A Genetic and Statistical Study of Psoriasis

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INTRODUCTION

Two excellent reviews of the literature on psoriasis have been published in recent years, the first by Lerner in 1940 and the second by Romanus in 1945. We shall, therefore, content ourselves with a discussion of the two most extensive statistical investigations of which we are aware, namely those of Hoede (1931) and Romanus (1945).

Hoede (1931) studied the records of 1,437 psoriatic patients seen by various physicians over a period of fifty years. Included among these were 539 patients seen by him in the five years previous to the publication of his paper and from whom he obtained detailed pedigrees. His genetic analysis is based on these pedigrees. His conclusions may be summarized as follows: Among the probands (index cases) males were more frequent than females (828:609); the frequency of the age at onset rises until 20 years and then falls off sharply, onset being earlier in females than in males (based on 959 cases); the proportion of diseased sibs is 4.48 per cent when both parents are healthy and 10.67 per cent when one parent is psoriatic; in families with male probands more male relatives than female relatives are affected with psoriasis, while in families with female probands more females than males are affected (the parents, sibs and children were treated separately; all others were grouped); these differences, while statistically insignificant, are always in the same direction; there is no significant association between the sex of a psoriatic parent and the sex of the proband. Finally, Hoede concluded that "psoriasis is an irregular dominant, which is incompletely sex-limited."

Romanus' (1945) material was composed of patients examined prior to 1922, in either of two hospitals in Stockholm. His follow-up study was begun in 1943: hence a patient to be included in this study had to have been examined at least 21 years prior to the commencement of the follow-up study and had to have survived until the follow-up study was begun. Consequently, of 1,417 patients whose records were examined only 768 (54%) were followed, 438 (31%) were dead, and 211 (15%) could not be traced. The follow-up examination and interview were thoroughly and carefully done. Romanus' conclusions may be summarized as follows: Among the original 1,417 probands, males were more frequent than females (943:474); this was also true among the patients followed, although to a lesser extent than in the larger original group (461:307); in the follow-up group one-half the males were affected before 19 years of age and three-fourths before 26 years, while one-half the females were affected before 12 years of age and three-fourths before 19 years (these values will be

discussed later). Romanus did not separate the probands and their families into groups depending on whether the parents were psoriatic or not, and in computing the frequency of psoriasis among the patients' sibs and children he used only those who were more than 30 years of age. Romanus reported the frequency of psoriasis among the patients' parents to be 8.3 per cent, among sibs 9.0 per cent, and among children 13.0 per cent; he found no evidence of a significant association between the sex of the patient and that of an affected parent or sib. Finally, he concluded that his data indicated "a dominant heredity with a manifestation probability (that is penetrance) of about 18 per cent."

The conclusions of these two workers will be examined in greater detail in a later section of this paper.

It should be stated that with very few exceptions workers in the field seem agreed that a predisposition to psoriasis is inherited via a dominant gene with reduced penetrance. Nevertheless a careful reading of the literature indicates that this hypothesis is based on biased or incompletely analyzed material and that the foregoing hypothesis does not account for such known facts as the increased frequency of psoriasis among the sibs of patients who have a psoriatic parent. We therefore decided to undertake the present investigation, hoping to be able to furnish a clearer picture of the situation than that which exists at present.

THE MATERIAL

The material on which this study is based consists of information concerning parents, sibs, spouses and children obtained from 464 consecutive, and therefore unselected, psoriatic patients examined by members of the Section of Dermatology. The information was collected on a special form, and particular pains were taken to obtain as accurate reports from the patients as possible. Nevertheless, the data undoubtedly contain uncertainties and errors with respect to the ages and to the presence or absence of psoriasis among the patients' relatives. We have exercised every effort to keep these errors to a minimum and know of no way of reducing them further short of interviewing and examining all of the individuals mentioned on the forms. This was not possible for two reasons: (*a*) the relatives were distributed all over the world, and (*b*) many of them were already dead. Although it seems probable that the frequency of psoriasis reported by the patients for relatives is too low, we believe that the errors of reporting made by the patients were of such a nature as not to affect materially any of the conclusions which will be drawn from the study.

Blood uric acid levels were determined for 177 patients and for the available immediate relatives of another 5 patients.[1] The details of this aspect of the study will be reported elsewhere; only the conclusion pertinent to this report will be referred to in this paper.

[1] We wish to express our gratitude to Dr. M. H. Power of the Division of Biochemistry for these determinations.

THE DATA

Age at Onset. The age at onset is that reported by the patient and is subject to many inaccuracies. Some patients came to the Mayo Clinic for reasons other than psoriasis and were unaware of the fact that they had psoriasis, in which event the age of onset is recorded as the age at which, according to the patient's statement, the lesion appeared. In other instances the patient was aware of his psoriasis and reported an age of onset. In some cases this was the age at diagnosis and in others it was the age at which the patient recalled the presence of the first eruption. An additional source of inaccuracy is introduced by the all-too-human characteristic of vagueness about dates. These uncertainties in our data are characteristic of all studies of this type. Hence, while it is possible to compare the results of various studies with each other, it is quite impossible to provide an accurate distribution of age of onset.

TABLE 1. DISTRIBUTION OF THE PROBANDS ACCORDING TO THE REPORTED AGE AT ONSET OF PSORIASIS

AGE, YEARS	TOTAL		MALES		FEMALES	
	Number	Per cent	Number	Per cent	Number	Per cent
0–9	43	9.3	14	5.6	29	13.6
10–19	104	22.5	47	18.7	57	26.8
20–29	100	21.6	62	24.7	38	17.8
30–39	93	20.0	57	22.7	36	16.9
40–49	59	12.7	36	14.3	23	10.8
50–59	48	10.3	24	9.6	24	11.3
60–69	15	3.2	10	4.0	5	2.3
70–79	2	0.4	1	0.4	1	0.5
Total.....	464	100.0	251	100.0	213	100.0

The distribution of the probands at the reported age of onset is shown in table 1. The modal age at onset in females occurs during the age interval 10–19 years and in males during the age period 20–29 years, the average ages of onset being 28 and 32 years, respectively.

Fifty-eight of the patients' sibs were reported to be psoriatic, and for 45 of these the age at onset was reported. The data (table 2) were examined for possible association between the age of onset in the patient and in his affected sib. While the data are few it is clear that they do not indicate any association between the ages of onset of the patient and his affected sib.

The age of onset was reported for only 31 of the 55 affected parents. The data are therefore too few to yield satisfactory information concerning a possible association between the age of onset in the patient and in his affected parent; however, they are presented in table 3 to make them available to supplement other data which may be collected in the future. More data would be necessary before the validity of the apparent correlation between the ages of onset in the

patient and the affected parent could be tested as was done in the case of diabetes by Harris (1950) and by Steinberg and Wilder (1950).

Sex Ratios. Reference to table 1 will show that 251 (54.1%)of the 464 probands were males. The excess of males in our sample is not statistically significant ($P \leqq 0.08$). However, the fact that the sample is relatively small, plus the fact that an excess of males (in some cases a significant excess) has been

TABLE 2. DISTRIBUTION OF PSORIATIC SIBS ACCORDING TO THEIR AGE AT ONSET AND THAT OF THE RELATED PATIENT

AGE OF PATIENT AT ONSET, YEARS	AGE OF SIBS AT ONSET, YEARS							TOTAL	MEAN AGE OF SIBS AT ONSET, YEARS
	0–9	10–19	20–29	30–39	40–49	50–59	60–69		
0–9	—	2	1	1	1	—	—	5	25
10–19	1	6	3	1	3	—	—	14	23
20–29	—	7	3	—	1	2	1	14	29
30–39	—	1	2	4	—	1	—	8	30
40–49	—	—	—	1	—	—	1	2	50
50–59	—	—	1	1	—	—	—	2	28
Total....	1	16	10	8	5	3	2	45	

TABLE 3. DISTRIBUTION OF PSORIATIC PARENTS ACCORDING TO THEIR AGE AT ONSET AND THAT OF THE RELATED PATIENT

AGE OF PATIENT AT ONSET, YEARS	AGE OF PARENTS AT ONSET, YEARS								
	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	Unknown
0–9	—	3	—	1	—	—	—	—	2
10–19	1	—	3	4	2	2	—	—	11
20–29	—	1	—	1	2	—	—	2	4
30–39	—	—	1	—	2	—	1	1	4
40–49	—	—	—	—	—	1	—	2	2
50–59	—	—	—	—	—	—	—	1	1
Total....	1	4	4	6	6	3	1	6	24
Mean age of patients, years.....	15	10	20	15	25	25	35	38	23

reported in almost all previous investigations (see Romanus, 1945, for a review of the literature), requires that a further examination of the data concerning the possible explanation of this excess be undertaken.

The 464 probands had 1,830 sibs. The sex was reported for 1,791 of them; of these 943 (52.6%) were males; the excess over 50 per cent is here significant ($P < 0.05$). A chi-square comparison of the sex ratio among the patients with that found among their sibs showed that a difference as great as or greater than

the one found would be expected to arise by chance in slightly more than 50 per cent of such comparisons. On the basis of this comparison there is no reason to assume a greater frequency of males among psoriatic patients than among their sibs. From this it follows that there is reason to question the biologic significance of the observed excess of males among psoriatic patients.

A further test may be obtained by comparing the frequency of psoriasis among all males in the study (patients and their sibs) with that found among all the females. These frequencies are 24.0 per cent (287/1,194) and 21.9 per cent (232/1,061) respectively. A chi-square test shows that at least as great a difference would occur by chance in about 20 per cent of such comparisons. Here again the analysis indicates that the observed excess of males among psoriatics is probably not of biologic significance. The analysis raises the question whether families of psoriatics tend to have more males in them than do families in general. Discussion of this question will have to be postponed until the data necessary for its analysis are available.

TABLE 4. RELATION BETWEEN THE SEX OF PATIENTS AND THAT OF THEIR AFFECTED PARENTS AND SIBS

PATIENTS	AFFECTED PARENTS		AFFECTED SIBS	
	Male	Female	Male	Female
Male	16	15	23	8
Female	13	11	13	11
Total	29	26	36	19

Table 4 shows the data concerning the relation between the sex of the patient and that of his affected parent (none of the patients reported both parents psoriatic) and sibs (3 sibs whose sex was not reported are not included in the table). Note that the male relative is the more frequently affected regardless of the sex of the patient. The differences, however, are not statistically significant.

Birth Order. Table 5 shows the distribution of the probands according to their order of birth. For obvious reasons the 25 one-child sibships are not included in the table. The rightmost column of the table shows the number of probands expected in each position if no relation between order of birth and susceptibility to psoriasis is assumed. The last row shows the number expected in the entire sample in each birth position. These figures are derived by summing the appropriate figures of the rightmost column. Thus for the first and second birth orders all the values in the rightmost column were totaled; for the order 3 all except the expected values for two-sib families were totaled; for order 4 all except the expected values for two-sib and three-sib families were totaled, and so on. The row above the last row shows the number observed in each birth

order. The deviations are clearly small. A chi-square test based on a 2 by 10 table (the values for birth orders 10–13 were combined) gave a chi-square value of 4.894 with 9 degrees of freedom, and $P > 0.80$.

Hyperuricemia and Psoriasis. Lobitz and Brunsting (unpublished data quoted in Ormsby and Montgomery [1948] and personal communication) found an increase in the concentration of uric acid in the serum of a high percentage of patients hospitalized for psoriasis. As a follow-up of this study the serum uric acid levels were determined for 177 patients (102 males, 75 females). Concentrations less than 6 mg. per 100 cc. of serum in the male and 5 mg. per 100 cc.

TABLE 5. BIRTH ORDER OF PATIENTS

SIZE OF FAMILY	BIRTH ORDER													TOTAL	NUMBER EXPECTED IN EACH BIRTH POSITION
	1	2	3	4	5	6	7	8	9	10	11	12	13		
2	29	31	—	—	—	—	—	—	—	—	—	—	—	60	30.0
3	32	31	21	—	—	—	—	—	—	—	—	—	—	84	28.0
4	17	20	18	14	—	—	—	—	—	—	—	—	—	69	17.2
5	10	6	17	14	18	—	—	—	—	—	—	—	—	65	13.0
6	4	5	13	7	5	6	—	—	—	—	—	—	—	40	6.7
7	2	9	4	6	3	10	2	—	—	—	—	—	—	36	5.1
8	3	3	6	2	1	6	4	1	—	—	—	—	—	26	3.2
9	3	1	2	7	4	3	4	1	1	—	—	—	—	26	2.9
10	3	1	4	0	1	0	1	2	2	2	—	—	—	16	1.6
11	0	0	0	1	2	0	2	0	1	1	1	—	—	8	0.7
12	0	0	0	0	0	0	1	0	1	0	0	1	—	3	0.3
13	1	0	0	1	0	1	1	0	1	0	1	0	0	6	0.5
Total observed....	104	107	85	52	34	26	15	4	6	3	2	1	0	439	
Total expected....	109.2	109.2	79.2	51.2	34.0	21.0	14.3	9.2	6.0	3.1	1.5	0.8	0.5	439.2	

of serum in the female were considered normal. Four male and 6 female patients were less than 20 years of age and were not included in this portion of the analysis because it has been shown that uric acid concentrations are not elevated in young persons possessing the genetic factor for gouty hyperuricemia (Smyth *et al.*, 1948). Among the males 48 per cent (47/98) and among the females 27 per cent (19/69) showed hyperuricemia. The data thus confirm Lobitz and Brunsting's findings.

Both parents of each of 4 unrelated patients were tested for hyperuricemia. All 8 parents had levels of uric acid well within the normal range of values. It thus appears that the relation between hyperuricemia and psoriasis is not the same as that between hyperuricemia and gout, where it has been shown that hyperuricemia is present in at least one of a gouty patient's parents and where it

has been shown also that hyperuricemia may be present prior to the development of clinical symptoms of gout (Smyth *et al.*, 1948; Stecher *et al.*, 1949).

Genetic Analysis. It has been shown in a previous section of this paper that there is no association between the sex of the proband and that of his affected parent or sib; hence for the discussion which follows we may ignore the sex of the individuals concerned. The sibship size and the number of affected individuals are presented in table 6 for those patients neither of whose parents were psoriatic and for those with one parent psoriatic. No patient reported both parents psoriatic. It is clear from the table that there is no tendency for a disproportionate number of the affected sibs to come from one or two families.

TABLE 6. SIZE OF FAMILY AND NUMBER AFFECTED, INCLUDING PATIENT

SIZE OF FAMILY	NUMBER AFFECTED						
	Neither parent psoriatic				One parent psoriatic		
	1	2	3	4	1	2	3
1	22	—	—	—	3	—	—
2	45	5	—	—	6	4	—
3	67	5	—	—	11	—	1
4	55	6	—	—	6	2	—
5	59	3	—	—	3	—	—
6	32	5	—	—	3	—	—
7	26	2	—	—	3	4	1
8	22	1	1	—	2	—	—
9	22	2	—	—	1	—	1
10	11	1	1	—	2	—	1
11	5	2	—	—	1	—	—
12	2	1	—	—	—	—	—
13	5	0	—	1	—	—	—
Total.....	373	33	2	1	41	10	4

No sibship had more than 4 affected members including the proband, and the one sibship with 4 affected contained a total of 13 children. Six sibships had 3 affected members each. These sibships consisted of one each with 3, 7, 8 and 9 members, and two with 10 members.

When neither of the patient's parents was psoriatic 2.45 per cent (40/1,630) of the sibs were psoriatic, while when one parent was psoriatic 9.00 per cent (18/200) were psoriatic. As mentioned previously, 55 (5.9%) of the patients' parents were psoriatic.

In our sample psoriasis occurs among the patients' sibs almost four (3.7) times as frequently when one parent is psoriatic as when neither parent is psoriatic, while in Hoede's sample the corresponding ratio is almost 2.5. While it cannot be said with certainty at this time what the increase in frequency is

when one parent is psoriatic, it can be stated that a marked increase does occur and that it is probably more than double. Although these data confirm the presence of an hereditary component in the causation of psoriasis they contradict the conclusion advanced by Hoede, Lerner, Romanus and others that this component is inherited as an irregular dominant—that is, as a dominant with incomplete penetrance. Such an hereditary pattern requires that the frequency of psoriasis among the patients' sibs be independent of the presence or absence of psoriasis in a parent.

What then is a likely genetic explanation of these data? We wish to state at once that a satisfactory answer cannot be given at this time. However, certain possibilities can be ruled out and we should like to consider them. Any hypothesis of sex-linked inheritance, either partial or complete, is incompatible with the data because of the independence of the sex of the patient and that of the affected parent and of the affected sibs; secondly, no single-gene hypothesis,

TABLE 7. FREQUENCY OF NON-CONSANGUINEOUS AND OF CONSANGUINEOUS MARRIAGES AMONG PARENTS OF PSORIATIC PATIENTS

TYPE OF MATING	NUMBER OF MARRIAGES		
	Non-consanguineous	Consanguineous	No information
One parent psoriatic	52	1*	2
Neither parent psoriatic	389	3†	17

* First cousins.

† One marriage of first cousins; one of cousins, degree not stated; one of uncle and niece.

dominant or recessive, with or without complete penetrance, can explain the present set of data, although a single *recessive* gene with incomplete penetrance could possibly explain Hoede's data. We are forced to assume more than a single gene to explain the observations.

One possibility is that the clinically observed group of psoriatic patients is genetically heterogeneous and that different loci are involved as units—one or more dominant and one or more recessive. In this case it would be reasonable to assume that the patients with non-psoriatic parents are predominantly homozygous recessive, while those with a psoriatic parent are heterozygous for a dominant gene. We should expect, therefore, in a sufficiently large sample, to find a greater (though perhaps not much greater) frequency of consanguinity among the parents of the former group of patients than among the parents of the latter group. Our sample is too small to enable us to test this point adequately, but the data—which, incidentally, lend no support to this view—are recorded in table 7 for future use.

On this same assumption we should expect also to find a greater frequency of psoriasis among the children of the patients who have a psoriatic parent than among those with healthy parents. We should like to point out that the fre-

quencies to be presented are low because the average age of the patients' children is low. It is not necessary for the present purposes to make corrections for this because the point at issue is not the absolute frequencies but the relative frequency of the disease among the children of patients with neither parent psoriatic as compared to that observed among the children of patients with one psoriatic parent. The frequency of psoriasis among the former group of children is 2.5 per cent (16/637) and among the latter 1.7 per cent (1/59). The figures are clearly not in accord with the prediction but there are too few offspring from patients with a psoriatic parent to establish the point with statistical certainty.

TABLE 8. CALCULATION OF THE NUMBER OF POTENTIAL PSORIATICS AND THE PERCENTAGE RECOGNIZED AS FRANK PSORIATICS

AGE, YEARS	1 PERCENTAGE OF THOSE STARTING A GIVEN DECADE WHO SURVIVE IT*	2 PERCENTAGE OF PATIENTS OCCURRING IN EACH DECADE OF AGE	3 RELATIVE NUMBER OF POTENTIAL PSORIATICS	4=2+3 TOTAL OF POTENTIAL AND FRANK PSORIATICS	5=2/4 PERCENTAGE IDENTIFIABLE
0–9	96.2	9.3	99.1	108.4	8.6
10–19	99.2	22.5	75.8	98.3	22.9
20–29	98.6	21.6	53.1	74.7	28.9
30–39	97.8	20.0	31.9	51.9	38.5
40–49	94.9	12.7	17.6	30.3	41.9
50–59	88.4	10.3	5.3	15.6	66.0
60–69	75.1	3.2	0.8	4.0	80.0
70–79	51.4	0.4	0.0	0.4	100.0

* Estimated for United States white population, July 1, 1948.

It has been noted that in the present sample psoriasis occurs among the patients' sibs with a frequency of 9.00 per cent when one parent is affected and with a frequency of 2.45 per cent when neither parent is affected. Because of the variability of the age of onset of psoriasis the frequencies observed are lower than they would be if all the individuals in the sample had reached, say, 70 years of age. Approximate corrections can be made for the fact that the ages of the individuals in the sample vary from the first through the ninth decade. A very useful method has been developed by Pincus and White (1933). It is based on the reasonable assumptions that the survival rate of those not frankly afflicted with the disease under review but genetically liable to it is not different from that of the general population and that the distribution of the age of onset derived from the present sample is representative of the age of onset in the patients' sibs.

The details of the procedure may be explained with the aid of tables 8 and 9. Column 1 of table 8 shows the percentage surviving each decade of life (based on life tables of the estimated United States white population as of July 1, 1941, published in *Vital Statistics of the United States*, 1948), and column

2 shows the percentage of the probands which became psoriatic in the indicated decade. The 0.4 per cent of the patients who became ill during the eighth decade of life represent 51.4 per cent (column 1, table 8) of those who were potential psoriatics in the seventh decade. This equals a relative total of 0.8 in the seventh decade who were potential but not actual psoriatics. This figure is entered in column 3 and added to the 3.2 who were actual psoriatics in the seventh decade to give the value 4.0 entered in column 4. These equal 75.1 per cent of the total who were potential psoriatics in the sixth decade. The corrected value, 5.3, is entered in column 3. The procedure outlined is repeated until columns 3 and 4 are completed. It is now possible to compute the proportion of actual psor-

TABLE 9. MEAN PROPORTION OF POTENTIAL PSORIATICS DETECTED AMONG THE PATIENTS' SIBS IN THE PRESENT SAMPLE

AGE, YEARS	NEITHER PARENT PSORIATIC			ONE PARENT PSORIATIC		
	1 Percentage of sibs of this age	2 Percentage identifiable	3 Relative number in percentage which would be detected	1 Percentage of sibs of this age	2 Percentage identifiable	3 Relative number in percentage which would be detected
0–9	4.6	8.6	0.4	8.3	8.6	0.7
10–19	5.5	22.9	1.3	16.6	22.9	3.8
20–29	12.3	28.9	3.6	13.5	28.9	3.9
30–39	18.3	38.5	7.0	18.6	38.5	7.2
40–49	22.6	41.9	9.5	19.2	41.9	8.0
50–59	20.8	66.0	13.7	16.1	66.0	10.6
60–69	12.0	80.0	9.6	6.2	80.0	5.0
70–79	3.5	100.0	3.5	1.0	100.0	1.0
80–89	0.4	100.0	0.4	0.5	100.0	0.5
Total.....			49.0			40.7

iatics realized at each decade from among the total of all psoriatics (potential as well as actual) present in the decade. This equals the number in column 2 divided by the number in column 4 and multiplied by 100 to give a percentage value. The results are entered in column 5. These values may now be used to compute the proportion of potential psoriatics among the patients' sibs who would be recognized as actual psoriatics. The figures are in table 9. The values in column 1 show the age distribution of the patients' sibs; the age of the sibs who were psoriatic was taken as that at which the onset of psoriasis occurred. Column 2 reproduces the figures of column 5 of table 8. Column 3 of table 9 is derived by multiplying column 1 by column 2 and dividing by 100, and shows the proportion of all potential psoriatics in this population of sibs that would be recognized in the indicated decade. The total of column 3 equals the total proportion of the potential psoriatics that would be recognized in this popula-

tion. Thus when neither parent is psoriatic 49.0 per cent of the potentially psoriatic sibs of the patient would be recognized as such. The corresponding value when one parent is psoriatic is 40.7 per cent. These figures may be used to correct the observed frequencies of actual psoriatic patients, namely, 2.45 and 9.00 per cent respectively, to obtain the total frequency of potential plus actual psoriatics in the sample. The corrected values are 5.0 and 22.1. It must be emphasized that these corrections are very approximate. They do, however, yield values which do not differ greatly from those which would be obtained if psoriatics were homozygous recessive for two pairs of genes, if it is assumed that among matings which yield psoriatic offspring those matings in which both partners are nonpsoriatic are predominantly between a double homozygote and a double heterozygote. Thus when both parents are normal the mating is $AaBb \times AaBb$, which would yield 6.25 per cent of potential psoriatics (the derived value is 5.0 per cent). When one parent is psoriatic the mating would be $aabb \times AaBb$, which would yield 25.0 per cent of potential psoriatics (the derived value is 22.1 per cent). We do not wish to imply that this hypothesis is the correct explanation of the data; we offer it merely as a *possible* explanation and use it to help emphasize that a single-gene hypothesis cannot explain the observations.

DISCUSSION

Age at Onset. The modal and the average ages of onset for the patients reported in the present study are in agreement with those published by previous investigators (Steinke, 1935; Romanus, 1945; and others—see Romanus for review) in that they show an earlier age at onset in females than in males. The values obtained (modes in the age interval 10–19 in females and 20–29 in males; mean ages of 28 and 32 years, respectively) are in agreement with Steinke's but differ considerably from the average ages at onset reported by Romanus, namely, 14 and 18 years in females and males, respectively. This difference is due to the manner in which Romanus selected his probands. As mentioned in a previous section, each patient in Romanus' study had to have been examined for psoriasis at least 21 years before Romanus began his study of him. It follows, therefore, that in general those with an older age of onset would be less likely to have survived the necessary twenty-one-year interval, and consequently the observed sample is biased in the direction of having an excess of individuals with early onset of psoriasis.

Sex Ratios. The analysis presented earlier in this paper indicates that the excess of males found among psoriatic patients in this as well as all other sizable studies probably does not indicate an increased susceptibility to psoriasis among males. We suggest that the excess of males found among psoriatics may not result from a greater susceptibility among males but rather from the fact that there are in these families more males available to become affected.

We have already indicated the necessity for investigating the reason for this excess of males among these families. Unfortunately data for such an investigation are not available at present.

Hoede (1931) reported an excess of affected males among the relatives of male patients and an excess of affected females among the relatives of female patients. Sibs, parents and children were tabulated separately, all other relatives were reported in a group. Our data for parents and sibs differ from Hoede's in that more male than female relatives (parents and sibs) were affected regardless of the sex of the patient (table 4). None of the differences found by Hoede or by us are statistically significant. They are mentioned only because of the stress that Hoede placed on them.

Hoede was sufficiently impressed by the fact that in four sets of comparisons (sex of parents, sibs, children, and all other relatives with the sex of the patient) no reversal occurred to lead him to postulate a sex-limited form of inheritance. However, Hoede's numbers are small, two of the comparisons differ by only one individual, and a third shows equality of numbers. Finally Hoede himself pointed out that a bias may arise because female patients are probably better informed about the occurrence of psoriasis among their female relations and male patients about its occurrence among their male relations, particularly among those more distantly related, and in fact the greatest difference reported in his data occurs among the group of more distant relatives.

In the light of the foregoing analysis of the sex ratios and of the relation between the sex of the patients and that of their affected relatives it seems unnecessary to us to assume sex linkage or sex limitation as a factor in the occurrence of psoriasis.

Genetic Analysis. Before entering into a discussion of our data we should like to discuss Hoede's statement that any investigation of the familial incidence of psoriasis which results in an incidence of less than 33 per cent is one in which the material has not been sufficiently studied. We wish to discuss the meaning, or rather the lack of meaning, of the term "familial incidence." The first difficulty that arises with this term is the meaning of "familial." Many investigators use this term to include any blood relation that can be traced. It is in this sense that Hoede used it. Unfortunately these authors generally fail to state how many of the patients' "uncles and his cousins and his aunts" (with apologies to Gilbert and Sullivan) they have traced. Clearly "familial incidence" depends on this point and in this sense, we suppose, Hoede's statement has some merit. But "familial incidence" depends also on family size. For example, if one were unfortunate enough to encounter only one-child families the "familial incidence" in his study—although worked out in greatest detail—would be much lower than that which would be found by an investigation of only ten-child families. This illustration is extreme, of course, but it does make our point. It is worth noting also that the current trend toward

smaller family size will inevitably lead to a reduction in "familial incidence." Obviously a measure as ill-defined and unstable as this should be abandoned. The statistics that should be reported are the frequencies of occurrence of the disease among the patients' parents, sibs (preferably separated into groups based on whether one or both parents are affected), children (again separated into groups based on whether or not the patient's spouse is affected), and other *specified* relatives, if available. Proper attention will, of course, have to be paid to the method of ascertainment and to corrections, where pertinent, for variable age of onset.

Our data confirm the conclusions of previous investigators that there is an important genetic component in the causation of psoriasis. They do not, however, confirm the hypothesis advanced by these workers that this genetic component consists of a dominant gene with incomplete penetrance or, as Hoede claims, a dominant gene with incomplete penetrance and sex-limited expression (see Romanus, 1945, for a detailed review of the literature). We find that the data (ours as well as Hoede's) cannot be explained by assuming a single dominant gene. It is most probable that any correct explanation will require more than one gene locus, and we have tentatively advanced a hypothesis involving two recessive genes because it approximates our data reasonably well.

Hoede, Lerner and others have advanced the argument that recessive heredity cannot be involved in the causation of psoriasis because the frequency of consanguinity among the patients' parents is too low. This argument is invalid because it does not take into account the fact that the expected increase in consanguinity is low when the gene frequency is high. There is no adequate information concerning the frequency of psoriasis in the population; however, an estimate by Gahan (1943) places the frequency at 1 per cent. This of course means a very high gene frequency and consequently only a slight increase in consanguinity would be expected. Another difficulty arises from our lack of knowledge of the frequency of consanguineous marriages in the United States as a whole or in any of the local areas. Data collected by Glass (personal communication) in Baltimore from pregnant women and by Steinberg (unpublished data) in Rochester, Minnesota, from women during the lying-in period indicate the remarkably low frequency of 0.05 per cent in these two widely separated cities. These figures, it must be emphasized, refer to relatively recent marriages and may be considerably lower than would be found for an earlier generation. Nevertheless, they do indicate a much lower frequency than had been supposed by many investigators.

Our discussion of the genetics of psoriasis is limited to the inheritance of a predisposition to the disease. We have not investigated the problem of the variability of the age of onset. It is possible that there is a genetic component involved in the determination of the age of onset. The analysis of this would require not only a large number of pedigrees with affected parents, sibs and chil-

dren (which we do not have) but also painfully careful attention to pertinent common environmental factors among the members of these families and to accuracy in the determination of the ages of onset.

SUMMARY

1. The data concerning 464 consecutive psoriatic patients and the information obtained from them concerning their parents, sibs and children were analyzed statistically and genetically.

2. The modal age at onset among the patients in this study is, in females, 10–19 years; in males, 20–29 years; the mean ages are 28 and 32 years, respectively.

3. The excess of male psoriatics found among the patients is shown to be essentially the same as the excess of males in these families as a whole. It is shown also that the frequency of psoriasis among the males in these 464 families is not significantly greater than that among the females. There is reason, therefore, to question the biologic significance of the excess of males found among psoriatic patients.

4. No relation was found between the sex of the patient and that of his or her affected parent or sib.

5. There is no relation between birth order and the occurrence of psoriasis.

6. Hyperuricemia occurred in 48 per cent of 98 adult psoriatic males tested and in 27 per cent of 69 psoriatic females tested.

7. All of the 8 parents of 4 psoriatic patients whose serum uric acid level was determined had levels well within the normal range.

8. The frequency of psoriasis among the patients' sibs when neither of the patients' parents was psoriatic was 2.45 per cent. It was 9.00 per cent when one parent was psoriatic. No patient reported both parents psoriatic.

9. The frequency of psoriasis among the patients' parents was 5.9 per cent.

10. The data indicate the presence of a hereditary component in the causation of psoriasis. This component is not—as has been postulated by previous workers —a single dominant gene with incomplete penetrance. It is necessary to assume a minimum of two genes to explain the data. A possible, but not necessarily correct, explanation based on two autosomal recessive genes, the double recessive being predisposed to psoriasis, is advanced.

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