution of intravascular volume (haemorrhage, water depletion, sweating, post operative metabolic response).

3 - Conditions associated with oedema and ascites.

4 - Endocrinal disturbances : Hyperthyroidism, hypothyroidism, pregnancy, insulin shock.

5 - Conn's Syndrome.

6 - Central nervous system disturbances : anxiety states, mid brain vascular lesions.

Pituitary Control of Aldosterone :

Endocrinological thought has been dominated by the concept that the pituitary gland is the conductor of the orchestra. It was natural to suppose that the secretion of aldosterone was primarily controlled by some trophic hormone, elaborated in the anterior hypophysis.

This speculation turned out to be inaccurate. The partial independence of the suprarenal cortex was proved after many clinical and experimental observations. Serious Na depletion which occurs in Addisons disease seldom if ever develops in panhypopituitarism. In hypophysectomised animals, there is atrophy of the inner two zones of the suprarenal cortex, but the zona glomerulosa, the outer most, remains intact. It was proved that

hypophysectomy whether surgical or medical by prolonged administration of cortisone has little effect on aldosterone production, (Davis et al., 1959; Farrell et al., 1956).

However, it seems that the independence of the zona glomerulosa is not complete, still it is a satellite of the pituitary. It is believed that some trophic pituitary factor is required to maintain the resposiveness of aldosterone secreting cells but it need not imply that such a factor regulates its secretion. There are also reports which indicate that ACTH may play a part in aldosterone production. It may enhance but does not initiate it, (Hermando et al., 1957).

The Role of the Pineal Gland :

Farrell has suggested and tried to prove that

the pineal gland may be the source of a humoral substance regulating aldosterone secretion, (Farrell 1959). The pineal extract increases aldosterone production (Farrell, 1956).

But it seems clear from subsequent experimental work that this extract is not essential for normal aldosterone response to Na^+ deficiency nor does it appear that the decrease in aldosterone production resulting from pinealectomy in similar preparations give a reason for regarding this structure as having other than its lartesian function, (Rauschkolb & Farrell, 1956; Farrell et al., 1959).

SODIUM LOSING HORMONE

The possibility of the presence of sodium losing hormone which would compete with Na retai-

ning hormone, aldosterone, was discussed by Bayliss (1958). There was some supportive evidence of its presence. A substance was isolated from urine during corticotrophin induced diuresis which promotes in animals the elemination of Na.

It was suggested that a similar substance may be formed in some patients with congenital adrenal hyperplasia. About 10% of these patients have a sodium losing syndrome with clinical picture like Addison's disease. The syndrome was aggravated by the administration of corticotrophin, (Prader et al., 1955). These patients excrete excess sodium in spite of a high rate of aldosterone excretion, (Luetscher, 1956).

Recently Neher et al., 1958 isolated a sodium excreting hormone from the urine of patients with

salt losing adrenogenital syndrome. In this condition a very low output of aldosterone occurs despite Na deficiency. This hormone has now been synthesised and may be a prototype of theraputic value in the treatment of oedema, (Blizzard et al., 1959; Neher et al., 1959; Desaulles, 1959).

GLUCO CORTICOIDS

Cortisone and other steroids of this group are secreted at a rate which is one hundred times greater than aldosterone. They are secreted by the inner zona fasciculata.

They have a weak aldosterone like action . The synthetic hormone, prednisone has still a weaker action. It is interesting to note that sometimes they have a natriuretic effect especial-

ly if a weak Na retaining one is administered after a more strongly active one. This effect may be partly due to increased glomerular filtration, (Carrod et al., 1955).

Another important action of cortisone from the clinical point of view is to maintain the normal response of the tubules to diurnal variation in water excretion and to respond normally to increased water intake by permitting diuresis, (Carrod & Burston, 1952).

SEX HORMONES

Androgens in large doses may produce Na and water retention. The amount retained exceeds what is required for their anabolic effect. Such effect was noticed during treatment with ' Nilevar'

(Mc Swingy & Prunty, 1957). Oedema and sudden weight gain were observed in treating eunochoidism with large doses of testosterone.

Preedy and Aitken (1956) proved that oestrogens can cause retention of water. Evidence suggested that the site of action is the renal tubules where more Na and accordingly more water are absorbed from the glomerular filtrate. The same conclusion was arrived at in animals, (Thorn et al., 1958).

While oestrogens seem to help the kidney to conserve Na, progesterone works in the opposite direction, (Prunty, 1959). It seems that it is through this effect, the natriuretic effect, that good results were obtained after its use in the treatment of premenstrual tension.

S E R O T O N I N

Recently a new hormone was discovered, new in structure and in origin. It was isolated simultaneously by Rapport and Espamer (Espamer & Asero, 1952; Rapport et al., 1958; Rapport et al., 1958). The chemical structure of serotonin, 5 hydroxytryptamine (5 H T) was identified by Espamer, (Espamer, 1953).

Serotonin or its immediate precursor is produced by the entero chromaffin system in man;that is why large amounts are produced in the intestines where argentaffin cells are widely distributed. The hormone accumulates in the blood platelets after its formation to be transported to various sites. It is detoxicated in the mitochondria of the hepatic cells by monoamino oxidase which also im-

activates catecholamines and other pressor substances, (Schayer, 1955).

Biological Action :

1 - Haemodynamic action, a vasopressor effect.

2 - Stimulation of smooth muscles.

3 - Espamer demonstrated that (5 H T) has a definite antidiuretic action which resulted in retention of Na, Cl and water in animals, (Espamer, 1953). Serotonin acts either by decreased filtration due to vasoconstriction of the afferent glomerular arterioles or by increased tubular reabsorption as was suggested by Spinazzola and Sherrod, 1957).

There is no doubt that hormones play a major role in the regulation of water and electrolytes in the human body.

THE ROLE OF THE CENTRAL NERVOUS SYSTEM

I N

WATER AND ELECTROLYTE METABOLISM

I . REGULATION OF BODY WATER.

What Releases A.D.H. ?

Verney demonstrated that the secretion of A.D.H. is stimulated by an increase in the effective osmotic pressure of the fluid reaching the receptors, which he called osmoreceptors,(Verney, 1947). He came to this conclusion after injection of concentrated Na Cl solution in the carotid brought under the skin of a dog, and demonstrating the resulting anti diuretic effect. He obtained the same result with glucose, sucrose but not with urea, which penetrates the cell membrane easily, so it does not increase the effective osmotic pressure.

It is interesting to note that salt deprivation leads to dilution of blood, but not to diu-

resis. It seems possible that when the change in the osmotic pressure develops very gradually, the osmo receptors become adapted and no longer respond in their normal manner. When water is administered in cases of simple salt lack, the osmo receptors do respond, but inadequately, as judged by delayed and drawn out water diuresis.

Where are the Osmoreceptors ?

It was concluded from the experimental work of Verney that the osmoreceptors are somewhere in the vascular area of the common carotid artery, probably in the hypothalamus.

In 1953 Euler measured a potential difference with electrodes placed in the frontal sinus and the exploring electrode in the supreoptic nucleus, in cats. A slow potential change was recorded in

response to an injection of 2% Na Cl solution into the carotid artery, and a potential difference in the opposite direction was noted when the same volume of tap water was administered.

In 1957 Jewell & Verney measured the antidiuretic response to intra carotid infusions during established water diuresis, before and after intradural ligation of one or more branches of the internal carotid, whereby the blood carrying an osmotic stimulus was deflected from or directed to defined regions of the brain. Their results showed that the only part of the brain from which osmotic antidiuretic response has been invariably elicited was the part of the hypothalamus well anterior to the mamillary body. This osmoreceptive zone contains the dorsomedial, ventromedial, supraoptic and the para ventricular nucleus.

There is evidence that the responsiveness of the osmoreceptors depends on nervous integrity of the paraventricular nucleus of the hypothalamus and that the posterior lobe of the pituitary serves as a storage site from which the hormone can be released to the general circulation.

II. REGULATION OF ELECTROLYTES.

The possibility of cerebral regulation of electrolytes was studied by crossed-circulation experiments in dogs. The head of one animal was isolated from its truck except for nervous connection, and perfused with the blood of another animal, (Foldi et al., 1957).

Using this humorally isolated head a reflex increase in sodium excretion followed intracaro-

tid infusion of hyperosmotic solution of Na Cl, (Kovach et al., 1959). This was due to diminished tubular reabsorption as the Na^+ concentration in the glomerular filtrate did not change. There was no change in K^+ excretion but there was a definite diuretic effect. It is clear that in such preparation the natriuretic and the diuretic results are independent of the A.D.H. action which is liberated as well after intracarotid injection of hyperosmotic saline, (Verney, 1947).

As such a response could not be reproduced in adrenalectomised animal maintained by cortisone, they concluded that the increase in Na excretion is due to discharge of neural impulses which act through the adrenals, by regulating the liberation of aldosterone and Na losing hormone.

At this stage two questions arise: the first question. Is there a centre regulating aldosterone secretion ? and if such a centre exists, where does it exist and how does it respond to variations in homeostasis ? Is it a direct response to change in osmolarity of the extracellular fluid ? Is it through direct nervous connections from the osmoreceptors or does A.D.H. play a part ?

Our state of knowledge is far from complete in spite of the extensive work done, (Holzbauer & Vogt, 1959; Mills et al., 1958; Davis et al., 1959; Bartter et al., 1959; Farrell et al., 1958). When decapitation and midcollicular decerebration greatly reduced the secretion of aldosterone in dogs, the possibility was raised that there is an area

in the mid brain crucial to aldosterone secretion, (Newman et al., 1958, Newman et al., 1959).

What is clear is that we have to wait for the final answers of many questions regarding the cerebral control of electrolytes.

- - - -

WATER METABOLISM DURING PREGNANCY

NORMAL AND ABNORMAL

Water is retained in the body during pregnancy. It is required for the growing foetus and for the liquor amnii. A total increase in the blood volume is necessary to fill the growing uterine vascular tree. More than 6 L of fluid must be retained during pregnancy to allow for cellular growth of the products of conception.

The Amount of Water Retained during Pregnancy :

Before the availability of isotopes for total body water measurement it was not easy to estimate how much water is retained during pregnancy. One way was to find out the amount lost during labour and puerperium. Chesley (1944) made an estimate of 6.1 L which accorded well with his thiocyanate estimation of extracellular volume of 6.3 L. Stander & Pastore (1940) found an average

weight loss of 8.41 Kg: 5.43 Kg. at delivery, 2.3 Kg. during the first 10 days of puerperium and .68 Kg. between the second and the sixth week.

Another method was to take the gain in weight as a measure for the amount of water retained. Chesley (1944) in an excellent paper analysed results from 19 articles comprising 11960 cases. He found an average total weight gain of 24 lbs. (range 13.3 - 37.4, S.D. 10.8 lbs.).

Rhodes (1960) calculated the average total weight gain in pregnancy to be 11 Kg. follows :-

Foetus	3.2
Placenta and membranes	.5
Liquor amnii	1.0
Uterus	1.0
Breasts	1.4
Extracellular fluid	4.0
	11.1

Distribution of Retained Water :

Chesley estimated the available water of the foetus as 80 % of its body weight. The water content of the placenta was estimated as 82 % of its weight, (Chesley & Boog, 1943).

Recently Hawkins & Nixon (1958) have examined biopsies of the uterus obtained at Caesarean Section and found that 80 % of its weight was water, and 75 % of its water was extracellular . At term the uterus weighs about 1 Kg., so it holds about 800 ml. of water.

The breasts gain about 1 Kg. although they contain much fat which is poor in water.

The blood volume expands in pregnancy by about 20.25 %. A normal blood volume of 4 - 4.5 L will expand by 1 - 1.5 L in pregnancy.

Chesley (1944) using the thiocyanate method found the mean increase in the extracellular fluid to be 6.3 L of which 1 L is held in blood, plasma one litre in the liquor amnii leaving 4.3 L to be accomodated in the tissue spaces.

Rhodes (1960) summarised the distribution of retained water as follows :-

Foetus	.96
Placenta	.41
Liquor	1.00
Blood	1.00
Uterus	.60
Breasts	.50
Maternal Tissus Spaces	1.40
	5.87

Oedema During Pregnancy :

It was only in 1797 that oedema and eclampsia were related by Demaret, (Nordenstrahl, 1952).

More detailed investigations of this question were undertaken between 1903 and 1916 by Zangenmeister who examined this relation from the clinical point of view. He coined the expression "hydrops gravidarum". He was the pioneer of the belief that water is the "toxin" of pre-eclampsia.

The total plasma proteins decrease during normal pregnancy. This is due exclusively to diminution of serum albumin. The total globulin may be slightly increased due to a rise in fibrinogen and beta globulin, (Eastman, 1930; Neuweiler, 1948).

There was an agreement that during pregnancy the capillary permeability is increased with consequent more filtration of fluid and increased protein concentration in the capillary filtrate.

The greatest changes were found in patients with massive oedema, (Albers, 1939; Micale and Bozzo, 19[illegible]; Szontagh, 19[illegible]9).

In pre eclampsia the tissue pressure is increased, (Dieckmann, 19[illegible]2). Tissue pressure may be higher than normal capillary pressure in certain cases of pre eclampsia, (Mukherjee and Govan, 1950).

Total Body Water and its Turnover :

The Study of turnover rates became possible after the availability of radioisotopes, (Haley & Woodbury, 1952). Hutchinson et al., (1953) studied total body water by repeated estimations during the course of pregnancy. The total body water expressed as % body weight exhibited no consistent changes during the second and third

trimester, but drops to its lower value in the immediate post partum period.

The turnover rate was studied in animals. In human beings it was originally investigated by Hevesy & Hofer (1934) and later by Schloerb et al., (1950). They found the disappearance constant to be .077/day or a turnover rate 7.7 % of total body water / day with a standard deviation ± 1.2 % with no difference between males and females.

Haley & Woodbury (1952) determined the turnover rate in 3 normal pregnant patients. There was no difference between the non pregnant and the normal pregnant patients.

Later Hutchinson et al., (1953) in a comparative study using pregnant women, normal, pre-

eclamptic and hypertensive found that the turnover rate is slow in pre-eclampsia. The turnover time in pre-eclamptic patients which is the average length of time of a molecule of water to remain in the body is considerably increased. This was attributed to the availability of a larger pool or an inherent defect in water metabolism. The turnover rate in hypertensive patients was considerably higher than in normals and pre-eclamptics as seen in the following table:-

Type	Number	λ	Turnover time/days
Pre-eclampsia	6	.058	18.4
Essential Hypertension	4	.090	10.9

They pointed that although such finding is compatible with the pathologic changes in essential hypertension yet the picture is complicated

by pre-eclampsia or heart failure the turnover rate will change.

Recently water metabolism particularly in relation to obstetric problems is receiving more attention especially after the availability of modern tools of research which deliver accurate information.

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ELECTROLYTE ECONOMY DURING PREGNANCY

In any anabolic process there is always retention of the necessary elements required for building a new tissue: nitrogen, water and potassium for cellular elements, water and sodium for the associated extracellular space. The most outstanding example of such anabolic process is pregnancy.

I. SODIUM .

What is the amount of sodium necessary for pregnancy ?

The extra amount of sodium required during pregnancy is partly foetal and partly maternal for the development of the uterus, placenta and expansion of the extracellular space. This amount was calculated by Rhodes (1960) as 20.5 g. Na_{Ex} as follows :-

Foetus	5
Liquor amnii	2.3
Breasts and placenta	3.6
Extracellular fluid	7.6
Uterus	2.0
	20.5 g. Na_{Ex}

These figures were obtained by simple calculations from different information. They remain to be checked by direct measurements. So the next question arises:

How much Na_{Ex} is retained during pregnancy ?

Gray & Plentl by repeated estimations on the same group of patients found that they retain 510 mEq. Na_{Ex} i.e. about 12 g. or 20 mEg. / week during the second and third trimester.

Macgillivray's figure was 756 mEq. of Na_{Ex} (Macgillivray & Buchanan, 1958). These figures

agree with what is to be expected by theoretical calculation within the range of experimental order.

Gray & Plentl used ^{24}Na and measured the Na_{Ex} in six pregnant women repeatedly during the course of pregnancy. The absolute value for the total Na_{Ex} increased during pregnancy but when these figures were expressed as mEq / Kg. they remained essentially unchanged (39.3 mEq. / Kg. with a range 31.9 - 49.5 mEq. / Kg.).

They found also that although the rate of sodium retention was inconsistent and that the maximum retention may occur at any time during the second trimester yet the net gain regardless of fluctuations appear to be reasonably constant.

Is this the only amount of sodium retained ?

The figures of sodium retention during pregnancy obtained by balance studies were variable but on the whole higher than those of Na_{Ex} (Taylor et al., 1939; Hummel et al., 1936; Coon et al., 1934; Freyberg et al., 1938; Thompson & Pommerenke 1939). Chesley (1944) suggested a figure of 3 g. / week. According to this figure if sodium retained is osmotically active, at least 28 L of water would collect in the body which is not the case. The only available explanation is that the difference between the total sodium retained and that retained in an exchangeable form is stored in an inactive form in the bone bank.

Distribution of Retained Sodium :

Between half and two thirds of the amount retained can be accounted for in the products of

gestation and the remainder is distributed in the expanded maternal extracellular space.

The concentration of sodium in the amniotic fluid is nearly equal to that of the plasma. As the average volume of the liquor amnii at term is 850 ml. i.e. it contains about 110 mEq. The newly born contains 47.5 mEq. / Kg. Na_{Ex}. It weighs 3.2 Kg. Thus it contains 152 mEq.

A high sodium concentration was found also in oedema fluid obtained through puncture in cases of pre-eclampsia with severe oedema, (Mukherjee & Govan, 1950).

Sodium Metabolism in Pre-eclampsia :

Until 1958 the trend of thought was always favoring the existence of abnormal sodium retention in pre-eclampsia. At the same time restric-

tion of salt in the diet which was originally advocated by Snoo (1938) was almost the rule in most centres. Two papers appeared which attracted much attention. The first demonstrated a controlled study using 2019 patients, (Robinson, 1958). She claimed that extra salt in the diet is essential for the health of the pregnant mother and her child. She treated twenty patients suffering of early pre-eclampsia by giving them extra salt in the diet. This work contradicted many previous contributions, all came to the same conclusion that administration of sodium in cases of pre-eclampsia aggravates the symptoms and precipitates the occurence of eclamptic fits, (Torbert & Cheney, 1936; Harding and van Wyck , 1931; Strauss, 1937; Dieckmann, 1950; Fuster, 19[illegible]).

The second contribution proved the existence of a statistically significant decrease in Na_{Ex}/ Kg. in pre-eclampsia, (Macgillivray & Buchanan, 1958). The following table demonstrates t h e average values of Na_{Ex} / Kg. :-

T y p e	Na_{Ex}/Kg.	S.D.
(1) Normal Pregnancy (late)	48.3	3.7
(2) Mild Pre-eclampsia	44.0	4.5
(3) Severe Pre-eclampsia	43.8	2.3

From the above mentioned figures they concluded:

There is no excessive storage of sodium in pre-eclampsia and water is stored without sodium.

Using ^{24}Na and denterium oxide Plentl & Gray (1959) measured the total Na_{Ex} and related it to total body water in order to minimise the dif-

ferences due to habitees. They found a significant increase in Na_{Ex} /Kg. and in sodium space related to total body water in pre-eclampsia. The average figures are in the following table :-

	Number of Patients	Na_{Ex}/Kg.
Non pregnant	16	40.2
Normal pregnant	18	39.6
Pre-eclampsia	15	46.0

All other workers agree that there is an abnormal retention of Na_{Ex} in pre-eclampsia and the difference is significant, (Dieckmann & Pottinger, 1957). It was found that this abnormal retention was directly proportional to the severity of pre-eclampsia (Moore, 1957). Others found that these biochemical disturbances continue to a certain extent in early puerperium, (McCartney and al., 1959). They concluded that individuals with

pre-eclampsia were unique in that they evidenced marked antepartum and post partum increase in Na_{Ex} / Kg. To get more accurate results their figures were related to lean body mass estimated by densimetric method.

In 1954 Gray & Plentl drew attention to an interesting point. When they were following their patients with repeated estimations of Na_{Ex} they found that in one patient who developed later pre-eclampsia there was an abnormal increase in Na_{Ex} /Kg. before the appearance of any of the clinical signs, (Gray & Plentl, 1954).

On both sides of the Atlantic the subject is receiving much attention.

II. POTASSIUM.

Potassium is retained for the development of

the foetus and the uterus. Rhodes (1960) estimated the amount required as 10.9 g. distributed as follows :-

Foetus	6.0
Placenta	1.0
Uterus	1.5
Breasts	1.9
Extracellular fluid	.5
	10.9

The amount of potassium retained every week was estimated by Coons et al., (1934) as 3.5 g /week. It is clear that the descripency is possibly due to its storage in the muscle and other tissues. If there is a generalised altered cell membrane permeability in pregnancy it is possible that the excess of sodium retained gains access to the cell interior and that potassium is held there to maintain the normal Na/K ratio. This

explanation was supported by the finding that in normal pregnancy, using muscle biopsy, the sodium content of the rectus abdominis and gastrocnemius rises, (Dieckmann & Pottinger, 1955).

Later it was found that the potassium content of the muscle does not increase in pregnancy (Dieckmann & Pottinger, 1956). This agrees with Hawkins & Nixon's finding in the myometrium for they found a rise in the intracellular sodium with no real loss of potassium.

MacGillivray & Buchanan (1958) using ^{42}K measured the K_{Ex} in non pregnant, normal pregnant and pre-eclamptic patients. Retention of potassium was found in normal pregnancy.

They found that the total amount of K_{Ex} retained in normal pregnant women is approximately

the same as in pre-eclampsia. The amount of K_{Ex} / Kg. was less in pre-eclampsia presumably owing to greater retention of water.

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WATER AND ELECTROLYTES

DURING

THE PUERPERIUM.

The puerperium is a period of tremendous physiological adjustment. Immediately after delivery of the foetus and the placenta, the body contains an excess of water and electrolytes, 3.5 L of water, 11 g. of sodium and 2.5 g. of potassium, (Rhodes, 1960). This excess is lost during the puerperium, mainly the first two weeks, (Stander & Pastore, 1940).

During the puerperium there are two additional sources of water and electrolyte loss : the milk and the lochia.

Milk Secretion :

Although the amount of milk secreted varies in different women, yet two weeks after labour the majority produce about 25 oz. daily, (Waller,

1959). Such daily output of about 550 ml. of milk means a loss of 6 mEq. of sodium, 8 mEq. of potassium, 8 mEq. of calcium and 8 mEq. of chlorides, which are covered adequately by an average normal diet.

Lochia :

The total quantity of the lochia is about 500 ml. (Greenhill, 1955) containing 40 - 45 mEq. of sodium, 20 mEq. of potassium and 40 mEq. of chlorides (Rhodes, 1960).

The excess of water left in the body is lost mainly during the first 4 days as follows :-

1- 300 ml. of blood is lost immediately after labour.
2- 375 ml. lochia lost during the first four days.
3- 720 ml. milk " " " " " "

This amounts to 1.5 L. The remaining 1.5 L. are dealt with by the kidneys. The kidney func-

tion was investigated during the puerperium. (Sims & Krantz, 1958). Although the renal plasma flow was significantly decreased yet the glomerular filtration rate was normal and the filtration fraction was slightly elevated. Normal kidneys can deal easily with such a water load.

The water turnover during puerperium was studied by Hutchinson et al., (1953). It was extremely slow over the first 24 hours. Then it increased rapidly to almost twice its ante partum level. It returned to normal sometimes between the 2nd and the 5th day. This was explained by the post partum diuresis which was followed by a compensatory water intake.

More work is required to investigate the changes in body water and electrolytes during the puerperium in normal and abnormal conditions.

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HORMONES AND ELECTROLYTES

DURING

PREGNANCY.

The Role of the Placenta :

Sodium retention during pregnancy was attributed to the high serum levels of oestrogen and progesterone. This view was held for some time. Recently administration of oestrogen to non pregnant women resulted in water retention, but this effect was not permanent, (Preedy & Aitken,1956). Rhodes (1960) suggested hepatic ischemia interfering with the catabolism of oestrogens to be a possible explanation of water retention in pre-eclampsia.

It is doubted if placental gonadotrophins play any major role in water and sodium retention. Their maximum production is during the early months when water and sodium retention is minimal . Even if they play a role it must be an indirect

one through the supra renal cortex, (Behrman & Nieman 1955).

Pituitary Hormones :

There is increasing evidence that the anterior pituitary hormone are very active during pregnancy. Their possible role in the genesis of pre-eclampsia must be borne in mind, (Kellar, 1955). Anybody who is familiar with Cushing's Syndrome realises the role of ACTH in retaining sodium and water. Govan has suggested that the amount of pituitary gonadotrophins excreted is increased in pre-eclampsia, (Govan, 1952).

Cushing (1933) described how the sudden pouring into the C.S.F. of the posterior pituitary extract caused almost an explosion and a very

marked rise in the blood pressure which could explain the etiology of pre-eclampsia. The hypothesis agreed with the views of Zangenmeister (1917), It was demonstrated later that intravenous pituitary extract causes marked elevation of blood pressure in pre-eclampsia but little effect in normal pregnant women, (de Valera and Keller, 1938; Browne, 1943).

Many reports suggested an increase of ADH in pre-eclampsia, (Anselmino & Hoffmann, 1931 ; Anselmino et al., 1932). Theobald (1955) does not agree that the oliguria associating pre-eclampsia is caused by ADH due to lack of convincing evidence.

In 1955, Hawker could inactivate the anti diuretic activity of the posterior pituitary by

placental extracts from healthy pregnant women, but not from patients suffering of pre-eclampsia. The inhibitor present in these extracts may b e the same as those found in the plasma of healthy pregnant women. This may help to explain the finding that the plasma ADH activity in normal preg. is less than that in pre-eclamptic patients. This observation can explain oedema and hypertention of pre-eclampsia to be due to deficiency of this placental enzyme, leading to the presence of high concentration of ADH which possesses both water retaining and pressor properties.

Hawker (1956) gave evidence that this inhibiting substance in the placental tissue is an enzyme, as boiling for 30 seconds destroys it s activity, there is no change of activity after

storage at 0°C and it has an optimum pH 7-8. Only recently the activity of ADH could be essayed in the peripheral blood of pregnant women. More work is expected to follow this experimenta achievement.

Aldosterone in Pregnancy :

At the moment aldosterone holds the centre of the stage. It was found that aldosterone excretion is greatly increased in normal pregnancy, (Venning & Dyrenfurth, 1956). The increase by the third trimester is on the average more than sixfold, (Kumar et al., 1958). The finding is interesting and the immunity of the normal pregnant woman calls for an explanation.

There is evidence that the maternal adrenals are responsible for such increase and not the pla-

centa or the foetal adrenals, (Baulieu et al., 1957; Laidlaw et al., 1958). If this is true one finds it difficult to explain the mechanism. The most important stimulus for aldosterone excretion cannot operate here as in fact the extracellular space as well as the plasma volume are increased during pregnancy, (Chesley, 1943; Caton et al., 1949; Tysoe & Lowenstein, 1950). The possibility of the presence of a mid brain centre controlling aldosterone production was discussed, (Farrell, 1958).

The immunity of the normal pregnant woman to aldosterone production is explained by a blocking mechanism caused by a placental factor, probably oestrogen and progesterone, on the peripheral action of the hormone.

It is interesting to note that recent reports indicate a tendency to lower aldosterone excretion in pre-eclampsia, (Kumar et al., 1958; Rinsler & Ribby, 1957; Wolff et al., 1958).

To draw any final conclusions is certainly unwise. There are many possibilities waiting for approval or disapproval. The role of the placenta is not clear. Does it produce any specific hormone controlling electrolytes ? Does it produce any aldosterone factor ? Does it produce factor which enhances the action of aldosterone in pre-eclamptic patients ?

Serotonin in Normal Pregnancy and Pre-eclampsia:

Krupp & Krupp (1960) studied the serum level in non preg. normal pregnant and pre-eclamptic women. There was no difference between the

normal pregnant and the non pregnant serum levels. In pre-eclampsia, although the average was higher than that in normal pregnancy, yet no correlation could be found. The results were not treated statistically. But relying on the experimental observations they came to the conclusion that there was no correlation between the secrotonin level and the severity of the condition.

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EXPERIMENTAL PART

(A) WATER METABOLISM.

I. MEASUREMENT OF TOTAL BODY WATER

USING

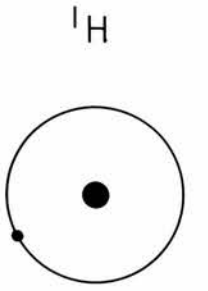
THE EXTRAPOLATION METHOD.

The measurement of total body water is important to study water metabolism and its disorders. It has been used as a reference standard item for exchangeable electrolytes. It is a more suitable reference than body weight, height or surface area until a simple and easy way of estimating total body fat is available for clinical research, (Plentl & Gray, 1959).

Apart from a few estimations of total body water on postmortem cases using chemical methods (McCartney, 1959 et al.,), the only possible clinical method is dilution technique (Moore 1946) which is well known.

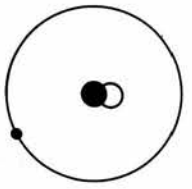
In fact there is no ideal method for measuring total body water. Fortunately hydrogen isotopes became available at a time when there was

Fig. 5.



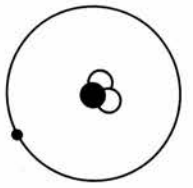
^{1}H

PROTIUM



^{2}H

DEUTERIUM
(Stable.)



^{3}H

TRITIUM
(Radioactive.)

HYDROGEN ISOTOPES.

Half Life	12·26 years.
Radiation	Beta.
Energy	0·18 MeV.
Available form	Tritiated H_2O
Price	£ 10 for 1 Curie.

a growing interest in metabolic studies. Both hydrogen isotopes, the stable deuterium and the radioactive tritium have been used in total body water measurement, (Schloerb et al., 1950) , (Prentice et al., 1952).

My aim was to use a method which combines both clinical simplicity and experimental accuracy. The commonest method which is recommended is to give the patient a tracer dose of radioactive water either orally or intravenously and then to collect a sample of body water using either urine or serum, after allowing for a certain time during which the tracer dose is equally mixed in different body compartments (Veall & Vetter, 1958). I will refer to this method as the "spot sample" method as it depends on counting a spot sample after the mixing time.

The other method is the extrapolation method. I believe this method could give more accurate information for reasons which I will discuss later. So I started measuring total body water in 20 pregnant women using both methods simultaneously to compare the results and to use the more efficient method which I found later to be the extrapolation method.

Material :

Twenty normal pregnant women attending the antenatal clinic at the Simpson Memorial Maternity Pavilion were studied. The estimations were done as an out-patient procedure.

Methods :

A. Clinical part:

The bladder is evacuated completely. The

patient receives .5 millicurie of THO tritiated water diluted with about 200 ml. of water or milk as an oral drink. The bladder is evacuated after two hours. An hour later the spot sample of urine is obtained which is here a three hours sample. It represents the activity after equilibrium. During the three hours of the test the patient is not allowed to have any drink. The weight and height of the patient are recorded. The data available from the previous steps are enough to determine the body water according to the following equation :

$$\frac{\text{activity administered - activity excreted}}{\text{activity after equilibrium /ml. x 1000}} = \text{Litre body water}$$

This is what is required to estimate the total body water by the spot specimen method which was done before by previous workers, (Langham &

al., 1956).

We continued to collect specimens of urine to determine body water by the Extrapolation Method. Each patient is asked to collect early morning specimens for five days. She is asked to evacuate the bladder before going to bed and to avoid a late drink so that the specimen will be obtained after a metabolic plateau overnight during sleep, (Stewart, 1959). By the end of five days the patient who was provided with labelled bottles each for a particular day will send them to the Out-patient Department of the Simpson Memorial Maternity Pavillion.

B. Laboratory part ;

1. Distillation of urine samples.

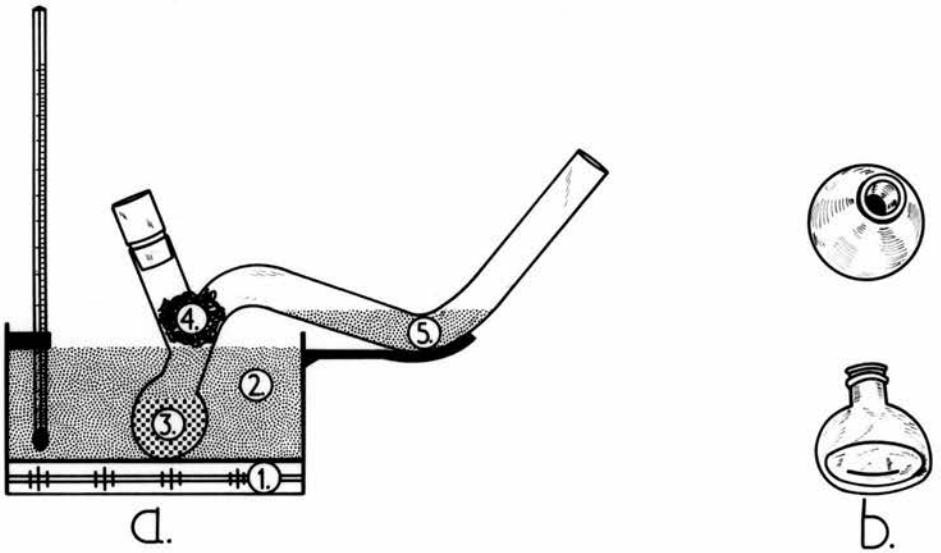
Before counting, the urine samples are puri-

fied by distillation. Since only one ml. of urine is required, specially designed tubes (Fig.6a) are used so that a good number of samples can be distilled in a short time. The distilled urine which is the sample of body water is kept in a test tube ready for the next step. It was proved that the distillation process does not cause any errors due to fractionation, (Simpson and Greening 1960).

2. Preparation of samples for counting.

One milliliter of distilled urine is mixed with 6 ml. of scintillation fluid. The latter consists of 1.2 % PPO and .05% POPOP in a mixture of dioxane, anisole and 1, 2-dimethoxyethane in the proportions 6:1:1 by volume (Davidson & Feigelson 1957). This particular scintillator was chosen because of its ability to mix with a

DISTILLATION APPARATUS AND COUNTING CELL.



a.

b.

1. Electric heater. 2. Tellus oil 69.
3. Urine in the bulb. 4. Glass wool.
5. Distilled urine.

Fig. 6.

relatively large proportion of water.

The samples are made up in specially designed cells (Fig. 6b). These are stopped pyrex glass bottles. For maximal light collection efficiency they are hemispherical in shape and covered with silver reflecting surface. These cells give over 25 % improvement in counting efficiency over the straight sided counting vessels.

The samples are kept in the dark for twelve hours in a special container which is included in a cooling system to allow for the decay of counts due to chemiluminescence.

C. Radio-active Measurement:

1. Counting.

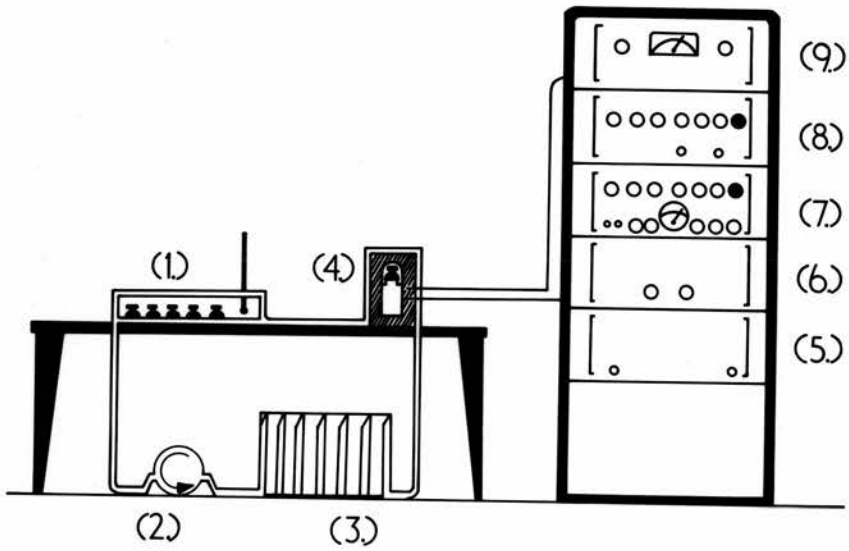
A Panax universal scintillation counter is used in conjunction with a Nuclear Enterprises

non-overloading amplifier and pulse height analyser. The high tension is supplied by an I.D. L. E.H.T. unit. These units as well as a Panax autoscaler are run from a constant voltage transformer to help to stabilise the counting conditions.

It was found that the sensitivity of the counting system greatly improved by making the measurements at a temperature of 1°C. This is achieved by a cooling system encircling the counting castle and the sample container, with continuously running ice-cold water circulated by a pump acting in conjunction with a refrigeration unit. The details of the counting and cooling systems can be seen in Figure 7.

Under these conditions it is possible to

TRITIUM COUNTING ASSEMBLY



1. Sample cooling chamber.
2. Pump.
3. Refrigeration unit.
4. Scintillation head.
5. Linear amplifier.
6. Pulse height analyser.
7 & 8. Autoscaler.
9. E.H.T. Unit.

Fig. 7.

count urine samples with an efficiency of about 12.5 % and a background of 10 counts per second. Thus in a patient of total body water of 35 litres who has received .5 millicurie THO 1 ml. of urine after equilibrium will give a count rate of 66.2 counts per second.

2. Standardisation of samples.

After counting each sample is standardised with an internal standard in order to correct for variations in cell efficiency. The internal standard consists of 50 millimicrocurie activity contained in .07 ml. of a mixture of water and scintillator in the same proportions as that used for counting.

After addition of the internal standard the samples are put in the container to cool and are

recounted. The activity of each is calculated in millimicrocurie.

Calculation.

In the Extrapolation Method the results of activity of the consecutive five days specimens are plotted on a semi log scale. The resulting linear relation is extrapolated to the time the patient received the dose (Fig. 8). The activity at that time is determined.

$$\text{Total body water} = \frac{.5 \times 10^6}{\text{activity by extrapolation} \times 1000}$$

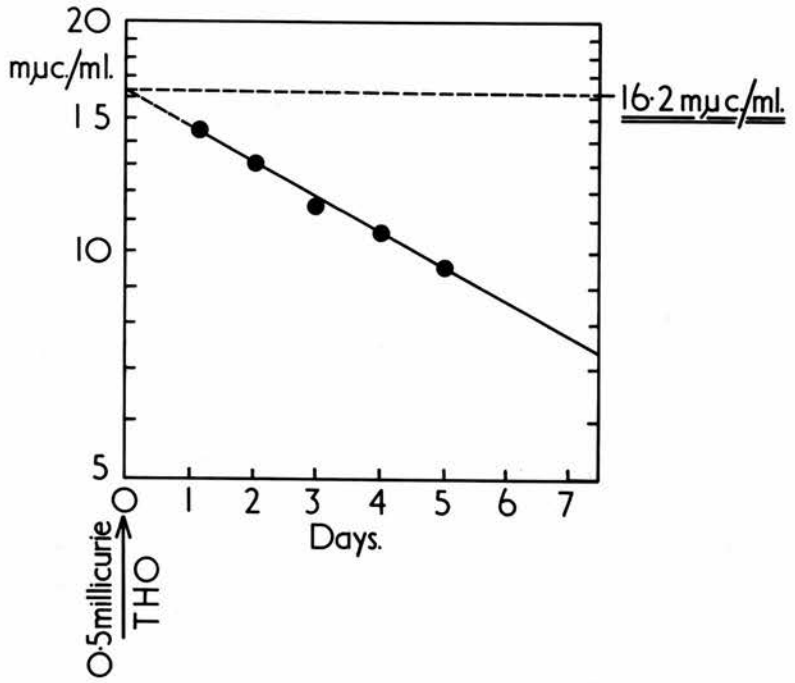
Results.

The result of total body water measurement in twenty normal pregnant women by the two methods are illustrated in Table 1.

The spot sample method has always been used for total body water measurement. The equilibrium

Fig. 8.

EXTRAPOLATION METHOD FOR BODY WATER MEASUREMENT.



ESTIMATION OF T.B.W. BY 3 HOURS METHOD X EXTRAPOLATION METHOD, USING TRITIATED WATER.

COMPARATIVE STUDY OF 20 CASES.

No.	Name.	Weight.(Kg.)	Total Body Water. (Litres.)		Difference.			Body Fat %
			3 Hours.	Extrapolation.	+	=	−	
1.	H. W.	61·5	50·7	35·8	14·9	—	—	
2.	I. D.	61·5	34·8	38·8	—	—	4	13·8
3.	E. M.	52·5	30·1	28·1	2	—	—	
4.	L. N.	68	37·6	37·6	—	same	—	
5.	B. K.	52	37·6	35	2·6	—	—	
6.	J. H.	61·5	43·5	43·5	—	same	—	
7.	J. S.	79	52·7	48·8	3·9	—	—	
8.	J. C.	68	39·4	43	—	—	3·6	13·4
9.	A. G.	57	48·6	39·2	9·4	—	—	
10.	I. G.	68·5	41·6	41·6	—	same	—	
11.	H. W.	71	64·5	63·3	1·2	—	—	
12.	A. C.	47	27·8	27·8	—	same	—	
13.	M. E.	57	28·3	33·8	—	—	5·5	18·4
14.	A. N.	63·5	36·2	36·2	—	same	—	
15.	R. G.	50·7	37·3	37·3	—	same	—	
16.	M. P.	52	38·4	29·1	9·3	—	—	
17.	A. W.	62·5	44·8	41·1	3·7	—	—	
18.	C. C.	57·6	47·6	33·4	15·2	—	—	
19.	B. A.	57·5	35	27	8	—	—	
20.	J. T.	54·5	34·7	37·9	3·2	—	—	
20 CASES =					11 + 6 + 3			

Table 1.

time was considered 2-3 hours. In one of our pilot experiments (Fig. 9) we found that equilibrium in this particular case took about two hours. We assumed that extending it to three hours would provide a range which would work for all the patients which proved to be wrong by this comparative study.

Comparatively the results can be classified in three groups:-

(1) Same result by both methods:

This was obtained only in 6 patients (30%).

In all of them the spot sample activity was on the extrapolated curve (Fig. 10).

(2) Spot sample measurement is below the extrapolated curve:

This is the case in 11 patients (55 %).

ABSORPTION EQUILIBRIUM CURVE AFTER ORAL ADMINISTRATION OF 0·5 MILLICURIE OF THO.

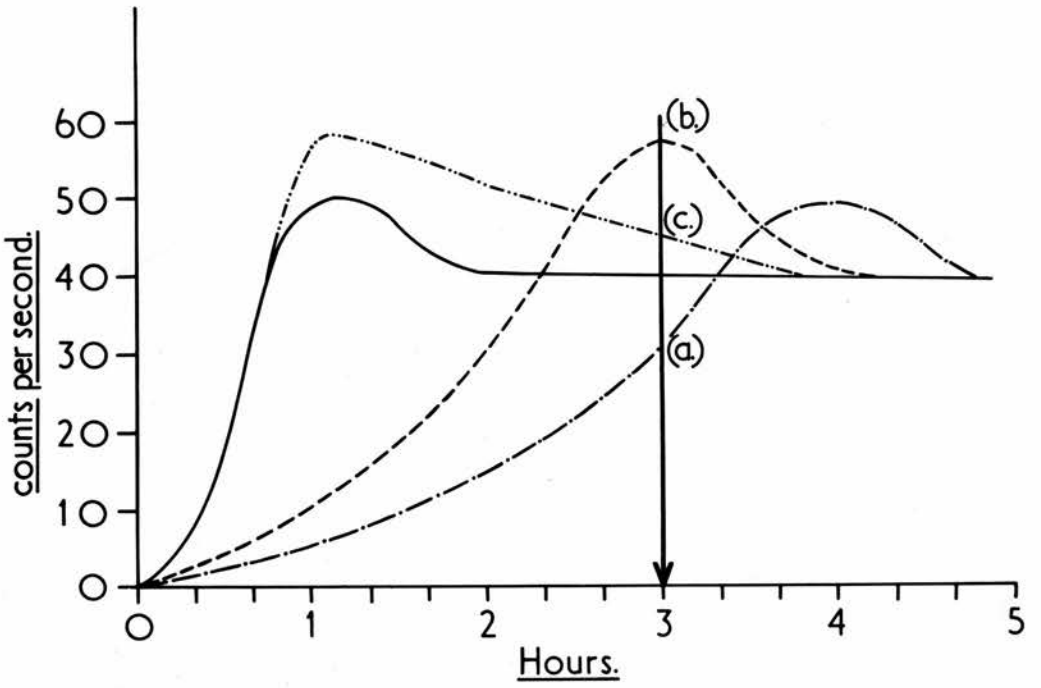


Fig. 9.

ESTIMATION OF TOTAL BODY WATER.

3 hour activity on the extrapolated curve.

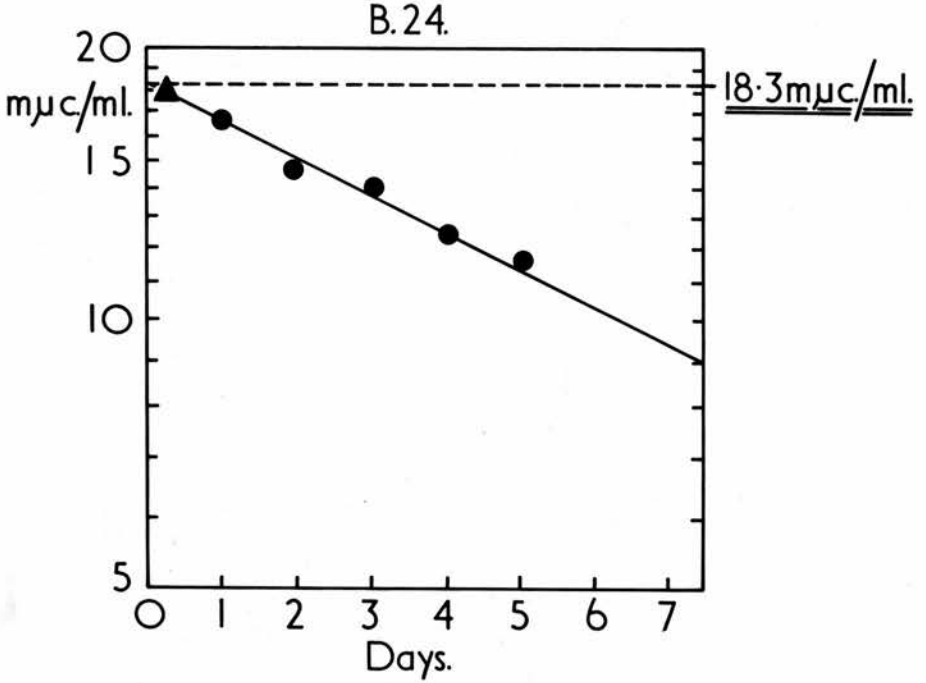


Fig. 10.

The 3 hours sample shows a lower activity than the one day specimen (Fig. 11). One explanation for such a situation, the tracer dose was not completely absorbed from the gastro-intestinal tract after 3 hours. It took the dose a longer time to be absorbed completely most probably after the patient started to drink after 3 hours period. Another possible explanation is failure to empty the bladder completely at 2 hours.

In this case the absorption-equilibrium curve is spread to the right and the activity of the 3 hours specimen is on the ascending limb of the curve not on the plateau as it should be (Fig. 9a).

(3) Spot sample measurement is above the extrapolated curve:

In 3 patients the spot sample activity has

ESTIMATION OF TOTAL BODY WATER.

3 hour activity below the extrapolated curve.

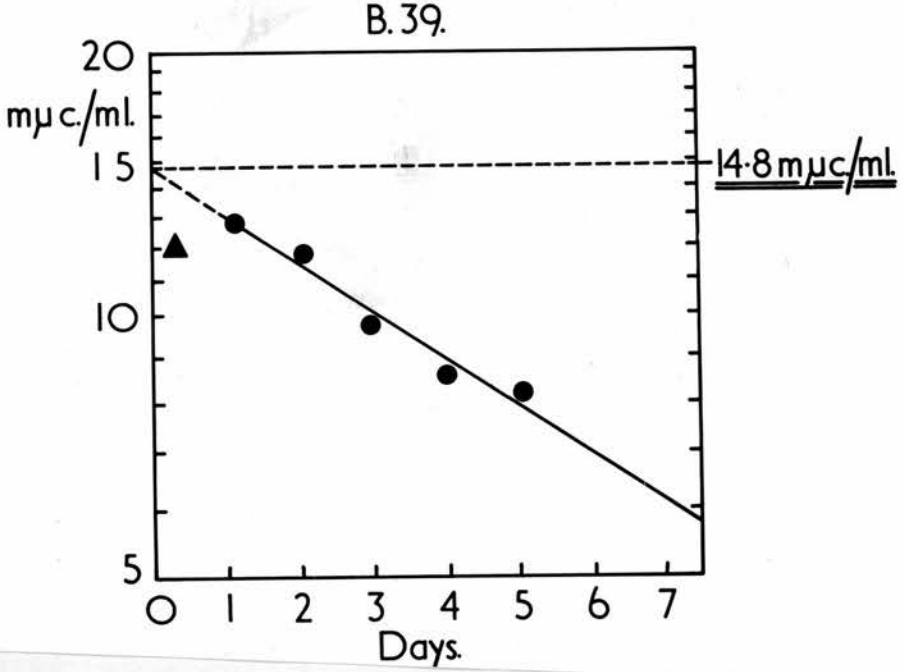


Fig. 11.

a higher value than that obtained by extrapolation (Fig.12).

This can be explained by one of two possibilities.

If the rate of absorption is slow, the absorption-equilibrium curve is spread slightly to the right and the activity of the spot specimen will be timed at the peak of the curve (Fig. 9b).

The rate of the absorption may be quick but the delay of equilibrium is due to delay in the spread of the isotope from the plasma to the rest of the body. When we use urine to represent the body water we are actually sampling from the plasma. In this case we get a higher reading of activity as the sampling time will be on the descending limb of the curve before a plateau is esta-

ESTIMATION OF TOTAL BODY WATER.

3 hour activity above the extrapolated curve.

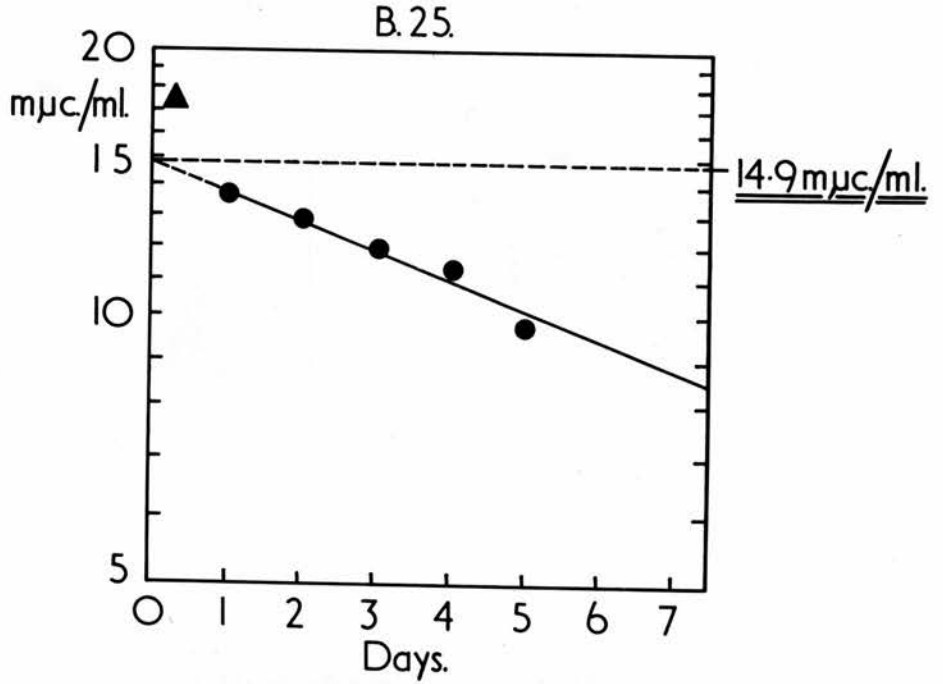


Fig. 12.

blished (Fig. 9c).

Discussion.

The main drawback of spot sample method is that the equilibrium time will vary from one person to another. It may vary in the same person under different conditions. Even if a special period of equilibrium is agreed upon in normal persons, it is expected to vary if one is dealing with patients with abnormal hydrodynamics.

It is clear that in 11 patients the dose was not completely absorbed in 3 hours. It is well known that the rate of absorption from the gut varies according to many factors. If this factor has been the only defect it would have been possible to by-pass the gastro-intestinal tract and administer the tracer dose intravenously but this is not the case.

In 3 patients it is clear that the tracer dose was completely absorbed by the end of 3 hours but it was not distributed to all the body fluid compartments. The isotope is diluted at first by the plasma, then it mixes with the extracellular compartment and finally the intracellular one. The rate of diffusion depends upon the composition of the body as well as the turnover rate. We presume that the amount of fat may effect the rate of diffusion. Adipose tissues contain only 31 % water in comparison to the lean body tissue which contains 72 %, (Keys & Brozck 1953). If one realises that the amount of fat varies considerably from one person to another (Wayne et al., 1959) a difference in the rate of diffusion is to be expected. As can be seen in table 1, in the 3 patients where the differen-

ce in the result is probably due to a delay in diffusion, the delay is proportional to the amount of fat.

In the Extrapolation Method the clinical part is easy to carry out. It includes giving the patient the tracer dose, recording the time and further collection of samples of urine. There is no need to keep the patient in for catheterisation as we used to do in the spot specimen method. This method I used in pregnant women at the Simpson Memorial Pavilion successfully as an Out-patient procedure. The method overcomes the drawbacks of the spot specimen method.

The use of extrapolation has been used with other tracer dilution techniques. Although it has been criticised for the use in case of biolo-

gically short lived tracers (Veall & Vetter, 1959) yet in case of THO where the biological half life is 8-9 days the method is quite suitable (Veall 1959).

The reading of the activity in body water at zero time, the time of administration, is the result of extrapolating a curve of five readings which minimises the possibility of chance error by depending on a single reading as is the case in the spot specimen method. Such accuracy is specially required if the water measurement is used as a reference item for exchangeable electrolytes.

Another advantage is that from the curve one can study the turnover rate which explores at the same time the dynamic aspect of the study.

I conclude that the extrapolation method is easier clinically, more correct and more informative as both static and dynamic aspects of water metabolism, although it entails more experimental work.

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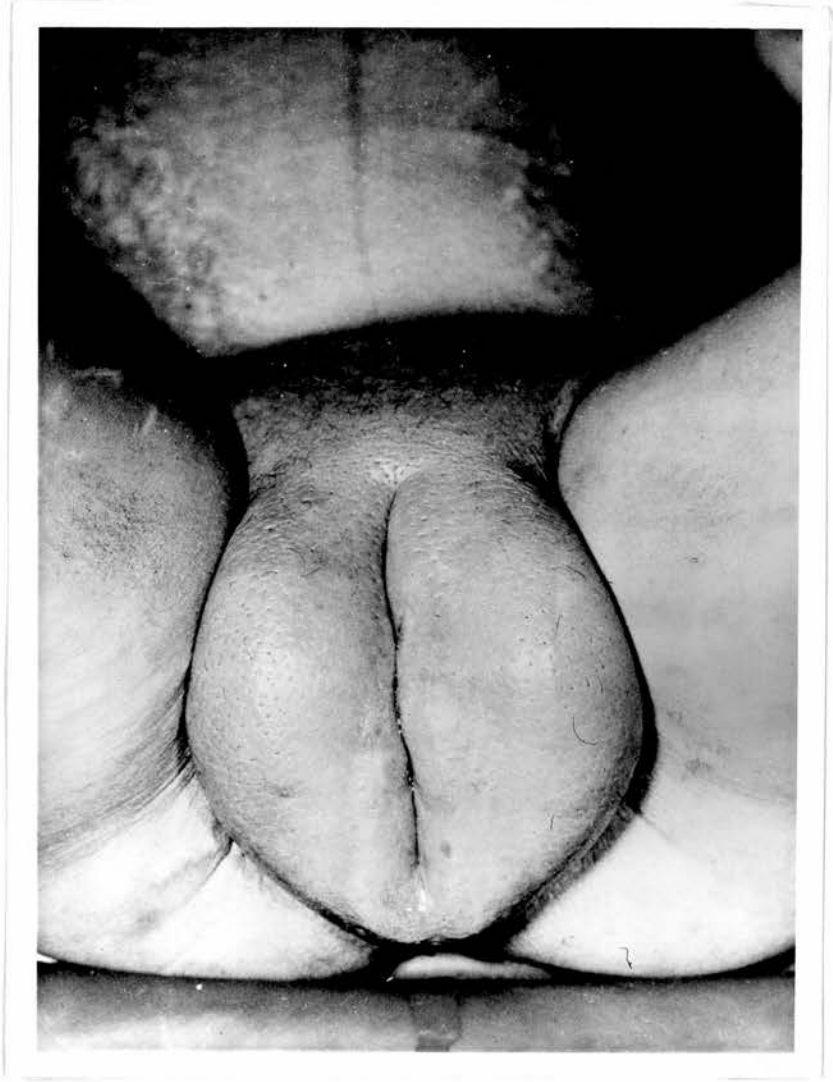
STUDIES IN WATER METABOLISM

IN

PREGNANT WOMEN

After establishing a working method for measuring total body water, my aim was to investigate some aspects of water metabolism during pregnancy.

That a relation does exist between pre-eclampsia and water metabolism does not need much evidence to prove it. Oedema is one of the classical trial by which we diagnose pre-eclampsia, and a very helpful one as well. What we want to know is the nature of this relation. How much water does the body retain ? Where is it kept ? Is it in the extracellular compartment where it could be demonstrated clinically, or is it in both extra and intracellular compartments ? How does the body deal with its water ? What happens in pre-eclampsia ? . . . . . To answer these



PRE ECLAMPSIA

A GROSS DISTURBANCE OF WATER METABOLISM

OEDEMA OF THE VULVA

Fig. 13.

questions I carried out this part of the work.

M A T E R I A L :

One hundred pregnant women cooperated to be the material for this work. They were 68 normal pregnant women, 26 suffering of pre-eclampsia and 8 were the subject of essential hypertension.

The normal cases were divided into two groups: 34 patients during the second trimester, all were attending routine Ante Natal Clinic in Professor Kellar's Unit and 32 patients in the third trimester, all were in-patients in ward 49 admitted for other ailments such as mild ante partum haemorrhage, twin pregnancy, repeated Caeserean Section ; ailments which cause minimal reflection on water metabolism.

PRE-ECLAMPSIA

A GROSS DISTURBANCE OF WATER METABOLISM

OEDEMA OF THE VULVA

I must mention here that when I use the word "normal" in relation to the latter group, I mean that they are clinically normal regarding their water and electrolyte metabolism.

The 26 pre-eclamptic patients were all in-patients in ward 49. They were all diagnosed clinically as pre-eclampsia. They all had a blood pressure 150/90 or more with oedema or albuminuria or both. They were all resting in bed receiving n o hypotensive or diuretic therapy. I had to exclude from the series 4 patients as their clinical condition necessitated starting them on chemotherapy, and another 3 patients who went to labour before the completion of the test.

The series includes 8 patients who were suffering of essential hypertension with pregnancy.

They were all attending the hypertension clinic and were supervised clinically by the Late Dr. R. Mackay.

Body water and its turnover rate measured by using tritiated water (THO) in all the patients (100 patients). Only 44 patients had their sodium space measured as well to represent the extracellular water. The following table summarises the material used:-

TYPE	NUMBER	T B W	Na SPACE
Normal (2nd trimester)	34	34	-
Normal (3rd trimester)	32	32	23
Pre-eclampsia "	26	26	21
Essential Hypertension	8	8	-
T O T A L	100	100	44

METHOD :

1 - Measurement of Total Body Water and its Turnover :

I used the extrapolation method which I discussed before. As I mentioned all the patients in the second trimester were Out-Patients. The tritiated water was supplied by the Atomic Energy Research Establishment at Harwell.

2 - Extra Cellular Space Measurement :

This was measured by estimating the Na Space. The details of the method are mentioned in the second part of the work which deals with electrolytes.

Both tritium .5 millicurie and ^{24}Na 30 μc were given orally to the patient. A sample of urine was collected for counting after 24 hours.

The presence of tritium does not affect the Well Scintillation counter for counting ^{24}Na as ^{3}H is a pure beta emittor of very short wave length.

Regarding tritium counting there were two ways : either to leave the specimen till ^{24}Na decays to undetectable amount or to count tritium after distillation. In conjunction with the Medical Physics Unit, we found that the process of distillation is very efficient, and none of the ^{24}Na could be detected in the distillate.

So the method I followed was to distill the urine specimens and count for tritium, while an undistilled specimen was used for ^{24}Na counting.

C A L C U L A T I O N :

1 - Total Body Water :

The method of calculating TBW was menti-

oned before the following equation :

$$TBW = \frac{.5 \text{ millicurie}}{\text{activity in millicurie at 0 time X 1000}}$$

2 - Water Turnover :

After plotting the curve from the data obtained of tritium counting in body water on a semi logarithmic scale, two points are chosen on the curve and the following equation is used to calculate λ which is the disappearance constant :

$$(THO)_t = (THO)_0 e^{-\lambda t}$$

This equation governs the turnover in compound biological systems.

= Disappearance constant = The fraction of total body water which is turned over or replaced during unit

of time (t).

$(THO)_0$ = is the concentration of tritium at the beginning of the period (t).

$(THO)_t$ = is the concentration of tritium at the end of the period (t).

e = constant.

3 - Extracellular Water :

$$ECW = \frac{^{24}Na \text{ dose administered} - ^{24}Na \text{ activity excreted in } 24 \text{ hours}}{\text{Activity of } ^{24}Na/ml. \text{ plasma} \times 1000}$$

= Litre of water

C A L C U L A T E D R E S U L T S :

1 - Gross Body Composition :

In normal pregnancy I attempted to get an idea about gross body composition using the following variables :-

a - Measured total body water (TBW)

b - Body weight in Kg. (Wt.)

c - Constant relation between TBW and Lean Body Mass (LBM) (Veall & Vetter,1958)

$$\text{Lean Body Mass} = \text{TBW} \times \frac{72}{100}$$

Fat = Wt. - LBM

Solids = LBM - TBW

2 - Distribution of Water in the Body :

TBW = measured.

ECW = measured.

ICW = Intracellular Water = TBW - ECW.

Both ECW & ICW have been related to TBW and body weight for comparative purposes.

3 - Water Turnover :

Total Turnover = TBW X = Litres of water

Turnover Time = the time taken by the body to change or to turnover an amount equal to TBW.

$$= \frac{1}{\lambda}$$

Half Life Time = the biological half life of tritium within the body.

$$= \frac{.693}{\lambda}$$

- - - -

RESULTS

TOTAL BODY WATER

MEASUREMENT & TURNOVER

IN

NORMAL PREGNANT WOMEN DURING

SECOND TRIMESTER

No.	NAME	AGE	PARITY	PREG.	WEIGHT Kg.	TBW L	λ
1.	M. Keegan.	24	P	20	72.0	38.4	.067
2.	S. REID	20	P	14	47	31.2	.110
3.	K. BAIN	19	P	24	60	30.0	.041
4.	E. WATSON	19	P	21	58	39.4	.086
5.	G. CONWAY	20	P	23	53	31.8	.070
6.	C. Robertson	20	P	24	53	27.8	.113
7.	A. HEATH	29	P	22	58.5	34.6	.067
8.	V. SHAW	19	P	14	45	25.0	.095
9.	D. Moffat	25	P	24	56	29.4	.054
10.	M. COOK	29	P	22	63.5	31.6	.067

NO.	NAME	LBM Kg.	FAT Kg.	SOLIDS Kg.	% BODY WEIGHT		
					W	F	S
1.	M. KEEGAN	53.3	18.7	14.9	53.3	26.0	20.7
2.	S. REID	43.3	3.7	12.1	66.5	7.9	25.6
3.	K. BAIN	41.7	18.3	11.7	50.0	30.5	19.5
4.	E. WATSON	54.6	3.4	15.2	68.0	6.2	25.8
5.	G. CONWAY	44.2	8.8	12.4	60.0	16.6	23.4
6.	C. ROBERTSON	38.6	14.4	10.8	52.0	27.2	20.8
7.	A. HEATH	48.0	10.5	30.4	59.0	18.0	23.0
8.	V. SHAW	34.8	10.2	9.8	55.6	26.8	17.6
9.	D. MOFFAT	41.0	15.0	11.6	52.6	25.0	22.4
10.	M. COOK	44.0	19.5	12.4	49.8	30.4	18.8

NO.	N A M E	AGE	PARITY	PREG.	WEIGHT Kg.	TBW	λ
11.	A. CHALMERS	28	P	23	74	36.3	.104
12.	D. TULLOCH	26	P	24	51	21.8	.095
13.	M. DAILY	26	P	14	45	27.0	.075
14.	J. McBAIN	22	P	23	54.5	21.7	.104
15.	J. LIDDLE	36	1	18	60	31.2	.081
16.	J. DORIAN	27	1	20	61	34.5	.074
17.	I. DUNCAN	22	P	14	61.5	38.8	.067
18.	E. McIntyre	28	2	19	52.5	28.1	.087
19.	L. Newcombe	19	P	24	68	37.6	.044
20.	B. KITE	32	P	12	52	55.0	.049

NO.	NAME	LBM Kg.	FAT Kg.	SOLIDS Kg.	% BODY WEIGHT		
					W	F	S
11.	A. CHALMERS	50.5	23.5	14.2	49.1	31.8	19.1
12.	D. TulloCH	30.3	20.7	8.5	42.8	40.6	16.6
13.	M. DAILY	35.5	9.5	7.5	66.0	21.2	12.8
14.	J. McBAIN	30.2	24.3	8.5	40.6	44.6	14.8
15.	J. LIDDLE	43.3	16.7	12.1	52.0	27.8	20.2
16.	J. DORIAN	48.0	13.0	13.5	56.6	22.2	21.2
17.	I DUNCAN	54.0	7.5	15.2	63.0	12.2	24.8
18.	E. McINTYRE	39.0	13.5	10.9	53.6	25.7	20.7
19.	L. NEWCOMBE	52.2	15.8	14.6	55.3	23.2	21.5
20.	B KITE	48.7	3.3	13.7	67.5	6.3	16.2

No.	NAME	AGE	PARITY	PREG.	WEIGHT Kg.	TBW L	λ
21.	J. HADDEN	28	2	24	73.5	43.6	.080
22.	J. CLARKE	29	2	14	68	43.0	.100
23.	A. GERRACHY	18	P	24	57	39.2	.066
24.	E. GRIEVE	30	P	24	68.5	41.6	.053
25.	A. CLARKE	17	P	16	47	27.8	.091
26.	M. ELLIOT	21	P	23	57	33.8	.078
27.	R. GALBREITH	23	P	22	53.3	37.3	.081
28.	E. McINTOCH	28	P	19	60.5	37.0	.140
29.	M. PHILP	20	P	23	57.2	33.4	.090
30.	C. CALBERSTON	24	4	26	63.5	23.4	.070

NO.	NAME	LBM Kg.	FAT Kg.	SOLIDS Kg.	% BODY WEIGHT		
					W	F	S
21.	J. HADDEN	60.5	13.0	16.5	59.4	17.7	22.9
22.	J. CLARKE	60.0	8.0	17.0	63.3	9.1	27.6
23.	A. GERRACHY	54.5	2.5	15.3	69.0	4.4	16.6
24.	E. GREIVE	57.7	10.8	16.1	60.7	15.8	23.5
25.	A. CLARKE	33.6	13.4	5.8	59.2	28.5	12.3
26.	M. ELLIOT	47.0	10.0	13.2	59.3	17.6	23.1
27.	R. GALBREITH	52.0	1.3	14.7	73.7	2.7	23.6
28.	McINTOCH , E.	51.5	9.0	14.5	61.2	14.9	23.9
29.	M. PHILP	46.4	10.8	13.0	58.3	18.9	22.8
30.	C. CULBERSTON	32.6	30.9	9.2	36.0	48.6	15.4

NO.	N A M E	AGE	PARITY	PREG.	WEIGHT Kg.	TBW L	λ
31.	M. STRACHAN	32	2	21	67	31.1	.075
32.	E. SCOTT	35	2	17	64	35.2	.080
33.	F. GUILD	36	P	21	64.5	36.3	.087
34.	J. HEPPENSTALL	28	2	13	52	29.1	.070
MEAN		22.3			58.7	33	.091
STANDARD DEVIATION $\pm$		6.1			7.6	5.7	.02

NO.	NAME	LBM Kg.	FAT Kg.	SOLIDS Kg.	% BODY WEIGHT		
					W	F	S
31.	M. STRACHAN	43.2	23.8	12.1	46.5	35.5	18.0
32.	E. SCOTT	50.0	14.0	13.8	57.6	21.9	20.5
33.	F. GUILD	50.5	14.0	14.2	57.5	21.8	20.7
34.	J. HEPPENSTALL	40.5	11.5	11.4	56.0	22.0	23.0
	MEAN				54.2	20.6	23.2
	S. D. $\pm$				8.5	9.0	4.2
	C. V.				15.7	43.7	18.0

T O T A L B O D Y W A T E R

MEASUREMENT, TURNOVER & DISTRIBUTION

IN

NORMAL PREGNANT WOMEN

(THIRD TRIMESTER)

NO.	NAME	AGE	Parity	Preg.	Weight Kg.	TBW L	TBW % Wt.	λ
1.	H. Webester	25	P	34	61.5	35.8	58.3	.104
2.	H. SCOTT	20	3	39	74.0	49.0	66.2	.084
3.	M. MALONE	29	2	36	74.0	42.7	57.7	.135
4.	R. SEDDON	29	3	34	73.5	53.6	73.0	.080
5.	I. STALKER	26	P	40	79.0	48.8	61.8	.067
6.	A. NICOL	24	P	40	63.5	38.2	57.1	.129
7.	A. WATSON	22	2	35	62.5	41.0	65.7	.070
8.	J. SMITH	22	P	32	77.0	44.4	57.7	.041
9.	C. SIMPSON	21	2	36	48.5	30.3	62.7	.075

NO.	N A M E	Age	Parity	Preg.	Weight Kg.	T B W L	T B W %Wt.	λ
10.	R. MULLEN	28	P	37	62.5	30	48.0	.1860
11.	A. COWAN	26	1	31	71.5	36.4	51.0	.1096
12.	B. STEWART	25	1	34	53.0	29.6	55.8	.1095
13.	I. ANDERSON	32	P	39	81.5	37.8	46.4	.085
14.	A. GRAHAM	42	3	34	67.0	34.6	51.7	.066
15.	J. CURRIE	26	1	34	63.5	32.1	56.7	.062
16.	E. ALLARDICE	22	2	34	51.0	25.0	49.2	.096
17.	M. CAIRNEY	21	1	41	80.0	32.7	41.0	.123
18.	B. GRANT	37	4	35	70.0	27.8	40.0	.092
19.	D. YOUNG	35	3	38	63.5	30.7	48.5	.115

NO.	NAME	ECW L	ICW L	ICW / ECW	% TBW		% Wt.	
					ECW	ICW	ECW	ICW
10.	R. MULLEN	24.4	6.0	.246	80.0	20.0	38.4	9.6
11.	A. COWAN	21.2	11.2	.528	58.2	41.8	29.6	15.7
12.	B. STEWART	16.8	12.8	.762	56.7	43.3	31.7	24.2
13.	I. ANDERSON	27.2	10.6	.390	72.0	28.0	33.4	13.0
14.	A. GRAHAM	22.3	12.3	.550	64.5	3.5	33.3	18.4
15.	J. CURRIE	20.0	12.1	.606	62.3	37.7	31.5	18.1
16.	E. ALLARDICE	17.7	7.3	.412	71.0	29.0	34.8	14.3
17.	M. CAIRNEY	24.9	7.8	.314	76.0	24.0	31.2	9.8
18.	B. GRANT	18.3	9.5	.520	66.0	34.0	26.2	13.6
19.	D. YOUNG	23.8	6.9	.290	77.6	22.4	37.5	10.9

NO.	N A M E	Age	Parity	Preg.	Weight Kg.	T B W L	T B W % Wt.	λ
20.	J. NISBET	39	1	39	72.0	29.8	41.5	.096
21.	W. DERRY	20	P	32	60	44.2	73.6	.0555
22.	I. CAMPBELL	30	P	32	69.5	47.7	63.6	.052
23.	M. LAIDLAW	20	P	32	61.5	35.6	58.0	.065
24.	S. SCRIMGER	27	P	35	69.5	47.6	68.5	.070
25.	M. BARNETT	30	2	32	62.0	37.9	61.2	.130
26.	S. MUNROE	31	P	39	69.0	49.7	72.0	.130
27.	H. DYER	20.	1	27	75.0	52.7	70.3	.070
28.	M. ELLIOT	27	2	32	60.0	34.0	56.7	.165
29.	D. SANDERS	26	3	34	71.5	46.3	65.0	.032

NO.	NAME	ECW L	ICW L	ICW / ECW	% TBW		% Wt.	
					ECW	ICW	ECW	ICW
20.	J. NISBET	23.4	6.4	.274	78.5	22.5	31.6	8.9
21.	W. DERRY	21.7	22.5	1.04	49.2	50.8	36.3	37.5
22.	I. CAMPBELL	25.4	22.3	.858	54.0	46.0	36.5	32.0
23.	M. LAIDLAW	13.3	22.3	1.680	37.4	62.6	21.7	35.7
24.	S. SCRIMGER	22.2	25.4	1.140	46.6	53.4	32.0	36.5
25.	M. BARNETT	17.6	20.3	1.150	46.4	53.6	28.4	32.6
26.	S. MUNROE	20.2	29.5	1.45	40.7	59.3	29.3	42.8
27	H. DYER	26.4	26.3	1.00	50.0	50.0	35.1	35.0
28.	M. ELLIOT	20.6	13.4	0.65	60.5	39.5	34.3	22.4
29.	D. SANDERS	22.3	24.0	1.08	48	52	33.3	33.6

No.	NAME	Age	Parity	Preg.	Weight Kg.	TBW L	TBW % Wt.	λ
30.	J. FLEMING	27	1	34	68.5	41.6	60.7	.063
31.	M. Jamieson	26	P	32	69.5	33.4	48.2	.140
32.	A. ALLEN	31	3	32	74.0	37.6	51.0	.071
	MEAN	27			62.8	36.5	57.5	.093
	S. D. $\pm$	5.8			8.4	7.4	9.4	.034

TBW = TOTAL BODY WATER

ECW = EXTRACELLULAR WATER

ICW = INTRA CELLULAR WATER

NO.	NAME	ECW L	ICW L	ICW / ECW	% TBW		% Wt.	
					ECW	ICW	ECW	ICW
30.	J FLEMING	22.7	18.9	.832	54	46	33.5	27.6
31.	M. JAMIESON	23.0	10.4	.450	69	31	33.1	15.0
32.	A. ALLAN	25.3	12.3	.490	67	33	34.1	16.6
	MEAN	21.3	15.2	.725	60	40	32	22.8
	S.D. ±			.38	3.7	3.8	3.7	15.0

TOTAL BODY WATER

MEASUREMENT , TURNOVER & DISTRIBUTION

IN

PRE ECLAMPSIA

NO.	N A M E	A G E	PARITY	PREG.	WEIGHT Kg.	T B W L	T B W % Wt.	λ
1.	M. WILLIAMSON	23	1	34	58.7	37	63.2	.091
2.	H. MESSER	28	1	37	84.5	50	59.2	.021
3.	E. McLEAN	33	1	36	70.0	33.3	47.7	.057
4.	W. CROMBIE	35	1	36	59.5	39.2	66.0	.066
5.	D. LOUDON	28	1	35	79.0	42.6	54.0	.024
6.	E. BROADFOOT	22	P	34	66.0	33.1	50.2	.072
7.	C. MORRISON	33	P	38	65.0	36.9	56.8	.066
8.	J. DARLING	30	1	39	74.0	51.0	69.0	.060
9.	A. MACKIE	26	P	32	54.0	40.0	74.2	.14
10.	W. PHEELY	21	P	30	48.0	48.0	83.0	.046

NO.	NAME	ECW L	ICW L	ICW / ECW	% TBW		% Wt.	
					ECW	ICW	ECW	ICW
1.	M. WILLIAMSON	26.7	10.3	.39	72	28	45.5	17.5
2.	H. MESSER	20.2	29.8	1.47	40.5	59.5	24.2	35.0
3.	E. MCLEAN	23.8	9.5	.40	71.5	28.5	34.0	13.7
4.	W. CROMBIE	25.1	14.1	.56	64.0	36	42.2	23.8
5.	D. LOUDON	26.6	16.0	.60	62.5	37.5	33.7	10.3
6.	E. BROADFOOT	23.2	9.9	.43	70	30	35	15.2
7.	C. MORRISON	26.9	10.0	.37	73	27	41.5	15.3
8.	J. DARLING	23.5	27.5	1.17	46	54	31.8	37.2
9.	A. MACKIE	18.2	21.8	1.20	45.5	54.5	33.7	40.5
10.	W. PHEELY	18.3	29.7	1.63	38	62	31.6	51.4

NO.	NAME	AGE	PARITY	PREG.	WEIGHT Kg.	T B W L	T B W % Wt.	λ
11.	J. STRANG	31	2	39	76	47.6	62.7	.038
12.	E. MANUEL	39	P	35	75	50.5	67.5	.034
13.	D. SMITH	35	1	35	74	47.7	57.7	.122
14.	E. PATERSON	41	P	36	81.5	44.5	54.6	.075
15.	M. BAISILLIE	22	P	38	68.0	53	78.0	.039
16.	E. SINCLAIR	37	6	33	68.5	51.6	75.4	.015
17.	J. BARR	36	P	40	75.5	41.7	55.2	.065
18.	M M. WISHART	31	P	38	63.5	32.8	51.7	.131
19.	E. FERNIE	25	P	37	84.0	43.8	52.2	.045
20.	C. LEATHLY	25	1	38	69	43.4	33.0	.063

NO.	NAME	ECW L	ICW L	ICW / ECW	% TBW		% Wt.	
					ECW	ICW	ECW	ICW
11.	J. STRANG	20.7	26.9	1.30	43.5	56.5	27.2	34.5
12.	E. MANUEL	26.9	23.7	.88	53.0	47.0	35.9	31.4
13.	D. SMITH	22.7	25.0	1.09	47.8	52.2	47.7	10.0
14.	E. PATERSON	29.3	15.2	.51	66	34	36	18.6
15.	M. BAISELLIE	21.6	31.4	1.46	40.7	59.3	31.8	46.2
16.	E. SINCLAIR	21.7	29.9	1.38	42	58	31.7	43.7
17.	J. BARR	24.8	16.9	.66	60	40	32.8	22.4
18.	M. WISHART	22.0	10.8	.49	67	33	34.6	17.1
19.	E. FERNIE	26.4	17.4	.66	60	40	31.5	20.7
20.	C. LEATHLY	24.6	18.8	.75	56.6	43.4	35.7	27.3

NO.	NAME	AGE	PARITY	PREG.	WEIGHT Kg.	T B W L.	T B W % Wt.	λ
21.	G. RICHARDSON	19	P	38	55	35.7	65.0	.032
22.	A. WARDHAW	28	P	38	87	44.4	51.0	.100
23.	E. INNES	29	2	38	65.5	39.6	60.5	.036
24.	J. THOMSON	39	9	36	54.5	34.7	63.8	.048
25.	E. WILSON	37.	3	40	77	46.5	60.5	.045
26.	E. HARVEY	30	2	36	77	50.0	65.0	.050
MEAN		30			70	43	61.8	.06
S. D. $\pm$		6.1			5.56	6.12	8.84	.031

NO.	NAME	ECW L	ICW L	ICW / ECW	% TBW		% WEIGHT	
					ECW	ICW	ECW	ICW
21.	G. RICHARDSON	21.4	14.3	.66	60	40	39.0	24.0
	MEAN	23.6	19.5	.84	56	44	35	27
	S.D. ±	2.9	7.48	.39	15.8	11.53	5.4	12.2

T O T A L B O D Y W A T E R

MEASUREMENT & TURNOVER

IN

Essentially Hypertensive Pregnant Women .

NO.	NAME	Age	Parity	Preg.	Weight	TBW L	TBW % Wt.	
1.	M. McDOGALL	32	2	33	74	46.3	62.7	.1386
2.	B. ADAMS	40	2	29	57.5	27.0	47.0	.1500
3.	B. SUTHERLAND	35	P	39	66.5	34.0	51.2	.0800
4.	B. CHRITON	23	P	39	67.0	32.5	48.6	.0750
5.	H. WHITE	24	1	38	77.5	34.4	44.4	.1030
6.	W. LUMSDEN	37	P	30	83	35.7	43.0	.0980
7.	A. CROZIER	40	P	34	50	23.2	46.5	.1800
8.	L. MURRAY	37	2	40	86	45.7	53.2	.1000
MEAN		33.5			70.2	34.8	49.6	.1156

WATER METABOLISM IN PREGNANCY

NORMAL & ABNORMAL

COMPARATIVE STATISTICS.

T O T A L B O D Y W A T E R A N D W A T E R T U R N O V E R

IN

N O R M A L A N D A B N O R M A L P R E G N A N C Y

(AVERAGE VALUES)

T Y P E	NO.	AGE	WEIGHT	T B W	T B W % Wt.		T T O	T T	H T
NORMAL (EARLY)	34	22.3	58.7	33	54.2	.091	13.0	11.0	7.63
NORMAL (LATE)	32	27	62.8	37.6	57.5	.093	3.5	10.7	7.46
PRE ECLAMPSIA	26	30	70	43.61	61.8	.06	4.2	16.7	11.55
E. HYPERTENSION	8	33.5	70.2	34.8	49.6	.115	4.52	8.7	6.03

T B W = Total Body Water

= Disappearance Constant

T T O = Total Turn Over

T T = Turnover Time

H T = Biological Half Life Time.

TOTAL BODY WATER AND ITS DISTRIBUTION

IN

NORMAL AND PRE ECLAMPTIC WOMEN.

TYPE	AGE	WEIGHT	T B W	E C W	I C W	T B W %Wt.	E C W % Wt.	I C W % Wt.	E C W %tBW	I C W % TBW	ICW / ECW
NORMAL	23	62.8	37.5	22.3	15.2	55.8	32	22.8	60	40	.72
PRE ECLAMPSIA	21	69.5	43	23.5	19.5	62.2	35	27	56	44	.84

T B W = Total Body Water

E C W = Extra cellular Water

I C W = Intra cellular Water

BODY WATER AND ITS DISTRIBUTION

(STATISTICAL TREATMENT)

	NORMAL		PRE ECLAMPSIA		t	p	Sig.
	MEAN	S.D.	MEAN	S.D.			
TBW % Wt.	54.8	9.9	62	9.4	2.41	.02	+
ECW % Wt.	32	3.7	35	5.4	2.31	.05	+
ICW % Wt.	22.8	15	27	12	.888	.4	-
ICW / ECW	.725	.38	.84	.39	1	.4	-

WATER TURNOVER RATE IN PREGNANCY

(STATISTICAL TREATMENT)

TYPE	NO.			t	p	Significance
		MEAN	S. D.			
NORMAL (EARLY)	34	.091	.05			
				.05	.9	-
NORMAL (LATE)	32	.093	.034			
				3.3	.01	+
PRE ECLAMPSIA	26	.06	.031			
				4.2	.001	+++
E. HYPERTENSION	8	.115	.03			

SUMMARY OF THE RESULTS :

NORMAL PREGNANT WOMEN : (2nd TRIMESTER)

The average value for the TBW was 33 L (range 21.7 - 43.6) in 34 pregnant women with average weight of 58.7 Kg. (range 45 - 74 Kg.) accounting for 56.2 % of their body weight (range 36 % - 73.3 %).

Using these figures the main body constituents which are, water fat and solids, were as follows : water 56.2 %, fat 20.6 % (range 2.7 % - 44.6 %) and solids 23.2 % (range 12.8 - 25.8 %) body weight.

The average disappearance constant was .091 (range .041 - .134) the total turnover of water was 3.1 Litre / 24 hours. The turnover time was

11 days, while the biological half time of tritium was 7.63 days.

NORMAL PREGNANT WOMEN : (3rd TRIMESTER)

In 32 normal pregnant women during the last trimester, of average weight 62.8 Kg. (range 48-81.5 Kg.), the TBW was 37.6 L (range 25-53.6L) accounting for 57.5 % of body weight (range 40 %-73.6 %).

The extracellular water estimated in 23 women was 22.3 L constituting 60 % of TBW and 35 % of body weight. The intracellular water was 15.2 L, accounting for 40 % of TBW and 22.8 % of body weight. The ratio ICW / ECW was .72 .

The average disappearance constant was .093 (range .032 - .18). The total turnover was

3.5 L / day, while the biological half life of tritium in the body was 7.46 days. The turnover time was 10.7 days.

PRE ECLAMPTIC PATIENTS :

The average weight of the 26 pre eclamptic patients was 70 Kg. (range 48 - 84 Kg.). The TBW was 43.61 L (range 33 - 53 L) accounting for 61.8 % of body weight (range 51 % - 83 %).

The ECW was measured in 21 patients. That was 23.5 L accounting for 56 % TBW and 62.2 % body weight. The ICW was 19.5 L, accounting for 44 % of TBW and 27 % of body weight. The ratio ICW / ECW was .84 .

The disappearance constant was low, only .06 (range .021 - .14) and accordingly the turnover

time was 16.7 days. The total turnover was 4.2 L / day. The biological half life for tritium was 11.5 days.

ESSENTIAL HYPERTENSIVE PATIENTS :

In 8 patients the average weight was 70.2 Kg. (range 50 - 86 Kg.), the TBW was 34.8 L (range 27 - 46.3) i.e. 49.6 % of body weight (range 43 % - 62.7 %).

The disappearance constant was .11 and the total turnover was 4.52 L / day. The turnover time was 8.7 days, while the biological half life was 6.03 days.

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DISCUSSION

COMPARATIVE RESULTS :

Total Body Water :

In normal pregnancy, water constitutes 56.2% and 57.5 % of body weight in the second and third trimester respectively. Although the body is more hydrated during the last trimester yet there is no marked difference between both groups. In pre eclampsia water is 61.8 % of body weight. Comparing this figure with that at a comparable period of normal pregnancy, a significant difference exists ($t = 2.41$, $P = < .02$). In essential hypertension the average body water is 49.6% body weight. The difference between water content of hypertensive and pre eclamptic patients is a significant one ($P = < .01$).

Distribution of Body Water :

Comparison is made between normal and pre-eclamptic patients at the same duration of pregnancy. In normal pregnancy the extra cellular water was 32 % body weight. In pre eclampsia it became 35 % body weight. In normal pregnancy the intracellular water was 22.8 % which rose to 27 % in pre eclampsia.

So it was clear that the gain in total body water in pre eclampsia was participated by both extracellular and intracellular water. The difference in extracellular water % weight is a significant one (t = 2.31, P = .05), while the rise of the intracellular water % weight was not associated with statistical confirmation because of the wide range of distribution (t = .888,

P = .4).

Comparing the distribution of water between both compartments it was interesting to find that the intracellular / extracellular ratio was .725 ± .38 in normal pregnancy and rose to .84 ± .39 in pre eclampsia (t = 1. P = .4). This again supports the finding that water is retained in the intracellular compartment as well as the extracellular compartment and the water gained in pre eclampsia is distributed between both compartments with a possibility of an intracellular shift. The intracellular retention of water was referred to by Dieckmann (1950) who described the sudden appearance of edema in cases of severe pre eclampsia and attributed it to the shift of the retained intracellular water to the extracel-

lular space.

Water Turnover Rate :

How does the body treat its water ? Comparing normal pregnant women in the second trimester (λ = .091 $\pm$ .05) with those in the third trimester (λ = .093 $\pm$ .03$\frac{1}{4}$) no difference existed. They both dealt with water at the same rate (t = .05 , P = .9).

This was not the case on comparing normal (λ = .093 $\pm$ .03$\frac{1}{4}$) and pre eclamptic patients (λ = .06 $\pm$ .031). A significant difference existed (t = 3.3 , P = .01). A highly significant difference existed (t = $\frac{1}{4}$.2 , P = .001) on comparing the last group with the hypertensive patients (λ = .115 $\pm$ .03).

It is obvious that pre eclamptic patients turnover body water at a much slower speed compared to normal and hypertensive patients, a point which could be of particular significance in distinguishing between pre eclamptic and hypertensive pregnant women.

Early Detection of Pre eclampsia by Measuring Water Turnover Rate :

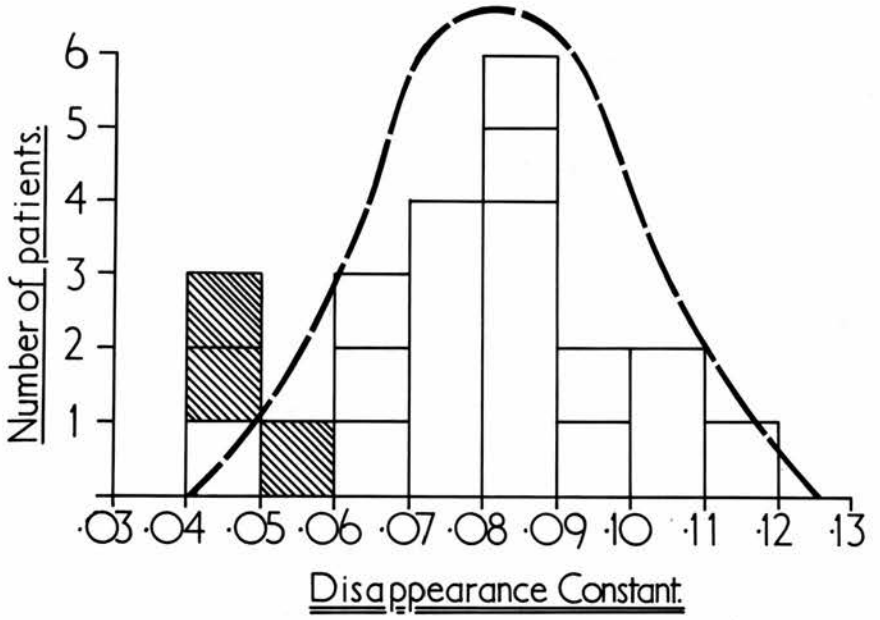
If such metabolic rigidity in water turnover exists in pre eclamptic women, how early does it start ? Is it possible that this measurable disturbance could happen before the appearance o f signs and symptoms ? To answer these questions 22 normal pregnant women belonging to the first group (2nd Trimester, No. 3 & from No.7 - No.27) who were attending routine ante natal care were

chosen. At the time of measuring the water turnover they were clinically asymptomatic, no hypertension, oedema, albuminuria or excessive weight gain. These patients were all followed up till labour. Four out of these 22 patients had a disappearance constant less than .06 (K. Bain .041, L. Newcombe .044, B. Kite .049 and E. Grieve .053). It was interesting to find that 3 of these patients developed signs and symptoms of pre eclampsia and were admitted as in-patients while the 4th one had excessive weight gain and was treated as out-patient.

I came to the conclusion that there is a pre clinical state during which the disturbance in biochemistry takes place, and that such disturbance could be detected by measuring the water

Fig. 14.

DISAPPEARANCE CONSTANT OF WATER TURNOVER IN CLINICALLY NON-TOXAEMIC PATIENTS.



water turnover before the appearance of any sign or symptom.

In our present state of knowledge about the etiology of pre eclampsia, the only effective measure to reduce the incidence and complications of pre eclampsia is early detection. Increased weight gain in pregnancy is still used to detect early cases, (Browne & Browne, 1960). It is an easy clinical method but one should be aware of two points : a patient can put on weight in fat with the same rapidity of retaining water ; the second point is that a patient may retain water and lose fat at the same time so she keeps the same weight.

In an attempt to discover the pre clinical pre eclamptic state, Dalton (1960) came to the

conclusion that symptoms as lethargy, vertigo , fainting, paraesthesia and depression were more common in patients who developed later pre eclampsia.

In conclusion I can say that early detection of pre eclampsia depends on symptoms, signs a s abnormal weight gain and investigations which is the measurement of body water turnover.

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PART II.

ELECTROLYTE METABOLISM

SODIUM AND POTASSIUM

The aim of this part was to investigate the exchangeable electrolytes in pregnant women, particularly in relation to pre eclampsia and essential hypertension. The relation of sodium to pre eclampsia is of particular interest. Light has been focussed on this point recently with the hope that facts will be known.

M A T E R I A L :

The material included 72 patients; all were in-patients in ward 49 at the Simpson Maternity Memorial Pavilion : 36 normal, 29 pre eclamptic and 7 essential hypertensive. All these patients were pregnant in the third trimester. The criteria of normality, pre eclampsia and of essential hypertension were the same as in the previous group.

All these patients had their total exchangeable sodium (Na_{Ex}) measured. In addition, 38 patients had their total exchangeable potassium (K_{Ex}) measured as well simultaneously. The following table shows the material used :-

Type	Number	Na_{Ex} Measurements	K_{Ex} Measurements
Normal	36	36	20
Pre Eclampsia	29	29	14
Essential Hypertension	7	7	4
TOTAL	72	72	38

METHOD :

The technique used is an established one . (Veall & Vetter, 1958; Miller & Wilson, 1953).

Tracer Dose :

^{24}Na & ^{42}K were supplied weekly by the Atomic Energy Research Establishment at Harwell . ^{24}Na has a short half life of 15 hours. It emits both beta & gamma rays but mainly the latter. ^{42}K is mainly a beta emitter with 12.5 hours half life time.

A stock solution of ^{24}Na was prepared with normal saline to contain about 5 micro curie/ml. Another similar stock solution was prepared with water. Both were kept in polythene bottles. The tracer dose was pipetted in a wax paper cup : 30 micro curie ^{24}Na & 30 micro curie ^{42}K. The dose was diluted with water or milk to be given to the patient as an oral drink. A standard solution

was prepared of the stock solution for counting later on with the clinical specimens.

Clinical Part :

The test was explained simply to each patient. The bladder was evacuated. The weight in Kg. and the height in cm. were recorded. Then the tracer dose was given to the patient orally. Each patient was supplied by a polythene bottle (two Litres capacity) so that all the urine should be collected during the subsequent 2¼ hours. Patients were kept on normal routine diet without particular restriction of salt.

After 2¼ hours the bladder was evacuated and the urine collected in a small polythene bottle (U_s = Spot Urine), 10 ml. of blood withdrawn

and kept in a dry test tube. As far as the patient was concerned the test was over at this step.

Laboratory Part :

(1) The amount of pooled urine was measured in millilitre and a small sample collected in a test tube labelled (U_p = pooled urine) and kept for radioactive counting.

(2) The Spot Urine sample (U_s) was kept for counting. Part of it was used for chemical estimation of potassium.

(3) The blood was centrifuged and the serum was separated.

(4) Using EEL Flame Photometer the serum

Na was measured as well as urine potassium after preparation of the standard solutions and the necessary dilutions of serum 1/1000 and urine 1 / 500.

Counting :

The method used for counting ^{24}Na & ^{42}K when used together was described by Veall & Vetter, (1958).

Beta Counting :

This was done in a Beta Counter (Liquid Sample Geiger) in the following order :

Background, U_s , U_p, Na Standard & then K standard.

Gamma Counting :

A Gamma Counter (Well Scintillation Counter)

was used. 10 ml. of each fluid were used. Counting was done in the following order :Background, U_s, U_p, K Standard and Na Standard. The counter had been adjusted before to the best counting position.

Corrections :

Counts were recorded and then corrected for dead time, background and radioactive decay. Using the following equations the Beta counts of ^{42}K and the Gamma counts of ^{24}Na could be calculated.

$$\text{Beta Counts of } {}^{42}K = \frac{\text{Counts in Beta Counter} - \text{Counts in Gamma Counter}}{1 - mn}$$

$$\text{Gamma Counts of } {}^{24}Na = \frac{\text{Counts in Gamma Counter} - \text{Counts in Beta Counter}}{1 - mn}$$

When

$$m = \frac{\text{Count Rate of } {}^{42}\text{K Standard in Gamma Counter}}{\text{Count Rate of } {}^{42}\text{K Standard in Beta Counter}}$$

$$n = \frac{\text{Count Rate of } {}^{24}\text{Na Standard in Beta Counter}}{\text{Count Rate of } {}^{24}\text{Na Standard in Gamma Counter}}$$

C A L C U L A T I O N :

Exchangeable Sodium :

^{24}Na in the body after ^{24} hours = activity admini-

= stered - activity excreted tracer dose

= (c.p.m.) - U_p volume (ml.) X U_p count

= /ml.

$$\text{Na Space} = \frac{^{24}\text{Na in the body after } ^{24}\text{ hours (c.p.m./ml.)}}{^{24}\text{Na in plasma (c.p.m. / ml.)}}$$

^{24}-hour $^{24}\text{Na}_{Ex}$ = Na Space (ml.) serum Na

concentration (meq. / ml.)

Exchangeable Potassium :

$$24\text{-hour } {}^{42}K_{Ex} = \frac{\text{dose administered} - \text{dose excreted}}{\text{activity / ml. Spot Urine}} \times \text{K concentration in } U_s \text{ (meq. / ml)}$$

For comparative reasons the total Na_{Ex} & K_{Ex} were related to body weight in Kg., height in cmm as well as to surface area in square meter which was calculated according to du Bois formula.

The technique was much easier in single determinations of Na_{Ex}, which was done in 34 patients, as the counting was done directly in the scintillation counter. I would like here to stress two points : The first is that the precision of the combined Na_{Ex} & K_{Ex} determination compared very favourably with that of single isotope method,

(James et al., 1954). The second point is that the combined simultaneous estimation is more valid when Na_{Ex} / K_{Ex} ratio is to be compared.

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RESULTS

E X C H A N G E A B L E SODIUM & POTASSIUM

IN

NORMAL PREGNANCY

NO.	NAME	Age	Parity	Preg.	Wt.	Ht.	S.A.	EX. SODIUM Meq.			
								Total	/ Kg.	/ cm.	/ s.m.
1.	I. REID	25	3	36	74	163	1.8	3100	42	25.8	2340
2.	R. MULLEN	28	P	37	62.5	166.5	1.64	2655	42.5	16.6	1620
3.	A. COWAN	26	1	31	71.5	172.5	1.85	3095	43.3	18.0	1607
4.	B. STEWART	25	1	34	53	160	1.54	2410	45.5	15.1	1570
5.	A. ANDERSON	32	P	39	81.5	167	1.89	3910	48.0	23.4	2060
6.	J. CURRIE	26	1	34	63.5	167	1.71	2782	43.8	26.2	2560
7.	M. STRACHAN	24	4	26	63.5	160	1.66	2730	43	26.9	2590
8.	E. ALLARDICE	22	2	34	51	158.5	1.36	2560	50.5	36.5	3720

NO.	NAME	Age	Parity	Preg.	Wt.	Ht.	S.A.	EX. SODIUM Meq.			
								Total	/ Kg.	/ cm.	/ s.m.
9.	I. SCOTT	32	2	21	67	161	1.71	2640	39.2	24.4	2290
10.	M. CAIRNY	21	1	41	80	169	1.91	3410	42.6	25.2	2230
11.	B. GRANT	37	4	35	70	146.5	1.62	2570	36.7	25.0	2270
12.	D. YOUNG	35	3	38	63.5	155	1.62	3205	50.5	32.6	3120
13.	E. NISBET	39	1	39	72	160	1.72	3240	45.0	28.2	2620
14.	E. MILLAR	23	P	30	61.5	148	1.54	2410	39	26.3	2530
15.	L. GREENWOOD	23	P	39	62	154	1.58	2440	39.4	25.6	2490
16.	J. SCOTT	26	P	30	76	157	1.77	2610	34.4	16.6	1480

NO	NAME	AGE	PARITY	PREG.	Wt.	Ht.	S.A.	EX. SODIUM Meq.				EX. POTASSIUM Meq.				Na / K
								Total	/Kg.	/ cm.	/ s.m.	Total	/ Kg.	/ cm.	/ s.m.	
17.	E. FEE	32	1	38	61.5	156	1.62	2795	45.5	17.9	1730	2315	37.7	14.85	1430	1.20
18.	J. WARD	29	2	35	68	156	1.68	2690	39.4	17.2	1600	2135	31.4	13.7	1270	1.25
19.	I. LEWIS	27	P	37	62	150	1.57	1950	31.4	13.9	1240	1390	22.4	9.3	886	1.4
20.	S. DINGWALL	34	P	34	66	167.5	1.67	2708	41	16.2	1620	1480	22.4	8.85	885	1.83
21.	W. DERRY	20	P	32	60	150	1.53	3130	50.5	20.9	2050	2100	35	14.0	1375	1.44
22.	A. CHAPMAN	38	1	34	61	156	1.60	3217	52.8	20.6	2000	2180	35.9	14.0	1365	1.47
23.	I. CAMPBELL	30	P	32	69.5	1585	1.7	3208	46.2	20.2	1890	2410	34.7	15.2	1420	1.33

NO.	NAME	Age	Par	Prg.	Wt.	Ht.	S.A.	EX. SODIUM Meq.				EX. POTASSIUM Meq.				Na/K
								T	/Kg.	/cm.	/s.m.	T	/Kg.	/cm.	/s.m.	
24.	M. LAIDLAW	20	P	32	61.5	149.5	1455	1685	27.8	11.3	1090	2410	39.6	16.1	1560	0.70
25.	S. SCRIMGER	27	P	35	69.5	163.5	1.7	2989	43	18.3	1760	2394	34.5	14.6	1410	1.25
26.	A. IRVINE	27	P	36	65.5	156	1.64	2500	38.2	15.2	1525	2450	37.5	15.7	1495	1.02
27.	M. BURNETT	30	2	32	62	160	1.63	2343	37.9	14.7	1440	2290	37.0	14.3	1405	1.02
28.	S. MUNROE	31	P	39	69	166	1.76	2792	40.5	16.8	1590	2790	40.5	16.8	1590	1.00
29.	H. DYER	20	1	27	75	160.5	1.79	3555	47.5	22.2	1990	2300	30.7	14.3	1285	1.55
30.	M. ELLIOT	27	2	32	60	153.5	1.58	2830	47.0	18.4	1790	2070	34.5	13.5	1310	1.36
31.	D. SAUNDERS	26	3	34	71.5	158	1.73	3200	44.8	22.0	1850	1870	26.2	11.8	1080	1.71

	NAME	AGE	PARITY	PREG.	WT.	Ht.	S.A.	EX. SODIUM Meq.				EX. POTASSIUM Meq.				Na/K
								Total	/Kg.	/cm.	/s.m.	Total	/ Kg.	/ cm.	/s.m.	
32.	J. FLEMING	27	1	34	68.5	162.5	1.74	3100	45.4	19.1	1780	2720	39.8	16.8	1560	1.14
33.	M. JAMIESON	26	P	32	69.5	157.5	1.71	3200	46.0	20.3	1870	2660	38.4	16.9	1500	1.20
34.	A. ALLAN	31	3	32	74.0	162.5	1.8	3670	49.7	22.6	2020	3200	43.3	19.7	1780	1.15
35.	J. HUTCHINSON	31	1	39	73	165	1.8	3390	46.5	20.6	1880	3520	48.2	21.3	1960	.97
36.	A. SNEDDON	27	2	32	60	148	1.53	2525	42.2	17.0	1705	2510	41.8	17	1640	1.01
	MEAN	27			66.2	158.4	1.67	2850	43	18.0	1709	2406	36.5	15.2	1440	1.18

EXCHANGEABLE SODIUM AND POTASSIUM

IN

P R E E C L A M P S I A

NO.	NAME	age	Parity	Preg.	Wt.	Ht.	S.A.	EX. SODIUM Meq.			
								Total	/ Kg.	/ cm.	/ s.m.
1.	M. GALBREITH	21	1	33	72	157	1.72	2880	40	18.3	1680
2.	A. CORMACK	20	P	39	72	155	1.70	2960	41	26.2	2405
3.	E. INNES	34	1	37	71	160	1.73	2470	34.8	26.9	2485
4.	M. ARTHUR	31	1	36	109.5	177	2.24	5230	48	27.1	1970
5.	C. BOYDE	31	P	36	69	147	1.62	3110	45	33.0	2780
6.	M. MONCRIFF	19	P	36	86.5	157	1.86	3820	46.4	24.3	2050
7.	E. MCLEAN	33	1	36	70	155	1.68	3455	49.5	21.6	2000
8.	W. CROMBIE	35	2	36	59.5	153	1.56	34.90	58.7	38.4	3770

NO.	NAME	Age	Parity	Preg.	Wt.	Ht.	S.A.	EX. SODIUM Meq.			
								Total	/ Kg.	/ cm.	/ s.m.
9.	D. LOUDON	28	1	35	79	162.5	1.84	3702	47.0	28.9	2555
10.	E. BROADFOOT	22	P	34	66	160	1.69	3420	51.8	32.4	3070
11.	C. MORRISON	33	P	38	65	158.5	1.67	3610	55	34.8	3800
12.	J. DARLING	30	1	39	74	163	1.8	3290	44.5	27.3	2470
13.	E. COWE	29	P	37	67	162	1.7	2780	41.5	25.6	2440
14	T. REID	35	P	36	98	166.5	2.06	3790	38.6	23.2	1930
15.	M. CURRIE	26	1	38	65	158	1.66	2916	44.8	28.4	2700

NO.	NAME	Age	Par.	Prg.	Wt.	Ht.	S.A.	EX. SODIUM Meq.				EX. POTASSIUM Meq.				Na/K
								T	/Kg.	/cm.	/s.m.	T	/Kg.	/cm.	/s.m.	
16.	E. HUTCHINSON	27	P	39	65.5	163.5	1.7	2940	45	18	1730	1690	25.8	10.3	1000	1.74
17.	A. MACKIE	26	P	32	54	155	1.51	2455	45.5	15.8	1625	1830	33.9	11.8	1210	1.34
18.	J. STRANG	31	2	39	76	166	1.83	2880	38.0	17.3	1575	2524	33.0	15.1	1370	1.15
19.	E. MANUEL	39	P	35	75	172	1.82	3690	49.2	21.5	2028	2608	34.8	15.2	1435	1.70
20.	M. DICKSON	27	1	36	65	165.5	1.7	2930	45.0	17.7	1720	2170	34.3	13.1	1280	1.31
21.	D. SMITH	35	1	35	74	161	1.78	3155	42.7	19.6	1770	2480	33.5	15.4	1390	1.27
22.	E. PATERSON	41	P	36	81.5	160	1.84	4140	50.8	25.8	22.5	2810	34.5	17.6	1530	1.47
23.	M. BAISILLI	22	P	38	68	151.5	1.54	3100	44.3	20.5	2020	2085	30.7	13.7	13.5	1.44

NO.	NAME	Age	Par.	Prg.	Wt.	Ht.	S.A.	EX. SODIUM Meq.				EX. POTASSIUM Meq.				Na./K
								T	/Kg.	/cm.	/s.m.	T	/Kg.	/cm.	/s.m.	
24.	J. BARR	36	P	40	75.5	163	1.81	3510	46.5	21.5	1940	2445	32.4	15.0	1350	1.15
25.	C. GREIG	21	P	38	64	165.5	1.71	3130	49.0	18.9	1830	1950	30.6	11.8	1140	1.63
26.	M. WISHART	31	P	38	63.5	160	1.66	3100	49.0	19.4	1870	1780	28.0	11.13	1075	1.75
27.	E. FERNIE	25	P	37	84	1555	1.82	3792	44.3	24.4	2080	2880	34.4	18.5	1580	1.29
28.	C. LEATHLY	25	6	38	69	163	1.75	3770	50	23.1	2150	2850	41.3	20.6	1920	1.21
29.	G. RICHARDSON	19	P	38	55	164	1.6	2820	51.2	17.2	1760	2380	43.5	14.5	1490	1.18
	AVERAGE	28.7			72	160	1.74	3325	46.2	20.8	1910	2469	34.3	14.6	1372	1.42

EXCHANGEABLE SODIUM AND POTASSIUM

IN

NORMAL & ABNORMAL PREGNANCY

COMPARATIVE STATISTICS

EXCHANGEABLE SODIUM IN PREGNANT WOMEN

NORMAL AND PRE ECLAMPTIC

(AVERAGE VALUES)

TYPE	NUMBER	AGE	WEIGHT	HEIGHT	S.A.	EX. SODIUM Meq.			
						Total	/ Kg.	/ cm.	/ s.m.
NORMAL	36	27	66.2	158.4	1.67	2850	43	18	1709
PRE ECLAMPSIA	29	28	72	160	1.74	3325	46.2	20.8	1910
TOTAL	65								

EXCHANGEABLE POTASSIUM IN PREGNANT WOMEN

NORMAL AND PRE ECLAMPTIC

(AVERAGE VALUES)

TYPE	NUMBER	AGE	WEIGHT	HEIGHT	S. A.	EX. POTASSIUM Meq.				Na / K
						Total	/ Kg.	/cm.	/ s.m.	
NORMAL	20	27	66.2	158.4	1.67	2406	36.5	15.2	1440	1.18
PRE ECLAMPSIA	14	28	72	160	1.74	2869	34.4	14.6	1372	1.42
TOTAL	34									

EXCHANGEABLE SODIUM IN PREGNANT WOMEN

NORMAL AND PRE ECLAMPTIC

(STATISTICAL TREATMENT)

TYPE	NUMBER	EXCHANGEABLE SODIUM MEQ. / Kg.					
		RANGE	MEAN	S. D.	t	P	Sign.
NORMAL	36	27.8 - 50.5	43	5.1	2.67	.01	+
PRE ECLAMPSIA	29	34.8 - 58.7	46.2	4.2			
TOTAL	65						

EXCHANGEABLE POTASSIUM IN PREGNANT WOMEN

NORMAL AND PRE ECLAMPTIC

(STATISTICAL TREATMENT)

TYPE	NUMBER	EXCHANGEABLE POTASSIUM MEQ. / Kg.					
		RANGE	MEAN	S. D.	t	P	Sig.
NORMAL	20	22.4 - 48.3	36.5	7.9	.8	.4	-
PRE ECLAMPSIA	14	25.8 - 43.5	34.3	5.1			
TOTAL	34						

EXCHANGEABLE SODIUM POTASSIUM RATIO

NORMAL AND PRE ECLAMPTIC

(STATISTICAL TREATMENT)

TYPE	NUMBER	EXCHANGEABLE SODIUM POTASSIUM RATIO					
		RANGE	MEAN	S. D.	t	P	Sig.
NORMAL	20	.7 - 1.83	1.18	.27	2.76	.01	+
PRE ECLAMPSIA	14	1.18 - 1.75	1.42	.19			
TOTAL	34						

SUMMARY OF THE RESULTS :

Normal Pregnancy :

The average age for this group was 27 years (range 20 years - 37 years). They had an average weight of 66.2 Kg. (range 51 - 81.5 Kg.), an average height of 158.4 cm. (range 138.5 - 172.5 sm.) and an average surface area of 1.67 sq.m. (range 1.36 - 1.89 sq.m.).

In 36 patients the total Na_{Ex} was 2850 meq. (range 3910 - 1685 meq.). Related to weight, height and surface area the Na_{Ex} was 43 meq. / Kg. (range 31.4 - 52.8 meq.), 18 meq. / cm. (range 11.3 - 36.5 meq.) and 1709 meq. / sq. m. (range 1090 - 3720 meq.) respectively.

In 20 patients the total K_{Ex} was 2406 meq.

(range 1390 - 3520 meq.), referred to body weight, height and surface area, the K_{Ex} was 36.5 meq./Kg. (range 22.4 - 48.2 meq.), 15.2 meq. / cm. (range 8.85 - 21.3 meq.) and 1140 meq. / sq. m. (range 885 - 1960 meq.).

The Na_{Ex} / K_{Ex} ratio was 1.18 (range .7 -1.83).

PRE ECLAMPSIA :

In 29 patients of average 28.7 years old and 72 Kg. weight (range 54 - 109.5 Kg.), 160 cm. height (range 147 - 166.5 cm.) and 1.74 sq.m. surface area (range 1.54 - 2.24 sq.m.), the average total Na_{Ex} was 3325 meq. (range 2455 - 5230 meq.). Referring Na_{Ex} to weight, height and surface area the average figures were 46.2 meq./Kg. (range 34.8 - 58.7 meq.), 20.8 meq. / cm. (range

17.2 - 38.4 meq.) and 1910 meq. / sq.m. (range 1575 - 3770 meq.) respectively,

In 14 patients the average K_{Ex} figures were: total K_{Ex} 2469 meq. (range 1690 - 2880 meq.), K_{Ex} /Kg. 34.3 meq. / Kg. (range 25.8 - 43.5 meq.), K_{Ex} /cm. 14.6 meq. / cm. (range 10.3 - 20.6 meq.), K_{ex} / sq. m. 1372 meq. / sq.m. (range 1000 - 1920 meq.). The Na_{Ex} / K_{Ex} ratio was 1.42 (range 1.15 - 1.75).

ESSENTIAL HYPERTENSION :

In 7 patients the average age was 32.4 years, the average weight was 72.2 Kg. (range 50 - 86 Kg.), height 160 cm. (range 151 - 163.5 cm.) and the average surface area 1.75 sq.m. (range 1.44 - 1.91 sq.m.).

The average total Na_{Ex} was 3065 meq. (range 2380 - 3750 meq.). Relating Na_{Ex} to weight height and surface area the average figures were 42.4 meq. / Kg. (range 37.8 - 47.5 meq.), 19.1 meq. / cm. (range 15.8 - 27.8 meq.) and 1805 / sq.m. (range 1650 - 2640 meq.).

K_{Ex} was measured only in 4 patients, were the average figures were : total K_{Ex} 2393 meq. (range 1690 - 2980 meq.), K_{Ex} / Kg. 34.5 meq. (range 27.7 - 40 meq.), K_{Ex} / cm. height 15 meq. (range 11.2 - 18.6 meq.), K_{Ex} / sq. m. 1385 meq. (range 1175 - 1685 meq.).

The Na_{Ex} / K_{Ex} ratio was 1.24 (range 1.01 - 1.36). The details of the results are in the following table :-

- - - -

NO.	N A M E	AGE	PARITY	Preg. Wt.	Ht.	S.A.	Na Ex total	Na Ex /Kg.	Na Ex / cm	Na Ex / sq.m	K Ex total	K Ex /Kg.	K Ex / cm.	K Ex / sq.m.	Na Ex / K Ex
1.	B. CHRITON	23	P	39	67	163	1.72	3015	45.3	27.8	2640				
2.	H. WHITE	24	1	38	77.5	162.5	1.89	3472	43.6	26.8	2380				
3.	W. LUMSDEN	37	P	30	83	163.5	1.83	3170	38.2	23.4	2020				
4.	A. CROZIER	40	P	34	50	151	1.44	2380	47.5	15.8	1650	1690	34.8	11.2	1175	1.36
5.	I. SINCLAIR	37	6	33	68.5	.57	1.7	3200	44	22	1880	2430	35.5	15.5	1430	1.24
6.	L. MURRAY	37	2	40	86	161	1.91	3750	27.8	23.3	1960	2380	27.7	14.8	1250	1.36
7.	G. GRAHAM	29	P	37	74.5	160	1.77	3000	40.3	18.8	1700	2980	40	18.6	1685	1.01
	M E A N	32.4			72.2	160	1.75	3065	42.4	19.1	1805	2393	34.5	15.0	1385	1.24

D I S C U S S I O N

Exchangeable Sodium in Normal and Pre eclamptic Patients :

In pre eclampsia there was an abnormal retention of exchangeable sodium. In 36 normal patients the Na_{Ex} /Kg. was $\overset{\sim}{4}3 \pm 5.1$ mEq., while in pre eclampsia it was $\overset{\sim}{4}6.2 \pm \overset{\sim}{4}.2$ mEq., with a significant difference (t = 2.67, P = .01).

Normal Pregnancy :

Dieckmann and Pottinger (1957) concluded that during normal pregnancy the body retains 10 percent more Na_{Ex} than non pregnant women but the figures related to Kg. body weight were $\overset{\sim}{4}2.3$ mEq. and $\overset{\sim}{4}0.2$ mEq. in the non pregnant and in the normal pregnant respectively,

Macgillivray and Buchanan (1958) found an increase from $\overset{\sim}{4}1.5$ mEq. Na_{Ex} /Kg. in non pregnant

state to 48.3 mEq. Na_{Ex} / Kg. during normal pregnancy. They concluded that these figures confirmed that there was retention of 755 mEq. Na_{Ex} during pregnancy. This amount is equal to that required to retain the extracellular water in the products of conception.

Plentl and Gray (1959) who were always interested in water and electrolytes in Obstetrics investigated the problem again. They estimated Na_{Ex} in 16 pregnant and 16 non pregnant women. The average figures were 40.2 mEq. Na_{Ex} / Kg. and 39.6 mEq. Na_{Ex} / Kg. respectively. He also concluded that the amount retained of Na_{Ex} is equal to what is required for foetal development. The following table summarizes these results :-

Author	Na_{Ex} / Kg.	
	Non Pregnant	Normal Pregnant
Dieckmann and Pottinger, 1957	~ 42.3	~ 40.2
MacGillivray & Buchanan, 1958	~ 41.5	~ 48.3
Pleutl and Gray ,1959	~ 40.2	39.6

The number of patients investigated was not mentioned in Dieckmann and Pottinger's paper and there was no statistical control for their results, but the difference between Na_{Ex} / Kg. in non pregnant and pregnant women was small. Their results agree with those of Plentl and Gray.

Comparing Plentl and Gray's results with those of MacGillivray and Buchanan it is interesting that they came to the same conclusion from diffe-

rent figures.

The question to be answered is : If a pregnant woman retains what is necessary for the products of conception, should there be any difference in Na_{Ex} / Kg. ?

As the patient who is retaining sodium is also gaining weight at the same time one would expect no significant difference in the Na_{Ex} / Kg. That was the case in Plentl and Gray's and Dieckmann and Pottinger's results. In spite of the fact that the figures of MacGillivray and Buchanan regarding Na_{Ex} / Kg. were contradictory to both the others, the results of the three present the same answer: that is, in normal pregnancy there is no abnormal retention of exchangeable sodium and all that is retained is accumulated in the products of concep-

tion.

Pre eclampsia :

It is interesting to read the comment of Eastman (1958) on Robinson's paper (1958) treating pre eclampsia with extra salt. He wrote: " To the modern obstetrician the contention set forth in this paper will appear a good deal like claiming that the best way to treat strychnine poisoning is to give the patient more strychnine. To say that it upsets all our concepts about the etiology and the treatment of toxaemias is an understatement. Indeed if this contention is valid we shall have to throw all our books out of the window and rush some new ones through the press recommending a high salt diet in pregnancy ".

As I have mentioned before MacGillivray and

Buchanan (1958) came to the conclusion that in pre eclampsia there is less Na_{Ex} / Kg. than in normal pregnancy.

The following table demonstrates that most workers agree that in pre eclampsia there is an abnormal content of Na_{Ex} in the body:-

A u t h o r	Na_{Ex} / Kg. Meq.	
	Normal Pregnant	Pre Eclampsia
Dieckmann and Pottinger, 1957	~40.2	~44.9
MacGillivray & Buchanan, 1958	~48.3	~43.8
Pleutl and Gray ,1959	39.6	~46.0
This work ,1961	~43	~46.2

We must be careful in comparing these figures. Although most workers agree about increased

Na_{Ex} content yet we do not know exactly when does retention occur. There is a possibility that this retention could happen before the appearance of the clinical signs. This was confirmed recently by Davey (1960). His series included 103 unselected primigravidae, 11 of whom developed later pre eclampsia. If this retention occur in the preclinical phase, there is a possibility that it may continue in severe cases or cease in mild cases after the appearance of signs and symptoms. That is why I kept away of border line cases in my series. Others found that this biochemical disturbrance continues to a certain extent during t h e puerperium (McCartney et al., 1959).

Working from another angle Chesley & Hellman (1957) and Chesley (1960) proved that in pre

eclampsia there is a reduction in glomerular filtration rate and an increase in tubular reabsorptive capacity which would provide a reason for salt retention.

Exchangeable Potassium in Normal & Pre eclamptic Patients :

There was no significant difference in the K_{Ex} / Kg. between normal and pre eclamptic patients. In 20 normal pregnant women it was 36.5 ± 7.9 mEq., while in 14 pre eclamptic women it was 34.3 ± 5.1 mEq. (t = .8, P = .4). The lower average figure in pre eclampsia could be explained by the increased body water content. This result is in agreement with MacGillivray and Buchanan's conclusion (1958).

In the 34 patients who had combined measure-

ment of Na_{Ex} & K_{Ex}, increased sodium retention was confirmed by a signigicant difference (t = 2.76, P = .01) between normal pregnant women Na_{Ex} / K_{Ex} ratio, 1.18 ± .27 and that in pre eclampsia which was 1.42 ± .19.

C O N C L U S I O N :

It seems therefore that there is agreement upon one aspect of this problem and that is that there is abnormal sodium retention in pre eclampsia. All the work hitherto done with few exceptions gives only a static aspect of the picture. The importance of the next step was stressed by Kellar (1960) and that is the need for a dynamic picture of the changes which take place during the development and progress of pre eclampsia . Such studies will enable us to understand when

the retention of sodium occurs, when re-excretion takes place and the relation of sodium metabolism to various degrees of severity of the disease.

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- In collaboration with the medical physics unit we established a method for measuring total body water by using tritiated water as a tracer. The extrapolation method was found more accurate and informative as the turnover rate was measured at the same time.

- Total Body Water was measured in 100 patients, normal, pre eclamptic and hypertensive. It was found that it constitutes 56.2 % and 57.5 % of body weight in the second and third trimester respectively. In pre eclampsia water was 61.8 % while in essential hypertension it was 49.6 % of body weight, with a significant difference between both groups.

- To study the distribution of water in different body compartments the total body water

S U M M A R Y

was measured by THO while the extracellular water was taken as sodium space measured by ^{24}Na. I found that retention of water in pre eclampsia is participated between the extra and intra cellular compartments.

- Using total body water as a method of estimating gross body composition, I found that in normal pregnant women the body contains: 56.2 % water, 20.6 % fat and 23.2 % solids.

- Water turnover rate was measured in normal, pre eclamptic and hypertensive patients. It was clear that in pre eclampsia the turnover rate was significantly decreased less than in normal and in hypertensive patients. I suggested the use of this method to differentiate between pre eclampsia and essential

hypertension.

- It was found that such metabolic rigidity in water turnover occurs before the development of clinical symptoms and signs of pre eclampsia and could be used for early detection of these cases.

- Using ^{24}Na the total exchangeable sodium was measured in 72 patients : normal, pre-eclamptics and hypertensive. A significant increase in the Na_{Ex} / Kg. was found in cases of pre eclampsia but not in cases of essential hypertension.

- Using ^{42}K the total exchangeable potassium was measured in 38 patients : normal, pre eclamptic and hypertensive. There was no significant difference in the K_{Ex} / Kg body

weight between the three groups.

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ACKNOWLEDGEMENTS

It is a pleasure to express my thanks to Professor R.J. Kellar for accepting me as a research student in his department, for suggesting the topic for research and for his continuous help and encouragement.

I would like to thank at first every patient at the S.M.M.P. who very kindly and willingly accepted to be the material for the research knowing well that it is for the sake of knowledge and science.

I am grateful for Dr. J.R. Greening, the director of the Medical Physics Unit for his kind encouragement and continuous help and supervision. The staff of the unit especially Dr. J. Simpson, Dr. P. Tothill and Dr. J. Simpson gave me every

possible help and technical advice without their cooperation it would have been impossible to do this work.

At the S.M.M.P. I received help from every body. The late Dr. R. Mackay, whose death came as a shock to every body, supervised and directed me in the Simpson Laboratory and have been always my reference in statistical problems.

Sister Herd in Ward 49 was a great help. She supervised personally the collection of the 24 hours specimens. She facilitated my work in the ward with a spirit full of proper understanding of research. I would like to thank her very much.

The technical staff of the Department of obstetrics & Gynaecology have been invariably wil-

ling and helpful.

I must thank very much Miss Laing and Miss Duncan for the daily help they gave to me.

I am most grateful to Miss Bell and her assistants in the Central Medical Library for their excellent service. They very willingly supplied me with all the references I needed and brought me some from other libraries in Britain and abroad. I acknowledge very much their help.

At last I wish to thank the Royal Infirmary of Edinburgh for the fund granted for this work.

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