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RADIATION FOR IMMUNOSUPPRESSION IN HUMAN ORGAN TRANSPLANTATION

II. Clinical experience

by

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At the Medical College of Virginia, radiation therapy is used routinely after transplant of the donor kidney following the recommendations of KAUFFMAN et coll. (1965). Using a high-energy source, 130 rad to the anterior surface of the kidney (calculated at 4 cm) is delivered on the first, third, fifth and seventh post-transplant days. The treatment field is outlined by silver clips placed at opposite poles of the kidney at the time of surgery. In addition to the irradiation, patients are also routinely placed on prednisone, 5 to 60 mg, and azothioprine, 3 to 5 mg/kg. A major problem, of course, in transplants is prevention of threatened rejection following the initial routine procedures.

From the fall of 1962 until January 1, 1970, a total of 140 patients have undergone kidney transplantation at our institution; 81 of these (57.8 %) are living (Table 1). Of these patients, 104 received a single transplanted kidney, with irradiation being used as a primary immunosuppressive agent. Table 2 reflects these results. Patients receiving a kidney from a near relative, all of whom

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Table 1

Kidney transplants from August 1962 to January 1970

	Number of patients		Total
	Living	Dead	
Single transplants			
Relative	48 (64 %)	27	75
Nonrelative	0	3	3
Cadaver	21 (53.8 %)	18	39
Total	69 (58.9 %)	48	117
Multiple transplants (53 kidneys)	12 (52.2 %)	11	23
Total number of transplants	81 (57.8 %)	59	140

were siblings or parents of the patient, had better survival than those who received either a nonrelative's kidney or a cadaver kidney. Twenty-two (58 %) of the 38 patients receiving single cadaver kidneys survived over one year and 46 of 66 (70 %) of single relative transplants have survived one year.

Thirty-five of the 104 single transplant patients, including 11 patients receiving cadaver kidneys, required only the initial course of 600 rad irradiation and are without evidence of rejection. Eight of these 35 are dead of this date, but the deaths were not related to kidney rejection (Table 3). The success rate using 600 rad was 24/66 (36 %) for relative kidneys and 11/38 (29 %) for cadaver kidneys.

Rejection is one of the major complications of organ transplantation. Clinically there is fever, swelling and tenderness of the transplant, mild anorexia, and decreased urinary output. Laboratory findings are multitudinous, including lymphocytes in the urine and blood serum lactic dehydrogenase (LDH) changes, depression of the C^2 fraction of the complement.

The most useful daily indices for the detection of threatened rejection are the sudden appearance of oliguria, associated with a rise in blood urea nitrogen (BUN), with or without fever. Sometimes the BUN will increase without concurrent rise in creatine, but the more severe crises are usually associated with elevation in the serum creatine and a fall in creatine clearances.

The primary treatment of threatened kidney rejection is prednisone (up to 400 mg daily) and actinomycin-D (200 to 400 mg daily for 3 to 4 days). If the impending rejection fails to respond to these initial measures, local irradiation to the graft is then utilized. Doses of 150 rad are given daily up to 1 500 rad if

Table 2

Patients with a single transplant receiving irradiation to the kidney only as adjuvant immunosuppression

Donor source	Total	Living	Dead	Survival				
				1 year	2 years	3 years	4 years	5 years
Relative	66	46 (70 %)	20	46 (70 %)	40 (60 %)	33 (50 %)	24 (36 %)	1 (21 %)
Nonrelative	0	0	0					
Cadaver	38	21 (55 %)	17	22 (58 %)	15 (39 %)	11 (29 %)	5 (13 %)	1 (2 %)
Total	104	67	37					

Table 3

Patients with a single transplant receiving 600 rad to the kidney and with no evidence of rejection

Donor source	Total	Living	Dead[2]	Survival				
				1 year	2 years	3 years	4 years	5 years
Relative	24	21	3	19	19	18	12	7
Nonrelative	0	0	0					
Cadaver[1]	11	6	5	6	4	3	1	0
Total	35	27	8					

[1] One patient also received antilymphocyte serum.

[2] Cause of death not related to kidney rejection (sepsis, myocardial infarction, auto accident, etc.).

Table 4

Single transplant patients who required additional radiation immunosuppression for threatened rejection after initial irradiation — The retreatments were all given to single allographs and this data does not include patients who received more than one kidney

Number of treatments	Number of cases	Average time from first to last irradiation (weeks)	Living	Dead	Average survival (months)
1	22	7.8	19	3	34.6
2	16	11.4	13	3	30.7
3	14	18.8	7	7	25.8
4	6	30.7	3	3	23.2
5	5	13.4	0	5	9.2
6	2	22.0	0	2	8.5

Table 5

Duration of graft survival of multiple kidney transplants

Patient	Number of transplants and donor				Transplant survival			
	First	Second	Third	Fourth	First	Second	Third	Fourth
R.A.	Relative	Cadaver			40 mo	[1]12 mo		
H.B.	Cadaver	Relative			2.5 mo	[1]24 mo		
G.B.	Cadaver	Relative			16 mo	[1]68 mo		
H.B.	Cadaver	Cadaver			11 mo	[2] 3 mo		
R.B.	Cadaver	Cadaver			10 mo	[2] 1 day		
J.C.	Nonrelative	Cadaver			2 mo	[2]57 mo		
B.C.	Relative	Cadaver			13 mo	[2] 4 mo		
M.D.	Relative	Cadaver	Cadaver	Cadaver	51 mo	[3] 0 mo	2 mo	[4]21 mo
K.E.	Cadaver	Cadaver			6 days	[1]64 mo		
S.G.	Cadaver	Cadaver			3 days	[2] 2 mo		
L.H.	Cadaver	Cadaver			5 mo	[2] 8 mo		
P.H.	Relative	Cadaver	Cadaver		15 mo	[1] 3 mo	[1]57 mo	
W.J.	Relative	Cadaver			2 mo	[2] 0 mo		
C.N.	Relative	Cadaver			27 mo	[1]44 mo		
D.P.	Cadaver	Cadaver			6 mo	[1]10 mo		
M.P.	Relative	Cadaver			31 mo	[1]14 mo		
R.R.	Cadaver	Cadaver	Cadaver		2 mo	1 mo	[4]2 mo	
R.R.	Relative	Cadaver			25 mo	[2]11 days		
E.R.	Relative	Cadaver	Cadaver		15 mo	13 mo	[2]7 days	
S.S.	Relative	Cadaver	Cadaver		8 mo	2 mo	[4]0 mo	
C.S.	Relative	Cadaver			12 days	9 mo		
H.S.	Cadaver	Cadaver			12 days	[1]40 mo		
P.S.	Relative	Cadaver	Cadaver	Cadaver	[3]0 mo	2 mo	1.5 mo	[2]18 days

[1] Living with good renal function at present.
[2] Patient deceased.
[3] Rejected kidney on day of transplant.
[4] Rejected last kidney on dialysis.

necessary. Each patient is evaluated utilizing clinical and laboratory data daily to determine the necessity for further irradiation. The results of repeat irradiation for the single kidney transplants are given in Table 4. It should be noted that the greater the number of treatments received by the patients, the less chance for success. This could be explained on the basis that the additional radiation was necessary because of continued rejection of the grafted kidney. Of the 65 patients receiving additional radiation attempting to reverse the rejection phenomena, 42 are living and 23 are deceased.

Table 6

Total body irradiation as primary immunosuppression

Year	Patient	Age (years)	Donor	Living	Dead	Dose in R	Survival
1963	E.A.	28	Relative		—	[1]150	1 mo
1962	G.B.	25	Cadaver	—		[2]150	7 yrs 2 mo
1962	J.C.	15	Relative		—	[3]300	1 mo
1962	M.D.	19	Relative	—		[4]150	7 yrs 1 mo

[1] Received 150 R to spleen as well.

[2] Received 200 R to transplanted kidney; second kidney transplanted in April 1964 and 600 R given to kidney.

[3] Received 400 R to kidney as well.

[4] Received 150 R to spleen and 100 R to kidney in November 1962, 150 R to kidney in March 1966 and 300 R in January 1967; had second and third transplants in May 1967 and received 600 R to kidney in May 1967; had fourth transplant in September 1967 and received 1 200 R to this kidney.

Twenty-three patients received more than one kidney due to rejection of previous allografts. Two patients received 4 kidneys, and one is still alive.

Twenty-one of the 23 patients with a second, or more, kidney allograft received the graft from a cadaver. Nine of these multiple transplant patients have good renal function at the time of this report, 11 have died, and 3 rejected their most recent cadaver transplant and are being maintained on dialysis. A total of 38 cadaver renal allografts were used in maintaining these 23 patients (Table 5).

The first 4 patients transplanted in late 1962 and early 1963 received total body irradiation prior to the transplant. These patients are listed in Table 6. The first patient, J.C., received 300 R measured in air to the midline axis of her body in one exposure. She died after slightly less than one month, her death complicated by evidence of marked bone marrow depression which was attributed to the total body irradiation. The next 3 patients received 150 R of total body irradiation. Two of these (G.B. and M.D.) still survive. G.B. received an initial graft from a cadaver and M.D. has received three successive cadaver kidneys after rejection of her mother's kidney.

A group of patients in 1963 and early 1964 received irradiation to their spleen in addition to the kidney irradiation. This was performed in an attempt to improve control of the immune response by the host against the transplanted kidney. It was believed that by irradiating the spleen of the recipients the afferent and efferent arcs of the immune response could be suppressed and that survival

Table 7

Irradiation of kidney and spleen as primary immunosuppression

Year	Patient	Age (years)	Donor	Living	Dead	Dose in R		Survival
						Kidney	Spleen	
1963	J.B.	20	Relative		—	750	150	5 mo
1963	B.B.	18	Nonrelative		—	600	150	2 mo
1963	D.B.	44	Nonrelative		—	900	1 050	3 weeks
1964	J.G.	10	Relative	—		750	150	5 yrs 6 mo
1963	S.G.	23	Relative		—	1 050	150	3 mo
1963	H.H.	37	Nonrelative		—	1 050	150	3 weeks
1963	P.H.[1]	11	Relative	—		1 050	150	6 yrs 9 mo
1964	W.L.	17	Relative	—		1 050	150	5 yrs 7 mo
1963	R.R.	35	Relative		—	1 100	150	4 mo
1963	C.S.	30	Relative		—	600	150	
1963	C.S.	30	Cadaver			900	150	11 mo
1964	R.S.	29	Cadaver		—	1 050	150	3 yrs 7 mo
1963	J.W.	15	Relative	—		600	150	6 yrs 7 mo
1963	A.W.	22	Relative		—	750	150	5 mo

[1] Has since had second and third kidney transplants.

might be improved. The early results did not substantiate this theory and the technique was abandoned in 1964 (Table 7).

Extracorporeal irradiation was first used in 1965 in patients undergoing rejection (Table 8). It has been used in a total of 7 patients to date. Six of these patients are deceased and one is living.

Antilymphocyte serum (ALS) was administered to 11 patients, who were undergoing rejection (Table 9). Five patients are still living with their first transplants for periods ranging from 19 months to 26 months.

This series of patients treated with routine irradiation post-transplant and irradiation for rejection crises is the largest group of kidney transplants treated in this manner. The majority of kidney transplant patients in other centers do not receive irradiation at any time.

The results of cadaver transplants at our institution using irradiation are superior to those of other centers not using irradiation, but other factors such as operative technique, methods of preservation, are also important in determining success of the transplant procedure.

Table 10, from the Sixth Report of the Human Kidney Transplant Registry, presents a summary of the results of all the accumulated kidney transplant in-

Table 8

Patients receiving irradiation to transplanted kidney plus ^{90}Sr shunt extracorporeal irradiation and anti-lymphocyte serum (ALS)

Patient	Donor	Number of transplants	Living	Dead	Period when ALS given		Survival
					Acute rejection < 4 months	Chronic rejection > 4 months	
H.B.[1]	Cadaver × 2	2		—	—		23 months
R.C.	Relative	1		—	—	—	6 months
S.G.[2]	Cadaver × 2	2		—	—		12 months
L.H.[3]	Cadaver × 2	2		—	—	—	14 months
E.R.[4]	Relative and cadaver × 2	3		—	—	—	45 months
S.S.[5]	Relative and cadaver × 2	3	—			—	41 months
P.S.[2]	Relative and cadaver × 3	4		—	—		25 months

[1] Received shunt for acute rejection of first and second kidneys.
[2] Received shunt for acute rejection of second kidney.
[3] Received shunt for acute and chronic rejection of first kidney only.
[4] Received shunt for chronic rejection of first kidney and acute rejection of second kidney.
[5] Received shunt for chronic rejection of first kidney.

formation as of January 1, 1968 (1 741 renal transplants). That report divided transplants as prior to January, 1966, and after that date, and evaluated the results accordingly. It was pointed out in that report that the host's acceptance of fresh cadaver kidney transplants had greatly improved in the past several months compared with experience prior to January, 1966, probably as a result of better pre-transplant organ preservation and better methods of immunosuppression. There had been little improvement in the parent kidney host's acceptance, but a moderate amount of improvement in the sibling kidney host's acceptance, was noted. This latter improvement was probably on the basis af perfecting methods of immunosuppression as well as the development of tissue-typing techniques. It should be pointed out, however, that in our experience, tissue-typing has not significantly improved transplant 1-year survival as evaluated at this time (Table 11). Finally we have evaluated the '5-year survival' in our kidney transplants: of the 52 patients transplanted during the period August 1962 to June 1964, 22 are living (5 of these have had multiple transplants) and 30 are deceased. The 5-year survival (through December 1969) was 42.3 %.

Table 9

Patients receiving irradiation to transplanted kidney and antilymphocyte serum (ALS)

Patient	Donor	Number of transplants	Living	Dead	Period when ALS given		Survival
					Acute rejection <4 months	Chronic rejection >4 months	
R.A.[1]	Relative and cadaver	2	—		—		54 months
M.A.	Cadaver	1		—	—		3 months
E.B.[2]	Cadaver	1	—		—	—	26 months
B.C.[1]	Relative and cadaver	2		—	—		19 months
M.D.[3]	Relative and cadaver × 3	4	—		—		85 months
W.F.[2]	Cadaver	1	—		—		20 months
H.F.[2]	Cadaver	1	—		—		19 months
C.J.[2]	Cadaver	1	—		—		26 months
E.J.	Relative	1	—			—	19 months
M.P.[4]	Relative and cadaver	2	—			—	47 months
P.S.[5]	Relative and cadaver × 3	4		—	—		25 months

[1] ALS given for acute rejection of second kidney only.
[2] ALS given on day of transplant.
[3] ALS given for chronic rejection of first kidney only.
[4] ALS given on day of transplant of third and fourth kidneys.
[5] ALS given for acute rejection of fourth kidney only.

Insofar as heart transplantations are concerned, no definite regimen for initial immunosuppression of prevention of rejection has been developed in the 5 heart transplants that have been carried out at this institution. The most important immunosuppressive agents are antilymphocyte serum, immuran and prednisone with radiation an adjunct. Rejection here is of course a major problem and is characterized clinically first by a precordial friction rub and then progressive congestive failure and by a fall in voltage and arrhythmia. Because of the possibility that fluid accumulation in the pericardium may be the cause of the low voltage, ECG changes from a myocardial electrode are felt to be more reliable. Current studies are underway to utilize enzyme changes. Preliminary investigation seems to demonstrate that elevations in bands I and II of the LDH (lactic dehydrogenase) isozyme and band I of the CPK (creatine phosphate kinase) isozyme may afford help in the detection of rejection crisis.

Table 10

Cumulative kidney transplant survival to January 1968 — (From Kidney graft survival rate improving, J. Amer. med. Ass. 206 (1968), 25)

Donor	Number of transplants	Survival (per cent)	
		1 year	2 years
Monozygotic twin	42	90	88
Dizygotic twin	14	79	51
Sibling	285	68	63
Parent	455	62	54
Other blood relative	34	61	61
Living unrelated	151	23	19
Cadaver	760	35	26
Total	1 741		

Table 11

Comparison of 1-year survival before and after the introduction of tissue typing

	Donor		Total	Number surviving one or more years
	Relative	Cadaver		
Patients transplanted in 1966 before tissue typing	14	10	24	19 (79.2 %)
Patients transplanted June 1967 to May 1968 after tissue typing	12	6	18	13 (72.2 %)

Our first patient was treated with the alternate day treatment technique utilizing ^{60}Co (80 cm FSD, 15 cm × 15 cm anterior thoracic field) commencing with the first post-transplant day. He only received 3 treatments of 150 rad surface dose each (100 rad each to the graft calculated at 10 cm) prior to rejecting on the seventh post-transplant day. It is now felt that his dose of antilymphocyte serum and steroids was not sufficient. In addition, the radiation dose was not equivalent to the dose used on the kidney since we were calculating maximum dose and not depth dose and this was not sufficient to help prevent rejection.

Since then, 4 more transplants have been done. One was not treated with irradiation and rejected. One was treated intermittently with 3 treatments 150 rad depth dose (through a 15 cm × 15 cm anterior thoracic port) each on nonconsecutive days for two rejection episodes and rejected on the second episode.

One patient was successfully treated with irradiation, increased prednisone, and antilymphocyte serum. He received 2 treatments of 150 rad (at 13 cm depth through a 15 cm $\times$15 cm anterior thoracic port) on alternate days at the time of his second rejection which occurred two months after transplant. He had a good response with reversal of the bundle branch block that had developed and is doing well now more than one year after the rejection and the transplant. Our 5th heart transplant patient was treated on the 9th and 10th days post-transplant because of threatened rejection as evidenced by lethargy, fatigue and a pericardial rub, a gallop rhythm and decreased voltage on ECG. He received 300 rad twice each day delivered through anterior and posterior 14 cm $\times$ 14 cm thoracic fields. He responded to this treatment in addition to other agents used. Approximately one month later he suffered another rejection crises and despite 2 more radiation treatments in addition to other immunosuppressive agents, he expired due to rejection. Despite this outcome this experience seems to confirm our findings in the dog heart transplant experiments that doses of 300 rad are more effective than lower doses in ameliorating the rejection.

Conclusion

Radiation has been used clinically as a method of immunosuppression in kidney transplants as total body irradiation, locally to transplanted kidney, and extracorporeally to the circulating blood. Because of high mortality of total body radiation, it has been abandoned in clinical practice. Local graft irradiation has been used successfully clinically in transplantation of the kidney and the heart. At our institution, it is used sequentially in the early kidney transplant period and is also used during periods of accelerated rejection. Experimental data supports its effectiveness as an immunosuppressive agent. Extracorporeal radiation of the circulating blood has also been shown experimentally to be an effective immunosuppressant. Its limited use thus far in man has shown that it is effective in reversing some episodes of accelerated rejection, but there is no effect on chronic rejection. Both of the latter methods of radiation serve as a useful adjunct to the basic immunosuppression armamentarium of the transplant. Thus far in the 5 human heart transplants at this institution, radiation has been used successfully in only two patients and this was for threatened rejection after a successful transplant. In future human heart allotransplants we would continue to use radiation in higher doses than we had before and earlier in the course of treatment.

It must be emphasized that radiation is a complementary method of immunosuppression in organ transplant and cannot sustain prolonged allogenic transplant survival when used alone.

SUMMARY

The human kidney and heart transplants performed at the Medical College of Virginia since 1962 are discussed. Out of 140 patients with kidney transplants 81 survived and of 5 heart transplants 1 survived. Kidney transplants are routinely treated with irradiation post-operatively to the graft site and receive further irradiation for rejection crises. Irradiation to cardiac transplants is used for rejection. Results of irradiation and other agents used in immunosuppression in the treatment of heart and kidney transplant rejections are discussed.

ZUSAMMENFASSUNG

Die menschlichen Nieren- und Herztransplantationen, die seit 1962 an der Medizinischen Hochschule von Virginia ausgeführt worden sind, werden besprochen. Von 140 Patienten mit Nierentransplantation haben 81 und von 5 Patienten mit Herztransplantation einer überlebt. Nierentransplantierte werden routinemässig postoperativ durch Bestrahlung der Transplantationsseite behandelt und erhalten weitere Bestrahlung bei Abstossungs-Krisen. Bestrahlung von Herztransplantierten wird bei einer Abstossung verwendet. Ergebnisse von Bestrahlung und anderen Mitteln, die zur Unterdrückung der Immunität bei der Behandlung der Abstossung von Herz- und Nierentransplantaten verwendet werden, sind besprochen.

RÉSUMÉ

Les auteurs étudient les greffes de rein et de cœur humains effectuées au Medical College de Virginie depuis 1962. Sur 140 sujets ayant subi une greffe de rein, 81 ont survécu et sur 5 sujets ayant subi une greffe de cœur, un a survécu. Les greffes de rein sont traitées de façon habituelle par une irradiation postopératoire du siège de la greffe et subissent une autre irradiation pour les crises de rejet. L'irradiation des greffes cardiaques est utilisée en cas de rejet. Les auteurs examinent les résultats de l'irradiation et des autres agents utilisés pour l'immuno-suppression dans le traitement du rejet des greffes de cœur et de rein.

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