RENAL FUNCTION, WATER, ELECTROLYTES AND OEDEMA IN PREGNANCY

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FOR several decades now the problem of kidney function in pregnancy has fascinated observers, particularly in relation to the occurrence of pre-eclampsia. The central position of the kidney in this condition, early considered as a renal disease, has been almost proselytized in recent years. At the same time the apparently inexplicable changes in salt and water metabolism have resulted in an enormous literature. The present writer makes no claim to provide an answer to these problems but rather to review the more important statements in the literature, bring certain facts into apposition, draw tentative if perhaps wrong conclusions and hope that by doing so, someone else may see light and produce a complete solution.

There are many factors which influence the composition of the urine and function of the kidneys in pregnancy. It is still to some extent a mystery how the kidney manages to deal with the products of metabolism and at the same time regulate the output of fluid and solutes in such a way as to allow for the continued growth of the conceptus and expansion of the circulatory space.

As a starting point one may consider a normal pregnancy of say 28 weeks. In such a patient the blood volume might have increased by 20% (Dieckmann and Wegner, 1934; Albers, 1939; Mull and Bill, 1945; Adams, 1954) and the cardiac output would have reached its maximum, being approximately one-third greater than in the non-pregnant (Hamilton, 1949; Adams, 1954). The renal plasma flow is therefore greatly increased (Bucht and Werkö, 1953; Sims and Krantz, 1959) from 500 ml./min. to 700 or 800 ml./min. Similarly, although varying figures are reported in the literature most observers are agreed that the glomerular filtration rate (GFR) is increased from approximately 110–120 ml./min. perhaps to as much as 150–180 ml./min. (Bucht and Werkö, 1953; Sims and Krantz, 1959; Page, 1957; Aubert, Charvet and Creysse, 1955). This means in effect that up to 100 extra litres of fluid may pass into the renal tubules each day. Assuming that the intake of fluid is within normal

limits, the pregnant woman would very quickly lose fluid and solutes and the body fluid volume be brought back to non-pregnant levels, or even below, if tubular reabsorption were unchanged.

As it is there is a slight diminution in the amount of urine excreted per day, and a reduction in the amount of many of the solutes.

It is apparent from these investigations that the renal tubules must make functional adjustments to cope with the increase in glomerular filtrate. Chesley (1943) has calculated that the total gain in extracellular water during pregnancy may amount to 6.3 l. MacGillivray (1960) using 'heavy water' techniques puts the figure at 7.4 l. and showed that water increased by 6.3% of the body weight. McCartney, Pottinger and Harred (1959) using similar techniques showed that total body water increased by 6.5% of the 'lean tissue mass'.

Control of Urine Volume

Abundant evidence exists to show that certain forms of renal tubular activity are altered during pregnancy. The question of water excretion is intriguing. Reports by several investigators (Dieckmann, 1941b) suggest that there is an increased reabsorption of fluid by the tubules. Theobald (1934, 1946) states that water-diuresis curves show that pregnant women are incapable of secreting urine at more than half the normal non-pregnant rate. Some modification of this statement must be made. If it were true one might expect all pregnant women to become progressively oedematous. Several points are to be noted in assessing the results of these tests. Smirk (1933a, b, c) has shown that approximately one-third of ingested water is distributed to the lower limbs and if the venous pressure in these is raised, the fluid becomes trapped (Baltes and Smirk, 1934). This can be seen in normal pregnant patients. Towards the end of pregnancy it is common to find patients complaining of swelling of the feet at the end of the day; this is found in 66% of all patients (Dexter and Weiss, 1941). The explanation is to be found in the increased

venous pressure in the lower half of the body produced by the pressure of the enlarged uterus on the veins, and by the influence of the arterio-venous fistula in the placenta. Almost all of the water-excretion tests reported have been carried out in one of two ways. Either a straightforward water-diuresis test has been performed with the patient in the dorsal position, which does nothing to relieve the venous pressure, or conclusions as to water excretion have been drawn from tests performed using solutions of sodium chloride. Janney and Walker (1932) and Walker, McManus and Janney (1933) compared excretion after a water load in non-pregnant normal patients with that in normal pregnant patients. In pregnancy the patient only excreted 55% if kept in the dorsal position, 32% if in a sitting position but 99% if turned on her side. In other words there is no evidence to indicate that there is any specific alteration in the handling of water by the kidney in normal pregnancy.

Sodium Metabolism

The position with regard to sodium metabolism is much more confused. The earlier literature seemed to indicate that an enormous retention of salt occurred in normal pregnancy (Coons, Coons and Schiefelbusch, 1934). Reported estimates of sodium retention vary from 4.8 mEq. to 55 mEq. per 24 hours, and of potassium from 0.26 mEq. to 36.5 mEq. per 24 hours. Hummel, Hunscher, Bates, Bonner and Macy (1937) in a balance study extending over 145 days found a retention of 207 g. potassium and 81 g. of sodium. Chesley (1944) summarised the findings of authors in the literature prior to 1944. These all showed a remarkable retention of sodium varying from 1.6 to 8.8 g. per week, which, if it were osmotically active, would lead to enormous water retention.

More recent studies have questioned the validity of these statements. Chesley, Valenti and Uichanco (1959) studied the output of water and sodium in the early puerperium. On the basis of their findings they came to the conclusion that pregnancy is not accompanied by any significant hydration of the tissues or by storage of osmotically active sodium. McCartney, Pottinger and Harrod (1959) demonstrated that the percentage of total body water did not alter during pregnancy, and the exchangeable sodium in terms of mEq./Kg. bodyweight was somewhat reduced. Plentl and Gray (1959) calculated that the increase in total sodium could be accounted for by the products of gestation and increase in blood volume. MacGillivray (1960) in careful experiments with deuterium oxide and radio-active cations proved that although there is an absolute increase in exchangeable sodium and chloride in normal

pregnancy the amount per litre of the total body water is the same as in the non-pregnant female. Although, therefore, there is no evidence of storage of osmotically-active sodium during pregnancy, the total amount is increased and it is natural to assume that this is achieved by an active renal retention. Since the glomerular filtration rate is increased, the process must be one of increased tubular reabsorption. It is however, difficult to prove this from results reported in the literature.

Most of the investigations have taken the form of balance studies without any specific test of the ability of the kidney to handle sodium. In addition they have been concerned with a comparison of normal and pre-eclamptic pregnancies, and provide no base-line for non-pregnant patients. One of the few communications which does give figures for non-pregnant as well as pregnant subjects is that of Smith, Hendrick and Miller (1957). With the same diet non-pregnant subjects excreted 174 to 218 mEq. of sodium in 24 hours whereas normal pregnant individuals only excreted 135 mEq. We have observed similar results in patients under what may be termed basal conditions. The patients are maintained on a standard diet of known sodium intake. On the day prior to the test no fluids are allowed from 7 p.m. At 7 a.m. in the morning the bladder is emptied and this urine is discarded. For the next three hours the urine is collected and the sodium content measured. Under these conditions it is found that the patient in the last trimester of pregnancy only excretes 80% of the total found in the urine of the non-pregnant subject. If these patients are then subjected to a loading test by injecting 10 g. of salt intravenously and collecting the urine for the following three hours, the comparative result is the same. Under these conditions the non-pregnant subject will excrete 58 mEq. of sodium compared to the 48 mEq. by the normal pregnant patient. The difference is even more marked if these tests are carried out on patients during the first two trimesters of pregnancy. This is also apparent from the results of a careful study made by Thomson and Pommerenke (1939) on a 28 year-old primigravid patient whose pregnancy was entirely normal. Estimates of sodium metabolism were made at the fourth month of gestation and again in the eighth and ninth months. During the fourth month the average daily retention of sodium was found to be 19.3 mEq. with an intake of 158 mEq. In the eighth and ninth months the average retention had declined to 11.6 and 13.2 mEq. respectively. This study was very carefully carried out, attention being paid to details such as the limitation of exertion in order to avoid sweating and thus

prevent excessive loss of sodium chloride in this manner.

It would appear, therefore, that during normal pregnancy the renal tubular cells have an increased avidity for the reabsorption of sodium. The mechanism is at present unknown but some tentative suggestions may be made. Sodium is reabsorbed from the tubule at four levels at least. According to Windhager, Whittenbury, Oken, Schatzmann and Solomon (1959) approximately 80 to 85% of the sodium is reabsorbed in the first convoluted tubule. The factors controlling this process are at present unknown. A further proportion of the sodium is reabsorbed in the ascending loop of Henle. This is the basis of the counter-current mechanism. (Gottschalk and Mylle, 1959). In the distal convoluted tubule sodium is exchanged for potassium, which is excreted. This mechanism is probably mediated through the action of aldosterone (Berliner, Kennedy and Orloff, 1951). Finally sodium is reabsorbed in the collecting tubules where it is exchanged for ammonium ions (Ullrich, 1960).

With the increase in GFR a greater volume of fluid is offered to the renal tubule. Under these circumstances proximal reabsorption of sodium tends to be limited, leaving more sodium to be dealt with lower down. Our knowledge of these mechanisms in pregnancy is very limited but from the available reports it appears that there is a great increase in the secretion of aldosterone (Venning, Primrose, Caligaris and Dyrenfurth 1957; Koczorek, Wolff and Beer, 1957; Martin and Mills, 1956; Rinsler and Rigby, 1957; Jones and others, 1959; Kumar, Feltham and Cornell, 1959). The values reported vary to some extent, probably due to different methods of estimation, but the results of Venning and others (1957), Koczorek and others (1957) and Rinsler and Rigby (1957) agree fairly well. According to these writers the output of aldosterone rises from a non-pregnant level of 6 μg . per 24 hours to values ranging from 16 μg . to over 100 μg . per 24 hours according to the stage of pregnancy.

In addition to these reports of increased excretion of aldosterone there is some indirect evidence that this substance is active during pregnancy. Both Rinsler and Rigby (1957) and de Alvarez, Bratvold and Harding (1959) have shown that the ratio of sodium to potassium in the urine is decreased during pregnancy and that this decrease runs parallel with the increase in aldosterone output. Further evidence is supplied by Kumar and others (1959) who have shown that salt restriction in normal pregnancy results in an increased output of aldosterone, and by Barnes and Buckingham (1958) who found that after

administering an aldosterone antagonist the output of sodium was greatly increased.

The question arises as to the reason for the increased output and activity of aldosterone during pregnancy. The simple answer is that more sodium is required for the expansion of the blood volume, the growth of the foetus and increase of the amniotic fluid. Yet increased aldosterone secretion in the presence of an increased quantity of body sodium and a raised blood volume does seem a paradox. Usually aldosterone secretion is reduced in these circumstances. In the normal individual it has been demonstrated that the immediate factors stimulating aldosterone secretion are a decrease in whole blood volume or effective blood volume (Bartter, Biglieri, Pronove and Delsa, 1957), a decrease in extra-cellular fluid volume, including blood volume, or a decrease in total body water (Strauss and Papper, 1959). So also the converse, diminution in aldosterone production, may be brought about by increase in extra-cellular fluid or total body water but not by increase in blood volume alone. Luetscher and Lieberman (1958) report that aldosterone secretion is also increased if there is a diminution in the sodium and therefore of the Na/K ratio of body fluids. In pregnancy the blood volume is increased, sodium is retained, and still aldosterone secretion is not only is high but goes on increasing throughout pregnancy. Three mechanisms may be at work even with a continually expanding vascular space: there may be a constant deficit of effective blood volume; secondly, there is a drain of sodium and fluid to the conceptus; and lastly, it is clear that it is not an overall volume change which influences aldosterone secretion and sodium metabolism. Pooling of blood in the limbs will increase aldosterone output and sodium reabsorption. Epstein (1957) has shown that the same occurs when an arterio-venous fistula is opened. The placental circulation is in a sense an arterio-venous fistula. In addition, it would be reasonable to suppose that there are receptors in that area engaged in regulating maternal blood volume and so maintaining placental blood supply.

Venning, Simpson and Singer (1954) and others have produced some evidence to suggest that the secretion of other salt-retaining factors in addition to aldosterone, possibly of placental origin, are increased in pregnancy. The results of pharmacological tests are interesting in this respect. Drugs, such as chlorothiazide and acetazolamide which inhibit tubular carbonic anhydrase and thus produce an acidosis have been administered to normal pregnant women. The body, in ridding itself of accumulated acids, uses sodium as a base and the sodium output is thus increased. Reports show however (Assali, 1960

Afonso, de Alvarez and Bratvold, 1960) that within a few days the activity of these drugs is lost. There may therefore be an over-riding control of sodium affecting more than one part of the renal tubule in normal pregnancy.

With the available evidence it would appear that the regulation of fluid exchange is achieved by control of the renal excretion of sodium. Water retention is geared to sodium reabsorption, perhaps passively or by interplay between sodium retaining steroids and anti-diuretic hormone.

Compartmental Distribution

Before proceeding to a discussion of sodium and water metabolism in abnormal pregnancy notice must be taken of certain changes reported to take place towards term which, if confirmed, may alter our outlook on these matters. In addition the question of oedema in normal pregnancy must be considered.

It has been known for some time that the plasma volume tends to fall during the last few weeks of pregnancy (Cope, 1958). Associated with this is a fall in the amount of total exchangeable sodium (Davey, O'Sullivan and McClure Brown, 1961). In 1949, however, Caton, Roby, Reid and Gibson, while reporting this same biphasic change in plasma volume, also noted alterations in the relationship between plasma volume and extravascular fluid. They found that while the plasma volume increased progressively until near term, when it fell, the extravascular fluid volume increased right up to term. In early pregnancy the rate of increase of the plasma volume greatly exceeded that of the extravascular fluid, but during the third trimester this ratio was reversed and when the plasma volume fell in the last month of pregnancy the relative size of the extravascular compartment was greatly increased. Confirmation of these findings would be of considerable interest.

Posture and Oedema

The significance of oedema in pregnancy is not clear, particularly when the patient is otherwise normal. Dexter and Weiss (1941) reported a 66% incidence of oedema in normal pregnancy. Even when overt oedema is not present most pregnant women will complain of shoes becoming tight-fitting and wedding rings being impossible to move, particularly at the end of the day. The findings of Janney and Walker (1932) quoted above suggest an explanation, and the process is initiated by means which are largely mechanical. McLennan (1943) has shown that the femoral venous pressure rises from 91 mm. H₂O in early pregnancy to 244 mm. in late pregnancy. These observations were made with the patient supine.

Previously, Rona (1935) had noted that with the patient standing the venous pressure varied from 792 to 1230 mm. H₂O. The maximum pressure noted by McLennan is not far short of the osmotic pressure of the plasma proteins in pregnancy, and the figures quoted by Rona are far in excess. In addition Payling Wright, Osborne and Edmonds (1950) found that during pregnancy there is a progressive slowing of venous flow in the lower limbs as pregnancy advanced, and McCausland, Hyman, Winsor and Trotter (1961) have demonstrated that there is a 150% increase in venous distensibility during pregnancy.

These changes alone would lead to retention of fluid in the limbs, but alterations in renal function take place which, under certain circumstances, would tend to make the fluid retention more or less permanent. Barger, Liebowitz and Muldowney (1959) dealing with non-pregnant patients have found that in the erect position sympathetic activity is increased and the rate of sodium and water excretion is 25 to 50% lower than that found when the patient is reclining. Assali, Dignam and Dasgupta (1959) report similar findings in pregnancy. In addition they showed that when the patient was erect there was a fall in the GFR and RPF. The aldosterone output rose markedly. The sequence of events would seem to be that fluid is trapped in the lower limbs and leaks into the interstitial tissues. The circulating volume is thereby reduced and aldosterone secretion is stimulated. This, along with the reduction in GFR and RPF results in retention of sodium and water in order to restore the blood volume. With most normal women the process is reversed on retiring to bed. The venous pressure is relieved, and as Theobald and Verney (1935) reported, the volume of night urine comes to equal that passed during the day. In some women, however, the process is more active, the fluid accumulates in the tissue spaces and the body may ignore it. This is particularly apt to happen if the patient is kept in the supine position. We have recently observed something of this kind in a patient admitted to hospital with oedema but no hypertension or albuminuria. Given a water-loading test she only managed to pass 24 % in the supine position. Repeating the test the following day with the patient on her side resulted in an output of 112%. Her oedema improved quickly with postural treatment of this kind.

Even in non-oedematous patients we have noted that, although they will excrete 100% or more of a water load while lying on their sides, the percentage output falls to around 50% when in the dorsal position and if made to stand or move about gently there is a further decrease to 30% or less.

The importance of this type of oedema in the

limbs cannot be over-emphasized if a proper appreciation of pre-eclampsia is ever to be attained. Many of the conflicting results reported in studies of renal function may well be due to this mechanism.

Pre-eclampsia

Oedema in pre-eclampsia tends to have a general distribution, although always more marked in the limbs and confined to that site in the early stage.

For long, problems of methodology have bedevilled the investigation of renal function and oedema in pre-eclampsia. Many of these problems have been overcome in recent years and we are now able to make a tentative evaluation although much remains to be done before the mechanisms are fully understood.

Clinically we are faced with two facts, albuminuria and oliguria in severe cases. The one argues for increased permeability of the glomerulus, the other for reduced permeability or increased tubular activity.

All investigators are of the opinion that the inulin clearance rate, which is normally supposed to measure GFR, is reduced in pre-eclampsia (Corcoran and Page, 1941; Dill, Isenhour, Cadden and Schaffer, 1942; Wellen, Welsh and Taylor, 1942; de Alvarez, 1950). The values quoted vary, but on average there is a fall from around 120 ml./min. in the non-pregnant state to 85-90 ml./min. in pre-eclampsia. Our own findings are similar. The results have been interpreted in several ways. For instance, Corcoran and Page (1941), from a consideration of histological findings, came to the conclusion that the glomerular membrane was less permeable in pre-eclampsia, but there are a number of arguments against this. For instance, the clinical finding of albuminuria might indicate *increased* permeability. In addition, Wellen, Welsh and Taylor (1942) compared the excretion of inulin with that of mannitol and sorbitol, both very much smaller molecules. In all three cases the clearance rates were identical. It is difficult to conceive that there is any hindrance to the passage of inulin in these circumstances and one must conclude that the clearance of this substance is a true measure of GFR. The view has also been put forward that the reduced filtration is due to spasm of the afferent arteriole, which would have to be of considerable magnitude in view of the hypertension. Again the pallor of the kidney at post-mortem in fatal cases of eclampsia lends some support to this argument. Unfortunately, investigations of renal blood flow do not support this idea of renal ischaemia. On the contrary all of the authors quoted above have found that the

effective renal blood flow is either normal or increased, and the kidney would therefore appear to be slightly hyperaemic.

It still remains to resolve the problem of reduced filtration in the presence of hypertension, and albuminuria. The filtration rate is the resultant of two main forces, the hydrostatic pressure in the glomerulus and the osmotic pressure of the blood. The pressure within the glomerulus is itself regulated by two factors, the pressure at the afferent end of the circulation and the tone of the efferent vessel. In pre-eclampsia the blood pressure is increased, the plasma proteins are diminished and one might therefore expect an increased filtration rate. One is forced to conclude, in the absence of any direct evidence of intense afferent spasm, that the reduced GFR is the result of a decreased hydrostatic pressure within the glomerulus achieved by relaxation of the efferent vessel. This has nothing to do with permeability, for the capillaries of the glomerulus might still leak protein although the filtration rate of water is reduced. This is an attractive hypothesis for if true it assures an adequate blood supply to the kidney, protects the glomerulus to a great extent from damage by high blood pressure and allows very effective reabsorption from the reduced filtrate which may be necessary.

Albuminuria remains a vexed question, but it is to be noted that the amount of protein passed by the kidney varies not only from day to day but from hour to hour during any one day. There is no doubt that arteriolar and glomerular damage does occur in the most severe cases and it seems likely that this is related to the high blood pressure (Govan, 1961). Pre-eclampsia is not a static condition and it seems to me possible that in the early stages of the disease the haemodynamic changes may not be sufficient to protect the glomerulus at all times. In the late stages it is my belief that the picture in most cases is dominated by the rising blood pressure and in these circumstances spasm of the afferent arteriole may play a greater part in the pathology of the disease.

In addition to finding a normal or increased renal blood flow Wellen, Welsh and Taylor (1942) and others have reported that the tubular excretory mass is normal, indicating that there is no reduction in tubular activity.

In summary, therefore, it would appear that apart from a moderate reduction in GFR the functional capacity of the kidney in toxæmia is normal. This does not mean that the renal function is qualitatively the same as in normal pregnancy and it remains to relate if possible the urinary findings with what is known of water and electrolyte balance in pre-eclampsia.

Volume Control

It has always been assumed in view of the accompanying œdema that water metabolism is upset in pre-eclampsia and for the past 30–40 years this has been linked with changes in sodium metabolism (Dieckmann, 1935). It is difficult to decide which factor, water or sodium, is the more important, and up to the present, impossible to determine whether these changes are of primary importance in the etiology of pre-eclampsia or merely secondary.

Recent work with 'heavy water' indicates that there tend to be changes in total body water. McCartney, Pottinger and Harrod (1959) found a rise in total water from 78.9% of the lean body mass in normal pregnancy at 37 to 39 weeks to 81.3% in pre-eclampsia in a pregnancy of the same duration. MacGillivray (1960) related his figures to the total body weight and showed that in mild pre-eclampsia there was a slight but not significant increase in total body water. In severe pre-eclampsia the increase was greater but still not statistically significant. Plentl and Gray (1959) on the other hand found little difference between normal and pre-eclamptic patients.

The difference in these reported views may well be due to variation in clinical material, such as the stage of the disease, and obesity of the patient. There is a fallacy, as MacGillivray has pointed out, in relating body water to body weight since it is impossible to determine the proportion of the weight which is fat. Chesley and Chesley (1943) showed that the amount of water, as measured by the thiocyanate method, may actually increase although the subject is losing weight. Clinically the disease is usually characterized by œdema, gain in weight and oliguria, therefore it seems reasonable to assume that the amount of body fluid is increased.

The occurrence of oliguria would suggest that the retention of fluid is of renal origin and there is some evidence to suggest that this may be so. Dieckmann (1935) and others have reported that there is a delay in excreting water. Our own studies support this idea. As noted above, a normal pregnant woman, will, when given a water-loading test, excrete at least 100% of the test dose in 3 hours provided she lies on her side. The same test carried out on a pre-eclamptic patient, with hypertension, albuminuria and œdema yields very different results. As in normal pregnancy, the output of water is reduced, frequently to 20%, when supine but repeating the test with the patient lying on the side may not increase the return to more than 50%.

This reduction in fluid output might be attributed to the fall in GFR but the decrease

reported in the latter is insufficient to account for water retention. The alternative is a specific reabsorption of water by the tubules, which would rather suggest anti-diuretic hormone (ADH) activity. This has long been a matter for contention among investigators. Anselmino, Hoffman and Kennedy (1932) were among the first to report an increase of posterior pituitary substance in pre-eclampsia. Indirect support for this idea is found in the work of Dieckmann and Michel (1937) who showed that pituitrin caused a rise in both systolic and diastolic pressures in pre-eclamptic patients. De Valera and Kellar (1938) also demonstrated that pre-eclamptic subjects were more sensitive to pitressin than normal. It has been shown that the serum of normal pregnant women contains an enzyme which inactivates posterior pituitary hormone *in vitro* (Barnes and Sawyer, 1960) and this enzyme is said to be diminished or absent in pre-eclampsia (Hawker, 1956). Assali, Dignam and Longo (1960) claim that whereas the GFR and RPF are not altered by pitressin in the non-pregnant they are diminished by this hormone in pregnancy. They could find no evidence for inactivation of the hormone *in vivo*. The controversy over posterior pituitary hormone has continued over the past two decades with an almost equal amount of evidence for and against its activity in this disease. In 1953, Arneil and Wilson reported the discovery of a polypeptide, isolated by chromatographic methods, in the urine of patients suffering from oliguria due to renal disease. This polypeptide appeared to have the same chemical composition as ADH. Paterson (1954) working in this department and using this technique, found the same substance present in the urine of pre-eclamptic and eclamptic patients. A further study (Paterson, 1960) demonstrated its presence in both plasma and urine, and a relationship between its occurrence and the presence of œdema. In this latter communication it is to be noted that in seven out of 86 cases of pre-eclampsia no polypeptide was found in the urine and these patients had only traces of œdema. This of itself tends to make one question the primary position of ADH in the etiology of pre-eclampsia. In addition, if ADH were operative from the beginning of the process any increase in available water would be by addition to the body stores and one would expect a gain in weight. Chesley and Chesley (1943) have shown that available water, measured by the thiocyanate method, is increased before any gain in weight is registered in patients who become pre-eclamptic. In other words a redistribution of fluid takes place prior to the onset of typical signs. If this is true then it is doubtful if posterior pituitary substance plays a part in the

genesis of the syndrome, although it may be of importance in the established disease.

Sodium Metabolism

Controversy has raged in a similar fashion in the field of sodium metabolism. The number of communications is vast. In the early years most of them dealt with balance studies which purported to demonstrate retention of salt in pre-eclampsia (Taylor, Warner and Welsh, 1939). Similarly, Dieckmann, Smither, Horner, Pottinger, Rynkiewicz and Lundquist (1951) reported that the oral administration of salt increased the severity of toxæmic symptoms in approximately 30% of pre-eclamptic patients. It is to be noted that in these patients there was apparently no restriction of fluid intake. Intravenous injections of large amounts of sodium chloride (Dieckmann, Pottinger and Rynkiewicz, 1952) produced marked increases in weight, œdema, hypertension and albuminuria.

It has been accepted for many years that the urine of pre-eclamptic patients contains less sodium chloride than that of normal subjects, although Chesley (1939) was inclined to believe that this might be the consequence of a salt-free diet. Dieckmann, Pottinger and Rynkiewicz (1952) showed that after a sodium chloride load pre-eclamptic patients only excreted 50% of the output of normal pregnant women. This was confirmed by Willson, Williams and Hayashi (1957). Using somewhat similar methods Halmágyi and Zelenka (1949) and Govan and MacGillivray (1954) reported similar findings and suggested that they were due to active tubular reabsorption of sodium. Subsequently, Chesley, Valenti and Rein (1958) repeated this work and carried out inulin clearances simultaneously with the infusion of sodium chloride. They found that although both fluid and sodium outputs were augmented, the increase in sodium output did not run parallel with the rise in GFR indicating that tubular reabsorption of sodium occurred. Indirect evidence of tubular activity is found in the results of hydrochlorothiazide therapy. Assali (1960) reported that the increased output of sodium was achieved without altering the GFR or RPF. It would appear then that the function of the renal tubule is changed as in normal pregnancy but possibly to a greater degree.

This result is peculiar in view of recent studies of aldosterone excretion in this disease. Martin and Mills (1956) reported that the amounts excreted in pre-eclampsia were within the normal range for pregnancy. On the other hand Rinsler and Rigby (1957), Koczorek, Wolff and Beer (1957) and Kumar, Feltham and Gornall (1959) have all found values lower than normal in pre-eclampsia.

This seems at odds both with an increased reabsorptivity for sodium and with the findings relating to blood volume. As long ago as 1918 Freis and Kenny pointed out that the blood volume is low in pre-eclampsia. Additional evidence was supplied by study of hæmatocrit readings (Skajaa, 1929; Crawford, 1940; Botella-Llusia and Arranz, 1941). Recently it has been confirmed using more modern methods by Rottger (1954) and MacGillivray (1960). It will be remembered that the main mechanisms in stimulating aldosterone secretion are a change in sodium/potassium ratio or changes in body fluid volumes, especially effective blood volume. One might conclude that the vascular system is well-filled in toxæmia although the blood volume is small. Although aldosterone output may be low compared with normal pregnancy it is still, according to Koczorek and others (1957) well above the non-pregnant range, and could be responsible for increased renal tubular absorption of sodium. Nevertheless Barnes and Buckingham (1958) found that anti-aldosterone substances had no influence on sodium output in pre-eclampsia.

Whatever the explanation of these findings may be, there is some doubt despite the increased reabsorptive capacity of the renal tubule for sodium, whether there is a true retention of sodium in pre-eclampsia. Recent work with radiosodium has yielded conflicting results. McCartney, Pottinger and Harrod (1959) found a marked increase of exchangeable sodium in pre-eclamptic patients. Plentl and Gray (1958) have reported similar findings. MacGillivray and Buchanan (1958) however, found the value for total exchangeable sodium in pre-eclampsia to be similar to that for normal pregnancy. Later MacGillivray (1960) by estimating body water simultaneously with sodium found that the ratio of sodium to body water was less than in normal pregnancy, indicating that water is retained without sodium chloride. Davey, O'Sullivan and McClure Browne (1961) agree with MacGillivray, but in addition, by repeated observations on patients throughout pregnancy they have uncovered some interesting facts. Patients who subsequently developed pre-eclampsia showed an excessive increase in total exchangeable sodium between the sixteenth and twenty-sixth weeks, but by the time pre-eclampsia became overt the total sodium showed a diminution compared to normals. This may explain to some extent the varying results reported by other authors.

Compartmental Distribution

Even more interesting than measurement of total sodium and water are the studies of compartmental distribution of these substances. Rosser

beck (1931) found, on analyses of eclamptic tissues that the sodium content was raised and the potassium diminished. Parviainen, Soiva and Ehrnrooth (1950) have made similar claims. These findings, however, may not be of etiological significance. Post-mortem findings represent terminal changes and histologically there is evidence of massive effusion of blood constituents into the tissues which would upset the chemical state in these cases (Govan, 1961). Nevertheless, Mukherjee and Govan (1950) and Tatum (1954) have both found the concentration of sodium to be higher in œdema fluid than in serum. On the other hand MacGillivray (1960) reported less sodium per litre of body water than normal. This refers to total body water and does not necessarily invalidate a compartmental distribution of sodium. There also seems to be a compartmental distribution of water. Reference has been made already to the low blood volume in these cases. It seems very doubtful if this lowering of blood volume can be the result of vaso-constriction. MacGillivray's (1960) results with thiocyanate, bromine and sodium indicate that the extracellular fluid is the same as in normal pregnancy. Since the total body water may be somewhat greater than in normal pregnancy this suggests that fluid is retained within cells, whereas Dieckmann (1941) had the view that there was a shift of fluid from the cells to the extracellular space, an opinion also held by McPhail (1939). Chesley and Chesley (1943) found that prior to the appearance of the classical triad of pre-eclampsia a gain in extra-cellular water was recorded without a gain in weight, again suggesting a movement from intra-cellular to extra-cellular fluid. These reports are interesting when one recalls that Caton and others (1949) have found evidence for somewhat similar changes in the last month of normal pregnancy. The changes occurring at this period of normal pregnancy would repay investigation and might well help to explain the complicated and apparently paradoxical volume changes in pre-eclampsia.

Although these changes in fluid volume and electrolyte concentration occur one must assume that the isotonicity of the body fluids is maintained and that, as in the normal, this is the main reason for changes in renal function. In this respect it is interesting to glance at the results of therapy involving manipulation of fluid and salt. Turner and Fair (1953) subject their pre-eclamptic patients to hydration therapy, involving the ingestion of almost 6,000 ml. of water daily. A low calorie diet containing 0.6 g. sodium chloride is given. This results in a water diuresis, but the excretion of sodium is diminished. First of all, these results indicate that the absorption of

water is normal, that the kidneys, in view of the diuresis are essentially normal, and that the centres for ADH control are sensitive and respond to a water load. With regard to the absence of a sodium diuresis, this is to be expected. Its retention is an indication of the body's attempt to maintain isotonicity, and of the fact that the kidney is carrying out its normal function in this respect. Similarly, with a salt-free diet, sodium disappears from the urine although a mild water diuresis may occur. Again the same process is at work. With a high-salt diet (de Alvarez, 1950) the excretion of sodium rises, but oliguria tends to occur, so that some of the salt is retained in isotonic solution and œdema will increase. Tatum (1955) found that the administration of various solutions to pregnant women produced a net gain in body water provided the solutions were isotonic. The changes were more marked in pre-eclamptic subjects.

It is at this point one comes to a full stop. Further speculation can only be of a very general nature. Œdema in the vast majority of cases is not markedly progressive. It is as if the fluid, having been retained for some purpose and that purpose being attained, the body ignores it. One gains the impression that these powers of the kidney to reabsorb sodium and water are largely potential, to be brought into operation when there is a threat to the isotonicity and electrolyte balance of the body fluids, as if the kidney is doing its best to maintain normal conditions in face of changes which are extra-renal. There seems to be a metabolic instability in pre-eclampsia and the co-ordination of salt and water metabolism and volume control is easily upset. This is implied in reports of hyponatræmia with continuing œdema following treatment with chlorothiazide (Miller, 1960). The apparent compartmental changes, if proved to exist, would tend to indicate an underlying fault in cellular metabolism. I have not considered the position of the plasma proteins in relation to œdema. Quite apart from the physical effect of their marked diminution in pre-eclampsia which must tend to create œdema, changes occur in the relative and absolute proportions of the various proteins, which probably indicate alterations in metabolism. It is known that peculiar changes occur in carbohydrate (Govan, Mukherjee, Hewitt and Harper, 1951) and nitrogen metabolism (Mukherjee and Govan, 1951) and that the glycogen stores of the liver are depleted (Mukherjee 1952).

Equally, I have not touched upon the possibility of altered adreno-cortical activity, as distinct from aldosterone, in relation to œdema. Adreno-cortical extracts are said to be diuretic and according to most observers the production of corticoids

is diminished in pre-eclampsia. A fact which may be relevant in this respect is that I have found the adrenals to be smaller than normal in fatal cases of eclampsia. It is interesting to note that a somewhat comparable situation in general medicine is met with in certain forms of cardiac failure. In these cases there is oedema with retention of large amounts of sodium but an even greater retention of water (Strauss and Papper, 1959). It has been suggested that there may be an element of adrenal failure in these patients.

Before a final assessment of oedema in pre-eclampsia can be made further information on the early changes prior to the onset of symptoms and signs is necessary. The factors involving volume control, even in late normal pregnancy, require investigation, and in all tests care will have to be taken that the methods of the investigator such as simple change in the patient's posture do not invalidate results, and that any results obtained are not related to prior manipulation of salt and water in the diet.

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