The characteristic, unmodified response to surgery by the kidney is an intense and prolonged reduction in the excretion of sodium and water. Anaesthetic agents and techniques, or regimens of water and electrolyte replacement, may modify this reaction. Many studies of the effect of anaesthesia on the kidney have failed to acknowledge that anaesthesia is an accompaniment of surgery (Deutsch et al., 1966; Deutsch, Pierce and Vandam, 1967). Thus, the effect of anaesthesia on the kidney must be considered in the way it affects the renal response to surgery.

Changes in renal function which have been described in association with premedication or volatile anaesthetic agents are non-specific and result from alterations in cardiac output and in renal blood flow and its distribution, with consequent secondary effects on glomerular filtration rate and tubular function. Changes in hormonal activity and in respiratory gas tensions may also be important. Methoxyflurane is the only anaesthetic agent known to have a specific effect on the nephron.

SODIUM EXCRETION

A series of complex and incompletely understood hormonal and vascular responses govern the postoperative excretion of sodium. Although several components of this response are recognized, the relative importance of each is controversial. It is now well established that sodium loading results in quite variable sodium excretion in different subjects and even in the same subject from day to day. The matter is complicated by the relatively long half-life of infused sodium in the body which may amount to many hours (Smith, 1957) even after intravenous infusion.

Adrenocortical hormones.

During and after surgery in adults there is a considerable increase in the secretion of both glucocorticoids and mineralocorticoids (Moore et al., 1955). These changes occur concurrently with reductions in the excretion of sodium and water, and the tenfold increase in the secretion of aldosterone has been assumed to account for the urinary sodium findings (Casey, Bickel and Zimmermann, 1957). Support for this view comes from the observation (Johnston, 1964) that patients pre-treated with an aldosterone antagonist, spironolactone, produced a sodium diuresis postoperatively. However, this has not been confirmed (Kay, 1968). It is known that adrenalectomized subjects maintained with cortisone supplements only still retain sodium after surgery (Mason, 1955) and that infants whose aldosterone production is impaired (Weldon, Kowarski and Migeon, 1967) tend to reabsorb nearly all the sodium filtered at the glomerulus (Aperia et al., 1972). All these findings are not necessarily inconsistent. It may be that aldosterone is responsible for sodium conservation after operation, but that, in its absence, other mechanisms can take over its role.

Natriuretic hormone.

Cross circulation experiments in dogs (de Wardener et al., 1961) suggest that factors other than glomerular filtration rate and the secretion of aldosterone are involved in the regulation of sodium excretion after saline infusion. “Natriuretic hormone” or “third factor” has a very short half-life and may originate in the brain, but there is evidence that intra-arterial injection of renal cortical extract has a similar action (Mills, 1970) which suggests the kidney as the site of production.

Pressure-sensitive site.

Intermittent occlusion of the renal vein results in natriuresis which could be explained by an increase in transmural pressure acting on a sensitive site (PSS) at the distal end of the afferent arteriole (de Bono and Mills, 1965) because the pressure there varies directly with arterial blood pressure and inversely with the tone of the afferent arteriole. Support for this view is provided by the observa-
tions that a natriuresis occurs during the post-operative period in patients who receive continuous extradural analgesia (Bevan, 1971) and when cardiopulmonary bypass is started in the course of open heart surgery (Bevan et al., 1973).

The mechanism by which changes at the PSS result in alteration of sodium excretion depends both on changes in the distribution of renal blood flow and on the difference in function between the superficial and deep cortical nephrons. Micropuncture studies show that the juxtamedullary nephrons are better able to reabsorb sodium than superficial cortical nephrons (Thurau, 1969); radioactive xenon washout studies have indicated that renal blood flow, under conditions of sodium retention, is diverted from the superficial cortical to the juxtamedullary region and such a redistribution occurs with surgery in anaesthetized dogs (Rosen et al., 1967).

**Intrarenal hormones.**

The cells of the juxtaglomerular apparatus secrete renin in response to renal ischaemia (Goormaghtigh, 1944). They are in close proximity to the sympathetic nerve fibres and to the afferent arterioles (Wagermark, Ungerstedt and Ljunqvist, 1968), and occupy the position of the PSS proposed by de Bono and Mills. Sympathetic stimulation accompanying surgery, or a fall in pressure at this site, leads to the release of renin. It has only recently been appreciated that there is sufficient renin substrate and converting enzyme in the renal cortex for angiotensin II to be produced locally (Hollenberg et al., 1972a). As the renal vasculature is exquisitely sensitive to the vasoconstricting properties of angiotensin II, this mechanism could account for the redistribution of blood from the superficial to the juxtamedullary cortex.

The renal extract of Mills referred to above contains kallikrein (Adeteyubi and Mills, 1972) which releases the vasodilator bradykinin from an a-globulin substrate in plasma. Also, vasodilating prostaglandins have recently been isolated from the renal medulla (Horton, 1972). Thus, a number of substances, all with powerful vasoactive properties, have been isolated from the kidney. The interrelationship of such rapidly acting compounds during and after surgery is uncertain and requires further study. However, it seems that they may be responsible for the immediate changes in water and salt excretion and their effect may be continued by substances with a slower onset of action such as aldosterone (Ross et al., 1959).

**FREE WATER EXCRETION AND ADH ACTIVITY**

"Free water" is any water in excess of that required to render a solute (sodium, in this context) isotonic. Thus, a litre of "fifth normal (0.18%)" saline would have 200 ml of osmotically obligated water and 800 ml of free water. The metabolic response to trauma greatly reduces the ability of the postoperative patient to excrete free water. The control of free water excretion is achieved normally by alterations in the rate of secretion of antidiuretic hormone (ADH) which are produced by the effect of sodium concentration on hypothalamic osmoreceptors. Normally, blood concentrations of ADH vary between 0.05–6 μg/ml. It is now known that higher concentrations of ADH than this occur during and after operation even when the normal control mechanisms would usually stop release of the hormone. A fall in serum sodium concentration is one of the commonest findings in the immediate postoperative period and this should result in renal excretion of free water in response to inhibition of ADH release: this does not happen for 48–96 hours after major surgery (Moran et al., 1964; Ukai, Moran and Zimmermann, 1968).

The mechanisms which result in continued release of ADH during and after operations can be summarized as follows (Moran and Zimmermann, 1967):

1. Left atrial receptors which initiate afferent impulses in response to a fall in left atrial pressure. The afferent arc is vagal and ADH levels of up to 60 μg/ml result.
2. Arterial baroreceptors which evoke blood levels of ADH of up to 600 μg/ml within 1–2 minutes of a fall in arterial blood pressure. These high levels are thought to have effects other than the normal inhibition of free water excretion, for example, sodium retention which can result from ADH release in man (Barraclough and Jones, 1970).
3. Nociceptive impulses transmitted by autonomic nerves and painful stimuli transmitted by somatic sensory nerves.

Very high concentrations of ADH only occur transiently during surgery and are attributed to the atrial and arterial pressure activated mechanisms. Postoperatively, the blood concentration of ADH falls gradually but is usually several times as high as the preoperative level until the third to the fifth day, the duration being related approximately to the severity of the trauma. If urine output is observed carefully after operation it will be found that there is a characteristic response when intake is maintained at 2 litres per day above measured.
losses. This is shown in table I where the cut-off of antidiuresis occurs between 48–72 hours after surgery.

**Table I. Urine output of 3 patients undergoing abdomino-perineal resection of rectum. Day 0 is the day of the operation which was performed in the early afternoon, so that the values do not represent a 24-hr output. The patients were catheterized.**

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Urine volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
</tr>
<tr>
<td>59</td>
<td>400</td>
</tr>
<tr>
<td>62</td>
<td>370</td>
</tr>
<tr>
<td>36</td>
<td>350</td>
</tr>
</tbody>
</table>

**MODIFICATIONS BY ANAESTHESIA**

The evidence given so far is in favour of both intrarenal and pituitary-adrenal hormonal responses which affect renal excretion of sodium and water during and after surgery. General and local anaesthesia may modify either or both of these responses. The immediate intrarenal adjustments are likely to be affected by any agent or technique which has an effect on either the cardiovascular or autonomic system. Most inhalational agents depress the cardiac output and some have an effect on the peripheral resistance vessels. Agents such as cyclopropane and ether, which cause peripheral vasoconstriction, might be expected to decrease renal sodium and water excretion whereas halothane may have the opposite effect.

Pituitary and adrenal responses may be modified by a number of factors. ADH secretion is stimulated by large doses of opiates (Papper and Papper, 1964) and occasionally by prolonged IPPV (Khambatta and Baratz, 1972). Adrenal cortisol secretion is inhibited by epidural analgesia (Lush et al., 1972). In addition, spinal and epidural analgesia may, by blocking lower thoracic sympathetic efferents, also inhibit the intrarenal response.

**Methoxyflurane.**

There are now several reports of an association between prolonged anaesthesia with methoxyflurane and either polyuria, with or without renal impairment, or acute oliguric renal failure (Crandell, Pappas and Macdonald, 1966; Mazze, Shue and Jackson, 1971). Fluoride ions, released during the metabolism of methoxyflurane, are probably responsible for the polyuria. They render the distal tubules and collecting ducts unresponsive to the action of ADH (Mazze, Trudell and Cousins, 1971). This results in a water and sodium-losing situation which, if extracellular fluid volume falls, causes under-perfusion of the kidney and a rise in blood urea. Most patients who survive such an episode make a rapid, complete recovery.

Acute oliguric renal failure after methoxyflurane is probably caused by an accumulation of calcium oxalate, another metabolite of methoxyflurane, in the renal tubules (Paddock, Parker and Guadagni, 1964). Three patients have now been reported with such a syndrome who showed no sign of recovery up to 25 months later (Hollenberg et al., 1972b).

Evidence of renal dysfunction after the use of methoxyflurane as an analgesic during labour has not yet been found (Rosen, Latto and Asscher, 1972). However, the renal disturbance seems to be dose-dependent because the use of methoxyflurane, even in small concentrations for a short time, results in a marked increase in the excretion of fluoride and oxalate in the urine.

**PRACTICAL IMPLICATIONS**

**Diagnosis of renal failure.**

It is clear that the patient who has undergone surgery is likely to have a lower urinary output than when in the normal state. When can we regard his intraoperative and immediate postoperative urine volume as representing a maladjustment rather than the expression of normal endocrine responses and of renal homeostasis to trauma? The two indices most commonly used for this purpose are changes in urine volume and blood urea concentration. Neither is free from problems of interpretation. Those who are concerned with the “small” volumes of urine passed during and after an operation under normal circumstances (i.e. flow rates of less than 0.3 ml/min) would do well to measure their own overnight urine output before ascribing this degree of oliguria to pathological circumstances. By contrast with this low volume under the influence of small solute loads and raised ADH secretion which occurs in health, the patient with a reduced nephron mass may be unable to excrete the solute and hydrogen ion load presented to the kidney, even though each nephron is operating under conditions of maximal diuresis and the urine volume is relatively high, perhaps up to 0.6 ml/min (36 ml/hr). In health, the excretion of urea can be regarded as a linear function of urine flow when flow rates are in the range 0.3–
2.6 ml/min; that this may not be a completely accurate physiological statement does not detract from its clinical utility. Thus, with a steady load being excreted at a given urine flow, increased water reabsorption in the distal tubule and a decline in final urine volume must result in an increase in blood urea concentration. An increase in load without an increase in free water will have the same effect. Both of these can accompany surgery. When a patient with a massive gastrointestinal haemorrhage has a rise in blood urea we do not necessarily call this renal failure; yet we are all too ready to assign similar oliguria and raised blood urea concentration in the postoperative patient to renal failure.

What yardsticks can be used? A urine flow of less than 20 ml/hr for two or more consecutive hours in a patient with a previously normal kidney should be regarded as outside the homeostatic range, for it is considerably less than the minimal urine volume encountered with maximal water conservation and a minimal solute load. However, it must be admitted that there are occasional patients who show anuria for several hours on the operating table, only to return at once to a normal postoperative flow. Not all such instances can be ascribed to a blocked catheter or kinked drainage tube, although these possibilities must be carefully eliminated before therapy is embarked upon.

When renal disease, severe intercurrent illness or an episode likely to produce renal damage are factors, a flow in excess of 20 ml/hr does not exclude renal failure, which may express itself merely as a rising blood urea concentration and a later fall in pH, or may become manifest at 48-72 hours after anaesthesia and surgery as acute oliguric renal failure. In such patients it is likely that the functioning nephron mass is reduced so that the urea load cannot be excreted. Consequently, the total urea excretion is small (less than 10 g/24 hr) and the urine urea concentration is low (less than 1 g%). These figures have been found useful in prognosis (Selmonosky, 1971); they are easy to obtain and bring greater precision to the diagnosis of impending disaster. Urine sodium concentrations are relatively high under such circumstances (40-80 m.equiv/l), unlike the situation in the immediate postoperative state where their concentration usually falls rapidly below 40 m.equiv/l and may reach levels as low as 5-10 m.equiv/l. The reason for this high concentration in the renal failure patient is not clear. All these observations on volume and composition may possibly permit therapy to be instituted which can arrest the progress of the disorder by treating an underlying cause.

**Causes and prevention of renal failure.**

The kidney is in failure when nephron function is inadequate to excrete a given load. This occurs when renal blood flow is reduced, or when tubules are put out of action temporarily by hypoxia or the accumulation of substances which are specifically nephrotoxic such as haemoglobin, myoglobin and possibly products of bacteria. Perfusion is in turn a function of afferent haemodynamic pressure and the peripheral resistance offered by the kidney, the latter being determined, at least in part, by those intrarenal mechanisms that have already been described. The prevention of renal failure lies in avoiding these injurious effects during surgery, or if there is a likelihood that they may occur, by putting the kidney into a physiological state where it is least at risk. Thus, the objectives of management during and immediately after operation are: to avoid circulatory insufficiency; to maintain urine excretion in the face of both changing endocrine influences and the production of nephrotoxic substances; and to minimize swings in balance for water and electrolytes in the immediate postoperative period. The general statements in relation to these objectives are: the volume of urine secreted is related to perfusion and filtration pressure; underperfusion results in a low volume uninfluenced by solute load; in the postoperative period it is normal for a healthy kidney to produce a small volume of highly concentrated urine because of the secretion of ADH; nephrotoxins may be concentrated in the distal tubule and so cause renal damage; and the ill patient is at high risk of renal failure.

**Fluid therapy.**

With these points in mind, a rational approach to water and electrolyte therapy in relation to operation appears possible. First, whole body and renal perfusion must be maintained. All are aware of this in connection with the replacement of whole blood loss; the only matter of controversy is on the haemodynamic effects which might be traceable to the cellular changes which permit the entry of sodium into the cell (Flear, 1970). The original evidence for reduction in effective extracellular volume (Shires, Williams and Brown, 1961) has been criticized (Lancet, 1969) and other work has failed to show changes that are likely to be of
haemodynamic significance (Roth, Lax and Maloney, 1969).

It seems probable that the great debate on effective extracellular volume will end with the recognition that the matter has been insufficiently analysed to permit dogmatic statements about management. The changes in membrane permeability do exist; they do not necessarily lead to the need for sodium replacement nor is it certain whether or not giving sodium aggravates cellular and transcellular oedema. Further experiment is needed to resolve these issues. When there is a considerable volume of tissue damage (e.g. burns, crush injury, long lasting exposure and handling of the gut) a third space is formed by transcapillary leakage and is indicated by a rising haematocrit unless this change is obscured by coexistent blood loss. The extent of such third space losses may have been underestimated in abdominal surgery; for example there is an easily measurable reduction in plasma volume in a patient undergoing a large dissection for removal of a colorectal cancer (Irvin et al., 1972). Such a reduction will intensify the extra- and intrarenal mechanisms for sodium and water conservation already described and so produce two effects: a more marked reduction in renal water and sodium output, and as a consequence of this an increased oxygen consumption by the kidney.

By contrast, maintenance of blood and extracellular volume will minimize the renal adjustments, and an over-expansion of extracellular space, by increasing sodium excretion, possibly will reduce oxygen consumption still further. However, the last manoeuvre carries a cost, in that only a percentage of extra administered sodium load will be excreted, because the fraction of a load which is eliminated remains constant at about a third under conditions of anaesthesia and injury (Pieber and Jones, 1966). Even if a diuresis is established with sodium, before induction of anaesthesia, the onset of surgery is still marked by an intense restriction of renal sodium excretion (MacKenzie and Donald, 1969). Thus, extra sodium as a means of protecting the kidney against the hazards of reduced perfusion is a two-edged weapon; the major surgical patient receiving a litre or more of 0.9% saline or its equivalent will normally go into progressive positive sodium balance (Irvin et al., 1972). In normal patients the intraoperative provision of sodium should be related to the magnitude of the procedure more than to the duration of operation (table II). After operation 75–100 m.equiv/day of sodium in addition to the replacement of extrarenal losses is the maximum required if overloading is to be avoided and intense renal sodium conservation is not to take place. This type of approach will result in relatively small intraoperative urine volumes (0.3–0.5 ml/min), and a total first day’s urine output of 800–1200 ml. More is not required unless there is a large urea load to be excreted, and even then the expansion of the e.c.f. will not augment urea output in the first 24 hours after operation sufficient to make the risks acceptable.

Protecting the kidney.

The actual or potential high risk situation has already been mentioned. If sodium is not being reabsorbed, renal blood flow can fall to 10% of

<table>
<thead>
<tr>
<th>Scale of procedure</th>
<th>Nature of provision</th>
<th>Quantities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–4 e.g. Bunions to elective appendicectomy</td>
<td>Water (5% dextrose)</td>
<td>Nil during operation 2 l./24 hr</td>
</tr>
<tr>
<td>5–7 Cholecystectomy–gastrectomy</td>
<td>E.c.f. replacement (Ringer-lactate) Water (5% dextrose) E.c.f. maintenance (Ringer-lactate)</td>
<td>Up to 1 l. during surgery 2 l./24 hr 500 ml./24 hr</td>
</tr>
<tr>
<td>7–9 Extensive oesophageal, colorectal surgery, cardiopulmonary bypass, multiple injuries</td>
<td>E.c.f. replacement (Ringer-lactate) Water (5% dextrose) E.c.f. maintenance (Ringer-lactate)</td>
<td>1–3 l. during operation, guided by c.v.p. and haematocrit. 2 l./24 hr plus allowance for evaporative loss of 250 ml/hr of visceral exposure. 500 ml./24 hr</td>
</tr>
</tbody>
</table>

The above table provides quantities and one method of administration using single solutions. Others may prefer to administer the same quantities using combined solutions (e.g. 0.18% NaCl in 4.3% dextrose). In all instances, allowance must be made for preoperative state.
normal before significant and potentially damaging hypoxia develops (Bradley and Coelho, 1972). Thus, any technique which reduces sodium reabsorption is of protective value, and drugs such as frusemide and ethacrynic acid, solute diuretics such as mannitol, and sodium itself can all produce this effect. The two diuretics mentioned also undoubtedly increase renal blood flow and glomerular filtration rate during conditions which prevail during surgery and anaesthesia (Stahl and Stone, 1970). Sodium-containing solutions may do the same by expanding the e.c.f. but mannitol is less effective in this regard. The problem is to decide when any of these agents should be given and which is to be preferred. The disadvantage of sodium administration in this context has already been discussed. Mannitol has been favoured for aortic surgery (Barry, Cohen and Le Blanc, 1961) and for the jaundiced patient (Dawson, 1968), but it has the theoretical disadvantage at least that if it is not excreted it has continuing powerful osmotic effects within the body. The agents of choice are thus frusemide or ethacrynic acid. The large diuresis produced, for example, by the use of frusemide 40 mg given 2-4-hourly should be replaced by dilute sodium chloride solution (0.45% saline in 2.5% dextrose) with added potassium if serum concentrations or the e.c.g. are disturbed (Stahl and Stone, 1970). A regimen such as this is justified only in major surgery under special circumstances (table III).

### Table III. Indications for, and methods of protecting the kidney during surgery.

<table>
<thead>
<tr>
<th>High risk situations</th>
<th>Methods of protection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiopulmonary bypass</td>
<td>Prime the patient with Ringer-lactate to raise e.c.f. by 1 litre</td>
</tr>
<tr>
<td>Aortic clamping above renal vessels</td>
<td>Administer mannitol 15 g/100 ml and repeat 2-hrly for duration of risk</td>
</tr>
<tr>
<td>Blood loss</td>
<td>Administer frusemide 40 mg 2-hrly with replacement of urine loss by 0.45% saline in 2.5% dextrose</td>
</tr>
<tr>
<td>e.g. aortoiliac surgery</td>
<td></td>
</tr>
<tr>
<td>Obstructive jaundice</td>
<td></td>
</tr>
<tr>
<td>bilirubin &gt;9 mg./100 ml</td>
<td></td>
</tr>
</tbody>
</table>

From time to time the surgeon and anaesthetist will be caught unawares by a patient in whom a period of reduced perfusion (consequent upon massive blood loss or water and electrolyte sequestration) and/or the production of a nephrotoxin (mismatched blood transfusion or a large production of a bile pigment) has occurred unexpectedly. Immediately after or during the procedure the patient becomes profoundly oliguric. It must be decided whether the situation requires measures other than the replacement of lost blood. Clearly the latter must have first priority; however, if a nephrotoxin is suspected there is ample experimental and clinical evidence that induction of diuresis may reduce the danger of progression to renal failure. It is doubtful if the diuresis affects nephrotoxin already present in the kidney; it is more likely that new molecules of the toxic agent arrive at a kidney which now does not concentrate them so greatly in the distal tubule and in which oxygen consumption is reduced. A rapid infusion of 100 ml of 15% mannitol or the administration of 80 mg of frusemide are used. However, if oliguria persists it must be assumed that many nephrons are non-functioning and that such urine as is passed emerges from a small number of survivors. These will respond to massive doses of frusemide but the diuresis produced is usually not quantitatively sufficient to influence blood concentrations of urea and potassium. The rising blood urea concentration will ultimately provide an adequate load per se and the patient must now be treated for oliguric renal failure until the damaged nephrons recover.

In the patient with profound hypovolaemia, renal vasoconstriction may occur from any or all of the influences on the renal circulation already discussed. In situations where intense peripheral vasoconstriction exists, often in association with a high core temperature (Ibsen, 1967), oliguria is often present. This particular combination is an indication for transfusion of blood and for the use of small, carefully regulated doses of chlorprothamide by the intravenous route.

**Free water replacement during and after surgery.**

The normal 70-kg human turns over approximately 2.5 litres of water every 24 hours of which up to 300 ml are produced by oxidation of calorie sources. Losses are about 1500 ml in urine and 1000 ml by insensible routes. Many factors in anaesthesia and surgery alter this balance.

The renal restriction of free water excretion by the action of ADH lowers urine volume to 800-1200 ml/day and usually towards the lower end of this range. In elective surgery on healthy patients neither water of oxidation, nor insensible losses, are greatly altered (see Kinney et al., 1970 for review). However, if massive injury, sepsis or fever is present there is not only a rise in metabolic water production, but also probably an extra mobilization of water from cells which enters the extracellular space and must be taken into consideration.
Excessive administration of water can easily occur in patients with large burns or who have no net losses from the lungs; or who has one of the described causes for increased loss. The patient undergoing intracranial surgery. Disorientation, hallucinations and even convulsions are readily provoked by an excess of free water.

CONCLUSIONS

Knowledge of renal responses to injury is still incomplete. In that the kidney is the most flexible controller of body water and electrolyte content and composition, our ability to prescribe wholly rational regimens must likewise be somewhat limited. Add to this that the kidney is threatened by pathological events in surgery outwith the homeostatic range, and the situation becomes truly complex. In the past 10 years many advances have been made, but unfortunately, in our view, therapeutic suggestions have tended to be made which focus unduly on one factor or hazard in what is a multivariate situation. There has also been a tendency to neglect the ability of the normal patient to undergo elective surgery of moderate extent with minimal manipulation of water and electrolyte intake or of renal function. We agree with the recent statement (Orloff and Hutchin, 1972) that "currently overhydration is a far more frequent and serious problem in surgical patients than is dehydration". Caution in water and electrolyte therapy, a due consideration of the inevitable consequences of injury, coupled with a recognition of specific hazards to the kidney during complicated procedures, should be the appropriate therapeutic prescription for the mid-1970s.

REFERENCES


