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LUPUS ERYTHEMATOSUS

Analysis of the Sex- and Age-Distributions of the Discoid and Systemic Forms of the Disease in Different Countries

P. R. J. Burch and N. R. Rowell

From the Department of Medical Physics and the Department of Dermatology, University of Leeds, Leeds, England

Abstract. We analyse the relative sex-specific and age-specific onset-rates of chronic discoid lupus erythematosus (DLE) and of systemic lupus erythematosus (SLE) in clinical series from the Netherlands. These rates are compared with those reported previously from other countries.

Further support is given to our earlier proposal that at least three main groups are predisposed to DLE, each with characteristic kinetics of initiation. The relative sizes of the groups in the Netherlands series differ from those in the combined series from Denmark, England, Sweden and the United States. Differences in the frequencies of predisposing genes are probably responsible. Within these main groups, however, another division can be made between "proper" and "transitory" forms of DLE. The kinetics of initiation of DLE in the Netherlands seems to be very similar, group by group, with those in other countries. This property of near-invariance is attributed to initiating somatic mutations, the average rates of which are independent of ordinary environments. Following Burnet, we propose that somatic mutations initiate the growth of "forbidden clones" of lymphocytes. These clonal cells attack cells in target tissues bearing complementary recognition factors.

Although the age-distributions of the onset of SLE in the Netherlands resemble those in two series from the United States, the sex-distributions differ markedly. The crude sex-ratio (F/M) in the Netherlands series is 142/80, that is, about 1.8, as contrasted with 7.3 for the combined U.S. series. A genetic interpretation of this difference is proposed. The age-distributions of SLE again support Burnet's forbidden clone concept. We suggest that the target tissue, both in DLE and SLE, comprises the endothelial lining of blood vessels.

Systemic lupus erythematosus is often described as *the* autoimmune disease *par excellence* and as such it has attracted much interest. Nevertheless, its pathogenesis remains obscure. In this paper, we pay special attention to the sex- and age-distributions of chronic discoid lupus erythematosus (DLE) and systemic lupus erythematosus (SLE) because we believe they have an important bearing on aetiology and pathogenesis. Those features of a disease that remain invariant with respect to widely-separated environments are unlikely to be determined by factors such as micro-organisms, allergens, drugs and atmospheric pollution.

In clinical series from four countries—Denmark, England, Sweden and the United States—the broad features of the sex- and age-distributions of DLE have been found to be strikingly similar (7). When the data from the four series were combined, the resulting sex- and age-patterns suggested that three genetically-distinctive sub-groups are predisposed to DLE, in each of the four countries (7). The kinetics of onset, group by group, appear to be very similar from one country to another. However, the relative sizes of the sub-groups differ between the series, and this indicates that the frequencies of the predisposing genes differ from country to country.

Details of the sex and age at onset of DLE patients in the Netherlands have now been made available to us by Dr Baart de la Faille-Kuyper and we shall compare the age-patterns in this new series with those from the other countries.

The sex- and age-distributions of systemic lupus erythematosus (SLE) in two large clinical series from the United States were analysed in an earlier paper (6). We shall also compare these patterns with those of the new series from the Netherlands. The sex-ratio in the Netherlands series of SLE patients differs strikingly from

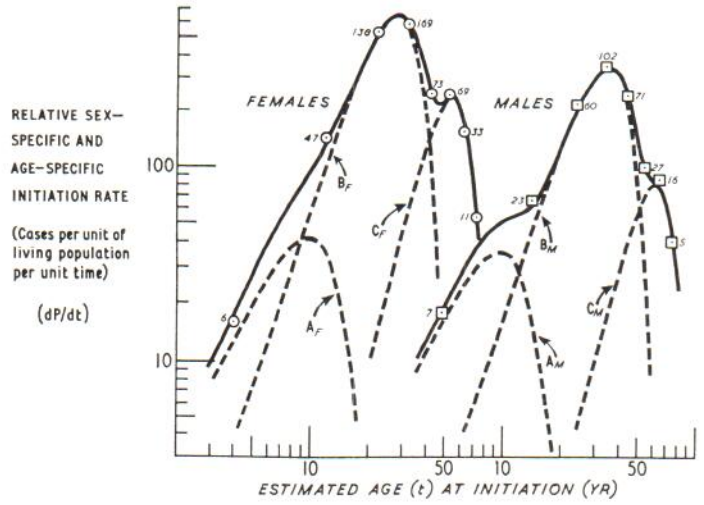

Fig. 1. Relative sex-specific and age-specific initiation-rates, (dP/dt), in relation to estimated age (t) at initiation, for chronic discoid lupus erythematosus. Results from our earlier paper (7) for combined series from Denmark (14), England (7), Sweden (20) and the United States (21).

those reported previously (11, 13, 16, 18, 19). Nevertheless, the *shape* of the curves of age-specific initiation-rates in relation to age remains closely similar. Differences in the frequency, and the dominant/recessive effect of predisposing X-linked genes might account for the unusual sex-ratio. Similar situations have been encountered previously in connexion with late-onset diabetes mellitus (3, 4), and with early-onset ulcerative colitis (5). We shall discuss a possible genetic interpretation of this phenomenon.

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Fig. 1, reproduced from our earlier paper (7), shows the sex- and age-distributions of DLE in the combined Danish (14), English (7), Swedish (20), and U.S. (21), clinical series. The stochastic equation which describes relative age-specific initiation-rates (dP/dt) for the early-onset group (sub-group A, curves A_F and A_M) is:

$$dP/dt \propto S_A t^2 \exp - k_A t^3 \quad (1)$$

This equation, taken in conjunction with many other considerations (3), suggests that in this sub-group, the disease is initiated by three somatic gene mutations, affecting autosomal genes, in a single stem cell. S_A represents the proportion of the population predisposed to this early-onset form of DLE; $S_{A,F}$ denotes the proportion of females predisposed at birth, and $S_{A,M}$ denotes the corresponding proportion of males. The symbol t represents age at initiation, and k_A is a kinetic constant (3, 7). Initiation-rates for this sub-group peak at about 9.5 years of age, both for males and females.

Curves B_F and B_M, for sub-group B, giving the major mode at $t = 28.0$ years (women), and $t = 34.3$ years (men), are based on the following equations (7):

$$(dP/dt)_F \propto 2k_B S_{B,F} t^3 \exp - 2k_B t^4 \quad \text{(for females)} \quad (2)$$

and

$$(dP/dt)_M \propto k_B S_{B,M} t^3 \exp - k_B t^4 \quad \text{(for males)} \quad (3)$$

These equations suggest that the disease is initiated in sub-group B by four somatic gene mutations, occurring in a single stem cell: one of the four initiating mutations in females occurs at double the rate of the corresponding event in males (7).

Late-onset cases (subgroup C, curves C_F and C_M) follow the initiation curves given by the equations:

$$(dP/dt)_F \propto 2k_C S_{C,F} t^4 \exp - 2k_C t^5 \quad \text{(for females)} \quad (4)$$

and

$$(dP/dt)_M \propto k_C S_{C,M} t^4 \exp - k_C t^5 \quad \text{(for males)} \quad (5)$$

In this sub-group, the disease appears to be initiated by five somatic mutations in a single stem cell. As in sub-group B, the average rate of one of the initiating mutations is twice as high in women as in men.

Following Burnet (8–10), we have proposed that in all sub-groups, the initiating somatic muta-

Table I. *Cases of chronic discoid lupus erythematosus (DLE) in The Netherlands, referred to Baart de la Faille-Kuyper (1)*[a]

Relative age-specific onset rates, by sex

Age-range (years)	Population, Utrecht Province, 31 Dec. 1967[b] (in hundreds)		Numbers of cases at onset						Relative age-specific onset-rates for combined groups	
			DLE "proper"		"Transitory" DLE		"Proper" and "Transitory" combined			
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
0–9	739	699	1	1	0	1	1	2	1.4	2.9
10–19	708	674	3	14	6	7	9	21	13	31
20–29	630	597	21	29	6	20	27	49	43	82
30–39	469	450	27	17	13	23	40	40	85	89
40–49	430	451	34	18	6	12	40	30	93	66
50–59	355	398	14	11	3	6	17	17	48	43
60–69	262	331	7	4	0	3	7	7	27	21
70–79	154	210	6	3	1	0	7	3	45	14
80–89	49	71	1	2	0	0	1	2	20	28
			114	99	35	72	149	171		

[a] The series given here has been extended slightly from the original (1).
[b] Patients have also been referred from outside the province of Utrecht and we assume that the relative sex- and age-structures of these other populations resemble those of Utrecht Province. Onset-rates given in the last column are therefore relative and not absolute; the units (cases per unit of population per year) are arbitrary.

tions cause a "forbidden clone" of lymphocytes to be generated from the mutant stem cell. An interval necessarily elapses before the attack by the forbidden clone on target tissues results in symptoms of disease. The latent period correction, which allows for the average interval between the occurrence of the last initiating somatic mutation and the first onset of DLE, is about 4 years for females and 2 years for males. During the first decade, the average latent period is probably shorter—about 1.5 years for girls and 0.75 years for boys.

Table I and Fig. 2 show the relative sex- and age-specific initiation rates of DLE ("proper" and "transitory") in the Netherlands population studied by Baart de la Faille-Kuyper (1). The distinction between the "proper" and "transitory" forms rests on the presence (in "transitory"), or

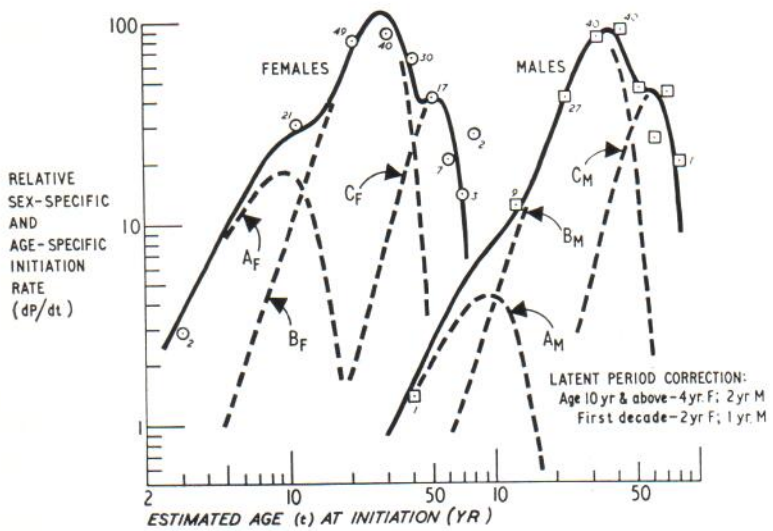

Fig. 2. Relative sex-specific and age-specific initiation-rates, (dP/dt), in relation to estimated age (t) at initiation, for chronic discoid lupus erythematosus. Findings for a series from the Netherlands. See reference (1) and Tables I and II.

Table II. *Relative sizes of sub-groups predisposed to DLE in Danish, English, Swedish, and US combined series (7), compared with those in a new series from The Netherlands*

	$S_{A,F}$	$S_{A,M}$	$S_{B,F}$[a]	$S_{B,M}$	$S_{C,F}$	$S_{C,M}$
Combined series (7)	3.4	2.8	100	67	61	23.5
Netherlands series (this paper)	8	2	100	102	59	72

[a] For both series, the size of the $S_{B,F}$ sub-group, the proportion of the female population predisposed to 'middle-onset' DLE, has been normalized to 100.

absence (in "proper") of immunoglobulin at the dermal-epidermal junction of the uninvolved skin (1). This has been called the basal membrane (BM) phenomenon (11). None of the patients in either of these sub-groups have overt SLE. In other clinical series (7) so-called "proper" and "transitory" forms were not distinguished, and both were diagnosed as DLE. Hence, for the purpose of intercomparison between different series, we have to combine the statistics for "proper" and "transitory" forms.

As can be seen from Table I, the age-patterns for "proper" and "transitory" forms are similar, although numbers are too small to be definitive. The kinetics of the "transitory" form differ appreciably from those for SLE and suggest that "transitory" DLE is not a sub-group of SLE. However, the sex-ratios for "proper" DLE differs from that for "transitory" DLE, and this suggests that the two forms of the disease are genetically-distinctive.

These new data are fitted to curves of exactly the same form as those described by equations (1) to (5), with exactly the same values of k_A, k_B and k_C. Hence, the modal ages of corresponding curves in Figs. 1 and 2 coincide. Numbers are somewhat smaller than for the combined series, but for most age-groups (except women above 80 years of age) the agreement with curves A, B and C is satisfactory.

We find that the ratios of the sizes of the different sub-groups: $S_{A,F}$, $S_{A,M}$, $S_{B,F}$ ... etc., in the Netherlands series differ appreciably from those for the combined series illustrated in Fig. 1—see Table II and Discussion.

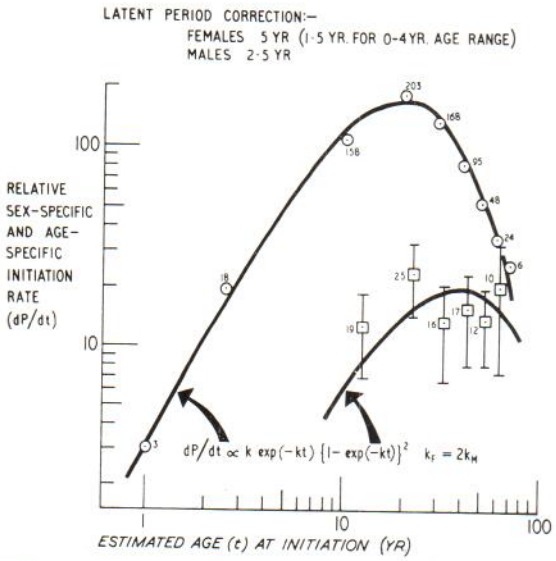

Fig. 3. Relative sex-specific and age-specific initiation-rates, (dP/dt), in relation to estimated age (t) at initiation for systemic lupus erythematosus. Results from our earlier paper (6) for two series (11, 17) from the United States.

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Fig. 3 illustrates relative sex-specific and age-specific initiation-rates for patients with SLE in two (combined) series from the United States (11, 17).

Data for females are fitted to the curve with the following equation:

$$(dP/dt)_F \propto 2kS_F(1-\exp-2kt)^2 \cdot \exp-2kt \qquad (6)$$

The curve for males is based on the equation:

$$(dP/dt)_M \propto kS_M(1-\exp-kt)^2 \cdot \exp-kt \qquad (7)$$

These two curves suggest that SLE is initiated in genetically-predisposed individuals by three independent and distinctive random events, and that the average rate of each event in women is double that in men (6). We have proposed that somatic mutation of X-linked genes initiates this

Table III. *Cases of systemic lupus erythematosus (SLE) in The Netherlands referred to Baart de la Faille-Kuyper (1)*

Relative age-specific onset rates, by sex[a]

Age-range (years)	Numbers of cases at onset		Relative age-specific onset-rates	
	♂	♀	♂	♀
0–9	2	7	2.7	10
10–19	7	20	9.9	30
20–29	18	31	29	52
30–39	13	34	28	76
40–49	19	27	44	60
50–59	12	15	34	38
60–69	9	8	34	24
	80	142		

[a] The footnotes to Table I also apply to this table. A population of the same sex- and age-structure is assumed here.

disease: one mutation in a single stem cell, in each of three distinctive sets of stem cells, leads to the growth of three forbidden clones (6).

The mode of the curve for females occurs at about 20 years of age, whereas that for males probably occurs at about 40 years of age. Above the age of 5 years, the average latent period between the end of initiation (marked by the third initiating somatic mutation) and the first onset of SLE, appears to be about 5 years in women, and 2.5 years in men.

Table III and Fig. 4 show the corresponding sex- and age-distributions for the series of SLE patients studied in the Netherlands (1). The solid curves are based on equations (6) and (7) and they therefore have the same form as those in Fig. 3. The fit of the data for males is much better than for the U.S. series. However, the k values differ slightly, and the initiation mode for females in the Netherlands series occurs at about 23 years—as compared with 20 years in the U.S. series. The mode for males occurs at about 46 years—as compared with 40 years in the U.S. series. In view of: (i) the rather small numbers, (ii) uncertainties in the age-structure of the population at risk, and (iii) diagnostic problems, we are unable to decide whether these differences are genuine, but they might be.

Latent period differences are also suggested. Above 10 years of age, the correction applied for the Netherlands series is 7 years for females—as compared with 5 years in the U.S. series; and 3.5 years for males—as opposed to 2.5 years in

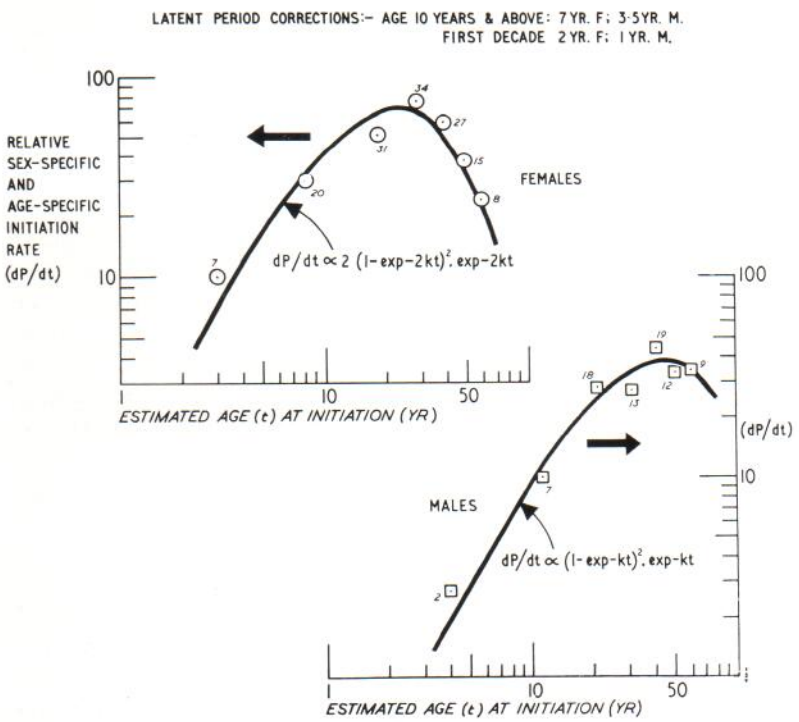

Fig. 4. Relative sex-specific and age-specific initiation-rates, (dP/dt), in relation to estimated age (t) at initiation, for systemic lupus erythematosus. Findings for a series from the Netherlands. See reference (1) and Table III.

the U.S. series. It has been found previously that in some diseases, the latent period can differ appreciably from one environment to another (3, 5). Clinical and epidemiological evidence reveals the precipitating and exacerbating action of various environmental agents—from microorganisms to drugs—and hence associations between latent period and environment can be expected.

DISCUSSION

The new data from the Netherlands for the age-patterns of DLE and SLE show certain features that resemble closely those of previously published series (6, 7). Thus, with DLE, the *form* of the sex-specific and age-specific initiation curves, for similarly predisposed sub-groups, appears to be much the same as in series from Denmark, England, Sweden and the United States. The age-pattern for the new series of DLE patients supports our earlier conclusion that at least three genetically-distinctive groups are predisposed to DLE. A further sub-division of DLE will probably be necessary in view of the presence/absence of immunoglobulin at the dermal-epidermal junction (1).

According to our unified theory of growth and disease (3–7), the number and type of somatic mutations initiating a specific autoaggressive disease, in similarly-predisposed individuals, should be independent of environment. When predisposing genes, and those undergoing somatic mutation are identical, the age at which peak rates of initiation occur should also be effectively independent of *ordinary* environments.

Although the age-patterns for DLE in various clinical series (7, 14, 20, 21) indicate that the kinetics of initiation for the three main subgroups A, B and C differ little, if at all, from country to country, the corresponding statistics for SLE suggest that the average rates of initiation of this disease might be slightly lower in the Netherlands community than in two U.S. communities (11, 17). Confirmation of this rather small difference will require careful and extensive epidemiological investigations, using strictly comparable diagnostic criteria.

Sex-ratio for SLE

Perhaps the most intriguing contrast between the Netherlands series and several others, relates to the sex-ratio of patients with SLE. The crude sex-ratio:—(number of female patients/number of male patients) is $142/80 \simeq 1.8$, in contrast to $723/99 \simeq 7.3$ for the combined (U.S.) series of Kellum & Haserick (17), and Dubois (11). These crude ratios depend on the sex- and age-structures of populations. A better comparison for genetic analysis is provided by S_F/S_M, which is the ratio of the proportion of females predisposed at birth, to the corresponding proportion of males. This can be calculated (3) from the curves in Figs. 3 and 4. For the Netherlands series, $S_F/S_M \simeq 0.9$; for the combined U.S. series, $S_F/S_M \simeq 4.5$.

We proposed (6) that the female preponderance in English and U.S. populations could be explained if three X-linked alleles, each with dominant effect, contribute to the SLE genotype. (Autosomal factors are also implicated in the polygenic predisposition (6).) On this view of the sex-difference, and from conventional genetic assumptions, the average frequency of each of the three predisposing X-linked alleles in the U.S. populations (11, 17) would need to be about 0.3_5 (6). To explain the sex-ratio $S_F/S_M \simeq 0.9$ in the Netherlands series, we have to introduce other ideas (3, 4).

Reversals in the sex ratio over a period of time, and with geography, for late-onset diabetes mellitus (3, 4); and reversals of the sex ratio with geography in early-onset ulcerative colitis (5) have been discussed previously, and they could have a bearing on our present problem. In certain communities, and at certain periods, an excess of females predisposed to these diseases has been observed. This could be explained if an X-linked allele, with dominant effect, features in the predisposing genotype. But in other communities, or in the same community at a different period, an excess of predisposing males has been observed and this could be attributed to a predisposing X-linked allele with recessive expression. That is to say, the same X-linked allele appears to have a 'dominant' expression in some situations, and a 'recessive' expression in others.

Hypothesis of genetic dichotomy

Reversals of the sex-ratio have been interpreted by the hypothesis of *genetic dichotomy* (3, 4). The frequency of alleles predisposing to autoaggressive ('autoimmune') diseases is usually high—often

between 0.2 and 0.8—and therefore indicative of genetic polymorphism (3). For several reasons (3, 4), we have suggested that one allele at such a locus corresponds to transcription from one strand of the DNA double-helix, and that the alternative major allele corresponds to transcription from the complementary, anti-parallel strand. The strand which is transcribed depends, perhaps, on a polypeptide chain or other factor, such as RNA, which complexes with the noninformational strand of DNA to block transcription from that strand (4).

Commonly, as in DLE (sub-groups B and C), and in SLE, the average rate of certain somatic mutations initiating autoaggressive disease is twice as high in women as in men (3, 6, 7). This rate factor of 2 to 1 probably arises when an X-linked gene undergoes somatic mutation. We have suggested that females who are genotypically heterozygous at such X-linked loci become, during embryogenesis, phenotypically homozygous in their central growth-control stem cells (3, 4). This change in gene expression might be achieved through a directed transition during embryonic induction (3, 4). The stem cells in which the induction takes place are at somatic mutational risk in autoaggressive disease and they are probably located mainly, or exclusively, in the bone marrow (3). Significantly, cells in this anatomical location do not exhibit Barr bodies (12), and hence, on cytogenetic grounds, there is no objection to the hypothesis that genes on both X-chromosomes are active, and at somatic mutational risk, in growth-control stem cells.

Genetic dichotomy and the sex-ratio for DLE and SLE

Suppose the two major alleles at a predisposing X-linked locus are designated *Xa1* and *Xa2*, and that in disease D, the allele *Xa1* mutates in somatic cells to *Xa2* to contribute to the initiation of the disease process. Consider females who are genotypically heterozygous (*Xa1*/*Xa2*) at this locus. Then, according to our theory, they become phenotypically either *Xa1*/*Xa1*, or *Xa2*/*Xa2*, in relevant growth-control cells, through an induction mechanism during embryogenesis. Alleles at other (autosomal) loci probably determine which one of these alternative transitions is effected (3, 4). If in one population the developmental transition $Xa1/Xa2 \rightarrow Xa1/Xa1$ predominates, then an excess of predisposed females will be observed, and *Xa1* will appear to be 'dominant' in action. However, if the transition $Xa1/Xa2 \rightarrow Xa2/Xa2$ predominates, then more males than females will be predisposed to disease D in that population, and *Xa1* will appear to be a 'recessive' allele. We also have to consider that, in certain genotypes, the transition $Xa2/Xa2 \rightarrow Xa1/Xa1$ might occur during embryogenesis.

One important consequence of this scheme should be stressed. Suppose the frequency of a dominant-effect predisposing X-linked allele is f_X. On the conventional view, and assuming equilibrium and no selection effects, the ratio S_F/S_M of predisposed females to predisposed males is given by $\{f_x^2 + 2f_x(1-f_x)\}/f_x$, which is $2-f_x$.

The maximum value of this ratio tends towards 2, as f_X tends to zero. If, however, directed transitions such as $Xa2/Xa2 \rightarrow Xa1/Xa1$ can occur during embryogenesis, this restriction in the ratio of S_F to S_M no longer holds, and values in excess of 2 become possible.

In the Netherlands series of DLE patients, the sex ratio ($S_{A,F}/S_{A,M}$) for sub-group A is about 4, and for the combined Danish, English, Swedish and U.S. series, the sex-ratio ($S_{C,F}/S_{C,M}$) for sub-group C is about 2.6. From the preceding arguments, each of these examples of relatively high (F/M) ratios could be accounted for in terms of a single predisposing allele at an X-linked locus.

Originally (6) we interpreted the high F/M sex-ratio in the U.S. series of SLE patients ($S_F/S_M \simeq 4.5$) in terms of three dominant-effect X-linked alleles, and we still believe this to be a plausible interpretation in view of the nature and number of the random events that initiate this disease. We equate these events with three independent somatic mutations, each of which presumably affects either the same or different X-linked genes, because the average rate of each somatic mutation in women is double that in men. However, we cannot as yet eliminate the possibility that a single predisposing X-linked allele is responsible for the high value of S_F/S_M in U.S. and English populations.

If we retain the hypothesis of three predisposing X-linked alleles then we have to account for the very low sex-ratio ($S_F/S_M \simeq 0.9$) in the Netherlands series (1). This can be done if we postulate that at least one of the predisposing X-linked

alleles behaves with recessive effect in the Netherlands population.

Experimental tests of these genetic hypotheses will require the identification of products of X-linked genes by immunological or biochemical techniques.

Target tissue

The question of the nature of the target tissue often arises in connexion with these diseases. According to our unified theory (3–7), the somatic mutations that initiate the growth of forbidden clones occur in stem cells of the central system of growth-control. Normally, the descendants of the non-mutant stem cells regulate the growth and size of target tissues throughout the body. The initiating somatic mutations change growth regulation into autoaggressive attack.

From age-analysis we have found that, for a given environment, the average latent period between the end of initiation and the first onset of symptoms is either of the same duration in men and women, or it is twice as long in women (3–7). In the latter instance, it seems likely that the target tissue lies on the blood side of blood-tissue barriers, and that the primary pathogens in the forbidden clone are small lymphocytes of the kind involved in delayed hypersensitivity and the allograft response (3, 4). We suggest, therefore, that in DLE and SLE, where the average latent period in women appears to be double that in men, the primary target tissue of the autoaggressive attack is the endothelial lining of blood vessels. This agrees with many earlier proposals along these lines, based on histopathological studies, which have been reviewed and confirmed by Baart de la Faille-Kuyper (1).

The question arises as to why a particular pattern of skin and organ involvement should arise in these diseases. According to our theory (3–7), the target cells of the autoaggressive attack bear recognition factors ("tissue coding factors") that are complementary to the mutant lymphocytes of the forbidden clone(s). The distribution of complementary target cells is determined, at least in part, by genetic factors (3, 15). Whether or not an attack at a specific vulnerable site develops, depends on the local concentration of the primary pathogens ("forbidden lymphocytes"). This local concentration will be affected by local vascular factors and by peripheral and central defence mechanisms (3, 6, 7). Defence mechanisms can be impaired by environmental factors—drugs, microorganisms, trauma and stress—which precipitate and exacerbate clinical manifestations of the disease.

Relation of DLE to SLE

The new data from the Netherlands add weight to our earlier concept that discoid and systemic lupus erythematosus are genetically-distinctive diseases (2, 6, 7). Not only the genetics of predisposition, but also the somatic mutations of initiation differ.

We have proposed that, when a genuine transition from DLE to SLE occurs, the affected patient is genetically-predisposed to both diseases (7).

Because predisposition to both nosological entities is probably polygenic (6, 7), one or more of the genes predisposing to one or more of the sub-groups of DLE may well predispose to SLE. That is to say, pleiotropism might be involved. In particular, the genetic relation between the "transitory" form of DLE on the one hand, and SLE on the other, requires further investigation. In one series (2), more than half the patients with DLE had serological abnormalities similar to those seen in patients with SLE, whereas in the remainder such abnormalities were absent. Nevertheless the sex-ratio and the prognosis were similar for both groups (2). It will be interesting to study the prognosis of a series of patients with "transitory" DLE—in which immunoglobulins are present at the dermal–epidermal junction of the uninvolved skin—in relation to those with "proper" DLE in which this abnormality is absent.

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REFERENCES

1. Baart de la Faille-Kuyper, E. H.: Lupus Erythematosus. An Immunohistochemical and Clinical Study of 485 Patients. Grafisch Bedrijf Schotanus & Jens, Utrecht N.V., 1969.
2. Beck, J. S. & Rowell, N. R.: Discoid lupus erythematosus. A study of the clinical features and bio-

chemical and serological abnormalities in 120 patients with observations on the relationship of this disease to systemic lupus erythematosus. Quart J Med, *35:* 119, 1966.
3. Burch, P. R. J.: An Inquiry Concerning Growth, Disease and Ageing. Oliver & Boyd, Edinburgh, 1968, University of Toronto Press, Buffalo, N.Y., 1969.
4. Burch, P. R. J. & Burwell, R. G.: Self and not-self. A clonal induction approach to immunology. Quart Rev Biol *40:* 252, 1965.
5. Burch, P. R. J., de Dombal, F. T. & Watkinson, G.: Aetiology of ulcerative colitis. II. A new hypothesis. Gut *10:* 277, 1969.
6. Burch, P. R. J. & Rowell, N. R.: Systemic lupus erythematosus. Etiologic aspects. Amer J Med *38:* 793, 1965.
7. Burch, P. R. J. & Rowell, N. R.: The sex- and age-distributions of chronic discoid lupus erythematosus in four countries. Acta Dermatovener (Stockholm) *48:* 33, 1968.
8. Burnet, F. M.: The Clonal Selection Theory of Acquired Immunity. Cambridge University Press, 1959.
9. Burnet, F. M.: Somatic mutation and chronic disease. Brit Med J *1:* 338, 1965.
10. Burnet, F. M.: Cellular Immunology. Melbourne University Press, Cambridge University Press, 1969.
11. Dubois, E. L.: Lupus Erythematosus. The Blakiston Division, McGraw-Hill, New York, Toronto, Sydney, London, 1966.
12. Hamerton, J. L.: Lyonisation of the X chromosome. Lancet *1:* 1222, 1964.
13. Harvey, A. M., Shulman, L. E., Tumulty, P. A., Conley, C. L. & Schoenrich, E. H.: Systemic lupus erythematosus: review of the literature and clinical analysis of 138 cases. Medicine (Balt) *33:* 291, 1954.
14. Hough, W.: Discoid lupus erythematosus. Acta Dermatovener (Stockholm) *46:* 240, 1966.
15. Jackson, D. & Burch, P. R. J.: Dental caries as a degenerative disease. Gerontologia *15:* 203, 1969.
16. Jessar, R. A., Lamont-Havers, R. W. & Ragan, C.: Natural history of lupus erythematosus disseminatus. Ann Intern Med *38:* 717, 1953.
17. Kellum, R. E. & Haserick, J. R.: Systemic lupus erythematosus. Arch Intern Med (Chicago) *113:* 200, 1964.
18. Larson, D. L.: Systemic Lupus Erythematosus. Little, Brown & Co., Boston, 1961.
19. Leonhardt, T.: Family studies in systemic lupus erythematosus. Acta Med Scand, Suppl. *416:* 1964.
20. Lodin, A. & Thyresson, N.: Discoid and disseminated lupus erythematosus. Acta Dermatovener (Stockholm) *35:* 429, 1955.
21. Rothfield, M., March, C. A., Miescher, P. & McEwan, C.: Chronic discoid lupus erythematosus. New Eng J Med *269:* 1155, 1963.

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N. R. Rowell, M.D., F.R.C.P.
Consultant Dermatologist
Department of Dermatology
The University of Leeds
The General Infirmary
Leeds 1
England