

Elevation in Urinary and Blood Histamine Following Clinical Renal Transplantation

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A SUBSTANTIAL amount of evidence has been gathered to suggest that an increase in the intracellular formation and release of histamine is involved in tissue and organ allograft rejection^{8, 10, 12, 13, 15, 19} and that pharmacologic measures to control these processes may lead to a prolongation of allograft survival and to a reduction of antibody formation in experimental situations.^{4-7, 11, 14, 18}

In 1968, the senior author, with Chang and Hume,⁹ reported the results of 65 random spot-checks of the 24-hour urinary excretion of histamine in 33 renal transplant patients. The studies were carried out from 7 days to 49 months after transplantation. These determinations were carried out too infrequently per patient and were too widely separated in time to indicate a trend in dynamic functional changes as related to the metabolism of this vaso-active amine. Nonetheless, the levels of urinary excretion of histamine did appear in the majority of patients to be lower than normal. Poorer renal function was associated with lower levels of excretion.

In the present study, frequent determinations of both blood and urinary levels of histamine were obtained in a smaller group of renal transplant patients and were concentrated largely in the initial month after transplantation.

Method of Study

Eighty-five blood histamine determinations and 131 24-hour urinary excretions of histamine were obtained in ten patients in the comparatively early period after renal transplantation. Three of the transplants were from related living donors and seven kidneys were cadaveric in origin. Three of the cadaveric kidneys were harvested elsewhere on the basis of cardiac death and had longer periods of shock and warm ischemia and four were harvested at this institution on the basis of neurological death with virtually no warm ischemia and very limited periods of cold ischemia.

From five to 30 urinary excretions of histamine studies and from three to 36 blood histamine levels were obtained per patient. Blood histamine levels were determined by the method of Shore, Burkhalter and Cohn.¹⁷ Twenty-four hour urine specimens were collected in 10 ml. of six normal HCl and were assayed for histamine by the ion-exchange butanol extraction method of Oates, Marsh and Sjoerdsma.¹⁶ The findings were placed on data flow sheets and correlated with other biochemical and physiological changes.

The senior author and associates, in the earlier study, found the normal range for the 24-hour urinary excretion of histamine to be from 30 to 85 $\mu\text{g.}$ with an average of 49 $\mu\text{g.}$ per 24 hours. Studies of 24-hour human urinary excretion of histamine, using this same method of Oates, Marsh and

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Sjoerdsma, in normal subjects by Oates and associates, by Beall¹ and by Gilbert and associates,³ gave values of 43.3, 46.4 and 42 μ g. per 24 hours.

The normal whole blood level of histamine in human subjects in our laboratory has been found to be 66.7 ± 9.4 nanograms per ml.

All patients received azathioprine and corticosteroids for immunosuppression. They also were given isonicotinic acid hydrazide (INH) and Histadyl, an antihistamine. All four drugs were started at the time of transplantation with the exception of the patient, A. Z., whose initial doses of INH and Histadyl were delayed three days. The dosages of INH and Histadyl were 300 mg. and 75 mg. daily given in split three times daily doses. Each patient received a total of 600 rads of local radiation to the transplant in the initial seven days after transplantation.

Results

All but one of the ten patients whose urinary histamine was studied had a clear elevation in the urinary excretion of histamine in the initial month after transplantation. The one recipient whose urinary excretion of histamine was not elevated had received a kidney which had been harvested elsewhere on the basis of cardiac death and which never functioned with a blood urea nitrogen below 130 mg./100 ml.

All of the elevations occurred during periods of reduction in the levels of corticosteroid administration. In six of the nine patients the elevation in urinary histamine excretion was associated with an increase in the creatinine or blood urea nitrogen. The creatinine was elevated in five of the six and in one only the blood urea nitrogen was elevated. Two of the three with increased urinary histamine excretion but no change in blood urea nitrogen or creatinine had cardiac death kidneys that were salvaged elsewhere and functioned poorly. One of these patients did not have a cre-

atinine below 5.0 in the first 30 days after transplantation. His 24-hour urinary excretion of 180 μ g. of histamine was based on a urinary output of 1,000 ml. 12 days after transplantation. The other patient with poor function did not have a urinary output above the 140 to 300 ml. per day level until 22 days after transplantation. The urinary excretion of this patient went from nine and 42 nanograms per ml. on days 4 and 6 after transplantation, and to 229 and 290 on days 9 and 11 before returning to 24 on day 13.

The time of the initial post-transplant elevation in the urinary excretion of histamine in the nine patients ranged from five to 24 days after transplantation and averaged 12 days post-transplant. In four patients, the increase in urinary histamine excretion occurred 1 and 2 days prior to the increase in creatinine or BUN levels and in one patient the increase in urinary histamine was observed on the day of an increase in creatinine. In one case it was not possible to determine clearly the temporal relationship because of insufficiently frequent urinary histamine and creatinine determinations at critical periods.

From two to 36 whole blood histamine determinations were obtained in eight transplant recipients. Seven of these also had had urinary histamine studies. Only one of the eight patients was found at any time to have an elevation in the level of blood histamine. This initially was at the onset of a severe rejection episode and later during the renal insufficiency associated with unremitting rejection.

In all of the eight recipients whose whole blood histamine was studied, the histamine level was depressed below normal, often in the 20 to 35 nanogram per ml. range, in the early post-transplant period when the level of corticosteroid administration was high. On tapering of the corticosteroid, the blood concentrations of histamine rose to more normal levels.

Alterations in urinary and blood histamine levels encountered in individual renal transplants are more meaningful when correlated with other related clinical and laboratory data. Several patients in this study have been selected for more detailed presentation as follows:

Case Reports

Case 1. J. M., a 21-year-old woman, received a C-match renal transplant from her father in October 1968. In the initial 51 days after transplantation, 30 24-hour urinary histamine and 18 whole blood histamine determinations were obtained. The transplant was slow to achieve normal levels of function. It was feared that corticosteroids had been tapered too rapidly and they were raised to the 200 mg. of prednisone levels on the 10th day. As they were being reduced from this point there was a great increase in the urinary excretion of histamine on the 13th day with a massive peak elevation to 1,840 µg./24 hours on the 14th day (Table 1). At this time there also was a temporary increase in the creatinine level.

A distinct, though mild, rejection episode occurred on the 49th day after transplantation. Two days earlier there had been a marked increase in the urinary excretion of histamine (Table 2).

In the early post-transplant period of high corticosteroid administration, ten whole blood histamine levels from three to 17 days after operation were in the subnormal 24 to 30 nanograms per ml. range. On the 42nd post-transplant day, 7 days after the prednisone dosage had been stabilized at 30 mg./day, the whole blood histamine was 81.

Twenty months after transplantation this patient's blood urea nitrogen is 15 mg./100 ml. and the creatinine is 1.0 mg./100 ml.

Case 2. S. C., a 49-year-old woman, received a B-match kidney transplant from her brother in September, 1969. Seven 24-hour urinary and three whole blood histamines were obtained in the first 24 days after transplantation.

There was excellent early function of the transplant. On the third post-transplant day, the BUN and creatinine were 20 and 1.2 and on the next day they were 15 and 1.0. An acute rejection episode occurred on the 15th post-transplant day. On the day before a marked increase in the urinary excretion of histamine had occurred (Table 3). The BUN was in the 15 to 19 range from the 11th through the 14th post-transplant day. On the 15th, 16th and 17th, the BUN rose to 23, 34 and 40 mg./100 ml.

TABLE 1. *Correlation of Urinary Excretion of Histamine with Creatinine Levels and Prednisone Administration in Early Post-transplant Period in Case 1 (J. M.)*

Post-op. Day	Urine Histamine (µg./24 hrs.)	Creatinine (mg./100 ml.)	Prednisone (mg./24 hrs.)
6	60	6.2	80
8	48	4.2	80
9	73	4.0	70
10		3.8	200
11	82	3.2	200
12	101	2.3	120
13	323	2.0	120
14	1838	2.5	120
16	315	1.4	100
18	50	1.3	90
19	78	1.4	90
20	101	0.9	80
22	72	1.0	60

The three blood histamine studies were done within the first 7 post-transplant days, during the period of high corticosteroid administration. They were lower than normal, in the 26 to 30 nanogram per ml. range.

Six months following transplantation, the patient's BUN is 19 and creatinine is 1.3.

Case 3. K. F., a 19-year-old woman, received a B-match renal transplant from her mother in Sep-

TABLE 2. *Urinary Histamine Excretion and Related Data in Second Post-transplant Month in Case 1 (J. M.)*

Post-op. Day	Urine Histamine (µg./24 hrs.)	BUN (mg./100 ml.)	Creatinine (mg./100 ml.)
39	48	18	1.0
40		20	1.0
41	83	22	
42	53	22	1.0
43		22	0.9
44		23	0.8
45			0.9
46	775	23	1.0
47		25	1.2
48		25	1.1
49		43	1.5*
50		40	1.4
51	170	28	1.5
52		32	1.3
53		32	1.2

* 30 mg./day of prednisone were given until this day, when levels were raised to 60 mg./day through the 53rd day.

TABLE 3. *Urinary Histamine Data in Case 2 (S. C.)*

Post-op. Day	Urine Histamine ($\mu\text{g.}/24$ hrs.)	Creatinine (mg./ 100 ml.)	Prednisone (mg./ 24 hrs.)
1	96	1.8	240
7	27	1.5	60
9		1.1	50
10		1.1	50
11	121	1.0	45
14	464		30
15		1.8	260
16	95	2.4	240
17		2.2	240
18		2.1	120
21	51	1.6	80
23	55	1.3	70

tember 1969. Eight 24-hour urinary histamine determinations were carried out in the initial 17 days after transplantation.

The early function of the transplant was good. In the 5 to 16-day post-transplant period, a significant increase in the urinary excretion of histamine occurred (Table 4). Although the BUN in this period rose from 10 to 27, the creatinine remained in the 0.8 to 1.0 range.

The patient lived in a distant and remote mountain community. On her release from the hospital to return home, four months post-transplant, her BUN and creatinine were 21 and 1.1. She recently returned to the hospital with a severe rejection episode of unknown duration and is being studied and treated for this at the present time.

Case 4. C. C., a 25-year-old man, received a D-match neurological death cadaver renal transplant in October 1968. Nineteen 24-hour urinary histamine excretions and 8 blood histamine levels were obtained. All but one of the determinations

TABLE 4. *Urinary Histamine Levels Post-transplant in Case 3 (K. F.)*

Post-op. Day	Urine Histamine ($\mu\text{g.}/24$ hrs.)	BUN (mg./ 100 ml.)	Prednisone (mg./ 24 hrs.)
3		12	180
4	98	10	120
5	165	18	120
6	76	18	120
7	182	23	100
9	134	26	70
11	312	25	60
13	312	27	50
16	181	15	35

were made in the initial 29 days after transplantation.

Good urinary outputs were achieved at once and there was steady improvement in function. A mild BUN elevation occurred in the 35 to 37 day post-transplant period and this episode was associated with a marked increase in the urinary excretion of histamine (Table 5). Unfortunately no urinary histamines were obtained in the 6 days before the day of the detected increase and it is not possible to identify that initial day of increased histamine excretion nor to correlate this temporally with the changes in creatinine levels. At the end of the 37th post-transplant day, after the creatinine level was reported, an additional 500 mg. of prednisone were given as a single one-day-only dose.

The blood histamine levels remained within normal limits. The patient currently has a BUN of 22 and a creatinine of 1.6 20 months after transplantation.

Case 5. D. H., a 35-year-old man, received a C-match neurological death cadaver transplant in June 1969. The transplant functioned well from the beginning. The creatinine was 1.7 on the third and 1.2 on the fifth post-transplant days. Nine urinary and two blood histamine determinations were carried out.

An increase in the 24-hour urinary excretion of histamine was observed on the 10th post-transplant day (Table 6). On this day the creatinine had risen to 1.7 from 1.2 on the previous day. A second series of elevations in urinary histamine excretion occurred in the 15 to 19 day post-transplant period. The BUN in this period rose from 27 to 35 while the creatinine remained essentially unchanged.

On the second post-transplant day the blood histamine during heavy corticosteroid administration was 59 nanograms per ml. and with tapering of the corticosteroids the level had risen to 104 on the 24th day. This patient has a BUN of 18 and a creatinine of 1.1 12 months after transplantation.

Case 6. D. B., a 19-year-old man, received a C-match neurological death cadaver renal transplant in October 1969. There was excellent early function and diuresis. Six urinary and three blood histamine levels were obtained.

An increase in the urinary excretion of histamine was found on the 13th and 16th post-transplant days (Table 7). This occurred during corticosteroid tapering but was not associated with any evidence of rejection.

Blood histamine levels were depressed to the 34 to 36 nanogram per ml. in the early post-transplant days of high corticosteroid administration.

This patient has a BUN of 26 and a creatinine of 1.4 eight months after transplantation.

Case 7. A. Z., a 30-year-old man, received a C-match neurological death cadaver renal transplant in May 1969. There was good early function with a satisfactory diuresis. The creatinine was 1.3 on the fourth post-transplant day and 1.1 on the seventh. Thirty-six blood and 27 urinary levels of histamine were obtained during the first 3 months after transplantation.

A very severe rejection episode started on the 24th post-transplant day. On the day before a marked increase in the urinary excretion of histamine occurred (Table 8). The BUN did not start to rise until the 28th day. A transplant biopsy on the 30th post-transplant day showed necrotizing glomerulitis. As transplant function deteriorated rapidly, the urinary excretion of histamine fell to low levels, the last ten determinations ranging from 3 to 9 $\mu\text{g./24 hours}$. Transplant nephrectomy was carried out 88 days after transplantation.

The blood level of histamine fell from 100 nanograms per ml. immediately before and after the transplant to 35 on the fourth post-transplant day in association with heavy corticosteroid administration. It increased to 89 with a significant fall in urinary output at the time of the mild first rejection episode on the 7th post-transplant day. A significant increase in the blood concentration of histamine was recorded on the 21st post-transplant day, two days before the massive 24-hour urinary outpouring of 3,200 $\mu\text{g.}$ of histamine. With progressive transplant failure and despite intermittent hemodialysis, the blood levels of histamine rose and remained elevated, reaching a peak elevation of 213 nanograms per ml. on the 72nd post-transplant day (Fig. 1).

This patient died, anephric, following hyperacute rejections of second and third cadaver donor renal transplants. Massive doses of heparin at the time of the third transplant did not prevent the hyperacute rejection of this kidney.

Case 8. R. W., a 22-year-old man, received a C-match neurological death cadaver renal transplant in April 1969. Early function was slow in returning to normal levels. Ten blood histamine levels were determined during the initial month after transplantation. Blood histamine levels were depressed during the period of heavy corticosteroid administration (Fig. 2). The level, which remained in the 29 to 32 nanograms per ml. range from nine to 15 days after transplantation returned to 97 eight days after the stabilization of prednisone dosage at 30 mg. per day. This transplant, after 14 months, functions with a BUN of 19 and a creatinine of 1.4.

TABLE 5. *Urinary Histamine Levels Following Cadaver Donor Transplant in Case 4 (C. C.)*

Post-op Day	Urine Histamine	Creatinine	Prednisone
13	88	2.0	160
14	98	2.0	160
15	71	1.7	140
16	48	1.7	140
17	97	2.0	120
18	106	1.6	120
19	73	1.6	100
21	84	1.6	90
23	66	1.3	80
25	66	1.4	90
27	59	1.6	60
28	66	1.7	60
30	96	1.6	50
32		1.6	50
33		1.7	40
34		1.7	40
35		2.2	40
36		2.1	40
37	1,061	2.8	540
39		2.2	40

Discussion

This study involved a more concentrated evaluation of histamine metabolism post-transplant in a smaller number of recipients than did the earlier report by the senior author, Chang and Hume. In the study reported here, both urinary and blood histamine levels were monitored by frequent de-

TABLE 6. *Urinary Histamine Excretions and Related Data in Case 5 (D. H.)*

Post-op. Day	Urine Histamine ($\mu\text{g./24 hrs.}$)	Creatinine (mg./100 ml.)	Prednisone (mg./24 hrs.)
5		1.2	90
8	30	1.2	80
9		1.2	80
10	465	1.7	80
11		1.2	200
12	51	1.1	170
14		1.2	100
15	778	1.2	80
17	850	0.6	80
19	1,028	1.2	70
22	70	1.1	60
24	33	1.0	50
26	54	1.1	50

TABLE 7. *Urinary Histamine Excretion and Related Data in Case 6 (D. B.)*

Post-op. Day	Urine Histamine ($\mu\text{g./24 hrs.}$)	Creatinine (mg./100 ml.)	Prednisone (mg./24 hrs.)
2	67	4.1	240
4	113	2.9	100
9	53	1.3	70
11	110	1.4	70
13	150	1.4	60
16	473	1.2	40

terminations. In the prior study, the average number of histamine determinations per patient averaged two, while in the present study they averaged 20. In the earlier study, all but four of the determinations were obtained more than 1 month after transplantation. In the present study the bulk of the determinations were in the first month after transplantation. Only two of the 11 recipients had more than four studies after the first month.

TABLE 8. *Urinary Excretion of Histamine and Related Data in Case 7 (A. Z.)*

Post-op. Day	Urine Histamine ($\mu\text{g./24 hrs.}$)	Creatinine (mg./100 ml.)	Prednisone (mg./24 hrs.)
4	108	1.3	100
7	109	1.1	50
8		1.7	100
9	77	1.7	100
10			100
11	84	2.0	200
14	108	1.3	100
15		1.2	80
17		1.1	60
18	54	1.2	60
21		1.0	45
22		1.1	40
23	3,200		35
24		1.4	30
25	610	1.5	30
26		1.8	60
29		2.7	120
30		4.0	190
31	5.3	3.9	500
32	25	4.3	150
33	19		120
35	15	7.5*	100

* Hemodialysis was started on the 37th post-transplant day.

In the study reported here, high doses of corticosteroids were found to be associated with depressed blood histamine concentrations and with lower urinary excretion of histamine. It also was of considerable interest that the increase in the urinary excretion of histamine, in all of the ten patients in which it occurred, took place at a time corticosteroid administration was being lowered. In many of the recipients, the elevation in the urinary excretion of histamine was associated with an upward change in the levels of creatinine, BUN or both. The increase in histamine excretion tended to occur one to two days before changes in BUN or creatinine could be detected.

The levels of urinary excretion of histamine when elevated, were markedly higher than the 45 $\mu\text{g./24-hour}$ average encountered in normal subjects. The increase, at times, was as much as 40 to 70-fold over normal values. This marked increase in the urinary excretion of histamine on withdrawal of corticosteroids also has been observed in human heart transplantation and in experimental canine heart transplantation.¹⁰

As observed in the previous clinical study, reduction in renal transplant function of a severe degree was associated with a marked depression in the urinary excretion of histamine. Reduced ¹⁴C histamine and histamine metabolites in the urine of a uremic patient after the injection of ¹⁴C histamine were reported by Beall and Van Arsdell² in 1960. Urinary excretion of histamine following renal transplantation and bilateral nephrectomy without immunosuppression in dogs has been found to be markedly depressed in the later stages of rejection and diminished transplant function.¹⁹

The blood concentration of histamine was of little help in monitoring histamine metabolic changes following transplantation. Blood levels were increased in only one recipient and then only at the time of a severe rejection episode with biopsy-con-

firmed necrotizing glomerulitis and late when transplant function largely had ceased (Case 7). We have encountered similar findings in unmodified canine renal allografts with bilateral recipient nephrectomy. Blood histamine levels in these dogs did not start to rise until several days after the rise in BUN and creatinine had started.¹⁹

None of the patients exhibited any systemic physiological changes which might be associated with an increase in histamine liberation. In this regard it should be pointed out that all of the recipients were receiving the anti-histamine, Histadyl, during the period of this study.

Daily 24-hour histamine excretion studies would appear to be of considerable value in the first month after transplantation and possibly at regular intervals thereafter. A clearer picture could be obtained of the temporal relationship between the elevation in the urinary excretion of histamine and the increases in the BUN and creatinine. Furthermore, this information might be considerably helpful in recognizing and treating episodes of acute rejection before significant transplant damage has occurred.

Summary

Repeated blood and urinary histamine determinations were carried out on eleven renal transplant patients largely in the first month following transplantation. On average 20 determinations per patient were obtained.

All recipients, but one who had essentially no transplant function, were found to have significant elevations in the 24-hour urinary excretion of histamine. In all cases, the initial elevation occurred during a period of reduction of high post-transplant levels of corticosteroid administration. In the majority of cases, this elevation in urinary histamine excretion was associated with and frequently occurred prior to increases in serum creatinine and blood urea nitrogen.

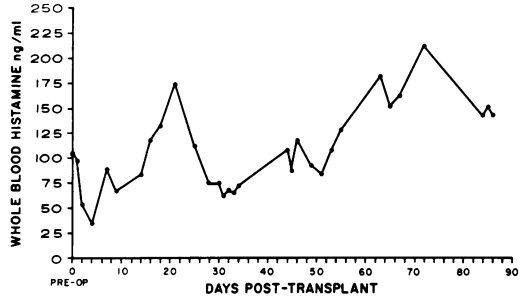


FIG. 1. Blood histamine levels following cadaver donor transplant in Case 7 (A. Z.). Histamine levels with high corticosteroid administration are depressed to the 35 ng./ml. level by Day 4. A moderate rejection occurred on Day 7 with increase in creatinine from 1.1 to 1.7. The very severe rejection episode of the fourth week which led to the loss of the kidney was initiated by the elevation in blood histamine on the 21st post-transplant day. A marked increase in urinary histamine excretion was encountered on the 23rd day. Two days later the creatinine and BUN started to rise. Blood levels of histamine remained high during the period of deteriorating transplant function which led to nephrectomy.

Large doses of corticosteroids appeared to depress both the blood levels of histamine and the amount of histamine excreted in the urine in a 24-hour period.

Severe reduction in transplant function reduced markedly the amount of histamine excreted in the urine. Only when this occurred or when there was an unusually severe rejection episode with diminished urinary output did the blood levels of histamine rise.

It was concluded that blood histamine determinations were of little practical value

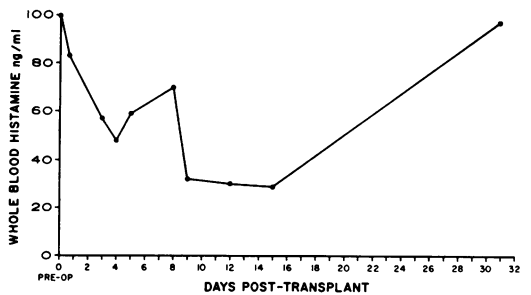


FIG. 2. Blood histamine levels following cadaver donor transplant in Case 8 (R. W.) showing depression in levels during early post-transplant period of high corticosteroid administration. Prednisone dosage was stabilized at 30 mg./day level on the 23rd post-transplant day.

in monitoring alterations in histamine metabolism in renal transplant patients in comparison with the information to be gained from daily 24-hour urinary histamine assays.

The 10 to 70 fold elevations in the urinary excretion of histamine above normal levels were impressive. Further studies may indicate more clearly the value and significance of these determinations.

The observed increases in the urinary excretion of histamine following transplantation suggest that the use of antihistamines may be of value, at least in the early post-transplant period as the large initial doses of corticosteroids are being reduced.

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