Urological Complications of Carcinoma of the Cervix Uteri

BY THE LATE

T. F. TODD, M.S. (Lond.), F.R.C.S. (Eng.), M.R.C.O.G.

Hon. Assistant Gynaecologist, Salford Royal Hospital; Research Fellow, Christie Hospital and Holt Radium Institute.

THE clinical study of a large series of cases of carcinoma of the cervix uteri before, during, and after treatment has revealed an incidence of urological complications that is surprisingly large. The discrepancy between impressions and findings is apparently accounted for by two reasons, namely the frequency with which such complications do not give rise to urological symptoms, and the rarity, in this country, of urological investigation of gynaecological cases. For these reasons I decided to investigate fully the urinary tract in carcinoma of the cervix uteri, and my cases fall approximately into three groups: (1) cases not previously investigated, but coming to investigation because of the development of some urological complaint following treatment; (2) cases recognized in the course of a thorough investigation as to the possible aetiology of severe pain occurring subsequent to treatment; and (3) cases submitted to urological investigation before, during, and after treatment for the purposes of finding out the incidence of urological complications and the effect of radiation therapy on the urinary tract. The bulk of cases of this group belong to either stage 3 or stage 4 (League of Nations Classification), and the whole series has been investigated at the Christie Hospital and Holt Radium Institute during the tenure of a Research Fellowship.

The portions of the urinary tract most subject to involvement by carcinoma of the cervix are the bladder and the pelvic portions of the ureters. Involvement of the urethra, of the abdominal portions of the ureters and of the kidneys is usually a secondary phenomenon, either due to advancing malignancy, in the case of the urethra, or to back pressure from ureteral obstruction. An exception was the solitary case of renal metastasis which will be described subsequently.

Résumé of Literature

The occurrence of urological complications in carcinoma of the cervix has been known for many years. Beatty[1] so far back as 1854 reported 3 patients dying of uraemia, and Wagner[2] in 1858 reported ureteral dilatation present in one-third of the cases of cervical carcinoma autopsied. Winter[3] in 1893 confirmed these findings in a similar study. Again, Williams[4] in 1895 reported a series of 78 autopsies on patients dying from carcinoma of the cervix and showing hydro-ureter and hydronephrosis in 86 per cent, but it is only recently that attention has been focussed upon them. Macalpine[5] states:

> Involvement of the ureter by carcinoma of the cervix is a very common complication of that disease, so much so that one-half of the mortality in unoperated cases is said to be due to renal back pressure and sepsis with its resulting uraemia. The importance of estimating the state of the upper urinary tract would seem to be sufficiently obvious, but this phase is still much neglected, though there are signs of an awakening to a realisation of its value.

That this is so is fully emphasized by the fact that practically all the literature on this subject has appeared in the last 12 to 15 years. Renand goes so far as to say that death from renal complications is only avoided when it is due to haemorrhage, peritonitis, or some such complication.

Series of autopsies on patients dying from carcinoma of the cervix have been reported by Warren,[6] Faerber,[7] and Behney.[8] Uraemia was the actual cause of death in 33 per cent, 11 per cent and 21 per cent respectively, but the incidence of hydro-ureter and hydronephrosis was much higher in each series. Holzbach[9] in 48 cases of carcinoma of the cervix studied at autopsy found 31 bilateral and 10 unilateral strictures. Pearson[10] in 57 cases studied post-mortem found 42 cases with unilateral stricture and associated hydro-ureter and hydronephrosis, 30 cases being bilateral and 12 unilateral. Infection is a frequent sequel to hydronephrosis and was present in 13 of these 42 patients. Ewing[11] stresses the frequency of renal failure as the actual cause of death in uterine cancer. He states that the pelvic ureters are commonly invaded from without from the parametrium, and while the wall long resists destruction partial or complete occlusion is readily established by cancerous infiltration or by inflammatory process. The ureter may also be invaded by extension through the vesical wall, and it may be occluded by inflammation extending upwards

from the bladder. Several writers confirm these opinions on clinical grounds. Hunner[12] says urological changes may be recognized in a large proportion of cases and may be an early feature. He stresses the importance of recognizing late obstructions, and the possibility of giving relief by ureteral dilatation. Graves, Kickham, and Nathanson,[13, 14] showed ureteral occlusion to be of common occurrence in carcinoma of the cervix once the disease had spread beyond the limits of the cervix itself. They fully endorse Macalpine's opinion, and consider that their findings justify complete urological investigation of all cases before treatment is instituted. Pomeroy[15] showed a pre-irradiation incidence of urological complications in 77 unselected cases of carcinoma of the cervix to be as follows:

Normal bladder	55 cases
Vesical wall involved	20 cases
Vesical mucosa involved	2 cases

Uroselectan findings.

Normal	63 cases
Double hydronephrosis	3 cases
Single hydronephrosis	3 cases
Functionless kidney	5 cases

By excretion urography, Colby[16] showed the presence of partial or complete ureteric obstruction in over a third of 34 cases; in none of these was the blood-urea raised—an important observation in view of the general acceptance of a normal blood-urea as indicative of normal renal function.

Bugbee[17] reported 6 cases of nephrectomy for pyonephrosis developing secondary to ureteral occlusion following irradiation treatment of cervical carcinoma, the earliest case 5 months after treatment, and the latest 9 years. Two additional cases of patients coming to autopsy were also described: the first developed bilateral ureteral obstruction 1 month after irradiation, the actual obstruction being due to carcinomatous involvement of the walls of the ureters some 3 cm. from the bladder; the second developed carcinomatous obstruction of the left ureter 3 cm. from the bladder over 4 years after irradiation. Bugbee stresses the importance of investigation of the urinary tract in follow-up examinations of treated cervical cancer, since the possibility of ureteral occlusion on one or both sides, resulting in slow destruction of renal function, and possibly necessitating nephrectomy, must be considered. He reported in 1938[17a] a follow-up of these

cases and a further series of 9 cases in which the patients had renal lesions. All of the patients operated on had died, though one lived for years. In the second series none were fit for nephrectomy. Bugbee states that it is questionable if urological complications shorten the individual's life, as in all of them there is evidence of metastasis at the time of their appearance.

The aetiology of these urological complications is imperfectly understood. Howes and Strauss[18] describe the aetiology of ureteral obstruction as fourfold: (1) Inflammatory parametritis; (2) carcinomatous infiltration; (3) post-irradiation oedema (transient); and (4) post-irradiation fibrosis. They report an incidence of 52 per cent of ureteral obstructions in a series of over 100 cases. The treatment advocated is dilatation of the affected ureter whenever the obstruction can be negotiated; when the obstruction is complete nephrectomy is considered preferable to nephrostomy or any type of ureteral transplantation. Schmitz[19] comments that radiation treatment has apparently contributed to an increase in the frequency of urinary tract complications, but points out that the determination whether complications are due to the disease itself, or result from radiation, can be made only by routine examination of the urinary system in the first instance. Behney found the incidence of complications higher in his series of 166 autopsies. Drexler and Howes[20] state that encroachment on the ureter does not appear to occur any more frequently now than before the advent of X-ray and radium therapy, whereas Hunner expresses the opinion that radium probably causes ureteritis and peri-ureteritis. Lewis[21] states that cervical carcinoma may surround the ureter which, however, seldom becomes invaded by growth, even though practically obliterated by pressure from it. Hufnagl[22] states that in the absence of infection ureteral obstruction is due solely to increase in size of the primary growth, but when infection becomes superadded a true ureteral stricture results. Hertzer and Schreiner[23] conclude that the high percentage of ureteral strictures in advanced carcinoma of the cervix is due to pressure on the ureter from invasion of the parametrium or vesical wall, which possibly may be made worse as the result of fibrosis in the healing of these lesions. Matusovszky[24] also considers fibrotic healing processes in the parametrium to be causal. Graves and others support this opinion, stating that in patients cured of malignant stenosis of the ureters may result from fibrosis alone, either from infection or as a result of a replacement fibrosis following the regression of the tumour in that region. They are also of the opinion that

oedema following radiation may precipitate complete obstruction when marked partial obstruction already exists.

There are two main schools of thought, one considering the majority of obstructions to be due to the encroaching tumour, while the other considers radiation fibrosis to be the major factor. The consensus of opinion appears to be that vesical involvement is frequent from advancing malignancy, whereas the ureters are, if anything, more commonly involved in parametrial thickening and fibrosis, not necessarily malignant. Martin and Rogers[25] describe a small series of experiments which showed that with well-filtered radiation up to 2.5 erythema does not produce any serious change in the dog's ureter in 6 weeks; these findings suggest that the ureter is more resistant than either the bladder or the rectum, and will probably not be damaged when the broad ligaments are extensively treated with heavily filtered radiation. In a further series of experiments the same observers[26] show that by implantation of vanadium steel needles containing 6.25 milligrammes of radium alongside the ureter in 7 dogs for periods of 4 to 8 hours a dose of 71 milligramme hours or more will cause complete stricture of the ureter, and hydronephrosis within 2 weeks. However, comparable radiation of the ureter does not occur in any of the ordinary technique of treatment commonly employed.

From the practical point of view several writers make constructive suggestions. Everett[27] suggests cystoscopy and urography prior to treatment, and frequent ureteral dilatation after treatment, to enable us to determine the damage due to irradiation, and to prevent serious late effects in the form of stricture and hydronephrosis. Hunner also stresses the importance of recognizing late obstructions and the possibility of giving relief by ureteral dilatation. Martin[28] stresses the frequency and severity of pain in the loins, groins and hips due to malignant ureteral stricture, and advises ureteral dilatation to give relief of pain. Holzbach[29] advocates transplantation of the ureters into the upper portion of the bladder in advanced carcinomata as a prophylactic against later obstruction, pain and uraemia. Band and Wade[30] are also advocates of cystoscopic examination of cases of carcinoma of the cervix, and they discuss the advisability in certain cases of diverting the urinary stream to prolong life and diminish discomfort. Gemmell[31] approached the problem from a surgical standpoint and in a detailed report of his findings at cystoscopy and ureteral exploration prior to surgical removal of the growth, plus the actual

findings at the time of operation, he concluded that these procedures are of value in estimating the operability of a case. His paper includes a valuable description of the morphology and pathology of the various stages of vesical involvement by underlying carcinoma of the cervix. Among others Hartmann[32] and Forsdike[33] also stress the value of cystoscopic examination in the determination of operability of carcinoma of the cervix.

Vesical complications, *per se*, form a more or less distinct group. They may result from the advance of the disease itself or follow treatment. There are two main lesions encountered, namely fistulae and late radiation ulcers. Vesico-vaginal fistulae occur commonly in the later stages of untreated cervical carcinoma, and their incidence is not increased by radiation, in spite of the fact that a certain number of late radiation ulcers are associated with sloughing and fistula-formation. The limit of vesical tolerance has been estimated by Neef and Hoff[34] to be approximately 7,000 'r' in 4 weeks. This may produce bullous oedema and fibrinous desquamation, progressing to healing in 4 weeks (their article is illustrated by several very good colour photographs).

Post-irradiation ulceration of the bladder occurring between 1 and 2 years after radiation treatment of uterine cancer has been described by several authors. Dean[35] gives particulars of 3 cases and deduces that a total dosage of 3,500 millicurie-hours of radium applied to the uterus with normal filters should be considered as bordering on the upper limit of safety. He states: "Urologists probably will be called on to treat an increasing number of patients for this condition, in which the history, symptomatology, and cystoscopic appearance strongly suggest carcinoma of the bladder, but no tumour is present. If the approved methods of treating carcinoma should be employed in these cases, it is likely that the results would be disastrous."

Dean considers the differential diagnosis to be from neoplasm, Hunner's ulcer, and possibly tuberculous ulceration. He thinks a biopsy should always be performed. Smith[36] said that the inflammatory zone of oedema existing around the periphery of post-radiation ulcers is a striking diagnostic feature from cancer, which assumes the form of ulcerative or proliferative process with abrupt transition into normal mucous membrane. Stacy[37] also stresses the occurrence of delayed ulceration in the bladder many months after pelvic irradiation, and points out the difficulty of differentiating from extension of malignancy. Schmitz,[38] in the discussion on Stacy's paper, described a case of late chronic

radiation ulcer in the bladder occurring 9 years after treatment. Ward[39] advocates the use of a self-retaining catheter in the bladder while the radium is *in situ*—the collapsed bladder is more remote from the radium than the full bladder.

Several French authors describe thoroughly the physical signs associated with the various states of involvement of the bladder by advancing malignancy, and the effect of irradiation on the vesical mucosa. Gouverneur and Fabre[40] stress that vesical symptoms are not an accurate guide to the presence of involvement by underlying malignancy (*cf.* Gemmell). They describe 4 essential features of carcinomatous invasion: (1) bombement; (2) transverse ridging; (3) oedema, either diffuse or bullous; and (4) ulceration. They point out that the first three manifestations are not specific to malignant disease—they may be seen in some cases of adherent pyosalpinx. In their experience the prognosis, despite treatment, once ulceration has occurred, even in the absence of vesical symptoms, is extremely bad—all their patients dying in 4 to 7 months. Aman-Jean[41] states:

> Cystoscopic examination is in our opinion as useful as vaginal examination, and appears to us the most useful auxiliary diagnostic aid to the gynaecologist who is a cancerologist, without necessarily becoming a genito-urinary specialist. In effect cystoscopy permits:
>
> (i) Precise limitation of the spread of the malignancy.
>
> (ii) Observation of the effects of treatment and the sequelae, and early evidence of recurrence.

He remarks that haematuria in association with cervical cancer is indicative of actual ulceration of the vesical mucosa. Two essentials of cystoscopic examination are the condition of the trigone and that of the ureteric orifices. He divides the trigonal changes into two: (1) submucosal changes—bombement (distortion); mamelonnement sans sillon (small projections without ridging); mamelonnement avec sillon (projections with marked ridging)—not necessarily only transverse; and mamelonnement avec sillon et bourgeon ou ulceration cancereuse (addition of projecting growth ulcerating through). (2) Mucous changes—vascular congestion, granular cystitis, ecchymoses, and bullous oedema. Examination of the orifices shows three features: situation; form, i.e. morphology, whether normal, vulviforme, or punctiforme; and function. An immobile orifice without contractions or ejaculations is indicative of ureteral stenosis, which can be confirmed by intravenous injection of methylene-blue.

Radiation reactions are fairly strictly confined to the trigone,

and consist at first of a diffuse congestion; any presenting mucosal changes are temporarily exaggerated, and then after a few days subside and may disappear completely; any submucous changes tend to retrogress *ab initio*. Radio-necrotic ulceration is described as commonly found; the prognosis is for gradual healing to occur with gross scarring, or for a vesico-vaginal fistula to develop.

Cystoscopy following treatment shows: (1) Any late effects of radiation; (2) whether or not growth has completely resolved; (3) the occurrence of any recurrence.

During treatment cystoscopy is of particular value in diagnosis and treatment of intercurrent infections due to cystitis or pyelitis. In presence of bullous oedema or cystitis he advises twice daily wash-outs with warm antiseptic. When ureteral compression exists, he advises an indwelling catheter during irradiation. This is an interesting and most comprehensive paper.

Marzetti, V.,[42] concurs that among pre-radiation cystoscopic findings elevation of the vesical floor (so-called bombement) is the most frequent. Bullous oedema usually signifies invasion. Schmitz[43] states that bullous oedema is indicative of invasion of vesical wall and advises use of radium in such cases, but X-rays alone as a preliminary. Should the initial response be good, then radium can be added; if the response is not good (e.g. persistence of oedema), then it is inadvisable to push treatment if it is wished to avoid fistulae.

Dean[41] describes three well-recognized radiation reactions in the bladder: primary erythema occurring within 24 hours of radiation; secondary erythema occurring within 3 to 4 weeks after radiation, and sometimes associated with fibrinous exudation—symptoms of frequency and dysuria occur; and tertiary reaction, or delayed radium burn. The latter is the most important destructive effect of therapeutic doses of radium. It occurs on an average some 2 years after treatment; rarely it occurs within a year, and sometimes not for several years after treatment.

The symptoms of late radium ulceration are frequency, dysuria, and haematuria: the latter may be very profuse, and deaths from this cause have occurred. The cystoscopic appearances may closely simulate those of malignancy, and biopsy is essential for diagnosis—it is as important as in cases of radiation ulcer of the rectum to avoid further irradiation. The prognosis is on the whole good; vesico-vaginal fistulae may form or sudden haemorrhage may kill, but usually healing occurs, with formation of atrophic telangiectatic mucosa. Treatment by lavage, plus

instillations of 15 c.c. 10 per cent argyrol, is advocated. An important diagnostic feature from malignancy in the bladder is the absence of induration in the anterior vaginal wall.

Schugt[45] described a case treated for menorrhagia with 2 castration doses of X-rays and 1 of radium (1,748 milligramme-hours) with the occurrence of severe haematuria within 6 months of treatment. Cystoscopy showed telangiectatic varices of the bladder, which were treated by cystotomy and excision of the affected portions of the bladder. Schmitz[46] thinks that many cases of vesical ulcer must be associated with special lessening of resistance to gamma radiation (as postulated by some authors in connexion with rectal ulceration following irradiation), i.e. the patient has a true idiosyncrasy. Alternatively he admits faulty technique as a possible factor. He advises against local treatment of these ulcers, and thinks the best method of relief is by ureteric transplantation.

Bladder Complications

In my experience vesical involvement occurs in three types of cases. First, it is found in advanced cases when cystoscopy is performed prior to treatment. Second, it occurs as a late phenomenon after treatment and is due to recurrent malignancy. Third, a specific post-radiation ulceration occasionally occurs.

In advanced carcinoma of the cervix, vesical involvement is relatively frequent because of the close juxtaposition of the base of the bladder to the cervix uteri. I have seen 110 cases of cervical carcinoma with signs of vesical involvement at their first attendance, while in a personal experience to date of over 1,000 cases of carcinoma of the cervix I have seen only 1 in which the growth was actually involving the rectum prior to treatment: the disparity is striking. The growth invades the muscle wall first, causing circulatory changes in the mucosa, then it spreads forwards into the mucosa, finally ulcerating through and progressing ultimately to a vesico-vaginal fistula. Except when the latter and obvious complication has occurred, diagnosis of involvement can be made only on cystoscopic examination, and vesical symptoms are quite valueless as a guide in this respect. The cystoscopic appearances of involvement are well described by Gemmell and Aman-Jean. Spread to the vesical wall produces first of all congestion and distortion of the mucosa. Further spread produces, in some instances, transverse ridging of the base—a series of transversely running hillocks. Isolated hillocks may occur. The next stage shows extensive bullous oedema, and this precedes

the final stage in which the growth ulcerated through the mucosa. From the point of view of staging the causes, I consider that ulceration alone or bullous oedema complicating ridging are indicative of a stage 4 growth in the League of Nations Classification.

Out of 195 patients who were grouped as stage 3 on clinical examination, no fewer than 44 showed involvement of the bladder on cystoscopy. In other words there may be an error of over 20 per cent on clinical staging, although in many of these involvement of the bladder was suspected and the need for cystoscopy before treatment was noted. This is a very strong argument for routine preliminary cystoscopy on all except early cases.

During treatment of cervical cancer with radium, the normal bladder does not show any marked change beyond a certain amount of injection of the basal mucosa. Very rarely an acute cystitis may apparently be precipitated by the treatment.

Following treatment either of two complications may occur: (1) recurrent malignant disease, or (2) post-radiation ulceration. Recurrent cancer shows the same lesion in the bladder as untreated cancer; there are no special features on cystoscopy. Post-radiation ulceration is a different entity. It is an uncommon but quite specific complication of radiation which appears to be more frequently encountered at other clinics.

In my experience it is relatively rare—during the past 5 years I have seen only 10 cases of late bladder reaction, and in only 4 of these did the reaction progress to ulceration: the other 6 presented merely an atrophic telangiectatic mucosa. This represents an incidence of approximately 1 per cent, and I doubt if it is appreciably higher, since every patient complaining of haematuria (the cardinal symptom) is forthwith cystoscoped.

The natural history of the condition is as follows: usually about 2 years or longer after radiation treatment the patient complains of an attack of haematuria which may, or may not, be accompanied by dysuria, and the passage of clots. Cystoscopy now reveals a bladder base with atrophic thin mucosa and numerous characteristic spider-web telangiectatic patches, one or other of which has caused the bleeding. The reaction may not progress any further and the haematuria cease spontaneously. Alternatively the condition may advance to actual ulceration. The four ulcers I have seen have all been situated immediately above the inter-ureteric bar. They have all had curious serpiginous heaped edges and a surrounding zone of bullous

oedema. The adjoining base mucosa is extremely blanched with scattered telangiectatic patches. The ulcer is usually occupied by a slough.

The diagnosis was made on the appearance of the ulcer and the absence of any definite malignant lesion. I did not make a biopsy for two reasons: (*a*) I feared that the trauma might lead to a vesico-vaginal fistula forming, and (*b*) on practical grounds little was to be gained, since if the ulceration was malignant further treatment should not be given, and if it was due to reaction spontaneous healing was the usual outcome. In 3 of my 4 cases the ulcer has healed spontaneously, leaving a rather scarred bladder base; the fourth patient unfortunately died of a sudden profuse haematuria some months after the initial symptoms had appeared: when admitted to hospital she was so exsanguinated that she was beyond aid.

Treatment of the haematuria is occasionally called for, and the best treatment is to cauterize the bleeding varices by cystoscopic diathermy. Clots may necessitate bladder wash-outs, but otherwise treatment is not called for once a diagnosis is made, since the natural tendency of the complication is towards spontaneous healing.

Vesico-vaginal fistulae are not infrequent terminal complications of the disease, but they may also result from radio-necrosis. Ulceration of the bladder base, just like ulceration of the rectum, may go on to complete destruction of the intervening tissues, though fortunately this is rare with our present techniques, and I can recall only two definite cases unassociated with recurrence. There is no treatment for the malignant cases. In the radio-necrotic type local repair is out of the question owing to the tissue non-vascularity and a diversion of the urinary stream is the only alternative. Colby expressed a general opinion when he stated that "It is a well-recognized fact that surgical attempts to close such fistulae are usually unsuccessful." However, Folsom and O'Brien[47] report a successful case of vaginal repair of a vesico-vaginal fistula occurring 6 months after radium treatment of carcinoma of the cervix. Eleven months after operation the patient was still well.

Ureteral Complications

These are frequent and may be considered in three groups, namely in untreated cases, and in cases treated (*a*) surgically, and (*b*) by radiation.

My experience with ureteral complications following the surgical treatment of carcinoma of the cervix is very limited as I practically never perform Wertheim's hysterectomy. That such complications are not rare may be judged from the experience of Webb-Johnson.[18] He details a scheme of treatment for ureterovaginal fistulae following hysterectomy and writes of a personal experience of 17 such cases. The only surgical complication I have met with was a uretero-abdominal fistula developing 5 years after a Wertheim's hysterectomy for carcinoma of the cervix. Following the operation the patient had had a urinary fistula from the lower end of the abdominal wound, but this had healed spontaneously in a few weeks. She was well for over 4 years, when a metastasis developed in the lower end of the wound and a urinary fistula reformed. Local radium implant was carried out, and 9 months later a supraclavicular metastasis occurred and was implanted with radium. The fistula persisted, and on further investigation it was found to be a left uretero-abdominal fistula. There was a large hydro-ureter and hydronephrosis above the site of leakage and bougies were passed through the cystoscope in an unsuccessful attempt to encourage spontaneous healing. Death occurred in a further 3 months, 1 year after the development of the fistula.

Ureteral Involvements in Untreated Cases

There is an appreciable incidence of upper urinary tract complications due to pressure or invasion of the ureter in advanced cases of carcinoma of the cervix, and present at the first examination. During 1937 and 1938 a preliminary investigation either by intravenous urography or by ureteric catheterization was made in 90 cases with the following findings:

Stage of disease	No. of cases	No. of complications	Hydronephrosis		Sluggish function	No function
			Unilateral	Bilateral		
1	2	0				
2	26	3	2	1	—	—
3	32	9	4*	1	2	3*
4	30	20	8*	2	2*	9

* Double lesion in one case.

Thus when unselected cases of stage 3 or 4 were investigated prior to treatment an incidence of nearly 50 per cent of upper

urinary tract complications were found. In the stage 4 cases such complications were nearly always present. A less reliable indication of a renal lesion was obtained from the blood-urea estimation. The average blood-urea in patients of the stage 3 cases with complications, in this series, was 40 mg. per cent (the highest being 56 mg. and the lowest 32 mg.) and in the stage 4 cases with complications, it was 58 mg. per cent (the highest being 225 mg. and the lowest 25 mg.); in both stages the amount is considerably higher than the normal, and suggests fairly considerable renal impairment.

Effect on Prognosis

Analysis of the sequelae of the 32 patients showing an upper urinary tract complication prior to treatment would suggest that the presence of such complications makes worse the prognosis in no small measure. Of the 3 patients of stage 2 with initial lesions, 1 was dead within 3 months of treatment, while the other 2 are alive and well a full year after. Among the 9 patients of stage 3, 1 died in 2 months, 1 in 3 months, 1 in 6 months, 1 in 9 months, and 2 others are dying within a year of treatment. Four patients of stage 4 are alive at the time of writing, 2 being 10 months alive, 1 a year and a half, and 1 just 2 years. Three have known

Table Showing the Prognosis in Patients with Renal Lesion.

Stage of disease	No. of cases	Alive over 1 year	Died within 1 year
1	0	—	—
2	3	2	1
3	9	3, and 2 cases alive for 9 months with recurrences	4
4	20	1 alive for 2 years and 2 for 10 months, but *all* have recurrences. One alive 18/12 with no obvious recurrence but vesico-vaginal fistula	16
Totals	32	11	21

recurrence of cancer. The other 16 patients all died within 12 months of treatment, and 15 of them within 6 months. The duration of life in these patients was:

11 months	...	...	...	1 case
6 months	...	...	...	2 cases
5 months	...	...	...	2 cases
4 months	...	...	...	1 case
3 months	...	...	...	4 cases
2 months	...	...	...	3 cases
1 month	...	...	...	3 cases

TABLE SHOWING THE PROGNOSIS IN PATIENTS WITHOUT INITIAL RENAL LESION

Stage of disease	No. of cases	Alive over 1 year	Died within 1 year
1	2	2	0
2	23	13	10
3	23	11	12
4	10	1	9
Totals	58	27	31

In the 10 patients of stage 4 in whom there was not any involvement of the renal tract the prognosis is shown in the following table:

TABLE SHOWING THE PROGNOSIS IN STAGE 4 PATIENTS WITHOUT RENAL LESION.

Case No.	Whether bladder involved or not	Alive	Died
1	Yes		3/12
2	Yes	18 months (7/1899)	
3	Yes		2 years
4	No		3/12
5	Yes		9/12
6	Yes		1 year
7	Yes		2 years
8	No		1 month
9	Yes		2 months
10	Yes		3 months

Stated in terms of months the prognosis is slightly better in this group.

A glance at the above tables suffices to show that the prognosis is virtually hopeless in practically every case with initial involvement of the renal tract in which the local malignancy is of stage 3

or stage 4. This raises the question of the advisability of giving other than palliative treatment to such patients, or alternatively of considering the question of treatment of the renal lesion as a preliminary measure. In the majority of cases evidence of the exact cause of death has not been available, but in a high percentage it is known to have been uraemia.

Surgical Treatment of the Renal Lesion

Surgical treatment has not been carried out before radiation in any case. In one case the development of acute pyelonephritis necessitated the interruption of radiotherapy while a nephrostomy was instituted. Treatment could not be completed, and this is the patient in stage 2 who died within the year. Suppression of urine in another patient some months after treatment also necessitated a nephrostomy. In another patient, too debilitated for nephrostomy, catheter drainage was established, and a ureterostomy was performed in a fourth patient with a vesico-vaginal fistula and but one functioning kidney. None of these patients lived more than a few weeks. Thus in my experience so far, the field of surgical intervention for this type of lesion is extremely limited in treated cases and is nil in cases prior to radiation.

Ureteral Complications following Radiation Treatment

Involvement of the upper urinary tract is a not infrequent finding in patients investigated some months or years after treatment, but so far I am not able to state with any precision the rôle played by the various factors described by Howes and Strauss. To obtain scientific evidence about this subject calls for very painstaking and detailed investigations, and up to the present I have been endeavouring to approach the problem along the following lines:

(1) An unselected group of patients suffering from carcinoma of the cervix, mostly in stage 2 or stage 3, were examined cystoscopically through a Kelly direct vision cystoscope, and radio-opaque catheters were passed into the ureters. A stereoscopic X-ray was then taken after the radium applicators had been inserted, and from the films the physicist at the Holt Radium Institute, Mr. W. T. Meredith, was able to make an exact reconstruction in space of the position of the ureters relative to the radium units.

(N.B.—This work remains incomplete. The dose on parametrium in the near neighbourhood of the ureter can be calculated and details of this

have been published,[49] but the individual doses for the cases described have not been measured.)

(2) During 1937 and 1938 90 patients had the urinary function investigated prior to treatment. Of these, 32 had demonstrable lesions and 58 showed normal renal function. A careful follow-up of these 58 patients showed the following findings: 31 died within a year and in only 2 did any urological condition become recognized. Three patients had further uroselectan examinations 6 months after treatment without any obstruction being shown. The exact cause of death is unknown in the majority, and the autopsy was unobtainable except in 2 cases. In 27 of the patients still alive 13 were treated over a year ago, and 14 over 2 years ago: in none of these has any urological complication been recognized so far, but urological investigation has not been carried out since treatment.

(3) Study of autopsy material: I have investigated the post-mortem records of the last 30 patients dying of carcinoma of the cervix in the Christie Hospital, Manchester. These include those who died during treatment from septicaemia, peritonitis, or embolism, and they are in consequence not a representative selection. Patients in whom the disease is more advanced and in whom recurrent cancer and metastases occur mostly die elsewhere, and it is in this group that a much higher incidence of urological complications would be found. The following table illustrates the type and incidence of 13 renal lesions in this selected relatively early group of 30 cases:

Lesion	No. of cases	Cause of death
Hydronephrosis		(1) Embolism (cerebral)
		(2) Septicaemia
		(3) Uraemia
Unilateral	6	(4) Haemorrhage
		(5) Haemorrhage
		(6) Peritonitis
		(1) Uraemia
Bilateral	3	(2) Metastases
		(3) Uraemia
Pyonephrosis		(1) Metastases
or	4	(2) Uraemia
Pyelonephritis		(3) Uraemia
		(4) Uraemia

In the remaining 17 patients without mechanical renal lesion, 5 had renal lesions—2 with fatty degeneration, 1 with sub-acute nephritis, 1 with arterio-sclerotic nephritis, and 1 with infarcts.

Thus even in such an unrepresentative group of cases the incidence of renal lesions is over 50 per cent, and the majority are indubitably due to the uterine malignancy.

Unfortunately, in the majority of these cases, beyond noting that there was dilatation of one or both ureters but little attention was paid to the exact cause of ureteral obstruction. In only one case was uterine obstruction noted to have been due to actual invasion of the ureter by the growth, while in several it was noted to have been due to fibrous tissue involvement. Exact determination of this point is difficult in the majority of post-mortems on these patients, since the pelvic tissues are very distorted and it would be necessary to take serial sections after fixing the whole pelvis. It is undoubted that non-malignant stricture of the ureter can occur in a certain percentage of patients, but in the majority active malignancy is present in the parametrial tissues surrounding the ureter.

(4) In patients in whom the occurrence of some upper urinary tract lesion was suspected some time after treatment urological investigations were made, and in a number pathological conditions were found, unfortunately the lack of precise information as to the renal function in the first instance prevents many deductions being drawn in this group. Again, it is striking how poor is the prognosis in the presence of a renal lesion. Eighteen patients have had a uroselectan examination in the course of investigation of the aetiology of severe pain subsequent to treatment. Fifteen had a renal lesion, either no function of a kidney or hydronephrosis. In 12 the renal lesion was associated with a parametrial high dose effect that was probably causative on some, if not all, of the ureteral obstructions. The prognosis in the whole series was extremely poor once a renal lesion had developed.

Case 1. Mrs. H. A. She was a stage 4 carcinoma of the cervix seen first in June 1937. *Inter alia* she had frequency and right loin pain. The right kidney was enlarged and easily palpable. Intravenous urography showed the right kidney low in position and hydronephrotic, and poor functioning of the left kidney. The blood-urea was 31 mg. per cent. Cystoscopy showed diffuse bulging and oedema of the base, with obstruction to bougie at 2 cm. up the right ureter. Two months later, after completion of full course of radium and X-ray treatment, further cystoscopy was performed because of persistence of pain and frequency, and now it was impossible to pass a bougie up the left ureter, though difficulty was not

found on the right side. The right ureter was seen to function, but not the left. Indigo-carmine did not appear in the bladder in ½-hour after injection. The blood-urea was now 104 mg., and the urine was heavily infected. The patient died of uraemia within 6 months of treatment.

CASE 2. MRS. F. E. She had a stage 2 carcinoma and was cystoscoped because of marked frequency. There was some trigonitis, and a bougie was obstructed at 2 cm. on the right side. Uroselectan showed gross hydronephrosis on that side. Blood-urea was 56 mg. per cent. There was thus considerable renal damage in a relatively early carcinoma of the cervix. Following a single radium insertion the hydronephrosis became infected, and nephrostomy was required. She died of this complication within 3 months of her first attendance.

CASE 3. MRS. A. L. Was first seen in December 1936, when she was found to have a stage 4 carcinoma because of widespread vesical involvement, as seen on cystoscopy. She was given a preliminary radium treatment and 3 months later a further cystoscopy done—this showed marked improvement in the condition of the bladder. Both ureters were patent and did not present any difficulty on bougie examination. Unfortunately urography was not performed at this time. A full course of X-ray and radium treatment was given in April and May 1937, and at the end of treatment a further cystoscopic examination was made. On this occasion the bougie introduced into the right ureter was firmly gripped just beyond the bladder. Urography did not demonstrate any activity in the right kidney, but normal functioning in the left one. Three months later (August 1937) a further uroselectan showed functioning of the right kidney now, though somewhat impaired. The investigations suggest a temporary suppression of function in the right kidney, precipitated by treatment and associated with an obstruction of the pelvic ureter—a subsequent cystoscopy one year after treatment showed that this obstruction had disappeared and uroselectan disclosed normal function of both kidneys.

CASE 4. MRS. F. H. This patient was treated with X-rays and radium in June and July 1934, for a stage 2 carcinoma. Preliminary urinary tract investigations were not made. One year later she developed pain in the right renal region and cystoscopy was performed in September 1935. The right ureter was found to be obstructed 8 in. from the bladder. Uroselectan disclosed complete non-functioning of right kidney with blockage of the right ureter just below the kidney. The kidney was palpable. Nephrectomy was decided upon in view of the patient's discomfort, and was carried out by Mr. Macalpine in September 1935. The whole of the upper two-thirds was infiltrated with tumour, which on microscopy proved to be squamous epithelioma, similar to the original primary cervical growth. (Metastasis to the kidney is a very rare manifestation in cervical carcinoma. A case was reported to the North of England Obstetrical Society in 1936.)

CASE 5. MRS. E. J. Stage 3 carcinoma treated in March and April 1937

with X-rays and radium. Investigation of urinary tract prior to and during treatment did not show any abnormality. Three months after treatment developed severe pain in left loin and back. On cystoscopy left ureteric orifice was golf-hole and bougie was obstructed at 2 cm. Uroselectan revealed hydronephrosis on the left side, with obstruction of the ureter at the level of the sacro-iliac joint. Mr. Watkins cystoscoped her bladder and found it possible to introduce a No. 5 olivary catheter past the obstruction. He diagnosed a tubular stricture some 4 inches long. The stricture was dilated, and there was appreciable relief of pain for a few days, when it recurred. On opening the abdomen the left ureter was found to be constricted from the pelvic brim to the bladder by a firm mass. The ureter was blunt-dissected free with difficulty, presacral neurectomy was performed, and an aortic gland removed for section—it proved to be malignant. Leakage occurred from the freed ureter, and the patient died in 4 days. Histological examination of the compressing parametrial tissue did not reveal any malignancy—it was purely organizing reactive fibrous tissue.

Case 6. Mrs. M. G. Stage 4 carcinoma (on bladder involvement) treated with radium and X-rays October/December 1937. Bladder involved at first treatment, but no obstruction in either ureter, and renal function (urography) normal. Cystoscopy just prior to termination of treatment revealed some obstruction to passage of bougie on left side. Six weeks later this obstruction was complete. Uroselectan now showed absence of function on left side. Six months later patient died of pulmonary embolus, but there was unquestionably widespread recurrent malignancy in the pelvis.

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