Asian Pacific Journal of Allergy and Immunology (1994) 12 : 87-93

Lupus Nephritis in Males: 8-Year Experience at Siriraj Hospital

Leena Ongajyooth, Chairat Shayakul, Paisal Parichatikanond*, Sumalee Nimmannit, Phisit Chirawong, Supat Vanichakarn, Somkiat Vasuvattakul, Prida Malasit and Sanga Nilwarangkur

SUMMARY **During 1984 to 1991, 54 out of 569 lupus nephritis patients at Siriraj Hospital were male (F:M sex ratio = 10:1). Mean age of the males was 29.8 ±14.6 years, range 12 to 69. The three most common extrarenal manifestations were anemia, cutaneous, and musculoskeletal involvement (74.5, 51.1, and 43.9%, respectively). The major renal manifestations were edema (75.9%) with heavy proteinuria over 3.5 g/day in 62.2% and nephrotic/nephritic findings in 51.9% of cases. Hypertension was found in 35.2%. Mean serum creatinine was 2.0 ±1.4 mg/dl while 60.5% of cases had creatinine clearance below 50 ml/minute. Mean serum albumin was 2.6 ±0.8 g/dl, cholesterol 262.8 ±129.5 and triglycerides 343.2 ±244.6 mg/dl. Interestingly, hypercholesterolemia (>250 mg/dl) was found only in 44.8% of cases with nephrotic syndrome. Antinuclear antibody was demonstrated in 91.5%, anti-dDNA antibody in 64.4% and LE cells in 40.4% of cases. Renal biopsy was done in 45 patients and 30 cases (66.7%) were classified as diffuse proliferative nephritis (WHO type IV), 15.6% of type II, 6.7% each of type III and V, with the rest of type V plus IV (4.4%). Tubulointerstitial inflammation was found in 77.3% of cases. During the follow-up period (42 ±35.8 months), 6 patients died. The causes of death were uremia in 3, infection in 2, and cardiac failure in 1. By life-table analysis, the probabilities of survival for 1 and 5 years were 89.5 and 80.6%, respectively. In comparison between sexes, except for a higher amount of urinary protein excretion (4.5 ±3.1 vs 3.5 ±3.0 g/day, $p < 0.05$), there were no statistically significant differences in clinical and pathological parameters, and probability of survival.**

Systemic lupus erythematosus (SLE) is widely regarded as a disease having female predominance. Some studies reported that the disease behaved differently in male and female patients and that a much more aggressive course and a higher morbidity rate could be observed in male SLE patients.[1-3] Although clinical reports of SLE in males have been published, studies concerned with male lupus nephritis are rare.[4,5]

The purpose of this investigation was to study the clinical and pathological findings of lupus nephritis in Thai male compared to female patients and their relative survival rates.

MATERIALS AND METHDOS

Patients

All patients who fulfilled ARA criteria for SLE[6] and who had been seen and followed up at renal unit with a diagnosis of lupus nephritis in the period 1984-1991 were incorporated into the study. Of the total 569 patients with lupus nephritis, only 54 patients were male. Information on patient characteristics, clinical manifestations, histology, treatment and outcome was derived from chart review.

Diagnosis

Lupus nephritis was defined by the presence of one of the followings: 1) urine protein greater than 1 g per day, 2) a 30% decrease in creatinine clearance over a 1 year period, and 3) a renal biopsy showing mesangial, focal proliferative,

From the Renal Unit, Department of Medicine, *Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand.

Correspondence : Leena Ongajyooth, Renal Unit, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University Bangkok 10700, Thailand.

diffuse proliferative or membranous glomerulonephritis or at least 3 of the followings in a 12-month period: 1) proteinuria of 2 to 4 plus, 2) persistent hematuria (>5 RBC/HPF), 3) oval fat bodies; granular, hyaline, or red blood cell casts in the urine, 4) serum albumin less than 3 g/dl.

Renal histology

Percutaneous renal biopsies were performed in 314 cases, 269 females and 45 males. They were classified into 5 groups on the basis of light microscopy, immunofluorescence and electron microscopy according to the World Health Organization classification system.[7,8] In class I, the kidneys were shown to be normal, Class II : mild to moderate mesangial changes, Class III : focal and segmental proliferative and/or necrotizing glomerulonephritis, Class IV : diffuse proliferative GN and Class V : membranous glomerulonephritis.

Statistical Analysis

All results are shown as mean ± SD. The unpaired two-tailed Student's *t*-test was used to compare the continuous variables. A p value of less than 0.05 was considered statistically significant. Life-table analysis and Kaplan-Meier survival curve were prepared using BMDP Statistical software. Comparison between sexes was made using a two sample log-rank test.

RESULTS

The 569 lupus nephritis patients in this study included 54 males and 515 females with the ratio of 1:10. The mean age in males and females was not different but males had shorter duration of symptoms (7.8 ± 11.8 months) and longer duration of follow up period (42.0 ± 35.8 months) as shown in Table 1.

The age at onset of the disease was most frequently between 20 and 30 in both sexes as shown in Fig. 1.

Table 2 shows the extrarenal manifestations at the first entry. Anemia was the most common finding (74.5%) in males, followed by skin involvement (51.1%) and musculoskeletal system involvement (30%), respectively. Approximately one half had a positive direct Coombs' test. The least common presentation was of nervous system symptoms. No laboratory criteria, including LE cells, antinuclear antibody and anti-DNA antibody were found to be related to gender. Clinical and biochemical data of renal manifestations of all 569 lupus nephritis patients are summarized in Table 3.

Edema and urine sediments corresponding to a nephrotic-nephritic picture were present in the vast majority of male patients (75.9% and 51.9%, respectively). Analysis of the clinical and biochemical data of renal manifestations showed similar disease patterns in males and females. The only clinical feature which differed significantly was the occurrence of more proteinuria (4.5 ± 3.1 vs 3.5 ± 3.0 g/day) in males compared to females

Table 1. Fundamental data of lupus nephritis patients (n=569).

	Female	Male
Number	515	54
Age	27.9 ±9.0	29.8 ±14.6
Duration (Month)	17.7 ±24.8	7.8 ±11.8*
Follow up (Month)	26.8 ±33.7	42.0 ±35.8*

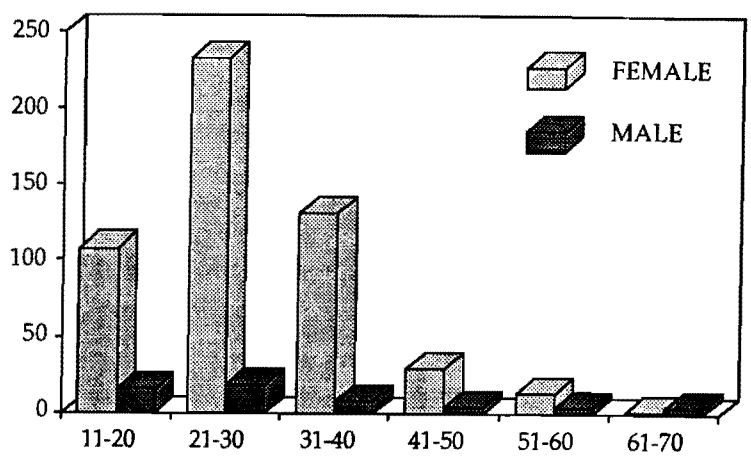

Fig. 1. Age and sex distribution of study population.

Table 2. Extrarenal manifestations at the first entry

	All (%)	Female (%)	Male (%)
Cutaneous system	346 (66.0)	323 (67.4)	23 (51.1)
Musculoskeletal system	315 (62.9)	297 (64.6)	18 (43.9)
Raynaud's	43 (32.1)	40 (32.3)	3 (30.0)
Nervous system	69 (12.3)	67 (13.1)	2 (3.9)
Cardiovascular system	52 (9.0)	49 (9.6)	3 (5.8)
Respiratory system	21 (3.7)	17 (3.3)	4 (7.84)
Ocular	85 (24.4)	81 (25.5)	4 (12.9)
Anemia (Hct≤30%)	448 (80.1)	410 (80.7)	38 (74.5)
Coombs' test + ve	236 (42.2)	220 (43.3)	16 (31.4)
Coombs' test-ve	212 (37.9)	190 (37.4)	22 (43.1)
LE cell + ve	191 (42.2)	172 (42.5)	19 (40.4)
Antinuclear antibody + ve	433 (90.0)	390 (89.9)	43 (91.5)
AntiDNA + ve	326 (67.2)	297 (67.5)	29 (64.4)

Table 3. Clinical and biochemical data of renal manifestation at the first entry.

	All (%)	Female (%)	Male (%)
Edema	413 (73.0)	372 (72.7)	41 (75.9)
Hypertension	183 (32.4)	166 (32.1)	19 (35.2)
Diastolic pressure 95 - 104 mmHg	127 (22.5)	115 (22.5)	12 (22.2)
Diastolic pressure >105 mmHg	56 (9.9)	49 (9.6)	7 (13.0)
Urinalysis			
nephrotic	153 (27.5)	144 (28.5)	9 (17.3)
nephritic	194 (34.8)	180 (35.6)	14 (26.9)
nephrotic/nephritic	159 (28.6)	132 (26.1)	27 (51.9)
telescopic	32 (5.8)	32 (6.3)	0
negative	19 (3.4)	17 (3.4)	2 (3.8)
24-hour urinary protein excretion (g/day)	3.6 ±3.0	3.5 ±3.0	45 ±3.1*
< 0.5 g/day	9.0	38 (9.0)	4(8.9)
0.5-3.5 g/day	47.4	208 (49.4)	13 (28.9)
>3.5 g/day	43.6	175 (41.6)	28 (62.2)
Serum Creatinine	2 ±2.1	2.0 ±2.2	2.0 ±1.4
K	4.4 ±1.0	4.3 ±1.0	5.0 ±0.9
HCO3	21.2 ±5.4	21.3 ±5.4	20.6 ±5.3
Albumin	2.6 ±0.8	2.6 ±0.8	2.6 ±0.8
Globulin	3.0 ±1.0	3.0 ±1.0	2.8 ±0.9
Cholesterol	273.6 ±132.8	274.8 ±133.3	262.8 ±129.5
Triglycerides	297.4 ±163.7	292.8 ±152.9	343.2 ±244.6
Creatinine clearance	50 ±33.4	49.6 ±33.0	54.1 ±37.5
>50 ml/minute	183 (42.0)	168 (42.2)	15 (39.5)
25-50 ml/minute	144 (33.0)	130 (32.7)	14 (36.8)
<25 ml/minute	109 (25.0)	100 (25.1)	9 (23.7)

($p < 0.05$). Mean serum creatinine in male patients was 2.0 ± 1.4 mg/dl while 60.5% of cases had creatinine clearance less than 50 ml/minutes. Mean serum albumin was 2.6 ± 0.8 g/dl, cholesterol 262.8 ± 129.5 and triglycerides 343.2 ± 244.6 mg/dl. Hypercholesterolemia (≥ 250 mg/dl) was found only in 44.8% of cases with nephrotic syndrome.

Three hundreds and fourteen patients (55.2%) underwent renal biopsy within 12 months of the onset of SLE. The most common renal histopathology (type IV) was the same in both sexes (61.5%). The other lesions in male patients were type II (15.6%), type V (6.7%), type III (6.7%) and mixed type IV and V (4.4%). Crescentic change was found in 46.6% of male cases. Moderate to severe tubulointerstitial involvement was described in 77.3% of male lupus patients (Table 4). No difference was demonstrated in renal histopathology between two groups.

Sixty-two percent of all patients received oral prednisolone 0.5-1 mg/Kg/day while 20 percent also had immunosuppressants. Methylprednisolone pulse therapy or pulse cyclophosphamide therapy was introduced in severe lupus nephritis, mainly in those with crescentic changes. Other therapeutic regimens included anticoagulants; antiplatelet aggregation therapy was given in 2 patients in addition to steroids and/or immunosuppressants.

The life survival in lupus nephritis patients was analyzed using life table analysis (Table 5) and Kaplan-Meier survival curves to compare difference between sexes (Fig. 2). The 5 year-survival in male patients was 80.6% compared to 76.25% in females. There was no statistical difference in life survival between male and female lupus nephritis patients.

Table 4. Renal histopathological findings.

		All (%)	Female (%)	Male (%)
Biopsy		314 (55.2)	269 (52.2)	45 (83.3)
Histology	type I	3 (1.0)	3 (1.1)	0
	type II	50 (15.9)	43 (16.0)	7 (15.6)
	type III	11 (3.5)	8 (3.0)	3 (6.7)
	type IV	193 (61.5)	163 (60.6)	30 (66.7)
	type V	49 (15.6)	46 (17.1)	3 (6.7)
	type V/IV	8 (2.5)	6 (2.2)	2 (4.4)
Crescentic change				
< 50%		92 (29.7)	77 (29.1)	15 (33.3)
50-80%		26 (8.4)	22 (8.3)	4 (8.9)
> 80%		21 (6.8)	19 (7.2)	2 (4.4)
Tubulointerstitial change		253 (81.9)	220 (82.7)	34 (77.3)
moderate to severe (%)		22.1	23.4	14.3

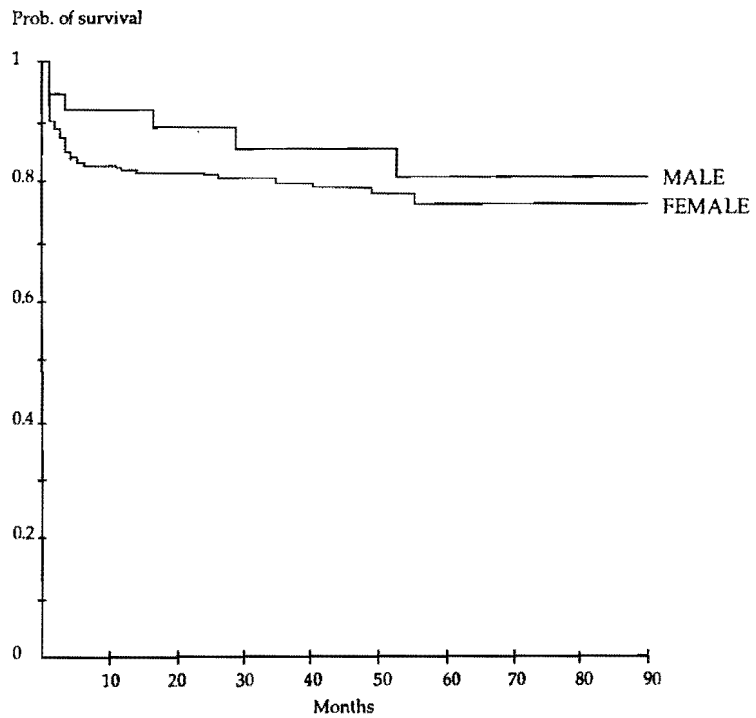

Fig. 2. Probability of survival in lupus nephritis comparing between male and female sexes.

Table 5. Causes of death in lupus nephritis patients.

	All (%)	Female (%)	Male (%)
Mortality rate	91 (16.0)	85 (16.5)	6 (11.1)
Causes of Death			
Infection	46 (50.5)	44 (51.8)	2 (33.3)
Uremia	26 (28.6)	23 (27.1)	3 (50.0)
Cardiovascular system			
: arrhythmia, heart failure	9 (9.9)	8 (9.4)	1 (6.7)
Nervous system			
: convulsion, cerebral hemorrhage	6 (6.6)	6 (7.1)	0
Others			
: GI hemorrhage, respiratory failure, etc.	4 (4.4)	4 (4.7)	0

DISCUSSION

In the present study, 54 of 569 patients registered as having lupus nephritis were males (9.49%). The incidence of disease in males in our study seemed to be higher than in reports from Italy by Remuzzi *et al.*[9] and from Japan by Hashimoto[10]; males represented 8.1% in the study of Tateno *et al.*[4] and in the multicenter study by Hirose *et al.*[11], 118 of 1614 patients (7.3%) were males. The mean age at the time of diagnosis in males was reported to be from 29 to 39 years,[2,3,12,13] which was similar in this study.

Even though males constitute only 4 to 18 percent of those with SLE, their clinical presentation is similar to that observed in women. Hochberg *et al.*[13] noted only a statistically significant increase in peripheral neuropathy, no other clinical, laboratory or HLA phenotyping differences could be found. Similary, Ward and Studenski[14] compared 62 men with 299 women followed at Duke University between 1969 and 1983; 23 clinical and laboratory variables were analysed. The only significant differences were more siezures and renal disease in men. Wallace compared 125 clinical and laboratory parameters among 30 men and 434 women seen in his office between 1980 and 1989.[15] Only four significant differences were observed ($p < 0.01$); men had less alopecia and fibrositis, but more nephritis and hypocomplementemia. Two other controlled studies have evaluated acceptably large members of males to make their data relevant. Fries and Holman[16] observed that men had more anti-DNA antibody and skin disease. Urowritz's group[17] found that men had more pleuritis but less photosensitivity, alopecia and thrombocytopenia. Thus, each study comparing men with SLE to women with the disease reached different conclusions so a typical "male" pattern cannot be defined.

In our series, the most common clinical manifestations in males were anemia, skin and musculoskeletal system abnormalities respectively which revealed also no statistically significant differences from females, as well as other extrarenal findings of SLE.

Renal manifestations including symptoms and signs of edema and hypertension were mainly found in male lupus. Urinalysis revealed nephrotic and nephritic sediments and heavy proteinuria in males than females significantly ($p < 0.05$). The mean serum potassium was also higher in male than in females although mean serum creatinine (2.0 ± 1.4 mg/dl) was similar in both groups.

Of 54 male lupus patients, 45 (83.3%) had renal biopsies, which were examined by three histological methods. The most important type was type IV according to WHO classification in 66.7% compared to 60.6% in females. Kaufman *et al.*[3] described that 76% of 52 male patients with SLE showed clinically active renal disease: 31% had diffuse proliferative glomerulonephritis (type IV). According to Sthoeger *et al.*[12], nine of 19 renal biopsies in males showed diffuse proliferative glomerulonephritis. Celermajer *et al.*[5] stated that 67% of male subjects showed diffuse proliferative lupus nephritis in contrast to 22% of female subjects ($p < 0.01$). In our study, the less common type was mild to moderate mesangial changes followed by membranous and mixed types (type IV and type V). It was of interest that 21 of 45 males showed cres-

centic formations which varied from less than 50% to over 80%. Tubulointerstitial changes were also noted in 77.3% of male cases; this was of moderate to severe degree.

Treatment regimens were similar in both male and female patients. Life table analysis revealed 96.3% survival within first month, 89.5% in one year and 80.6% in 5 years. No statistical difference was found in survival between male and female lupus nephritis patients. In this study, six patients died, 3 from uremia, 2 from sepsis, and one from cardiovascular complications. The comparative survival rates for males with SLE showed that 5 and 10 year survival was 90% and 78%, respectively, which was similar to that reported by Kaufman *et al.*[3] (91%, 71%) but higher than that reported by Wallace *et al.*[1] (77%, 75%) and by Sthoeger *et al.*[12] (85%, 79%). However, the overwhelming preponderance of female patients in nearly all of the studies has made it difficult to compare accurately the survival of male patients with that of females.

An increased prevalence of renal disease among males with lupus has been noted in both pediatric and adult populations.[3,5,18-21] This was true even for studies in which there was no difference in survival between males and females. There were reports which also found that male gender was a poor prognostic variable for the nephritis of lupus.[5,20-22]

It is likely that differences in survival and clinical patterns of disease are multifactorial in origin. Genetic factors related both to disease susceptibility and response to therapy, ascertainment bias from primary care *vs* tertiary referral hospitals, socioeconomic status and aggressiveness of therapeutic intervention impact on data collection and underlie the heterogeneity of different patient populations. HLA typing revealed increased frequencies of B8 and DR 3 antigens in SLE males compared with normal controls.[2] In murine models of lupus, there is generally an acceleration of disease activity following therapy with estrogens or castration.[23] Similarly in man the use of estrogens has been associated with a flare of disease.[24] However, 45% of the men had elevated plasma estrogen levels.[2] Although abnormalities of estrogen metabolism, including an increase in the 16-alpha-hydroxylation of estrone, have been identified in both men and women with lupus,the plasma levels of hormones do not correlate with disease activity.[25]

In conclusion, male lupus nephritis in Thailand showed a favourable clinical course despite severe renal histological finding at the time of initial renal biopsy. Among patients with lupus nephritis, gender does not appear to influence the prevalence of individual clinical manifestations and outcome to a major extent.

REFERENCES

1. Wallace DJ, Podell TE, Weiner JM, *et al.* Lupus nephritis-experience with 230 patients in a private practice from 1950-1980. Am J Med 1982; 72 : 209-12.
2. Miller HM, Urowitz MB, Gladman DD, Killinger DW. Systemic lupus erythematosus in males. Medicine 1983; 63 : 327-32.
3. Kaufman LD, Gomez-RTeino JJ, Heinicke MH, Gorvic PD. Male lupus : retrospective analysis of the clinical and laboratory features of 52 patients with a review of the literature. Sem Arthritis Rheum 1989; 18 : 189-92.
4. Tateno S, Hiki Y, Hamaguchi K, Tsuchida H, Shigematsu H, Kobayashi Y. Study of lupus nephritis in males. Q J Med, 1991; 296 : 1031-9.
5. Celermajer DS, Thorner PS, Baumal R, Arbus GS. Sex differences in childhood lupus nephritis. Am J Dis Child 1984; 138 : 586-8.
6. Tam EM, Cohen AS, Fries JF *et al.* The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982: 25 : 1271-7.
7. Pollak VE, Pirani CL. Lupus nephritis. Pathology, pathogenesis, clinicopathologic correlation and prognosis. In: Wallace DJ, Hahn BH eds. Dubois' Lupus Erythematosus. 4th ed., Philadelphia: Lea and Febiger, 1993; 525-49.
8. Pirani CL, Pollak VE. Systemic lupus erythematosus (SLE) Glomerulonephritis (lupus nephritis) In: McClusky RT, Andres GA, eds. Immunologically mediated renal diseases. New York : Marcel Dekker 1978; 11-69.
9. Remuzzi G, Gruppo Haliano per lo Studio della Nefrite Lupica (GISNEL). Lupus nephritis: Prognostic factors and probability of maintaining life supporting renal function 10 years after the diagnosis. Am J Kidney Dis 1992; 19 : 473-9.
10. Hashimoto H, Tsuda H, Hirano T, Takasaki Y, Matsumoto T, Hirose S. Differences in clinical and immunological findings of systemic lupus erythematosus related to age. J Rheumatol 1987; 14 : 497-501.
11. Hirose S, Hashimoto H, Kabasawa K. A multicenter study on disease classification of SLE. The first report. In : the 1988 annual report by the investigational study groups on autoimmune diseases in specified diseases by Ministry of Health and Welfare 1989 : 141-3.
12. Sthoeger ZM, Geltner D, Rider A, Bentwich Z. Systemic lupus erythematosus in 49 Israeli males : a retrospective study. Clin Exp Rheumatol 1987; 5 : 233-40.
13. Hochberg MC, Boyd RE, Ahearn JM, Arnett FC, Bias WB, Provost TT, Stevens MB. Systemic lupus erythematosus : A review of clinicolaboratory features and immunogenetic markers in 150 patients with emphasis on demographic subsets. Medicine 1985 Sept; 64(5) : 295-95.
14. Ward MM, Studenski S. Systemic lupus erythematosus in men: a multivariate analysis of gender differences in clinical manifestations. J Rheumatol 1990; 17 : 220-24.
15. Pistiner M, Wallace DJ, Nessim S, Metzger AL, Klinenberg JR. Lupus erythematosus in the 1980s: A survey of 570 patients. Semin Arthritis Rheum 1991 Aug; 21 : 55-64.

16. Fries J, Holman H. Systemic lupus erythematosus : A clinical analysis. Philadelphia : Saunders, 1975.

17. Miller MH, Urowritz MB, Gladman DD, Tozman ECS. Chronic adhesive lupus serositis as a complication of sytemic lupus erythematosus. Refractory chest pain and small bowel obstruction. Arch Intern Med 1984 Sep; 144 : 1863-4.

18. Studenski S, Allen NB, Caldwell DS, *et al.* Survival in systemic lupus erythematosus : a multivariate analysis of demographic factors. Arthritis Rheum 1987; 30 : 1326-32.

19. Jousson H, Nived O, Sturfelt G. Outcome in systemic lupus erythematosus : a prospective study of patients from a defined population. Medicine 1989; 68 : 141-50.

20. Austin AA, Muenz LR, Joyce KM, *et al.* Prognostic factors in lupus nephritis. Am J Med 1983; 75 : 382-91.

21. Tareyeva A, Janushkevitch TN, Tuganbekova SK. Lupus nephritis in males and females. Proc EDTA 1984; 21 : 712-6.

22. Folomeev M, Alekberova Z. Survival pattern of 120 males with systemic lupus erythematosus. Letter to the editor. Rheumatology 1990; 17 : 856-7.

23. Ansar Ahmed S, Penhale WJ, Talal N. Sex hormones, immune responses, and autoimmune diseases : Mechanisms of sex hormone action. Am J Pathol 1985; 121 : 531-9.

24. Jungers P, Dougados M, Pelissier C, *et al.* Influence of oral contraceptive therapy on the activity of systemic lupus erythematosus. Arthritis Rheum 1982; 25 : 618-23.

25. Lahita RG, Bucala R, Bradlow HL, *et al.* Determination of 16 alpha hydroxyestrone by radioimmunoassay in systemic lupus erythematosus. Arthritis Rheum 1985; 28 : 1122-7.

THE SECOND ASIAN PACIFIC CONGRESS OF ALLERGOLOGY AND CLINICAL IMMUNOLOGY

The 2nd Asian Pacific Congress of Allergology and Clinical Immunology will be held in Taipei, Taiwan on November 18-22, 1995. For more information, please write to : The Second Asian Pacific Congress of Allergology and Clinical Immunology. P.O. Box 84-583, Taipei, Taiwan, Republic of China. Fax no. 886-2-3972031 or 886-2-3217921

THE SECRETARIAT: THE SECOND ASIAN PACIFIC CONGRESS OF ALLERGOLOGY AND CLINICAL IMMUNOLOGY P.O. BOX 84-583, Taipei, Taiwan, REPUBLIC OF CHINA
TEL:886-2-3970800 EXT. 8630 FAX:886-2-3972031, 3217921