different types of myocardial infarction had different mortality rates and few of the papers which he cited described their diagnostic criteria in great detail, so that comparison between papers was difficult.

One point which he had not mentioned was that while patients who had had a previous myocardial infarction had a higher mortality rate during surgery, often as a result of a second myocardial infarction, this increased risk extended to patients suffering from other cardiovascular disease short of infarction. Thus coronary artery disease, hypertension – particularly untreated hypertension – and ECG abnormalities all suggested a greater than normal risk factor.

It was usually said that postanæsthetic infarction had a much higher mortality than 'medical' infarction. The figures of course were artificially loaded because many patients who died immediately after a 'medical' infarction never reached hospital. However, it had been clearly shown that the mortality rates for 'medical' infarction could be drastically reduced by proper treatment in a coronary care unit. This had been achieved mainly by the detection and correction of arrhythmias, little progress having been made in the treatment of 'pump failure'.

He thought this told several important things to anæsthetists. Because postoperative infarction was commonest on the third day and because we knew that postoperative hypoxia extended over this period, patients particularly at risk needed to be carefully watched over this period, perhaps with ECG monitoring and oxygen administration. Secondly, because the diagnosis of infarction was difficult, the observer should always have a high index of suspicion. Thirdly, if the patient did have an infarct, the correct place for him to be nursed was in a coronary care unit.

There was really no good evidence to show that one form of anæsthetic was better than another for these patients. Hypotension had, however, been shown to be harmful, as obviously hypoxia must have been. Our management of these patients during anæsthesia should, he thought, be modelled on the cardiac surgery or intensive care style which implied comprehensive monitoring and meticulous care of the circulation.

Meeting 1 June 1973

Registrar's Prize Essay

The Sodium Story: Effects of Anæsthesia and Surgery on Intrarenal Mechanisms Concerned with Sodium Homeostasis

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Anæsthesia and surgery are usually accompanied by severe sodium retention (Le Quesne & Lewis 1953, Snyder *et al.* 1952). The duration and degree of such retention seems to be related to the severity of the operative procedure (Moore *et al.* 1955). Although many reports (Shires *et al.* 1961, Fieber & Jones 1966, Deding *et al.* 1971) suggest that large volumes of balanced salt infused during surgery may prevent the sodium retention, its etiology remains unexplained.

In 1952, the powerful salt-retaining adrenal steroid, aldosterone, was isolated (Simpson & Tait 1952). Since Casey (Casey *et al.* 1957) showed that aldosterone excretion was increased tenfold postoperatively, it was assumed that aldosterone secretion was the cause of this sodium retention. This appeared to be confirmed when Johnston (1964) showed that patients pretreated with an aldosterone antagonist, spironolactone, produced a sodium diuresis postoperatively. Kay (1968), however, was unable to confirm this. In addition, it is known that adrenalectomized patients, maintained only with cortisone supplements, still retain salt after surgery (Mason 1955). Also in infants whose aldosterone production is impaired (Weldon *et al.* 1967), nearly all the sodium filtered at the glomerulus is reabsorbed (Aperia *et al.* 1972). Thus, it seems that other factors are important in the etiology of postoperative sodium retention. Intrarenal mechanisms have received little attention in surgical patients.

During the last ten years, enormous progress has occurred in the understanding of sodium homeostasis by the kidney. In 1961, de Wardener *et al.* showed that urinary sodium excretion could

be increased in animals, despite pretreatment with sodium-retaining steroids and despite a fall in glomerular filtration rate. Thus the classical view that urinary sodium excretion was determined only by changes in glomerular filtration and aldosterone secretion was now inadequate.

More recently it has been shown that urinary sodium excretion can be regulated by changes in the transmural pressure at a site at the distal end of the afferent arteriole (de Bono & Mills 1965). Increase in pressure at this site is associated with a natriuresis and a fall in pressure with sodium retention. The pressure varies directly with mean arterial pressure or cardiac output and inversely with the tone in the afferent arteriole. There is little support for their views in clinical practice apart from studies in patients with orthostatic hypotension (Wilson *et al.* 1969). These patients with defective vascular reflexes develop hypotension and sodium retention whilst standing and sodium diuresis on lying down. These changes in sodium excretion are compatible with the hypothesis that they result from changes in pressure at the pressure-sensitive site (PSS).

This paper reports two recent studies in which changes in the anæsthetic technique or the surgical procedure may be expected to change the pressure at the PSS. The changes induced are then related to the sodium excretion, during and after operation, in an attempt to determine whether de Bono & Mills' hypothesis can be related to changes in sodium excretion accompanying surgery.

In the first study (Bevan 1971), peripheral vascular tone was decreased by high extradural blockade (Kennedy *et al.* 1966). This fall in tone should result in a net increase in pressure at the PSS with an accompanying natriuresis. In the second study (Bevan *et al.* 1973), a group of patients undergoing cardiopulmonary bypass was studied. Institution of bypass in these patients with an impaired cardiac output should similarly result in a natriuresis.

Study 1: The Effect of Extradural Analgesia on the Metabolic Response to Surgery

Eighteen fit, healthy subjects undergoing vagotomy and pyloroplasty were studied. Ten patients, who were anæsthetized in a conventional manner with a barbiturate, N_2O/O_2 and relaxant sequence served as a control group. Their intravenous fluid intake was carefully controlled for forty-eight hours postoperatively. Two patients received 2% of their body weight by volume per twenty-four hours, 2 others received 3%, 2 received 4%, 2 received 5% and 2 received 6%. One-third of the total fluid was normal saline or Hartmann's solution and the remainder was 5% dextrose. This regime produced a daily fluid load between 1200 and 4500 ml, and a sodium load between 60 and 240 mEq. During operation, Hartmann's solution was infused at a rate of 2 ml/kg per hour.

Eight patients were anæsthetized in an identical manner and received a similar graduated fluid regime. In addition, an epidural cannula was introduced before surgery via a lower thoracic interspace and a band of analgesia covering the sixth to twelfth thoracic segments, maintained by frequent injections of bupivacaine 0.5% for forty-eight hours postoperatively. All urine and gastric aspirate was collected. Its volume and electrolyte concentration were measured.

Results: All patients, in both control and extradural groups, showed a retention of fluid in the postoperative period. Sodium retention was prominent in the control group but abolished in the epidural group (Fig 1). This difference was highly significant ($P<0.001$).

These results confirm that sodium and water rention is marked in patients undergoing upper abdominal surgery with conventional anæsthesia. Its presence, even in those patients who received a high fluid load, suggests that it is not due to falls in plasma or extracellular fluid volumes. Patients treated with epidural analgesia still showed some metabolic response to surgery, in that they still retained fluid. However, as they no longer retained sodium, this suggests that water and

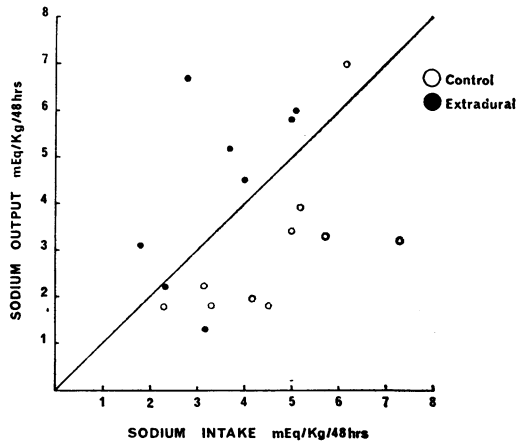

Fig 1 *Postoperative sodium balance in the control and extradural groups*

sodium retention act through different, unrelated mechanisms.

The stimuli of anæsthesia and surgery normally result in activation of the sympathetic nervous system. This produces peripheral vasoconstriction and an increase in circulating catecholamines (Price *et al.* 1959). High epidural analgesia, by blocking thoracic efferent sympathetic fibres, would prevent this increase in vascular tone. The sympathetic stimulation of surgery alters renal hæmodynamics by producing vasoconstriction of the afferent arteriole. This would lead to a fall in pressure at the PSS, resulting in sodium retention. Abolition of this fall by extradural blockade should then lead to undisturbed sodium excretion.

Study 2: The Effect of Fluid Loading on Salt and Water Excretion During Cardiopulmonary Bypass

Twelve patients undergoing cardiopulmonary bypass (CPB), for a variety of cardiac operations, were studied. They were arbitrarily divided into two comparable groups. Half of them (fluid-loaded group) received a fluid load of Hartmann's solution, 20 ml/kg body weight, infused during the time between the induction of anæsthesia and the start of CPB. The remainder (control group) received no additional fluid at this time, although in both groups all blood lost was replaced with whole blood.

Extracorporeal perfusion was provided by a de Bakey roller pump and a Temptrol oxygenator. The circuit was primed with 1 litre 5% dextrose, 500 ml Hartmann's solution and 2 units of blood to which was added 120 ml 4.2% sodium bicarbonate. A calculated flow of 2.4 l./m² was given which was increased in a number of cases to maintain the mean systemic arterial pressure above 60 mmHg. No sympatholytic or diuretic drugs were given until CPB was discontinued.

Urine was collected over the following periods: from the time of induction of anæsthesia until the start of CPB, and at half hourly intervals during CPB. The urine volume and its electrolyte concentration were measured.

Results (Fig 2): (1) Urine volume and electrolyte excretion were very low in all patients in the pre-perfusion period. (2) There was an immediate sodium and water diuresis from the start of CPB. (3) This diuresis was not maintained in those patients with a perfusion time of more than 60–90 min. (4) Fluid loading in the pre-perfusion period made only a very slight and statistically insignificant increase in sodium and water excretion.

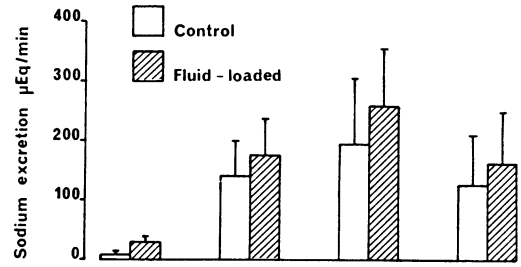

Fig 2 *Mean sodium excretion (±s.e.m.) in the control and fluid-loaded groups during the pre-perfusion 0–30 min, 30 60 min and 60–90 min periods of cardiopulmonary bypass*

These results demonstrate that the prompt sodium and water retention seen after induction of anæsthetic and the beginning of surgery is not altered by fluid loading. Thus, the correction of possible plasma or extracellular fluid deficits was either insufficient or such deficits do not exist.

All these patients with cardiac disease had an impaired cardiac output which was further decreased by the induction of anæsthesia (Prys-Roberts *et al.* 1971). The sodium diuresis occurring with the onset of CPB, is compatible with the hypothesis that CPB restores a normal cardiac output. In the kidney, this would have the effect of raising the pressure at the PSS. This view is strengthened by the observation that the natriuresis is not maintained after 60–90 min. It is established that renal vascular resistance progressively increases, at least in experimental animals, during perfusion with nonpulsatile flow (Jacobs *et al.* 1959). The increased resistance is achieved by constriction of the afferent arteriole, leading to a fall in pressure at the PSS with resulting sodium retention.

It is unlikely that the natriuresis during CPB was the result of hæmodilution alone, as suggested by Nashat (Nashat & Portal 1957), although it may have been partly responsible. No natriuresis was seen in the fluid-loaded group in the pre-bypass period, despite the infusion of a similar quantity of crystalloid solution by the dilute bypass prime.

DISCUSSION

The studies reported here substantiate the hypothesis of de Bono & Mills that changes in renal hæmodynamics may be responsible for changes in sodium excretion. Measures taken to prevent vasoconstriction, by the sympathetic blockade produced by high extradural analgesia, or to increase cardiac output, as in the patients during CPB, will both result in an increase in pressure

at the PSS and lead to natriuresis. These studies demonstrate the importance of the kidney in monitoring the hæmodynamic state of the individual and adjusting his sodium excretion accordingly.

Previously, the sodium retention associated with all forms of trauma, of which surgery is one of the most severe, has been interpreted as being due either to adrenal cortical steroid production or to secondary changes in the distribution of body fluids following stress.

Since Moore described the enormous output of adrenal steroids during and after surgery (Steenburg *et al.* 1956), this has been confirmed by many authors (Johnston 1964, Hume *et al.* 1962, Zimmerman 1965), and since Casey (Casey *et al.* 1957) showed that the output included aldosterone, it has been assumed that this was the cause of the sodium retention seen after surgery in adrenalectomized patients. More recently, it has been realized that changes in aldosterone secretion take sixty minutes before any change in urinary sodium excretion occurs (Ross *et al.* 1959). Thus aldosterone, although it may be important in the postoperative period, cannot explain the immediate sodium retention seen in the early surgical period in the present study of cardiac patients.

In 1961, Shires (Shires *et al.* 1961) suggested that salt and water retention following major surgery was due to significant deficits in the patient's functional extracellular fluid space. Although Roth (Roth *et al.* 1969) was unable to confirm the presence of Shires' 'lost fluid', many authors (Fieber & Jones 1966, Boba 1966 and Trudnowski 1966) have recommended that the urine volume and sodium excretion may be maintained by the use of large volumes of balanced salt solution during surgery. More recently Irvin (Irvin *et al.* 1972) suggested that plasma volume was reduced after surgery and that if it was maintained with Hartmann's solution, infused during and after surgery, then the urine volume and sodium concentration were undisturbed. Unfortunately, in their study their control group was depleted of fluid and electrolytes. In addition, when balance studies are constructed from their data they reveal a cumulative positive sodium balance of more than 350 mEq by the third postoperative day (Bevan 1972).

If it could be shown that these high infusion regimes, as well as maintaining normal urine volume, also maintained normal tissue perfusion and function, then they would be beneficial. No such data exists. On the contrary, the maintenance of urine volume and electrolyte excretion conceals the fluid overload which is occurring. Such overload, by increasing the interstitial fluid volume, may well be partially responsible for the impairment in lung function seen when such regimes are used (Adriani *et al.* 1967). It is probable that such studies may be misleading, in that they have ignored renal factors in the cause of alteration in sodium excretion.

Recently, investigation of the renal handling of sodium has been concerned with the distribution of renal blood flow and the effect of circulating substances on proximal tubular reabsorption. Although this is a very rapidly changing field, it is possible to produce some generally agreed principles.

Vascular Reflexes

The infusion of ^{85}Kr (Thorburn *et al.* 1963) or ^{133}Xe (Barger & Herd 1971) into the renal artery, now makes it possible to measure the distribution of renal blood flow. Analysis of the wash-out curves, determined with an external scintillation counter, enables four components to be recognized. These components correspond to flow in the cortex, juxtamedullary region, medulla and hilar fat. Studies in salt-restricted and salt-loaded subjects (Hollenberg *et al.* 1970) demonstrate that sodium retention is associated with a decrease in cortical flow and an increase in juxtamedullary flow. These changes are reversed with saline loading to produce a natriuresis. Micropuncture studies by Thurau (1969) have demonstrated that juxtamedullary nephrons are better able to reabsorb sodium than cortical nephrons. This gives some functional correlation of the changes in sodium reabsorption with the changes in distribution of blood flow. Thus factors tending to divert renal perfusion from the cortex to the juxtamedullary region lead to sodium retention. Mild stimulation of the renal nerves leads to such a redistribution of flow and retention of sodium (Pomerantz *et al.* 1968). In some respects the sodium retention in animals with artificially induced heart failure, resembles that seen during surgery in man. Barger (1966) has shown that the sodium retention in these animals is associated with decreased cortical blood flow. Phenoxybenzamine or frusemide will reverse this redistribution and abolish the sodium retention.

There is little evidence concerning the distribution of renal blood flow during anæsthesia and surgery. Rosen (Rosen *et al.* 1967) showed in animals that laparotomy was associated with a decrease in cortical flow, whilst cortical flow was normal in denervated transplanted human kidneys (Rosen *et al.* 1968).

Some recent studies have suggested that the timing of the changes in the redistribution of renal flow may not coincide with the alteration in sodium excretion (Hollenberg *et al.* 1972). Also, if renal perfusion is measured with radioactive microspheres, then such changes are less pronounced (Blantz *et al.* 1971). Stein (Stein *et al.* 1972) was unable to confirm Thurau's suggestion that superficial and deep nephrons had different rates of sodium reabsorption. Nevertheless, in certain circumstances, there seems to be no doubt that changes in the distribution of renal perfusion can affect sodium excretion. These changes are probably mediated by adrenergic mechanisms (Gill & Barger 1966).

Hormonal Changes

Renin-angiotensin: It has been known for some time that the cells of the juxtaglomerular apparatus contain renin granules. These cells are in close proximity to the sympathetic nerve fibres and the afferent arterioles (Wagermark *et al.* 1968). Thus, they occupy the position of de Bono and Mills' PSS. Sympathetic stimulation by surgery or a fall in pressure at this site leads to release of renin. Renin could then produce angiotensin-1 from renin substrate in the plasma, which is converted into angiotensin-2. This, by stimulating the release of aldosterone (Cannon 1969), would lead to sodium retention. Unfortunately, aldosterone acts too slowly for such a hypothesis to be tenable.

More recently it has been appreciated that there is sufficient renin substrate and converting enzyme in the renal cortex for angiotensin-2 to be produced locally (Hollenberg *et al.* 1972). As the renal vasculature is exquisitely sensitive to the vasoconstricting action of angiotensin-2, this mechanism could be responsible for the redistribution of blood from the cortex to the juxtamedullary region.

Natriuretic hormone-kallikrein: de Wardener *etal.* (1961) showed that the efferent factors then known to determine renal sodium handling – glomerular filtration rate and aldosterone secretion – were inadequate to explain the saline diuresis in fluid-loaded animals. They suggested, from cross-circulation experiments, that a circulating natriuretic hormone was responsible. No such hormone has yet been found.

Mills (1970) showed that when renal cortical extract is injected into the renal artery, a natriuresis results. He suggested that the kidney was the site of formation of the natriuretic hormone. Further work (A Adetuyibi, N A A MacFarlane & I H Mills, unpublished) showed that renal extract contained kallikrein, an enzyme which releases bradykinin from an alphaglobulin substrate in plasma. Bradykinin infusion had already been shown to produce a natriuresis (Barraclough & Mills 1965). Adetuyibi & Mills (1972) confirmed that sodium excretion in man can be related to urinary kallikrein excretion. This has recently been confirmed by Marin-Grez (Marin-Grez *et al.* 1972).

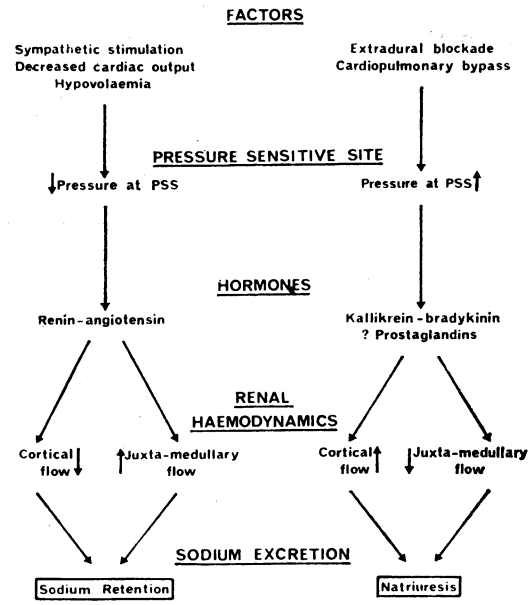

Fig 3 *Factors and pathways involved in the renal control of sodium excretion during and after surgery*

Prostaglandins: Prostaglandins have been isolated in the renal medulla (Horton 1972). Although there is as yet no information about their role in sodium excretion, it is reasonable to assume that they will result in a natriuresis, as they are powerful vasodilating agents.

Thus a number of substances, all with powerful vasoactive properties, have been isolated from the kidney. Any of them may be released in response to changes in pressure at the PSS. A fall in pressure at this site can lead to the release of renin and angiotensin which decreases cortical flow and causes increased sodium reabsorption. An increase in pressure leads to the release of the vasodilating kallikrein-bradykinin system and possibly also prostaglandins. These restore cortical perfusion and cause a natriuresis. The integration of such changes in relation to sodium excretion during anæsthesia and surgery is shown in Fig 3.

Conclusion

These studies emphasize the role of intrarenal mechanisms in the changes in sodium excretion, during and after surgery. Previously it was believed that the kidney's role was a passive one of effecting changes, produced primarily by the rest of the body. It is now realized that, in addition to this role, it also plays a part in monitoring the hæmodynamic state of the individual – particularly when the individual's integrity is threatened by any form of trauma.

Zimmermann (1965) has interpreted the responses of the kidney to stress on a teleological basis:

'As terrestial animals evolved from their ancestors in the seas, they became further away from their ready supply of salt and water. As any form of injury would make it more difficult for them to return to the sea, it is only appropriate that their earliest responses are those of retention of water and salt.'

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The following papers were also read:

Oxygenation During Bronchoscopy

Dr I M Bali
(*Royal Victoria Hospital, Belfast*)

REFERENCE

Bali I M, Dundee J W & Stevenson H M (1973) *British Journal of Anæsthesia* (in press)

The Cost of Bleeding Cut by Inflation: Control of Hæmorrhage by Application of Infradiaphragmatic Pressure

Dr D G Lewis
(*Royal Victoria Infirmary, Newcastle upon Tyne*)