

RADIATION NEPHRITIS

by

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In 1952 (KUNKLER, FARR & LUXTON) we published a paper based on a study of radiation nephritis occurring in 20 men after prophylactic irradiation of the abdomen following orchidectomy for seminoma testis. These cases will now be briefly reviewed along with 34 other patients including 5 women. A more detailed clinico-pathological study of 27 patients has been published (LUXTON 1953) and also a long-term review of the whole series, some cases now having been watched for a period of 14 years (LUXTON 1961).

Three techniques employing daily fractionation had up to 1948 been used in succession to treat the abdominal drainage areas.

Method 1. Opposing circular fields 30 or 40 cm in diameter.

Method 2. Three field trunk bridge technique: two anterior rectangular fields at 120 degrees to each other, opposing a posterior circular field, HVL 1.5 mm Cu, central dose 3 000 r in four to five weeks.

Method 3. Four field trunk bridge technique: the two anterior rectangular fields were opposed by an identical posterior pair, central dose 2 500 r in four to five weeks.

While these methods had progressively improved the distribution of dose in the transverse central plane, they had not remedied the fall in dose parallel to the long axis of the fields and in particular in the region of the aortic nodes. The next method aimed at overcoming this criticism.

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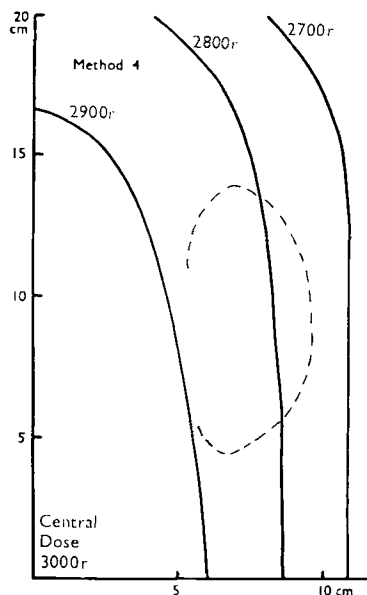


Fig. 1. Dose distribution to kidney from four field trunk bridge: field length 45 cm and width 17 cm, beam flattening filters, central dose 3 000 r in five weeks (treatment 6 days per week), HVL 1.5 mm Cu.

Method 4. Four field trunk bridge: field length 40 to 45 cm and width 17 cm, beam flattening filters introduced at the same time, central dose 3 000 r in five weeks.

Method 4 resulted in the delivery to the kidneys of a greater proportion of the prescribed dose and a high incidence of renal damage (Fig. 1). The dose distribution in the region of the kidneys was investigated for each of the treatment methods and the isodose curves in the mid-coronal plane were calculated (KUNKLER et coll. 1952).

As a man is able to survive with a third of his total renal mass (80 to 100 g), the average doses received by the upper third of the kidney volume were calculated. In methods 2 and 3 there was a gradient of dose through the kidneys. The upper poles received 1 700 r and their lower poles 2 700 r and 2 300 r respectively. Renal failure did not follow treatment by these two methods. If renal failure is to be prevented it is not wise to assume that the 'average' dose or the integral dose received by the kidneys in methods 2 and 3 is a 'safe' dose (Table 1).

It is only from the dose in the parts of the kidneys which received the least radiation that reasonably reliable data on renal tolerance to roentgen rays are obtainable.

A dose of 1 700 r or less delivered to the kidneys over a period of five weeks or more (daily treatment six days a week HVL 1.5 mm Cu), could on this basis be considered a tolerable dose. It must not, of course, be assumed that there has been no diminution in renal reserve. From cases presented by others,

Table 1

Kidney doses not causing overt renal damage — treatment 6 days a week — overall time 4 to 5 weeks — HVL 1.5 mm Cu

Method	Upper third	Lower third
2	1 700 r	2 700 r
3	1 700 r	2 300 r

and from our own experience, it is clear that hypertension can result from high dose irradiation of a limited volume of kidney tissue, and may respond to nephrectomy. From our dose calculations in method 2 it is unlikely that severe hypertension in healthy young adults would often be induced by such limited irradiation if the doses were of the order of 2 700 r in five weeks, although significant local renal damage must be inflicted. No case of severe hypertension was proven to occur among the 24 patients treated by method 2, although the lower poles received 2 700 r in four to five weeks.

However, from method 4 it was concluded that a dose of 2 800 r or more delivered to the whole of both kidneys in five weeks or less would lead to renal failure in a high proportion of cases.

Further experience suggests that where it is imperative to include the whole of both kidneys within the irradiated volume in a patient with malignant disease, a dose of 2 300 r over five weeks may be acceptable.

Table 2 gives the five-year crude survival rates for each year from 1947 to 1953 at the Christie Hospital, Manchester, for seminoma testis without known metastases. This table shows how, at least in the case of seminoma testis, it is possible to avoid this serious complication and maintain survival rates. Of the 27 patients treated in 1949, however, by method 4 (the abdominal bath with four large fields) only eight were alive at the tenth year (29.6 %). Two of the ten year survivors have died subsequently with renal damage and four have proteinuria.

Table 2

Seminoma testis — 'healed' cases 1947 to 1953 inclusive

Year of treatment	Number treated	Number alive	Crude 5-year survival rate %
1947	11	9	81.8
1948	23	16	69.6
1949	27	9	33.3
1950	16	13	81.3
1951	21	14	66.7
1952	17	14	82.4
1953	26	22	84.6

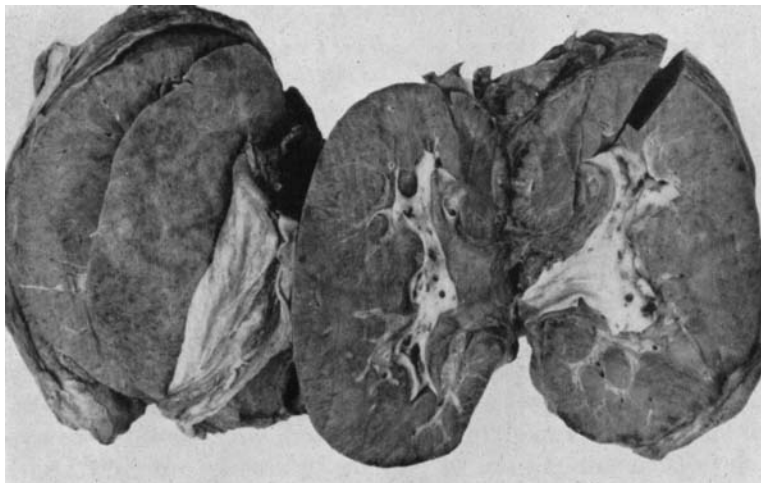


Fig. 2. Kidneys in acute radiation nephritis.

Clinical and pathological aspects of radiation nephritis

The clinical and pathological features fell into a spectrum ranging from fulminating malignant hypertension to asymptomatic proteinuria. Five syndromes have been defined: (1) acute radiation nephritis, (2) chronic radiation nephritis, (3) benign hypertension, (4) late malignant hypertension, (5) asymptomatic proteinuria.

1. *Acute radiation nephritis.* Between the commencement of radiotherapy and the first symptom of renal involvement there is a latent period of 6 to 13 months in adults (average 8 1/2 months) although the latent period is shorter in children. Before the first symptom appears, however, clinical examination may reveal proteinuria, anaemia and hypertension. The onset of symptoms is gradual, but most patients are incapacitated within one month.

Hypertension is always present, but may not be the first sign of nephritis. The blood pressure usually reaches its highest level within six months of the first symptom. In about half the patients who recover from acute radiation nephritis the blood pressure returns to normal levels within two years after the onset. Malignant hypertension occurred in 8 of the 20 patients with acute radiation nephritis, of whom 6 died. The other 2 recovered without specific treatment, although one died 6 years later in chronic uraemia.

Anaemia is severe and refractory to all treatment except blood transfusion.

Kidneys in acute radiation nephritis are illustrated in Fig. 2. They are of normal size; the capsule may or may not be thickened; subscapular petechiae may be seen. Histologically there is widespread injury to glomeruli and tubules, and the interstitial tissue between the tubules is increased.

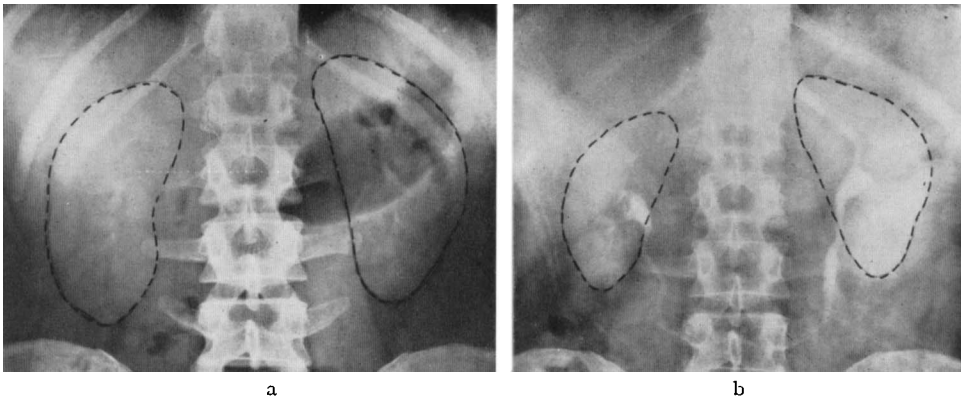


Fig. 3. Renal outlines in a patient: a) during acute radiation nephritis, and b) eight years later.

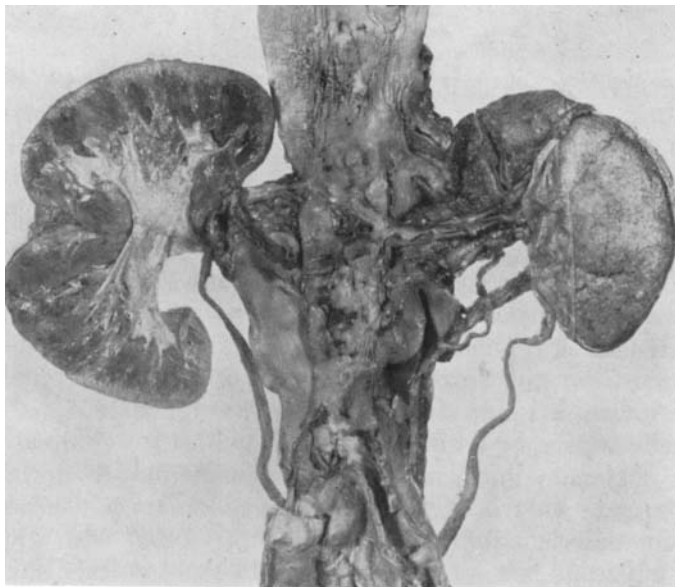


Fig. 4. Shrunken kidneys from patient who died in chronic renal failure 11 years after acute radiation nephritis.

Malignant hypertension is the main immediate threat, but fortunately it responds to hypotensive drugs. All patients who survive the acute stage are left with chronic radiation nephritis.

2. *Chronic radiation nephritis.* Irradiation sclerosis may succeed acute radiation nephritis or it may occur without the acute stage.

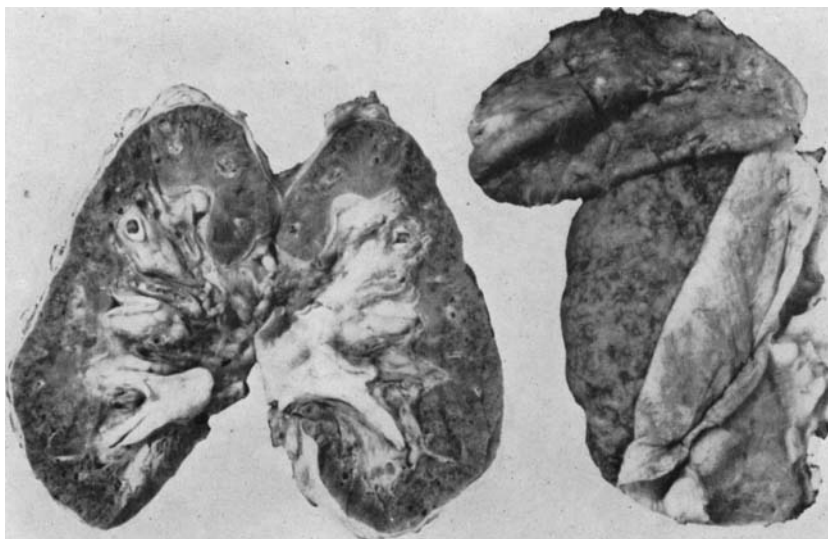


Fig. 5. Shrivelled kidney of a man who died in chronic uraemia eight years after renal irradiation.

The renal outlines in a patient, during acute radiation nephritis, and 8 years later, are shown in Fig. 3. The similarly shrunken kidneys of another patient, who died in chronic renal failure 11 years after acute nephritis, are shown in Fig. 4. In Fig. 5 the shrivelled kidney of a man who died in chronic uraemia 8 years after irradiation is illustrated. Each kidney weighed 45 g; the adrenal gland seen is about twice the normal size. In Fig. 6 the contracted kidney of a man who died in chronic uraemia 3 years after renal irradiation is shown. There was no acute stage; this kidney weighed 100 g.

The clinical features of chronic radiation nephritis comprise proteinuria, hypertension, anaemia, and azotemia. Some patients are normotensive for years and complain only of lack of energy and nocturia. Chronic radiation nephritis is compatible with many years of life, often with almost normal activity, and of 22 patients, 14 are alive after 10 to 14 years. Others have died of chronic renal failure.

3. *Benign hypertension.* A few patients (5 out of 54) developed the clinical features of benign essential hypertension, the signs being hypertension and a variable degree of proteinuria. The condition is not so 'benign' as at first appeared, however, for one of the 5 patients died of cardiac failure and another developed malignant hypertension 11 years after his radiotherapy.

4. *Late malignant hypertension.* The malignant hypertension of acute radiation nephritis may be regarded as 'early' malignant hypertension, commencing as



Fig. 6. Contracted kidney of a man who died in chronic uraemia three years after renal irradiation.

it does within 12 months of the start of radiotherapy. Seven of 54 patients developed 'late' malignant hypertension, i. e. 1 1/2 to 11 years after radiotherapy. It may be stressed that renal irradiation has an astonishing tendency to cause malignant hypertension. Of 54 patients, 15 (28 %) developed malignant hypertension sooner or later. Once begun, the condition may progress rapidly. It responds well to hypotensive drugs and thus it is important that all patients with chronic radiation nephritis or hypertension due to renal irradiation should be kept under review so that the significance of a rising blood pressure is not missed.

Pathologically, three groups of cases of late malignant hypertension are seen: (1) with kidneys of normal size, (2) in chronic radiation nephritis with both kidneys equally contracted, (3) with one kidney having suffered a greater radiation injury than the other.

When late malignant hypertension is associated with gross disproportion in size of the two kidneys, relief of the hypertension may follow excision of the smaller kidney. Careful roentgen investigation of the kidney size and conformation are needed, and also studies of renal function. It is illustrated in Fig. 7 how cure of late malignant hypertension may be attained in such a case, even when both kidneys have been severely damaged by roentgen radiation.

Discussion

For the moment we have to rely upon the knowledge we have gained of the tolerance levels of the kidneys for treatment regimes, which have usually employed daily fractionation. In planning therapy in the region of the kidneys, there must be a clear decision determining the volume to be irradiated and

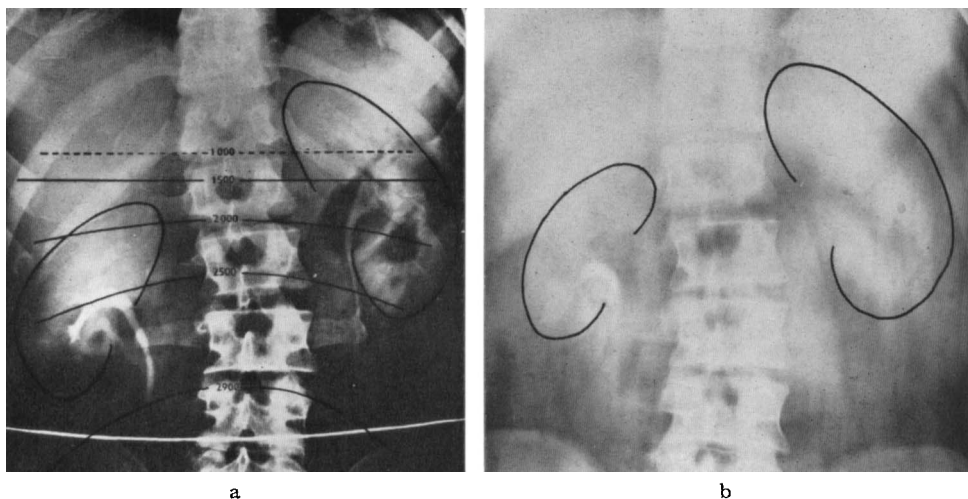


Fig. 7. Renal outlines in a patient: a) 1952 before roentgen therapy, and b) four years later. The right kidney is low-lying.

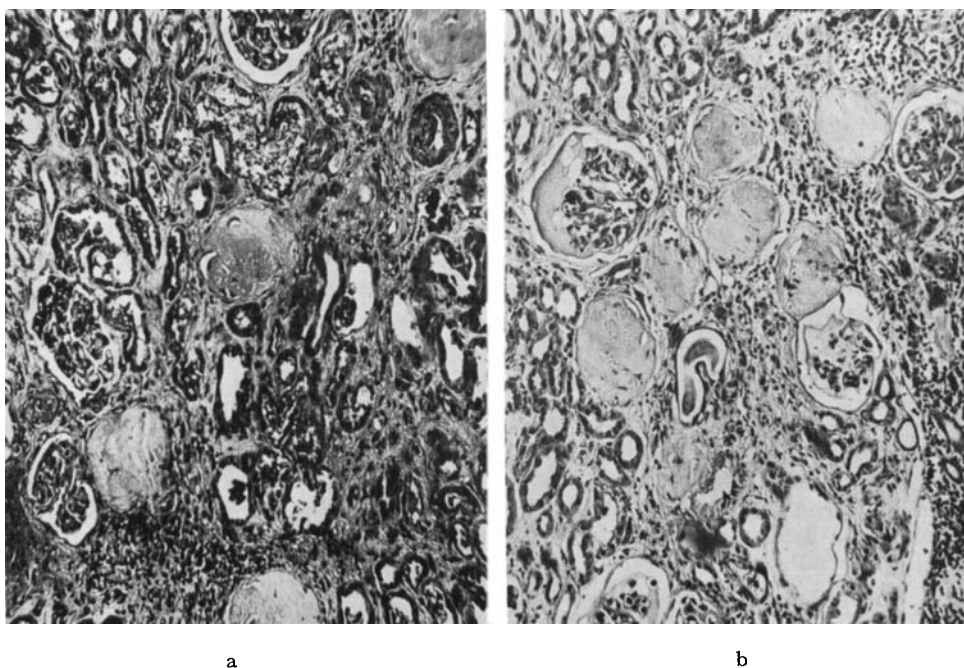


Fig. 8. From same patient as in fig. 7. (The right kidney was excised and weighed 80 g.) a) Histologic section of excised kidney. b) Biopsy from lower pole of left kidney.

accurate localisation of the kidneys. The problem frequently presents itself in relation to ovarian carcinoma (ZIEGERMAN 1957), Wilms' tumour, and other lesions, apart from seminoma testis. Thus radiation nephritis has occurred following treatment of the lower dorsal and lumbar spine (LEVITT 1957, DAVEY et coll. 1952). DEAN & ABELS (1944) describe the case of radiation nephritis following upper abdominal irradiation for a lymphoma. ZUELZER et coll. (1950) pointed out that the kidney of the infant may be more radio-sensitive than that of an adult. BECK (1958) has reported a case of a child, 2 1/2 years old, who received 3 000 r over three weeks to a metastasis in the right perirenal fat from a Wilms' tumour of the left kidney which had been removed nine months previously. Irradiation nephritis developed four months later. GROSSMAN (1955) has described this complication in an infant nine months old following unilateral nephrectomy for Wilms' tumour and a kidney dose estimated at 2 000 r.

From our evidence in adults with treatment six days each week, we must conclude that 2 800 r in five weeks to the whole of both kidneys is associated with a high risk of initiating radiation nephritis which is often fatal. It is therefore essential that, when treatment involves the upper abdomen, the position and function of the kidneys should first be determined. It should be remembered that certain clinical factors predispose to radiation nephritis, factors such as congenital renal lesions, malposition of one or both kidneys, tumour masses adjacent to the kidney which may interfere with its blood supply, preceding chronic nephritis and urinary tract infection.

With detailed treatment planning it is still possible to carry out a rational policy of surgery and radiation therapy with minimal risk of radiation nephritis.

SUMMARY

From the dose distribution calculated in the region of the kidneys, in a series of patients treated for seminoma testis, an estimate has been made of the limits of renal tolerance. The clinical and pathological features of radiation nephritis, based on a long term review of 54 cases, are outlined.

ZUSAMMENFASSUNG

Die Bestrahlungsnephritis in einer Reihe von Patienten, die wegen eines Seminoms der Hoden bestrahlt worden waren, und deren Strahlendose in der Nierengegend bekannt war, wurde mittels Bestimmung der Nierentoleranz untersucht. Die klinischen und pathologischen Erscheinungen der Bestrahlungsnephritis werden an Hand einer langen Beobachtungszeit von 54 Patienten besprochen.

RÉSUMÉ

Se basant sur la distribution de dose calculée dans la région des reins pour une série de malades traités pour séminome du testicule, les auteurs donnent une estimation de la limite de la tolérance rénale. D'après 54 cas suivis pendant longtemps, ils décrivent les signes cliniques et anatomo-pathologiques de la néphrite des radiations.

REFERENCES

- BECK J. S.: Acute radiation nephritis in childhood. *Brit. med. J.* 2 (1958), 489.
- DAVEY P. W., HAMILTON H. D., and STEELE H. D.: Radiation injury of the kidney. *Canad. med. Ass. J.* 67 (1952), 648.
- DEAN A. L., and ABELS J. C.: Study by the newer renal function tests of an unusual case of hypertension following irradiation of one kidney and relief of the patient by nephrectomy. *J. Urol.* 52 (1944), 497.
- GROSSMAN B. J.: Radiation nephritis. *J. Paediat.* 47 (1955), 424.
- KUNKLER P. B., FARR R. F., and LUXTON R. W.: The limit of renal tolerance to X-rays: An investigation into renal damage occurring following the treatment of tumours of the testis by abdominal baths. *Brit. J. Radiol.* 25 (1952), 190.
- LEVITT W. M.: Radiation nephritis. *Brit. J. Urol.* 29 (1957), 381.
- LUXTON R. W.: Radiation nephritis. *Quart. J. Med.* 22 (1953), 215.
- Radiation nephritis. A long term study of 54 patients. *Lancet* 1961: II, p. 1221.
- ZIEGERMAN J. H., TULSKY E. G., and MAKLER P.: Post-radiation nephritis syndrome; report of a case. *Obstet. Gynec.* 9 (1957), 542.
- ZUELZER W. W., PALMER H. D., and NEWTON JR. W. A.: Unusual glomerulonephritis in young children, probably radiation nephritis: report on three cases. *Amer. J. Path.* 26 (1950), 1019.