AN UNUSUAL CLINICAL RECOVERY FROM SYSTEMIC LUPUS ERYTHEMATOSUS

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This case is reported for two reasons. First, it illustrates that lupus nephropathy with renal failure and severe hypertension is not necessarily fatal, and that the hypertension may be reversible; secondly, the patient's unexpected recovery followed the menopause.

Case Report

A housewife aged 51 came to hospital in July, 1955, complaining that for the previous 2 months she had suffered from attacks of pain in her right arm; these occurred principally at night, but were also provoked by peeling potatoes or carrying shopping. On direct questioning it appeared that for about 3 months she had not been completely well: her appetite had been poor and, contrary to her usual custom, she had been getting up at night to pass urine. Some 3 weeks previously she had had transient painful swelling of her right ankle, and for 1 week she had noticed a patchy non-irritating rash on her face and neck. She also mentioned that all her life her skin had tended to become blotchy after exposure to sunlight.

On examination she was febrile (99.8° F.). Her face and neck were covered by a symmetrical red scaling macular rash, sparing only the area around her eyes. Around the nail-folds of her fingers were red chilblain-like lesions. Her blood pressure ranged from 130 to 140/70 to 80. The urine contained 0.3 per cent. protein, with numerous red and white blood cells. X ray of the cervical spine showed clear evidence of disc degeneration, and this was presumed to have caused the pain which brought her to hospital.

Her erythrocyte sedimentation rate (Westergren) was at first 18 mm./1 hr, but within 2 weeks it had risen to 66 mm. Other tests showed: Hb 75 per cent., red blood cells 3.9 million/mm.³, white blood cells 5,000/mm.³ (neutrophils 2,600/mm.³). Blood urea 63 mg./100 ml. Plasma proteins 6.9 g./100 ml. (albumin 3.7, globulin 3.2). Paper electrophoresis: increase in gamma-2 globulin (14 per cent.). L.E. cells were seen in peripheral blood. A urine concentration test showed a maximum urinary specific gravity of 1.022. Chest x ray and intravenous pyelogram were normal.

A diagnosis was made of systemic lupus erythematosus (S.L.E.) with renal involvement, and treatment with cortisone was started on August 12, 1955. She was discharged from hospital 3 weeks later on 150 mg. cortisone daily. Her rash faded quickly, well-being and appetite improved, and the erythrocyte sedimentation rate fell to 14 mm./1 hr. Proteinuria and microscopic haematuria persisted.

On September 13, 1955, her blood pressure was found to be 180/105, and by November 22, 1955, it was 250/145. She was now re-admitted to hospital. Both optic discs were swollen, although there were no haemorrhages or exudates. Her face was moon-shaped, her complexion greasy, and her ankles oedematous. The blood urea had risen to 92 mg./100 ml.; the maximum urinary specific gravity after dehydration was 1.018, and the urea clearance values were 29 and 33 per cent. or normal.

Because of the oedema, cortisone was replaced by prednisone, stabilizing at 50 mg./day. The hypertension was moderately controlled by oral pentolinium tartrate. Her general condition gradually improved, the appearance of the optic discs became normal, and by June, 1956, the blood urea had fallen to 47 mg./100 ml. The dose of prednisone was reduced progressively. By February, 1957, the urine was free of protein, although it still contained granular casts and red and white blood cells.

During 1958 the patient's menses ceased, and during the next 2 years she was troubled by hot flushes and sweats.

In August, 1958, prednisone was withdrawn altogether. The patient, however, "felt awful", and complained much of muscle and joint pains. The blood pressure at the end of this 6-week steroid-free period was still 140/110, despite pentolinium. Prednisone 2.5 mg. daily was re-started, but 3 months later it proved possible to withdraw both steroid and hypotensive drugs.

The patient was seen regularly for a period of 18 months after therapy was stopped. After some initial fatigability, she gradually regained a feeling of normal fitness and returned to full-time employment. Her blood pressure has averaged 140/87 (range 125 to 155/80 to 90). Her erythrocyte sedimentation rate has ranged from 10 to 15 mm./1 hr, and her blood urea from 42 to 49 mg./100 ml. The urine has usually been protein-free, though

a faint trace has been detected on occasion; the deposit has consistently revealed increased numbers of white blood cells and some granular casts.

Discussion

In their account of lupus nephritis, Muehrcke, Kark, Pirani, and Pollak (1957) noted that, in two patients with only mild renal injury, exacerbations of disease seemed to be associated with reversible hypertension; but in their experience severe hypertension, or hypertension associated with severe renal injury, was never reversed. Harvey, Shulman, Tumulty, Conley, and Schoenrich (1954), in their description of 138 cases of S.L.E., mentioned only one patient in whom the hypertension disappeared, and even then it had never been great, having ranged from 160 to 175/90 to 110. Recovery from severe hypertension does not seem to have been recorded hitherto in any case of S.L.E.

In the patient described here, the blood pressure level showed some correlation with steroid dosage; the pressure began to rise 1 month after treatment was started, and the highest pressures coincided with the highest doses. On the other hand the hypertension was also correlated with the severity of the nephritis, as judged by renal function and proteinuria. The relative importance of these two factors cannot be properly determined, but certain relevant observations may be stressed. First, malignant hypertension is an unlikely complication of steroid therapy *per se*; and similarly it is unlikely that the daily dose of 10 mg. prednisone given during the 3rd year could have been wholly responsible for diastolic pressures which—despite pentolinium—rose on occasion to 125 mm. Secondly, when at the end of the 3rd year steroid therapy was stopped, the diastolic pressure 6 weeks later was still 110 mm.—again despite pentolinium. For these reasons it seems likely that this patient's hypertension was due primarily to lupus nephritis, although it may have been aggravated by steroid treatment.

At one stage of her illness she had florid generalized disease, azotaemia, malignant hypertension, heavy proteinuria, and oedema. Her ultimate recovery is still not assured, and she has certainly suffered a measure of irreversible renal injury. But the fact that she is symptomatically a fit person leading a normal life indicates that the physician faced with such a case should not wholly despair nor pursue only half-hearted therapy.

This unusual recovery occurred at approximately the same time as the patient's menopause. A number of other observations also suggest that the female

sex hormones may exert an unfavourable influence on the dissemination and course of this disease:

(1) Discoid lupus erythematosus shows only a slight female preponderance in incidence. Gold (1960) reported 105 cases of clinically uncomplicated discoid disease. After the exclusion of cases with a raised erythrocyte sedimentation rate, the female/male ratio in the remainder was only 1.3. Furthermore, there was no clear rise in this ratio during the female reproductive years: the ratio for the 3rd and 4th decades was the same as that for the rest of life.

The incidence of systemic lupus erythematosus, on the other hand, shows a heavy female preponderance. Table I combines the data from two large series, totalling together 212 cases (Harvey and others, 1954; and Medical Research Council, unpublished). There is a striking rise in the female/male ratio during the 3rd and 4th decades, although at all ages (except for the 1st decade) the ratio is higher than for discoid disease. A steadily progressive fall after the 3rd decade is interrupted by a rise in the 60+ age group. This may be a vagary due to small numbers; but there was a similar trend in a series of discoid cases reported by Gold (1960), among whom there were ten females aged 60 and over, but no males.

TABLE I
INCIDENCE OF SYSTEMIC LUPUS ERYTHEMATOSUS BY AGE (AT DIAGNOSIS) AND SEX, BASED ON COMBINED DATA OF HARVEY AND OTHERS (1954) AND THE MEDICAL RESEARCH COUNCIL (UNPUBLISHED)

Decade of Onset	Number of Cases		Female/Male Ratio
	Female	Male	
1	2	3	0.7
2	28	8	3.5
3	46	4	11.5
4	46	7	6.6
5	27	8	3.4
6	14	5	2.8
7+	13	1	13.0
Total	176	36	4.9

(2) It has been suggested by Soffer, Ludemann, and Brill (1955) and by Rupe and Nickel (1959) that systemic lupus erythematosus tends to be more severe among women than among men. There appear at present, however, to be no factual observations to confirm this suggestion.

(3) Some clinicians have formed the impression that, among females with the disease, mortality is higher during the reproductive years. Again, figures to support this contention do not seem to be

available. Merrell and Shulman (1955) estimated the prognosis in their series of cases of systemic lupus erythematosus, using a life table procedure. Their data may be used to form separate estimates of prognosis in women aged respectively under 45, or 45 and over, at diagnosis (Table II). The estimated survival rates at 2 years from diagnosis are not significantly different. (The true risk of dying from S.L.E. among the older group of women is probably less than appears in the Table, because of their relatively greater risk of dying from other causes.) It thus appears that a higher case fatality rate among younger women cannot at present be substantiated. On the other hand, Pollak (1961) has found that the risk of exacerbation of S.L.E. is very much greater during the first 8 weeks *post partum* than it is during pregnancy.

(4) Through the courtesy of the United States National Office of Vital Statistics, figures were made available for the numbers of deaths from lupus erythematosus in the United States, by age and sex, for the period 1956-58. In Table III these are presented as age-specific death rates. It can be seen that the male rate rises more or less steadily throughout life. At the extremes of life, the female rates are very similar to the male; but they are a great deal higher than the male rates for the quinquennia from 10-14 up to 50-54, and especially for the period between 20 and 49 years of age.

In order to obtain a more specific measure of the true mortality excess among females, one may deduct from the female rate at each age the corresponding male rate. (This procedure is based on the assumption that the changes in male rates with age represent a non-specific age effect which is likely to be common to both sexes.) The results are shown graphically in the Figure (overleaf), which also

TABLE III
DEATH RATES FOR LUPUS ERYTHEMATOSUS BY AGE
AND SEX, UNITED STATES, ALL RACES, 1956-58
(FROM UNPUBLISHED DATA OF NATIONAL OFFICE OF VITAL STATISTICS)

Age (yrs)	Deaths per 10 ⁶	
	Female	Male
< 5	0.04	0.03
5-	0.30	0.18
10-	1.33	0.13
15-	2.79	0.61
20-	3.59	0.33
25-	2.66	0.48
30-	3.08	0.73
35-	3.86	0.40
40-	3.45	0.90
45-	3.60	1.03
50-	3.29	1.55
55-	2.34	1.96
60-	2.30	1.78
65-	1.83	2.02
70-	2.10	2.23
75 and Over	2.24	1.34

indicates the age-specific means for urinary oestrogen excretion, as determined by a study of 704 normal women by Pedersen-Bjergaard and Tønnesen (1948). The correspondence between the changes in excess female mortality from lupus erythematosus and the changes in oestrogen levels is quite close.

This remarkable mortality phenomenon is not shown by any other disease, apart from diseases of the female reproductive organs and the complications of pregnancy. The complete contrast between the age and sex patterns for systemic L.E. incidence and mortality on the one hand, and discoid L.E. incidence on the other, presents difficult but stimulating problems.

These observations favour, although they do not prove, the hypothesis that the female sex hormones tend to provoke or aggravate systemic lupus erythematosus. The evidence might be considered sufficient to justify the trial of androgen therapy or

TABLE II
LIFE TABLES SHOWING PROBABILITY OF SURVIVING AMONG WOMEN WITH SYSTEMIC LUPUS
ERYTHEMATOSUS, AGED UNDER 45 YEARS, AND 45 YEARS AND OVER
(DATA OF MERRELL AND SHULMAN, 1955)

Age (yrs)	Period from Diagnosis (mths)	No. of Cases				Probability of Dying in Period	Probability of Surviving	Cumulative Probability of Surviving
		Entering Period	Follow-up Terminated in Period	Dying in Period	At Risk, Estimated			
Under 45	0-	66	9	8	61.5	0.130	0.870	0.87
	6-	49	12	3	43	0.070	0.930	0.81
	12-	34	7	3	30.5	0.098	0.902	0.73
	18-23	24	6	1	21	0.048	0.952	0.69
45 and Over	0-	18	1	4	17.5	0.229	0.771	0.77
	6-	13	2	1	12	0.083	0.917	0.71
	12-	10	1	1	9.5	0.105	0.895	0.63
	18-23	8	3	0	6.5	0.000	1.000	0.63

Figure.—(Female-male) death rates from lupus erythematosus, by age, United States, all races, 1956-58 (National Office of Vital Statistics, unpublished data) and mean oestrogen excretion rates, by age, in normal women (Pedersen-Bjergaard and Tønnesen, 1948).

(perhaps more appropriately) oöphorectomy in menstruating women with severe S.L.E.—especially perhaps, in cases of lupus nephritis with azotaemia. It also indicates a need for detailed studies in individual patients on the relation between the activity of S.L.E. on the one hand, and pregnancy, menstruation, and hormone levels on the other.

Summary

(1) A case of systemic lupus erythematosus is reported in which severe nephritis was followed after 3 years of steroid therapy by reversal of azotaemia, hypertension, and proteinuria.

(2) This unusual recovery coincided approximately with the menopause. Statistical evidence related to sex differences in this disease is presented and found to be consistent with the view that the female sex hormones may exert an adverse effect.

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Cas peu fréquent de rétablissement de lupus érythémateux généralisé

RÉSUMÉ

(1) On décrit un cas de lupus érythémateux accompagné d'une néphrite grave qui fut suivie, après trois ans de thérapie stéroïde, par l'inversion de l'azotémie, de l'hypertension et de l'albuminurie.

(2) Ce rétablissement extraordinaire coïncidait à peu près avec la ménopause. On présente des données statistiques concernant le sexe dans cette maladie et on les trouve compatibles avec le point de vue que les hormones féminines peuvent y exercer un effet peu favorable.

Un caso poco frecuente de recuperación clínica de lupus eritematoso generalizado

SUMARIO

(1) Se describe un caso de lupus eritematoso, con nefritis grave, que fué seguida después de 3 años de terapéutica con esteroides por una reversión de la azotemia, hipertensión y proteinuria.

(2) Esta poco usual recuperación coincidió aproximadamente con la menopausia. Se presentan datos estadísticos de esta enfermedad con relación al sexo, que son compatibles con la hipótesis de que las hormonas sexuales femeninas pueden ejercer un efecto adverso.