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☐ Orginal Article ☐

Studies on Lymphocyte Subpopulations and Cell-mediated Immunity in Patients with Chronic Renal Failure

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Several parameters of cell-mediated immunity in thirty-eight patients with end stage chronic renal failure were measured including total lymphyocytes, B-and T-lymphocytes, T-cell subsets and the mitogenic response to PHA and Con A at three different times; before dialysis, 3 months and 12 months after dialysis treatment. There were no significant differences in the absolute numbers of peripheral leukocytes between each patient and the control group. But the absolute numbers of lymphocytes of each patient group were significantly reduced compared to the control group (p<0.01). The proportion of peripheral blood active T cells and helper T cells was significantly reduced both in the predialysis uremic and dialysis populations compared to the control group, although the helper/suppressor (OKT4/OKT8) ratio was not different between each patient and the control group except for a lower ratio in the hemodialysis 12 month follow-up group (HD 12M). With respect to the PHA and Con A stimulation tests, the stimulation indices of the predialysis and hemodialysis groups were significantly lower than those of the control group. However, patients on continuous ambulatory peritoneal dialysis (CAPD) exhibited a normal mitogenic response and a lower suppressor cell removal index compared to the patients on hemodialysis, suggesting an improved cell-mediated immunity in the patients undergoing CAPD.

Key Words: Uremia, lymphocyte subset, mitogenic response, hemodialysis, continuous ambulatory peritoneal dialysis (CAPD)

Chronic renal failure is associated with significant functional alterations of the immune system (Boulton-Jones *et al.* 1973; Goldblum *et al.* 1980; Morrison 1983). Many of the complications experienced by these patients can be attributed to these altered immunologic functions. Although these defects include both the humoral and cellular immune systems, the dominant defect resides in the cell-mediated immunity which primarily involves T-lymphocytes (Morrison 1983; Osaki *et al.* 1983; Smith *et al.* 1983). The major manifestations of this suppressed cell-mediated immunity are frequent infections (Dobbelstein, 1976; Andrew *et al.*, 1980; Rutsky & Rostand, 1980), cutaneous anergy (Selroos *et al.* 1973), prolonged allograft survival (Morrison *et al.* 1963; Dammin *et al.* 1957), and an altered tumor surveillance system (Matas *et al.* 1975).

This suppressed cellular immunity can be explained by a decrease in absolute T-lymphocyte numbers, an increase in T suppressor cell activity and the inhibitory effect of uremic serum on lymphyocyte blastogenesis (Elves *et al.* 1966; Newberry *et al.* 1971; Smith *et al.* 1983). The mechanism which underlies this impairment of the cellular immune response in uremia is not well understood. The possibility has been raised that the metabolic abnormalities present in uremia may lead to an increased amount of T-suppressor substances or lead to deficiencies of substances necessary to the mounting of an immune response (Morrison, 1983). Altered adrenal cortical functions and/or protein-calorie malnutrition may also play an important role in the genesis of this defect.

The recent discovery of suppressor T cells represents a major advance in the understanding of immunoregulations (Benacerraf, 1978). Although the potential role of suppressor cell abnormality in various autoimmune disorders has been widely studied, little work has been done concerning uremic patients.

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Even though changes in the T-cell subpopulation and altered suppressor activity were reported in patients with chronic renal failure and in patients undergoing hemodialysis as compared to normal controls (Osaki *et al.* 1983; Smith *et al.* 1983), no sequential measurements of these changes were reported comparing results before and after the initiation of chronic dialysis.

Moreover, few studies are available yet concerned with these T-cell functions in patients undergoing chronic ambulatory peritoneal dialysis (CAPD) which has a greater clearance of middle molecular uremic toxins compared to hemodialysis. Middle molecules already have been shown to suppress PHA-induced lymphocyte transformation (Touraine *et al.,* 1975).

The main objective of this report is to elucidate the exact nature of the altered immune functions seen in uremic patients by studying the sequential changes in the T-lymphocyte subpopulations and lymphyocyte blastogenic responses to mitogens in these patients both prior, during and after initiation of chronic maintenance hemodialysis and peritoneal dialysis. In addition to the quantitation of numbers of suppressor and helper T cells, suppressor cell activity was measured to further characterize altered cellular immunity. An additional objective is the determination of the role of middle molecular uremic toxins in inducing altered cellular immunity by comparing the different effects of two separate dialysis methods, hemodialysis and peritoneal dialysis, on these parameters of the immune system.

SUBJECTS AND METHODS

Subjects

Thirty-eight patients with end-stage chronic renal failure were selected from among those who gave informed consent to this study at the dialysis center of Severance Hospital, Yonsei University Medical Center. They ranged in age from 22 to 67 years. Five patients were lost after the initial measurement of immunologic parameters. Twenty-four patients were managed by chronic maintenance hemodialysis and nine patients by CAPD (Table 1).

Total lymphocytes, B lymphocytes, T lymphocytes, T-cell subsets and lymphocyte mitogenic response to Phytohemagglutinin (PHA) and Concanavalin A (Con A) were measured at three different times; before dialysis, 3 months and 12 months after dialysis treatment. Normal control values for these parameters were already available from previous studies done at the Immunological Laboratory of this hospital.

Table 1. Age and sex distribution of the patients by group

Group	No. of patients (male, female)	AGE	
		Mean	Range
Predialysis	38 (28, 10)*	43.7±11.0	22-67
Hemodialysis	24 (16, 8)	43.0±11.0	22-60
CAPD	9 (6, 3)	46.0± 9.0	30-67

Data are presented as the mean ± SD

* Five patients were lost after the initial measurement of immunologic parameters.

Peripheral blood lymphocyte preparation

Lymphocytes were separated from whole heparinized blood on a Ficoll-Hypaque density gradient. The cell layer was washed 3 times in Hanks solution and suspended in McCoys 5A medium. The final cell count was adjusted to 5×10^3 cells/ul (Boyum, 1968).

The proportion of B lymphocyte was determined by the EAC-rosette forming technique. The lymphocyte suspension (0.05 ml) was added to an equal volume of a sensitized 1% sheep RBC suspension. The mixture was incubated for 30 minutes at 37 C and then centrifuged for 5 minutes at 500 x g. A drop of the suspension was placed on a glass slide and the EAC-rosette forming lymphocytes were counted (Moretta *et al.,* 1975).

Total and active T lymphocytes determinations

The lymphocyte suspension (0.05ml) was mixed with the same amount of Hanks solution containing 1% sheep RBC and 10% fetal calf serum. The mixture was centrifuged for 5 minutes at 500 X g and then incubated for 90 minutes at room temperature. The cells were left overnight and a drop of the suspension was placed on a glass slide. Total T cell count was calculated by the percent of erythrocyte (E) rosette forming cells.

Another 0.05 ml aliquot of the lymphocyte suspension was mixed with an equal amount of 10% fetal calf serum and incubated for 1 hour at 37 C. After that 0.05 ml of 1% sheep RBC suspension was added and centrifuged for 5 minutes at 500 X g. A drop of the suspension was placed on a glass slide. The active T cell count was calculated by the percent of erythrocyte (E) rosette forming cells (Moretta *et al.,* 1975).

T lymphocyte subpopulations

T cell subset of helper and suppressor cells were estimated by using specific monoclonal antibodies to these cells. After 100 ul of the lymphocyte suspension was mixed with 50 ul of phosphate buffered saline, it was stained with 10 ul of isothianate fluorescein-labeled OKT4, OKT8 monoclonal antibodies (Ortho Pharma. Corp., Raritan, N.J., USA) at 2-8 C for 30 minutes. The nucleated cells were collected by centrifugation at 300 X g for 10 minutes and the cells were resuspended in 1 ml of phosphate buffered saline, then counted under a fluorescent microscope (Reinherz & Schlossman, 1980).

Proliferation studies with mitogens

Peripheral blood lymphocytes were isolated on a Ficoll-Hypaque density gradient as described above and resuspended in McCoys 5A medium at 1000 cells/ul. We determined the blastogenic response of 2 X 10^5 cells in triplicate in a microtiter culture system with optimal concentrations of mitogens (10 ug/ml of phytohemagglutinin and concanavalin A). The cultures were labeled overnight with H3-thymidine (New England Nuclear), 1 u Ci/well and the radioactivity was measure in a beta counter (Packard Tricarb 300, Packard Co., Ill., USA) following 72 hours of incubation. The blastogenic response was expressed as a stimulation index according to the following formula:

$$\text{Stimulation Index (SI)} = \frac{\text{Counts Per Minutes in Stimulated Cultures}}{\text{Counts Per Minutes in Control Cultures}}$$

Suppressor cell removal index

The effect of spontaneous removal of suppressor cell activity during the 24 hour preincubation was measured by the subsequent responsiveness of lymphocytes to mitogens. Lymphocytes were stimulated with Con A, either at the initiation of the culture or after 24 hours of culture at 37 C. Cultures were terminated 4 days after the addition of mitogens and harvested. Uptake of H3-thymidine was measured by a beta counter, and the suppressor cell removal index was calculated according to the following formula:

$$\text{Suppressor Cell Removal Index (SRI)} = \frac{\Delta\ \text{CPM (24 h)}}{\Delta\ \text{CPM (0 h)}}$$

Δ CPM (24h); CPM preculture (24h) with mitogen–CPM preculture (24h) without mitogen

Δ CPM (0h); CPM preculture (0h) with mitogen–CPM preculture (0h) without mitogen

The lower half of the formula refers to the mitogen-induced blastogenesis of the lymphocyte (Δ CPM 0h), as in a typical blastogenesis assay with mitogen added at the onset of incubation. The upper portion of the formula refers to the mitogen-induced blastogenesis of the lymphocytes which were precultured for 24 hours in a plain culture medium before the addition of the mitogen (Δ CPM 24h). The enhancement ratio, an indicator of suppressor cell activity, was obtained by comparing the radioactivity of the two different culture plates from the 0-hour and 24-hour incubations (Aoki *et al.*, 1979).

RESULTS

Absolute Numbers of Peripheral Blood Leukocytes and Lymphocytes

The white blood cell and lymphocyte counts in the

Table 2. Absolute numbers of peripheral blood WBC and lymphocytes between each patient group and the control group

	Predialysis (n=38)	HD 3M (n=24)	CAPD 3M (n=9)	Control (n=24)
WBC	7155±2740	7082±2635	7178±1178	7433±1635
Lymphocyte	1754± 673[a]	1419± 740[a]	1493± 743[a]	3271±1218

Data are presented as the mean ± SD
HD 3M; Hemodialysis 3 Month Follow-Up Group
CAPD 3M; CAPD 3 Month Follow-Up Group
a; $p<0.01$, compared with values in the Control
n=number of subjects

Table 3. Mean percentage of total T cell, active T cell, B cell, and T cell subsets and OKT4/OKT8 ratio between each patient and the control group

	Predialysis (n=38)	HD 3M (n=24)	HD 12M (n=19)	CAPD 3M (n=9)	Control (n=10)
Total T cell	70.4±14.0	68.0±10.0	66.0± 9.3	62.0± 8.9	73.3±3.8
Active T cell	44.3±13.5[a]	36.0± 7.6[a]	36.0±10.0[a]	36.0± 9.3[a]	53.6±6.3
B cell	21.0± 7.4	21.0± 6.8	16.0± 6.7	21.0± 4.6	18.3±8.3
OKT4	46.4±14.3[b]	44.0±18.0[b]	37.0±15.0[b]	39.0±17.0[b]	62.3±6.5
OKT8	22.7± 9.5	25.0±12.0	22.0± 9.8	22.0±10.0	21.8±6.5
OKT4/OKT8	2.40±1.23	2.43±2.32	1.85±0.74[c]	2.38±1.46	2.90±0.7

Data are presented as the mean ± SD
HD 3M; Hemodialysis 3 Month Follow-Up Group,
HD 12M; Hemodialysis 12 Month Follow-Up Group
CAPD 3M; CAPD 3 Month Follow-Up Group
a; $p<0.05$, Compared with values in the control
b; $p<0.05$, Compared with values in the control
c; $p<0.05$, Compared with values in the control and other patients group
n=number of subjects

peripheral blood of end-stage renal failure patients were examined. The results as shown in Table 2 demonstrate that although the total white blood cell counts are not significantly changed in the patient groups as compared with the control, the patient groups show significant lymphopenia. The differences in the total lymphocyte counts between the patient groups and the control are statistically significant at 1% level based on t-test ($p<0.01$).

Peripheral Blood Lymphocyte Subsets

The total T-cell, active T-cell, B-cell, and T-cell subsets were examined by using the E-rossette technique, EAC-rossette technique, and OKT4 and OKT8 monoclonal antibodies. The average percentages of total T cells, active T cells, B cells, helper and suppressor T cells in the total lymphocyte population are shown in Table 3.

It is apparent that the average relative proportions of total T cells, B cells and suppressor T cells do not differ between the uremic patient groups and the control. However, the average proportions of active T cells and helper T cells are significantly decreased in the uremic patient groups compared to the control at 5% significance level based on t-test ($p<0.05$).

There is no difference in the ratio of the helper/suppressor (OKT4/OKT8) cells between the patient groups and the control except in the hemodialysis 12 month follow-up group which shows a significantly lower ratio, mainly due to decreased helper T cells (Table 3).

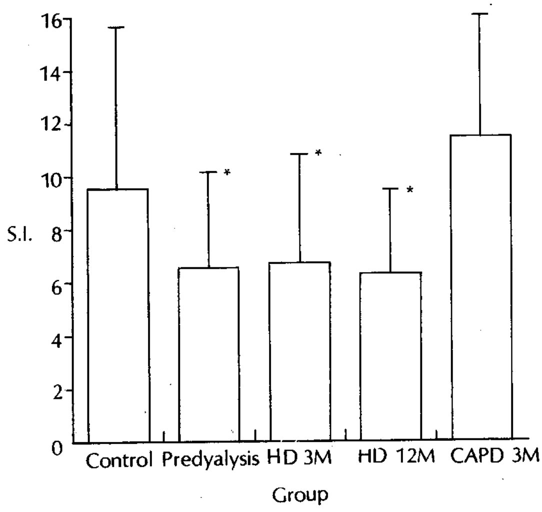

Fig. 1. *Comparison of Peripheral Blood Lymphocyte Mitogenic Response after PHA Stimulation.*
Values are mean ± SD
HD 3M; Hemodialysis 3 Month Follow-Up Group
HD 12M; Hemodialysis 12 Month Follow-Up Group
CAPD 3M; CAPD 3 Month Follow-Up Group
S.I.; Stimulation Index
**; p<0.05, compared with values in the control and CAPD 3M group*

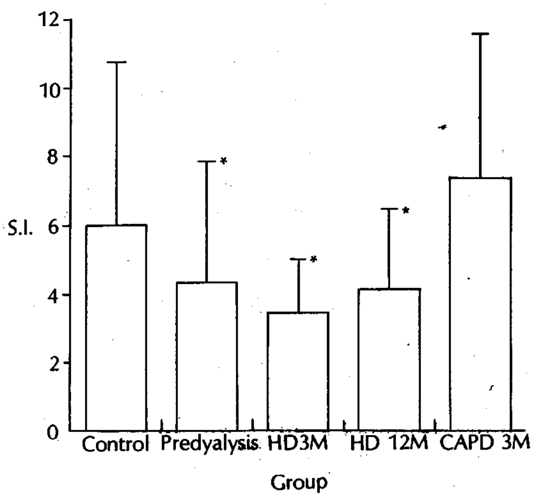

Fig. 2. Comparison of Peripheral Blood Lymphocyte Mitogenic Response After ConA Stimulation.
Values are mean ± SD
HD 3M; Hemodialysis 3 Month Follow-Up Group
HD 12M; Hemodialysis 12 Month Follow-Up Group
CAPD 3M; CAPD 3 Month Follow-Up Group
S.I.; Stimulation Index
**; p<0.05, Compared with values in the control and CAPD 3M group*

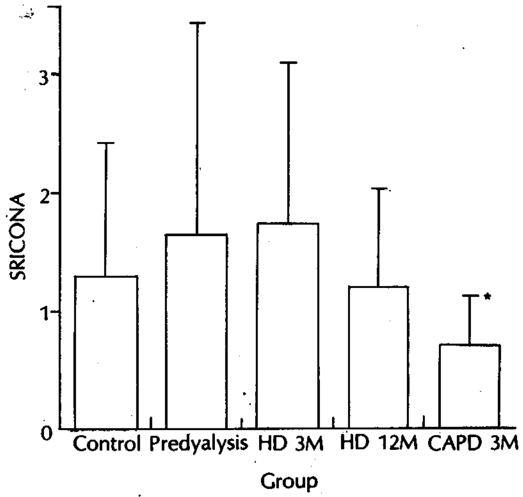

Fig. 3. Comparison of Suppressor Cell Removal Index After ConA Stimulation.
Values are mean ± SD
HD 3M; Hemodialysis 3 Month Follow-Up Group
HD 12M; Hemodialysis 12 Month Follow-Up Group
CAPD 3M; CAPD 3 Month Follow-Up Group
SRICONA; Suppressor Cell Removal Index of Con A
**;p<0.05, Compared with values in the control and other patient group*

Peripheral Blood Lymphocyte Mitogenic Response after PHA Stimulation

Lymphocytes were stimulated with PHA at 37 C to delineate the effect of a nonspecific mitogen to T cell blastogenesis. After PHA stimulation, stimulation indices of the predialysis and hemodialysis group were significantly lower than the control and CAPD group ($p<0.05$). These data indicate that uremic lymphocytes from patients with CAPD have a normal or even enhanced activity to respond to PHA stimulation (Fig. 1).

Peripheral Blood Lymphocyte Mitogenic Response after Con A Stimulation

As described above, lymphocytes were also stimulated with ConA. After ConA stimulation, we also noted that the stimulation indices of the predialysis and hemodialysis groups were significantly lower than the control and CAPD groups ($p<0.05$). These data also indicate that the CAPD group has a normal or even enhanced ability to respond to PHA stimulation (Fig. 2).

Suppressor Cell Removal Index after Con A Stimulation

In order to delineate suppressor cell functions in uremic patients, lymphocytes were stimulated with ConA, either at the initiation of culture or after 24 hours of culture at 37 C. As shown in Fig. 3, the suppressor cell removal index after ConA stimulation (SRICONA) of the predialysis and HD 3M groups was slightly higher than the control value, although the difference was not statistically significant ($p>0.1$). Interestingly, SRICONA of the CAPD 3M group was significantly decreased compared to the control and other patient groups ($p<0.05$). This ratio is even lower than one. These findings suggest that the CAPD group has a normal or even lower suppressor cell activity than other patient groups.

DISCUSSION

Previous studies of immunity in patients with chronic renal failure have emphasized the findings of lymphopenia (Wilson *et al.*, 1965; Jessen, 1958), reduced cutaneous hypersensitivity to antigens (Wilson *et al.*, 1965; Huber *et al.*, 1969; Serloos *et al.*, 1973; Casciani *et al.*, 1978), frequent infections (Dobbelstein, 1976; Andrew *et al.*, 1980; Rutsky & Rostand, 1980), prolonged skin allograft survival (Dammin *et al.*, 1957; Morrison *et al.*, 1963; Smiddy *et al.*, 1961), depressed antibody production (Boulton-Jones *et al.*, 1973) and increased incidence of malignancies (Linder *et al.*, 1981; Matas, 1975).

Although these defects include both the humoral and cellular immune systems, the dominant defects reside in the cell-mediated immunity which primarily involves T lymphocytes. Recently, using monoclonal antibodies, the T-cell subsets in the peripheral blood of uremic patients have been examined (Lortan *et al.*, 1982; Collart *et al.*, 1983; Raskova *et al.*, 1984; Bender *et al.*, 1984). Much research has already been done concerning the alterations of T cell subsets in uremic patients and the mitogenic response of uremic lymphocytes (Kauffman *et al.*, 1975; Miller & Stewart, 1980; Kunori *et al.*, 1980; Selroos *et al.*, 1973; Kasakura & Lowenstein, 1967; Daniels *et al.*, 1971). However, no sequential measurements of these changes were reported comparing results before and after initiation of chronic dialysis. Moreover, few studies are available yet concerned with T cell functions in patients undergoing CAPD which has a greater clearance of middle molecular uremic toxins compared to hemodialysis.

Our data on the white blood cell and lymphocyte counts are in excellent agreement with those of others (Wilson *et al.*, 1965; Riis P & Stougaard J, 1959). The total white blood cell count was not reduced in the uremic patient groups, as has also been noted previously. The total numbers of lymphocytes were significantly reduced in the uremic patient groups and these findings were also in good agreement with others (Jessen, 1958; Wilson *et al.*., 1965; Kim JS & Rha HY, 1986).

We have demonstrated through the use of the E-rossette technique and monoclonal antibodies reactive with T cell surface markers that the average percentages of peripheral blood active T lymphocytes and helper T cells were significantly decreased in the uremic patient groups than in the control ($p<0.05$). The present study confirms early reports that uremic patients have lymphocytopenia and a decreased proportion of OKT4 cells (Wilson *et al.* 1965; Riis & Stougaard, 1959; Quadracci *et al.*, 1976; Lortan *et al.*, 1982; Bender *et al.*, 1984; Kim JS & Rha HY, 1986). The lymphocyte subsets of helper cells, defined by the monoclonal antibody OKT4, play a central role in the body's immune system. The OKT4 subset provides the inducer/helper function of T-T, T-B and T-Macrophage interactions and its presence is required for a maximum in vitro proliferative response to mitogens and antigens. Decreased OKT4 cells have been recently associated with a variety of immunodeficiency states in which an increased incidence of infections and tumors are the predominant features (Reinherz *et al.*, 1981).

Suppressor cells are now known broadly as cells which have inhibitory effects in any immunological phenomena and they presumed to play a critical role in immune regulation. The average percent of suppressor cells in uremic patient is normal according to some authors and decreased according to others (Lortan *et al.*, 1982; Raskova *et al.*, 1984; Bender *et al.*, 1984; Collart *et al.*, 1983). We found a normal percentage of OKT8 cells in the uremic patient groups and these data were in excellent agreement with those of others (Lortan *et al.*, 1982; Raskova *et al.*, 1984; Bender *et al.*, 1984).

Earlier studies of the in vitro response of uremic lymphocytes to mitogens and allogeneic antigens in human patients have reported controversial results: the mitogenic responses have been variously reported as reduced (Birkeland *et al.*, 1976; Selroos *et al.*, 1973; Kauffman *et al.*, 1975; Kunori *et al.*, 1980; Miller & Stewart, 1980), normal (Sengar *et al.*, 1975; Byron *et al.*, 1976), or even increased (Daniels *et al.*, 1971). Our sequential study, observing thirty-eight uremic patients, indicated that the blastogenic responses of lymphocytes from the predialysis and hemodialysis groups were significantly lower both after PHA and Con A stimulation than that seen with the control and CAPD groups. CAPD seems to improve cell-mediated immunity, producing a normal or even an enhanced mitogenic respose in the lymphocyte after PHA and ConA stimulation but there are no changes in the average percentages of helper and suppressor T cells. Giacchino *et al.*, in 1982 reported that 3-5 months after CAPD treatment, six of 16 CAPD patients showed a positive response to the DNCB test and E-rosettes had increased significantly indicating an improvement in cellular immunity, but patients on hemodialysis showed no change. The same author in 1983 also reported that CAPD patients showed an improvement in cellular immunity with a significant increase in the E-rossette count and delayed hypersensitivity reactions 3 months after treatment started, while no difference was observed in the hemodialysis patients. Langhoff *et al.*, in 1983 also demonstrated the beneficial effect of CAPD on the mitogenic response of uremic lymphocytes. They showed that the proliferative response of the peripheral blood lymphocytes and T cells to PHA and ConA were identical in CAPD and control cultures and significantly higher than in HD cultures. Our present data are in good agrement with Giacchino *et al.*, (1982, 1983) and Langhoff *et al.*, (1983), although our study showed no significant changes in the proportion of T cell and T cell subsets in the CAPD patients. The mechanism(s) underlying the observed improvement in cell-mediated immunity in uremic patients undergoing this particular dialytic therapy is not clear at the present time.

Recently augmented suppressor cell activity has been described in mononuclear cell preparations both in experimental uremic animals (Raskova *et al.*, 1976; Raskova & Raska, 1983) and in dialysis patients (Guillou *et al.*, 1980). We measured suppressor cell activity using the suppressor cell removal index described by Aoki *et al.* (1979). Suppressor cell function was monitored using a delayed culture method in which suppressor cells preexisting at the intiation of a culture could be functionally removed after 24 hours of preculture, leading to the acquisition of increased responsiveness to Concanavalin A(ConA) by peripheral mononuclear cells compared to cells without preculture. The method is an application of the observation by Dutton (1975) that suppressor cells are short-lived or become functionally ineffective after 24 hours of incubation. Our results as shown in Fig. 3 suggest a slightly enhanced suppressor cell activity in the predialysis uremic patient and HD 3M group compared to the control group but statistically not significant. However, this enhanced suppressor cell activity has been normalized or even decreased in the CAPD 3M group.

In conclusion, the data given above suggest that the dereased proportion of helper cell and/or altered suppressor cell activity may be the main causes of immunoparesis in uremia. Several parameters of this suppressed cell-mediated immunity can be improved by manitenance on CAPD, but not by hemodialysis. Further studies are needed to clarify the functional derangements of T cell subsets in uremia.

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