THE SALVAGE OF KIDNEY FUNCTION

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THE battle for survival of spinal cord injury patients is a recent development in the history of medicine which has continued through the professional lives of most of us here assembled. During that time there can never have been any doubt of the identity of the chief enemy. Infection of the upper urinary tract, leading to sepsis or renal failure, or both, used to kill most of these patients; it remains responsible for about half the current mortality. There has, however, been a significant change. In former years most of the deaths could be laid directly to sepsis; more recently, the lethal factor has been failure of kidney function. The availability of antibiotics and other modern methods of management, not to mention our better understanding of the pathophysiological processes involved, are usually, if not always, sufficient to stay the onslaught of overwhelming bacteremia. But the insidious destruction of renal parenchyma by chronic infection, enhanced by occasional acute or subacute exacerbations, often continues beyond our control, sometimes even without our knowledge.

To begin our consideration of the salvage of kidney function we must ask ourselves first, whether infection is indeed the only culprit. As we review upper urinary tract complications in these patients, three elements become apparent; infection, inadequate drainage and calculus formation. These are closely interrelated; they react upon each other and, since none is likely to be observed alone, its treatment cannot be independently considered. What we encounter, therefore, is not a single morbid process but a chain of events which, unless interrupted, becomes a vicious cycle. A digression is here necessary for mention of a fourth element, which can also be identified, namely, secondary amyloid disease. In our most recently studied autopsy series this was found in 16 of 43 subjects, an incidence of 37 per cent. In three of these no other kidney disease was present, but death resulted from renal failure. In 13, amyloid and pyelonephritis were both present, and nine of these died of renal failure; the relative contribution of the two morbid processes to the outcome could not be determined. It is clear that amyloid disease may develop independently of the pathogenetic sequence involving kidney infection. It has been our impression, supported by clinical evidence, that it hardly ever results from kidney infection alone, the usual precursor having been extensive suppurative disease of bone associated with severe pressure ulcers. In only two of 16 cases was this finding absent from the history, although the precursor lesion had frequently been cleared up before the patient died.

Calculus formation may play an important role in renal destruction, and spinal cord injury patients are twice vulnerable. The migration of calcium from the skeleton and its excretion in the urine is one hazard. This is particularly the case soon after the injury, especially if recumbency is undisturbed and hydration is inadequate. The vigorous prophylactic measures which must be undertaken are well understood and need not concern us at this time. The other factors that increase the likelihood of stone formation are, once again, infection and poor

drainage of the upper urinary tract. The relationship of these to each other has been the subject of a number of my previous reports. Rather than to repeat those observations, it is my purpose here to review in very general terms the implications of this relationship and the extent to which they may be useful in the care of our patients.

As in any other organ system, infection of the urinary tract may manifest itself by the evidence of sepsis and alter function by tissue destruction. In this particular case, however, it has another effect which contributes to the first two and creates new problems of its own. It can impair the dynamics of evacuation—particularly of transport through the ureter—upon which the integrity of renal function depends. This too has been described before and need not be elaborated now. What is immediately relevant to our present purpose is to emphasise that these alterations in dynamics may be a hazard to the kidney and that, to the extent that they can be recognised and evaluated, so may that hazard, threatened or actual, be identified and possibly averted.

Having seen all too many of my patients succumb to renal insufficiency, I was for years preoccupied with finding a means to detect alterations in renal function while they were still, if not reversible, at least not severe enough to be a hazard to health or life. The ideal I sought was a method of examination which could be performed serially at frequent intervals with no inconvenience or danger to the patient, at no more than reasonable expense and which, above all, would yield results which would be accurate, reproducible, and capable of measurement for purposes of comparison. I must here report that no such method is as yet known to me. My efforts, therefore, have gradually become directed to acquiring a better understanding of methods already available to us and long in use, with, occasionally, some refinement of those methods and a more sophisticated approach to analysis. In consequence, although we continue to use all the accepted chemical tests of renal function, we place our main dependence, for clinical guidance, upon radiographic studies. More recently we have found the radioactive hippuran renogram of considerable value.

Such an approach is applicable to our patients because, in most of them, impairment of kidney function is accompanied or preceded by detectable structural changes somewhere in the urinary tract. In this respect we are rather more fortunate than nephrologists who deal with glomerulonephritis and other so-called medical diseases of the kidney which carry no such structural imprints. It has also been an obvious advantage to be able to study our patients over long periods, generally starting before renal disease appeared so that its development could be traced serially over months or years.

Radiography has so far provided the most reliable and certainly the longest tested means of detecting and following these changes. In a symposium on pyelonephritis some years ago, a good deal of discussion was devoted to procedures for determining whether, in a given patient with bacteriuria, renal infection was or was not present. A number of methods were described and it was of particular interest to me that they were evaluated in terms of radiologic findings, and none was more reliable. In the series of autopsies to which I have already referred there was a high correlation (0·84) of reported positive X-ray evidence to actual pathologic findings. This was a retrospective study and the actual films were not re-examined. At the time the patients were under observation, no such review was contemplated. Since then, we have scrutinised our films with even greater

care and acquired more sophisticated equipment for fluoroscopy. Dynamic studies sometimes reveal details not observable on still films, especially if they can be taped or filmed and thus made available for repeated review.

Two things are necessary if this method is to achieve its full usefulness. Our radiologic examinations must be minute and complete. We are in the habit of making the most meticulous inspections in search of a stone, knowing that its importance may be out of all proportion to its size. I am reminded of a mathematician's venture into urology when Pascal wrote, 'Cromwell was about to ravage all Christendom; the royal family was undone, and his own forever established, save for a little grain of sand which formed in his ureter. Rome herself was trembling under him; but this small piece of gravel having formed there, he is dead, his family cast down, all is peaceful, and the king is restored.'

With no less zeal than is applied to searching for calculi, it is necessary to search also for other abnormalities, however slight.

The second requirement is continuing close observation of the patient's clinical course. Granted that our concern is to recognise signs that might antedate clinical manifestations, it remains a fact that intimate familiarity with the clinical background will help us to establish their meaning. Acute febrile episodes which, after careful examination cannot be otherwise explained, are usually due to exacerbations of urinary tract infection and will respond promptly to appropriate treatment. In the series already quoted, the high correlation between X-ray and pathological findings was matched by the history of such episodes. At the same time, 128 living patients then in the hospital were reviewed according to the same criteria. Judging by these, the proportion of patients without evidence of upper urinary tract infection was about the same as in the autopsy series, and once again the coincidence of clinical with radiologic findings is striking.

These radiologic observations have been discussed elsewhere and need not be described again in detail, but they merit a few general remarks. They are seen on plain films, intravenous urograms and cystograms. Except in the instances of delayed or totally absent excretion of the contrast medium, when the damage may well be beyond repair, they are not direct evidence of disturbed kidney function. Rather, they represent alterations in the architecture of the urinary tract caused by infection ascending from the bladder and up through the wall of the ureter. This poses a dual hazard; it can advance directly into and destroy the substance of the kidney; it can so impair the function of the calyces, pelvis and ureter as to make adequate drainage impossible, resulting ultimately, if the process continues unchecked, in infected hydro-ureter and hydronephrosis; or it can do both. Not unnaturally, since this is an ascending invasion, the first indication will appear in the lower ureter, usually as a dilatation unassociated with intraluminal obstruction. Because of the important part played by the lower ureteral segment in the valve action at the uretero-vesical junction, such a finding strongly suggests that there may be vesico-ureteral reflux, which can often then be demonstrated by cystogram.

Reflux thus becomes important not so much for itself as for what it may portend. If it is trivial in degree, or transitory, it may be unimportant, although it will always bear watching. If established irreversibly it is a serious dysfunction almost always associated with major disturbances or complete failure of ureteral peristalsis. Because infection may wax and wane, the functional embarrassment may be reversible. But severe or long-standing infection may lead to fibrosis of

such degree that, even after the active inflammatory process has subsided, the dysfunction remains. Studies of the dynamics of the upper urinary tract thus become essential in order to evaluate the risk to the kidney and to suggest appropriate treatment.

So we have two important criteria by which to judge, not so much the actual status of kidney function but, which is perhaps more useful, the extent to which it is endangered by advancing infection. Before moving on to their interpretation it is appropriate to refer to yet another method which may be employed to the same end. This is the I^{131} Hippuran renogram. The procedure is cheap and innocuous and the results are reproducible. It is, therefore, well adapted for use in serial studies over prolonged periods. Our method has been to compare changes in the tracings with those observed in intravenous urograms and various chemical parameters taken at the same time. To date, we cannot claim that the renograms have provided us with a dependable direct measure of renal function. They can, for instance, help in distinguishing between possible causes of azotemia or oliguria, but a reliable quantitative index of progressive renal failure is not yet possible. We are attempting to achieve something of the sort by selecting certain points on the curve to which numerical values can be assigned and, through these, subjecting large numbers of tracings to computer analysis. A mass of data from the first run showed that our impression of reproducibility was correct and that the correlation with the results of our other studies was good. Although we had frequently observed changes in the renograms anticipating those seen on X-ray, the frequency of such instances was not found to be statistically significant. It might become so if the renograms were done more frequently, which is entirely practicable. For the moment the method is adjuvant to other studies. We have not placed our sole dependence upon it, in any case, but it has been very useful in some.

The integration of ureteral with bladder function provides a basic concept of great importance. It is a common observation on the intravenous urogram that the contrast medium, seen in the renal pelves throughout the examination while the bladder is filling or filled, is evacuated promptly after bladder emptying. This is seen in normal subjects as well as those with disturbed vesical function. The ureter, as Gould and his associates point out, may continue to force urine into the bladder during micturition, but it is unlikely that an elaborate mechanism should exist to ensure this during so brief and occasional an event. Thus, during the elevated pressures developed during micturition or distension, contraction of the lower segment will block the upward thrust of pressure and so protect the upper tract. In normal circumstances, the resulting obstruction is transitory and unimportant. As long as no infection is present, this mechanism remains effective; if the bladder remains chronically distended, it may persist to the point of hydroureter and hydronephrosis, since the lower segment possesses the thickest musculature and exhibits the highest muscle tone. Such a mechanism may operate to produce the hydronephrosis seen in patients with long-standing prostatic obstruction, without reflux or infection. It is a hazard to be considered in judging how far the bladder may be permitted to fill during management by intermittent catheterisation.

With infection, the process is quite different. Then, as I have already indicated, the lower segment of the ureter becomes incompetent and reflux develops. The upper portions of the ureter and the renal pelvis become subject

not only to abnormal pressures, producing dilatation, but also to advancing infection which impairs or abolishes muscular contractility. During this march of events, various types of peristaltic dysfunction may appear, including retrograde peristalsis. Meanwhile, infection spreads from the ureteral and pelvic walls directly into the interstitium of the kidney and an infected stream of sluggishly flowing urine bathes the entire upper tract. Every stage of this process may be traced by X-ray.

No dilatation of the urinary tract can be taken casually. To any conscientious urologist the sight of hydronephrosis is like a red rag to a bull; it is a signal for immediate attack and, in ordinary circumstances, this is sound enough. Even when no infection is present, continued distension of the renal pelvis is a threat to kidney function; the obstruction causing it must be identified and, if possible, eliminated. This, however, will not be enough unless the musculature proximal to the obstruction is still capable of resuming its propulsive activities. Prolonged overdistension, even without the ruinous element of infection, may have wrought irreversible damage. When the obstruction has been of brief duration it is reasonable to assume that function will return after its removal. When it has been present for months or years, surgical intervention should be preceded by an attempt to determine the likelihood of good peristaltic activity after operation. For this reason, radiologic studies of the dynamics are always indicated, and should be supplemented, during surgery if it is done, by direct electrical stimulation. It must be noted that the results of such pre-operative studies may be ambiguous. If peristalsis is demonstrated one may be resonably assured of a satisfactory functional result, after correction of the obstruction. If not, operation may still be helpful, for there is a striking but unpredictable capacity for functional restoration even after long-standing insult. In such cases, the indications for intervention may depend upon purely clinical considerations and one will at least be prepared for disappointment. If functional return is considered in advance to be impossible, or if operation has been attempted and proved unsuccessful, a diversion may be indicated but, as I shall point out later, this must begin proximal to the level of dysfunction.

In only a few of the patients here considered, however, are we so fortunate as not to encounter the element of infection. As compared to the occasions of purely mechanical obstruction, this may operate either to the patient's advantage or disadvantage, unhappily more often the latter. The brighter possibility rests on the fact that inflammatory processes resolve and the functional alterations they cause may, therefore, be transitory. But, in chronicity or by the legacy of fibrosis, or both, they produce permanent structural changes with irreversible functional loss. Even this, however, may not be disastrous. The disorder may be trivial or it may be well compensated. In vesico-ureteral reflux, for instance, the retrograde column of urine may ascend for only a short distance up the ureter and drain promptly when the bladder is emptied. Such a situation, if the patient is clinically well, calls for no intervention, since structural rearrangement of the uretero-vesical junction will not in itself remedy the inflammatory change in the ureteral wall that causes the reflux. If the patient is voiding and there is no residual urine, I do not consider it necessary, in such a case, to put him on constant catheter drainage. He must, of course, be re-examined at frequent intervals—not longer than three or four months. I have followed a number of such patients for many years and the great majority have done very well, showing no further deterioration of function.

Some, however, undergo regression and we must be on guard for the signs by which it may be announced, either radiological or clinical. The latter are of great importance, for febrile bouts, reflecting exacerbations of urinary tract infection, commonly anticipate radiologic change; this is particularly so when they are recurrent. No patient in our series who showed changes in his X-ray studies has escaped such febrile episodes. They must be considered ominous because they represent a failure of host-resistance to organisms with which the patient has previously lived in comfortable symbiosis.

In most cases the acute episode can be resolved promptly. Our customary treatment is copious intravenous infusion containing 5 gm. daily of sodium sulfadiazine. If this is not effective within two or three days, a complete radiologic study is undertaken, usually an infusion urogram or, if this is unsatisfactory, retrograde pyelography. A renogram is now done as well. Not uncommonly, no evidence of impaired drainage is apparent, and intraluminal obstruction of the ureter is practically never found. In the rare cases in which an obstructing stone or stenosis may be encountered, it can be handled by an appropriate surgical procedure. Even when the lumen is totally unobstructed, it may be assumed that there is an impairment of drainage based upon functional failure. (This is usually an assumption rather than a demonstrated conclusion because the patient at this stage is frequently too ill to be subjected to further dynamic studies.) With this in mind, the renal pelves are drained through indwelling ureteral catheters and, with very few exceptions, defervescence and marked general improvement will be evident in 48 hours or less. The catheters are generally left in place for a week or 10 days.

The question arises as to the administration of antibiotics, and the decision should be based entirely upon clinical considerations. If the temperature is only moderately elevated, the sodium sulfadiazine is continued. If the constitutional symptoms are severe, with high temperature and chills, an antibiotic is usually given. Positive blood cultures are very rare but more than one organism is usually cultivated from the urine. Since *in vitro* sensitivity determinations are far from reliable, selection of the best agent may be difficult. When no choice is obvious we use chloramphenicol, given intravenously, in doses of 4 gm. per day for the first day or two and 2 gm. daily for the next four or five. In spite of its known dangers, we have so far avoided difficulty, although we have been using it for years, by watching the white blood cell count every day and limiting its administration to a period of a week. Prolonged administration of any antibiotic seems to me to be unwise in these situations because it may result in the emergence of resistant strains. Recently, however, we have begun to experiment with the use of amphicillin in this fashion in selected cases.

For the rare instances in which ureteral catheter drainage fails, surgical drainage is indicated, preferably by nephrostomy, occasionally by pyelostomy. If one side can be specifically incriminated, a unilateral operation will suffice; if not, bilateral drainage must be undertaken. It has already been noted that there may be no X-ray changes when clinical symptoms first appear, but when the process is severe they are likely to develop rapidly. Studies should, therefore, be repeated as frequently as every other day if necessary, and marked changes are often apparent within a few days or a week. Taking the form of dilatation in some portion of the upper tract or impaired excretion of the contrast medium, or both, these can be helpful in locallising the disease to one side or the other.

Following drainage of an acute process, whether surgical or through a catheter, there is usually a remarkable return to normal or nearly normal appearance and function, as definite and striking as that which follows removal of an intraluminal obstruction. This has been puzzling to many observers unfamiliar with these patients, who cannot account for recovery when, as they say, no obstruction has been removed. The fact is, however, that there was physiological obstruction which was relieved by control of infection and temporary drainage. The nephrostomy or pyelostomy tube is usually removed after three to eight weeks, but only following demonstration of the adequacy of pelvic and ureteral peristalsis. A number of patients so treated have been followed for years and had no further difficulty. A few have gone on to progressive chronic deterioration.

Much more frequent than these fulminating outbursts, and more difficult to evaluate in terms of treatment, is the appearance of radiologic evidence of impaired dynamics, either with no concurrent clinical manifestations and with a history of only brief and infrequent subacute febrile episodes which the patient may not have reported at the time. We seldom see the ballooning hydronephrosis common in urologic practice. These changes appear gradually; a slight dilatation of the calyces or even one calyx, a little puffiness of the pelvis, some irregularity or widening of the ureter, particularly in its lower segment, all these are signs demanding further investigation. Careful comparison with previous films is necessary. Among patients who are examined regularly and at frequent intervals, the alterations are so insidious that they may be overlooked on their first appearance; only after they are picked up does it become evident, in retrospect, that they were present at the previous examination. It is in the case of the patient who has missed his follow-up examinations for some time that we are likely to find full-blown definitive signs. These may be easier to interpret but it is unfortunate for him since the damage may already be beyond remedy. On the other hand, we are not in a position to take advantage of the dictum that the sooner pathology is recognised the better, since it may then be promptly attacked. Because of the possibility—or even the likelihood—that the disorder may be reversible, we are required to adopt an expectant attitude unless the clinical manifestations demand action. To decide even upon this is difficult, for there is always the nagging fear that unless something is done soon, it may be too late to do anything. Yet action for its own sake is not justifiable either. There must be a clear rationale to suggest that it represents the best possible course, and this can seldom be established beyond doubt.

How, for instance, shall we manage a patient who comes in showing a slight dilation of the pelvis of one kidney which has clearly developed since his last examination a year before? He looks well and is asymptomatic; he voids without residual urine. He has had bacteriuria for years but there has been no change in the flora. Fluoroscopic studies show no dysfunction; blood chemistry studies are normal. My own decision in such a case is to do nothing but to see the patient again in six months, or sooner if he has any symptoms. One of three things may happen as regards the X-ray findings. They may improve, remain the same or get worse. In the case of the first two, I stay with expectant treatment. In the case of the third a reappraisal is in order, and to make this adequate I must again review the negative findings listed above. Almost always, one or more will have departed sufficiently from normal by this time to provide some clue to appropriate management. The most important is the clinical course. The patient who has

had frequent attacks of acute or subacute renal infection, but who still shows good urinary tract dynamics, is perhaps the likeliest candidate of any for a diversion. The fact is, however, that this situation is seldom encountered. Another discovery may be that the alteration in the upper tract is secondary to inadequate drainage of the bladder, and drainage by an indwelling catheter may result in prompt improvement. This may be necessary only temporarily; a transurethral resection of the vesical neck may be all that is required. But even permanent catheter drainage, should it be necessary, is an acceptable method of treatment and many so managed have gone for years without regression.

There remains the most serious situation of all as represented by the patient with definite changes in the upper urinary tract which have persisted or got worse during a reasonable period of observation and with demonstrated functional deficiencies uninfluenced by adequate bladder drainage. He will usually, in this circumstance, show or have shown clinical signs of infection. But even if he has escaped these, and although the chemical parameters of renal function remain normal, he may be in serious trouble, for experience has shown us that a certain number of these patients eventually succumb to kidney failure.

Inevitably the advisability of diversion through an ileal conduit must be considered. The indication for this operation may exist, but it is not absolute. It is apparent that the fundamental need is to provide adequate drainage, but this is not guaranteed by a structural rearrangement of the urinary flow, however ingeniously designed or skilfully executed. A most meticulous evaluation of ureteral function is necessary. If ureteral peristalsis is insufficient to force urine into the bladder, it may be equally incapable of delivering it into a segment of ileum. With an obviously inadequate ureter, a direct pyelo-ileostomy may be performed. The dilated pelvis which is usually present in such cases makes the operation technically easier but is also an indication of poor function. My limited experience with this operation has not been satisfactory. With good peristaltic function in the upper tract, the operation will generally lead the way to good drainage, but ultimate judgment depends upon accurate timing. If done too soon it may have been unnecessary because improvement would have occurred without it. If done too late, the damage to kidney function may already be beyond recovery. I believe that there is a place for this operation in selected patients, but I do not consider it should be lightly undertaken. It has certain inherent disadvantages, the chief of which is that it leaves the kidneys no longer accessible. Although it can be performed safely by any competent surgeon, it is a formidable procedure for most patients and the post-operative course is frequently stormy. Post-operative complications are not infrequent and the care required by the stoma is usually far greater than that involved for an indwelling catheter. On my service, the incidence of this type of intervention has been about 0·05 per cent.

Any type of diversion carries its own disadvantages. The most useful, in my experience, has been permanent bilateral nephrostomy. I have a number of patients who had this operation because an ileal loop diversion was for one reason or another contra-indicated, usually because they were too ill, because the upper tract was functionally inadequate, or because kidney function was already so far impaired that the procedure was considered only as short-term palliation. The majority of these have done exceptionally well. Skin ureterostomy has also in my opinion, a wider application than is now generally recognised, although it too has its obvious drawbacks.

Ultimately, the salvage of kidney function in these patients depends upon control of infection and maintenance of adequate drainage of the upper tract. Because advancing infection produces structural changes that impair this function, the two are inextricably tied together and cannot be considered separately. Surgical procedures may, in selected cases, improve drainage sufficiently to remove the hazard to renal function. In general, however, the guiding principle of treatment must be to find means whereby the normal restorative process may be encouraged. The emphasis must be upon functional considerations, with structural alterations undertaken only when they contribute to functional recovery. There can be no short cuts in this process, no substitute for prolonged careful study by every means available. Our understanding of normal and pathological physiology and our ability to interpret clinical and radiological signs in terms of their threat to kidney function must be our guides to the choice of treatment, and our assurance that if surgical intervention is undertaken it will be an adjuvant to and not a substitute for the innate restorative capability of the organism.