Acta Dermato-Venereologica, Vol. 40, p. 285–306 (1960)

PRURIGO BESNIER (ATOPIC DERMATITIS) WITH SPECIAL REFERENCE TO THE ROLE OF ALLERGIC FACTORS

I. The influence of atopic hereditary factors

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Much work has been carried out concerning the allergic factors in Prurigo Besnier (PB)[1] especially by use of intracutaneous and scratch tests (Cooke, Sulzberger and Baer, Hill, Haxthausen, Hellerström, Schnyder and others). There has been a great deal of discussion on the subject and as the problem is not yet entirely resolved it seemed justifiable to contribute to this as yet incompletely elucidated problem with experiences gained from a considerable follow-up series of patients. This series comprises 1,200 individuals with PB among the in-patients of the Karolinska Sjukhuset during the years 1953—59; patients treated in 1959 and 1960 are also included in some instances. The 1954 portion of this patient material was elaborated on by Hellerström and Lidman (33) from several viewpoints, which the author also in part discusses in the following. As many considerations arose in the above group of subjects the author will divide the study in several parts which will be published in several communications. In this first communication the influence of hereditary factors is considered. Only mention of the most essential literature references has been made.

Wise and Sulzberger (91) were the first to place PB in the atopic group of *Coca* one of the important characteristics of which is heredity; the atopic manifestation develops on the basis of hereditary disposition. By now it is almost unanimously accepted that it is not the allergic manifestation itself that is inherited, but the allergic disposition (18). The mechanism of the latter is much discussed in the literature. An argument against a recessive (1, 84) mechanism is the fact that often only non-allergic children are born in marriages where both parents are allergic, while it is an argument against dominance (18, 80, 11, 28) that there can be allergic descendants even if both parents are non-allergic. Nor does it facilitate a solution to assume allelomorph gene pairs (93, 88) or double gene factors (36). It seems most reasonable to assume an intermittent dominance (65, 74). The modern opinion (14) is that the limit between dominant and recessive gene is not very sharp since the difference between homo- and heterozygotes in certain "hereditary" diseases is only quantitative. According to Schnyder (72), patients with PB or respiratory allergy depend on the same alleles at the gene locus additioning each other.

[1] Other synonyms of this disease are atopic dermatitis, constitutional neurodermatitis, endogen eczema, späteksudatives Eczematoid etc.

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From the point of view of penetrance about every fourth gene carrier attracts PB (72). This seems a reasonable figure, considering that besides sensitization numerous other causes contribute to the manifestation of an allergic symptom and that even non-allergic mechanisms can play an important part in PB.

It should be mentioned that the age of the patients examined is important in judging the allergic manifestations, as certain allergic manifestations only appear in later years. The age of twenty-one must be considered as decisive from this point of view (10, 38). As a rule there is no sexual disposition in connection with the heredity. Some writers assume heredity of shock organs in order to explain that certain allergic manifestations in some families appear through several generations, or assume that among the family traits of, e. g., asthmatics mainly asthma occurs while among those with allergic rhinitis mainly rhinitis occurs (15, 79). But according to Urbach (86) the circumstances of exposure and some psychological factors can influence the organ-heredity. A contribution of decisive importance would seem to be the recent statement of Schnyder (72) that atopia is different in conception from the genetic and the allergy points of view, since (a) the atopic allergy factors play different roles in various atopic pathological pictures, (b) PB patients and PB patients with respiratory allergy show a different family pathology picture and (c) it can be proved from a hereditary point of view that intracutaneous test-positive and negative PB (resp. asthma) patients behave identically.

In connection with the latter question the author attempts to furnish further data:

in Part I he will elucidate the relationship between intracutaneous tests and the heredity factor,

in Part II, the connection between vasofunctional tests and heredity is examined in view of the aetiological importance of other factors in PB,

in Part III a contribution is made to the problem by elaborating the data on twin pairs in the patient material.

Part I

Relationship between intracutaneous tests and the heredity factor

Introduction

The problem of the relationship between skin tests of the immediate type and heredity already arose in connection with bronchial asthma, where Adkinson (1) found that there was no difference from the point of view of heredity between test-positive and test-negative asthmatics. Schwartz (74), also, found that from this point of view there was no difference between allergic asthmatics (patients with positive skin test agreeing with the history) and non-allergic asthmatics. As already mentioned, the same was found by Schnyder, whether respiratory allergy or PB occurred in the history of the test-positive or test-negative patient (72).

The proportion of positive heredity in PB patients is a matter for discussion, the divergences being mainly due to data being composed in different ways or to the inclusion of different manifestations. If only asthma, atopic rhinitis and

PB (atopic heredity) are taken into consideration, the following grouping can be made:

Rost-Marchionini	(66)	67 %
Sulzberger-Goodman	(83)	50 %
Nexmand	(53)	43 %
Walzer	(89)	58 %
Baer	(2)	62 %
Korting	(40)	71 %
"	(41)	63 %
Hellerström-Lidman	(33)	68 %

Of course even within the atopic diseases proper a number of sources of error are possible in regard to anamnestic data, such as in the differentiation of eczema and the evaluation of old age asthma.

According to numerous opinions (18, 80, 43, 4) the appearance of the atopic symptom is influenced by heredity, so that the allergic manifestation will be noticeable earlier for instance in the case of bilateral hereditary taint. Thus when the hereditary taint is only unilateral, the atopic manifestation will only appear in the course of the 10th year of life in one-third of the cases, and when there is negative heredity only in one-fifth (88). Other writers deny on statistical grounds the influence of heredity factors in the onset (60, 57, 74). This question is of obvious importance as the effect of the hereditary factors as against exposure will be considerably enhanced if a manifestation occurs very early e. g. immediately after birth. Maternal reagin transmission and diaplacentary sensitization have also been mentioned as reasons for early atopic manifestations in infants (61) and even the influence of mother's milk was considered. The majority of writers take a negative attitude to this incompletely settled question; thus it can be proved that from the point of view of the onset of infantile eczema the difference between artificial nutrition and mother's milk is not significant (Edgren, 23). Many communications are known also concerning the onset of PB. On the basis of extensive statistical data complete agreement concerning onset before the fifth year of life can be emphasised:

Nexmand	(53)	80 %
Siemens-Jagtman	(77)	$^2/_3$ + 20 %
Oddoze	(56)	86 %
Hellerström-Lidman	(33)	86 %

In this connection the question of the relationship between *eczema infantile* (EI) and PB has also been much discussed in the literature. Thus, from the point of view of heredity Schnyder only includes cases of PB above the age of 16 years (73) and excludes cases of child eczema in his statistics. The same is true of Quarles van Ufford (58). Evidently EI does not necessarily imply PB, but on the basis of a good deal of experience the point of view can be accepted which considers EI with certain characteristics (heredity, morphology, localization, itching, positive skin tests, etc.) as the infantile phase of PB (atopic dermatitis) (Hill-Sulzberger, 31). It must, however, be stated first, that few PB patients of infantile age occurred in the author's material and, second,

that in most examinations the relationship between age groups and PB was taken into account and furthermore that patients in age groups III and IV (older than 12 years) were the basis for most of the comparisons.

In regard to the onset of respiratory allergies Williams (94), states that in about 38 % of approximately 25,000 asthmatics it takes place under the age of 5 years. This statement agrees well with earlier statistics (10, 58). On the other hand, the first manifestation of allergic rhinitis occurs mostly between the age of 10 and 30.

The writer's investigations

The data of the 1,200 PB patients treated during the years 1953—59 are presented in Table 1 according to age groups. The heredity of these patients are shown in Tables 2 a, b and c. The data concerning heredity were obtained as

Table 1. *The patient material.*

1200 patients	only Prurigo Besnier		643 cases
	combined with respiratory manifestations		557 cases
	Prurigo Besnier + Asthma bronch.	144 cases	
	Prurigo Besnier + Atopic Rhinitis	264 cases	
	Prurigo Besnier + Asthma + Rhinitis	149 cases	

Age groups		
Group I	0— 6 years	158 patients
Group II	7—12 years	204 patients
Group III	13—18 years	321 patients
Group IV	19—45 years	492 patients
Group V	over 46 years	25 patients
	Total	1200 patients

Table 2 a. *The distribution of atopic heredity in 100 patients with only Prurigo Besnier (Groups III—IV).*

parents	16 times
siblings	10 times
other relatives	18 times
multiple heredity	24 times
no heredity	32 times
Total	100 times

Table 2 b. *The distribution of paternal-maternal heredity in 100 patients with only Prurigo Besnier (Group III—IV).**

maternal heredity	49 %
paternal heredity	38 %
heredity on both sides	13 %
	100 %

* excluding first cousins

Table 2 c. *The distribution of atopic manifestations in the familial heredity of 100 patients with only Prurigo Besnier (Groups III—IV).*

Prurigo Besnier in familial heredity	61 times	48.8 %
Asthma bronchiale in familial heredity	36 times	28.8 %
Atopic Rhinitis in familial heredity	28 times	22.4 %
		100.0 %

Table 3 a. *Correlation between intracutaneous tests and atopic heredity in 1100 cases of Prurigo Besnier.*

positive heredity and positive i. c. test	in 565 patients
positive heredity and negative i. c. test	in 153 patients
negative heredity and positive i. c. test	in 283 patients
negative heredity and negative i. c. test	in 99 patients
Total	1100 patients

Table 3 b. *Correlation between intracutaneous test and atopic heredity in 100—100 grouped cases of patients with Prurigo Besnier only.*

A. Heredity-positive		i.c. tests		B. Heredity-negative		i.c. tests	
	Neg.	1–3 pos	Sev. pos.		Neg.	1–3 pos.	Sev. pos.
25 patients, Group I	6	12	7	25 patients, Group I	13	10	2
25 patients, Group II	12	9	4	25 patients, Group II	12	11	2
25 patients, Group III	11	5	9	25 patients, Group III	9	9	7
25 patients, Group IV	6	9	10	25 patients, Group IV	4	13	8
100	35	35	30	100	38	43	19

χ^2 test and significance: A. to B.: 3.395 degree of freedom: 2 P: 0.20—0.10

Abbreviations:

Neg.: negative i. c. test
1—3 pos.: 1—3 positive reactions in the i. c. test
Sev. pos.: several positive reactions (more than 3) in the i. c. test

Table 4. *Correlation between atopic manifestations and atopic heredity in 50—50 patients (Groups III—IV).*

	Heredity-positive	Heredity-negative
A. 50 patients with Prurigo Besnier	35	15
B. 50 patients with Prurigo Besnier + Asthma	35	15
C. 50 patients with Prurigo Besnier + Rhinitis	40	10
D. 50 patients with All three Symptoms	35	15

χ^2 test and significance: B. to C.: 1.333 degree of freedom: 1 P: 0.25

part of the history of the patients. Those doubtful or difficult to evaluate were excluded. From the heredity point of view only PB, bronchial asthma and allergic rhinitis were considered, i. e. atopic heredity. The relationship between heredity and skin reactions of the immediate type in patients suffering from PB only was the object of the survey in 1,100 cases (Table 3 a). Divided in four age groups the i. c. results of 25 patients each were compared from the point of view of positive and negative heredity (Table 3 b). The relationship between heredity on the one hand and PB or PB plus respiratory allergic manifestations on the other are presented in Table 4. In Table 5 are given, in addition to this, the results of the i. c. test according to groups. The relationship between hereditary factors and the onset of PB is presented in Table 6 a. For comparison data are also given on the onset of PB (Table 6 b) or respiratory manifestations (Table 6 c).

Table 5. *Correlation between intracutaneous test, atopic heredity and atopic manifestations in patients with Prurigo Besnier (Groups III—IV).*

Manifestation	Familial heredity	1. Positive intracutaneous reactions*				2. Negative reaction
		Animal hair	Fungi etc.	Foodstuffs	Pollen	
A. Prurigo Besnier 50 cases	Prurigo Besnier	5	10	3	9	8
	Prurigo Besnier + respiratory atopy	3	6	4	4	7
	Respiratory atopy	3	3	2	2	6
	Total	11	19	9	15	21
B. Prurigo Besnier + respiratory atopy 50 cases	Prurigo Besnier	4	7	6	9	1
	Prurigo Besnier + respiratory atopy	12	18	9	13	2
	Respiratory atopy	8	10	5	12	—
	Total	24	35	20	34	3

χ^2 test and significance: A. to B. concerning 1. and 2.: 17.763 degree of freedom: 1 $P < 0.001$

* one patient has several positive i. c. reactions

Abbreviations:
fungi etc.: fungi, dust and staphylococcal extracts

Table 6 a. *Correlation between atopic heredity and onset of Prurigo Besnier in 150 children with Prurigo Besnier (Groups I—II).**

	Onset of Prurigo Besnier												
	Months:							Years:					
A. Positive heredity 100 cases	−1	1−2	3−4	5−6	7−8	9−10	11−12	1	2	3	4	5	6
Unilateral heredity:													
Prurigo Besnier	2	9	8	5	2	1	1	3	—	1	—	—	—
Prurigo Besnier + respiratory atopy	6	10	6	—	2	1	—	6	—	—	—	—	—
Respiratory atopy	1	2	2	5	—	2	—	2	4	1	—	—	—
Bilateral heredity:													
Prurigo Besnier	—	—	—	—	1	—	—	1	—	—	—	—	—
Prurigo Besnier + respiratory atopy	1	5	2	1	1	—	—	2	—	—	—	—	—
Respiratory atopy	—	—	2	—	1	—	—	1	—	—	—	—	—
B. Negative atopic heredity 50 cases	5	10	5	7	2	2	1	12	5	—	—	—	—

χ^2 test and significance A. to B.: 4.062 degree of freedom: 2 P: 0.20—0.10

* for the problem Prurigo Besnier — Eczema infantile (see text)

Table 6 b. *Onset of Prurigo Besnier in the patient material.*

Onset in years	Males	%	Females	%
— 1	328	60.2	360	55.0
1— 5	159	29.4	201	30.7
6—10	26	4.8	47	7.2
11—15	8	1.5	23	3.5
16—20	14	2.6	14	2.1
21—25	5	0.9	6	0.9
26—30	1	0.2	1	0.2
30—40	—	—	—	—
40—50	—	—	1	0.2
Uncertain	4	0.7	2	0.3
Total	545	100	655	100

Table 6 c. *Onset of Asthma bronchiale and Atopic Rhinitis in patients with Prurigo Besnier.* (557 cases: 261 males, 296 females)

Onset in years	Asthma bronchiale			Rhinitis atopica			Astma bronchiale+Atopic Rhinitis					
	males	females	total	males	females	total	males	females	total	males	females	total
— 1	3	7	10	14	6	20	4	6	10	4	8	12
1— 5	35	26	61	18	15	33	25	26	51	13	13	26
6—10	6	10	16	24	15	39	5	15	20	9	11	20
11—15	3	7	10	7	28	35	8	7	15	8	11	19
16—20	8	5	13	18	23	41	4	8	12	3	7	10
21—25	4	2	6	4	4	8	5	3	8	2	1	3
26—30	—	2	2	1	3	4	—	—	—	—	2	2
31—35	—	1	1	2	1	3	2	2	4	1	—	1
36—40	—	1	1	1	1	2	—	1	1	1	1	2
40—50	—	1	1	—	—	—	—	1	1	—	—	—
Sum	59	62	121	89	96	185	53	69	122	41	54	95
Unknown	13	10	23	34	45	79	13	14	27	25	29	54
Total	72	72	144	123	141	264	66	83	149	66	83	149

Results and Discussion

The data of Group V in connection with Table 1 will be elaborated in the subsequent communication. The occurrence of manifestations of respiratory allergy in PB patients is between 25 %—50 % as follows:

Rost-Marchionini	(66)	25 %
Blumenthal-Jaffe	(6)	33 %
Sulzberger-Goodman	(83)	50 %
Haxthausen	(29)	21 %
Müller	(51)	31 %
Bonnevie	(7)	29 %
Edgren	(23)	33 %
Nexmand	(53)	31 %
Schnyder	(72)	ca 50 %

In accordance with the data of Table 1 50 % is given in the author's material. Concerning the morbidity and the occurrence of PB in the material of dermatological clinics the literature contains abundant data (72, 74 and 53, 33).

Concerning the distribution of heredity the author's data agree in the main with those in the literature. Thus, for example, Tables 2 a and 2 b agree with the data of Hellerström-Lidman (33) i. e. maternal heredity is higher; owing to their number most of the atopic manifestations are to be found in relatives, followed by parents and finally brothers and sisters. Kochs finds that PB plus asthma occurs more frequently among brothers and sisters than among parents (39). Positive heredity could be proved in about two-thirds of the cases (Tables 2 a and 3 a). This corresponds exactly to the data of Hellerström-Lidman, already mentioned. Table 2 c also brings out that PB can originate from any family with atopic manifestations (71). Others have obtained values similar to those in Table 2 c: Hellerström-Lidman (33): (PB 40 %, bronch. asthma 30 %, allergic rhinitis 10 %), and Korting (40): (45 %, 42 %, 13 %).

As shown in Table 3 a positive heredity can be demonstrated in the majority (about two-thirds) of the PB cases. In most of these cases the skin tests are also positive. These results agree with the data of Hellerström-Lidman (33). The small differences in the figures are due to the exclusion of epicutaneous test results from the calculation. Only included are the i. c. test. But if the results of 100 positive-heredity and 100 negative-heredity patients from various age groups are compared according to table 3 b, it becomes clear that there is no decisive divergence. This seems to indicate that hereditary factors do not exercise a decisive influence upon the result of the i. c. test in PB. On the basis of this and of asthmatic experiences Adkinson (1) and Schnyder (72) also distinguish between atopy from the allergic and from the genetical points of view.

Table 4 shows that the heredity factor does not *a priori* "influence" the combination of PB with asthma or allergic rhinitis. Or: the hereditary data of patients suffering from PB combined with manifestations of respiratory allergy or from PB alone are fairly similar.

Table 5 presents the distribution of the various i. c. reactions. It shows a significant difference between Groups A. and B. according to positive or negative reactions. Thus more positive i. c. reactions appear in Prurigo Besnier patients with than without a respiratory allergic combination. Among the positive reactions those predominate due to fungi-dust and to pollen respectively.

Thus in summarizing the findings with PB in Tables 3 b, 4 and 5 it can be said that:

(i) between i. c. test results and atopic heredity there exists no close parallelism,
(ii) between respiratory allergic combination and atopic heredity no close parallelism exists,
(iii) between i. c. test results and respiratory allergic combination a parallelism does exist.

Table 6 a shows the data of 100 children suffering from Prurigo Besnier with detailed atopic heredity and of 50 without atopic heredity. The PB appears in a majority in both groups during the first six months of life. According to the statistical data, however, there are no significant differences between these two groups, that is to say that PB does not appear earlier in families with an atopic hereditary taint.

The data regarding the onset of atopic symptoms which Hellerström-Lidman (33) discussed in detail and with which the author's data agree, are given in Table 6 b and 6 c for comparison. The sex differences in certain age groups shown in this connection will be discussed in a following communication.

Part II

Relationship between vasofunctional tests and heredity

Introduction

(a) Vasofunctional investigations.

The discovery of the delayed blanch symptom in PB patients (Lobitz-Campbell, 44) and the divergent behaviour of PB patients when applying nicotine acid esters (Illig 34 and others) were of special interest. Even earlier the occurrence of white dermographism instead of red reaction on light stroking was known in such patients (92) and the non-appearance of flare after i. c. histamine (68, 25) or protein allergenes (55, 81). The following is a summary outline of the most important facts in this field:

(1) White dermographism (without urtica) occurs even as a result of mechanical stimuli of medium strength, (2) there is absence of the flare in general after i. c. histamine, (3) an anaemic zone is found after an initial erythema around the area of the i. e. injection of acetylcholine (delayed blanch), (4) no erythema response is observed after dermal application of nicotine acid esters (5) decreased vasodilatation occurs on i. c. injection of serotonine (16), (6 a) increased vasoconstriction occurs in the acrae upon cold stimuli, (6 b) hypersensitivity is observed in the old pressor test, (6 c) delayed vasodilatation takes place on heat application and (6 d) increased vasodilatation occurs in the flexural areas after hot and cold stimuli (90).

Items (1) — (6 b) favor an increased vasoconstrictor tendency. Yet it is so far undecided whether this is due to real vasoconstriction or to exudative edema which constricts the skin capillaries (pseudo-constriction). In the latter case the appearance of the exudative edema would be preceded by vasodilatation and increased capillary permeability. Although the supposition of vasoconstriction harmonizes better with the observations made (67, 48, 49, 3), yet (a) under capillary microscopy Davis-Lawler (22) found no reduction in the number of active capillaries, (b) hyaluronidaze suspends the delayed blanch (75), (c) the edema reaction to acetylcholine shows the tendency to occupy the area of the delayed blanch (82), and (d) PB patients do not have more peripheral vascular diseases than normal material. On the other hand, Lobitz (45), for example, was unable to establish the formation of edema after acetylcholine injection on the samples of excised skin.

A special effort was made to investigate the tests made on PB patients under (1), (3) and (4) above and to utilize them for diagnostic purposes. In order to facilitate a survey of the literature on this question Table 7 is presented, which shows there is no universal, or entirely specific vasofunctional test in PB. It is thus desirable from a diagnostic point of view to carry out several tests (82).

It is also mentioned that the nicotine acid ester anaemia can appear in acute rheumatic diseases (69, 52, 87, 50) and in certain cases of insufficiently controlled diabetes (50). Furthermore the erythematous reaction can be suspended by applying steroids (59, 85).

It seems undecided whether these findings are constant or varying. The first view is supported by Illig (34) and Stüttgen-Krause (82), and in Rothman-Bloom's investigations (67) it was not found possible to influence them by medical therapy, including steroids. On the other hand, others have observed that white dermographism (63) and delayed blanch (75) can disappear in healed PB patients. If we really have to do with a "constant" symptom, the significance of the hereditary factors can be considerable. Stüttgen and Krause mention exudative diathesis of families — about one-third of their cases — in their investigations, but do not establish a necessary relationship in connection with the results of their investigations (82). According to Clendenning *et al.* (16) the diverging vascular response of atopics is an hereditary abnormality.

(b) hereditary problems in other investigations.

Other PB investigations have also been mentioned in connection with heredity. Thus Kochs explains the disturbances in the function of sebaceous glands with heredity factors and assumes that a sebaceous hypofunctional factor is inherited in connection with ichthyosis (39).

On 25 PB patients Lutz and Korting (46) have shown, by means of investigations of pulmonary functions, that 60 % had latent susceptibility for asthma. Of these no heredity occurred in the history in 12 cases. In 8 of these even disposition to asthma could not be proved. This allows conclusions in favour of both the influence of heredity on disposition to asthma and of separation of PB and PB plus respiratory allergy as shown also by Schnyder (71) However Kraepelien (42) found normal values in lung volume studies on 16 children with PB.

The author's investigations

In the years 1959/60 investigations were carried out on 100 PB patients by applying histamine 1 : 10.000 i. c., acetylcholine 1 : 1.000 i. c., 5 % trafuril ointment percutaneously for 30 and 60 seconds respectively and by means of mechanical stroking. The results of this investigation are shown in Table 8 a, while Table 8 b shows similar investigations carried out on patients with asthma or with rhinitis allergica. The author examined the trafuril reaction on 50 controls suffering from acne or other skin diseases than PB. In Table 8 c the possible hereditary connections were investigated after grouping the results on the basis of the acetylcholine reaction.

Results and Discussion

Similarly to most other date in the literature, white dermographism and the trafuril reaction gave most of the reactions "characteristic of PB" as shown in Table 8 a. As already stated by Illig (34) the numerous border cases are confusing in the trafuril reaction. It is for this reason only that his cases entirely lacking in hyperaemia were included in Table 7. By border cases are meant the

Table 7. *Reports from the literature on vasofunctional tests in patients with Prurigo Besnier.*

Author	Material	White dermographism	Anaemia to nicotinic acid esters	Delayed blanch
Illig (34)	47 Prurigo Besnier		21	
	178 Other dermatoses		5	
Borelli (8)	97 Prurigo Besnier	1/3—1/4		
	44 Prurigo Besnier		34	
Callaway (13)	18 Prurigo Besnier		18	
	33 Other dermatoses		4	
	10 Normal persons		—	
Rothman & Bloom (67)	15 Prurigo Besnier	15	(100%)	7
	11 Other dermatoses	2		1
Stüttgen & Krause (82)	42 Prurigo Besnier		34	31
	33 Asthma bronch.		17	20
	36 Controls		7	7
Scott (75)	30 Prurigo Besnier	20	25	15
	30 Eczema		16	—
	30 Normal persons		—	—
Reed *et al.* (63)	80 Prurigo Besnier	76		
	24 Diss. neuroderm.	24		
	69 Other dermatoses	49		
Reed & Kierland (64)	41 Prurigo Besnier			37
	15 Diss. neuroderm.			1
	18 Other dermatoses			—
Murrell & Taylor (50)	15 Prurigo Besnier		13	
	37 Other dermatoses		—	
Jillson *et al.* (35)	Prurigo Besnier		85—100%	50—65%
	Other dermatoses		50%	—

cases in which hyperaemia arises, although to a limited extent, or e. g. only after applying trafuril for 60, but not for 30 seconds. Most "typical" reactions were thus obtained on mechanical stimulus. But 19 certain PB patients did not give this response, and in the course of the analysis it could be shown that the vasofunctional investigations were not parallel and also that in 10 % none of the vasofunctional tests gave a PB type of reaction. It was not possible to evaluate the material diagnostically from this point of view, and the histamine reaction was therefore not even considered in this analysis. Thus from the diagnostic point of view it would seem beyond doubt that the application of acetylcholine, of trafuril and the mechanical stroking should be carried out simultaneously.

On comparison of Tables 8 a and 8 b there is a significant difference and the not altogether specific character of these investigations is clear from the point of view of PB. In the controls erythema was obtained after having applied trafuril in every case.

On the basis of Table 8 c it can be stated that no essential differences can be ascertained amongst the hereditary relations of patients with delayed blanch.

Table 8 a. *Vasofunctional tests in 100 patients with only Prurigo Besnier (Groups III—IV).*

Histamine reactions	Acetylcholine reactions	Reactions to stroking	Trafuril reactions
38 without erythema	67 delayed blanch	81 white dermographism	59 anaemic reaction
17 minimal erythema	5 without erythema		26 weak reaction
	4 minimal erythema		
45 erythema	24 erythema	19 red line*	15 erythema

* Analysis of these 19 cases: 4 weak trafuril reactions
1 negative trafuril reaction
3 delayed blanch
1 delayed blanch but negative trafuril reaction
10 erythematous reactions in all tests

Table 8 b. *Vasofunctional tests in 40 patients with Asthma bronchiale and/or Atopic Rhinitis.*

Histamine reactions	Acetylcholine reactions	Reactions to stroking	Trafuril reactions
1 without erythema	4 delayed blanch	4 white dermographism	2 anaemic reactions
	1 without erythema		5 weak reactions
	1 minimal erythema		
39 erythema	34 erythema	36 erythema	33 erythema

Table 8 c. *Correlation between vasofunctional tests and atopic heredity in 100 patients with Prurigo Besnier (Groups III—IV).*

	Atopic heredity	
	positive	negative
67 cases with delayed blanch after acetylcholine	36	31
9 minimal or no erythema after acetylcholine	7	2
14 erythema after acetylcholine but white dermographism to stroking	9	5
10 erythematous responses to all vasofunctional tests	7	3

Furthermore there are relatively more patients with positive heredity amongst the individuals who do not give response to acetylcholine more or less typical of PB.

The author was not able to show parallels with other data or characteristics in PB patients in the course of the vasofunctional investigations. Thus there was no parallelism between the result of the vasofunctional investigations and between the age, sex, PB history, exacerbation, i. c. test results or combinations of respiratory allergies. Also according to Illig the trafuril reaction had no connection with the spread of the skin disease (34). But according to the author's observations the characteristic pallor of the face of patients who respond with

vasoconstriction seems to be a more or less constant quality. In the course of a few repeated investigations it has not been possible to observe any normalization of the pathologic vasofunctional results on our PB patients, although there has been no opportunity to examine individuals whose PB had been cured for a long period, or permanently.

The vasofunctional investigations are carried out and evaluated on the diseased skin of PB patients. Although the same technic is used it is emphasized that parallels to this was often found on seemingly healthy skin areas of the patients. Scott, too, mentions similar observations (75), while Reed *et al.* (64) state that the response only occurs on diseased skin areas. Murrell-Taylor (50) asserts that when examining PB patients with trafuril, normal reactions are found on intact skin areas.

Part III

Data of twin pairs with Prurigo Besnier

Introduction

In considering the relationship between hereditary factors and peristasis in allergic manifestation, twin research is of decisive importance. Monozygotic twins can be evaluated, unless they live completely apart, while the importance of dizygotic twins from the genotypical point of view equals that of siblings. Yet in case of identical sex the exposition is very similar in this group too. Two points of view can be distinguished when studying twins and their allergic manifestations:

(a) *Inheritance of allergic disposition.* This may vary with different allergic manifestations. Thus, acording to Spaich-Østertag's considerable material, the concordance of monozygotic twins for example in regard to allergic rhinitis is 100 %, and to asthma 57 % (79). According to this, each member of the twin pairs examined for allergic rhinitis suffered from some kind of allergic manifestation, but in those with asthma only about half of them did so. Not infrequently does only one member of a twin pairs suffer from some allergic manifestation, while the other is free from it (9, 17, 37, 26).

(b) *Identical allergic manifestation.* As shown in a considerable monozygotic twin series, identical allergic manifestations were shown in 7/59 (Bowen, 9), 6/7 (Criep, 20), 3/6 (Cooke and van der Veer, 18). Opinions diverge concerning smaller series, as some have found concordance (5, 26), while others speak of discordance, so that only one member of the twin pairs suffers from the allergic disease in question. Here, too, it is important to know the kind of manifestation in question, as the concordance is for example 80 % with allergic rhinitis, but only 28.6 % with asthma (79). According to considerable statistical surveys in the case of asthma there is concordance ($22/27 = 81.5$ %) in the majority of cases (Schwartz, 74). It is interesting to note that the aetiology can be different even in the cases of identical manifestation (19), whilst the skin reaction can be identical even in the case of varying manifestations or manifestations of differing degree (20, 30, 12, 78). As a rule the time of onset is similar, but the degree of allergic manifestation can vary (20).

There are comparatively few data on PB in literature. After critical evaluation the following data about PB monozygotic twins has been collected:

3	cases, Bowen	(9)	
3	" Buffum-Feinberg	(12)	
2	" Spaich-Ostertag	(79)	
1	" Criep	(20)	(PB + asthma)
1	" Egea Bueon	(24)	
1	" Mayr	(47)	
1	" Schmidt-Kehl	(70)	
1	" Illig	(34)	
1	" Frain-Bell & Koblenzer	(27)	

But extensive investigations have not been carried out in these cases, with the exception of those of Illig where a trafuril test and in some other instances where i. c. testing was undertaken (20, 47, 24, 12).

The author's investigations

Five monozygotic and 9 dizygotic cases occur in the author's material (5 of these were twins of differing sex). They were distinguished in accordance with usual methods. These twin pairs were as far as possible subjected to katamnestic control and when studying their data the onset of PB, its history, localization, characteristics, combinations with respiratory manifestations, i. c. and epicutaneous tests, vasofunctional tests and other allergic or further symptoms were considered. The information is summarized in Table 9. To simplify the presentation the author has also divided the data into smaller tables, with particular reference to convergences and divergences. Thus the data are presented from the point of view of allergic disposition (Table 9 a), combination with respiratory manifestations (Table 9 b), onset and history (Table 9 c), i. c. investigations (Table 9 d), vasofunctional tests (Table 9 e). Finally there is a table showing the twin data as regards familial heredity (Table 9 f).

Results and Discussion

The results of Table 9, and Tables 9 a—9 f are, of course, too limited in number to permit exact conclusions. Yet they point towards a few noteworthy facts, particularly in connection with monozygotic twins.

Thus from the point of view of allergic disposition (Table 9 a) there is no doubt a tendency to convergence, but this does not go so far as is postulated by, e. g., Spaich-Ostertag (79). It was surprising to see that when comparing monozygotic and dizygotic pairs of identical sex only from the point of view of allergic disposition and PB convergence (see Table 9), this was found contrary to expectations, to be higher in the dizygotic group. As already stated, such a limited number is insufficient for statistical evaluation, and may explain the mentioned feature. Yet this observation seems to indicate that PB cannot be explained by heredity factors *alone*, as in that case the occurrence of PB in monozygotes should be significantly higher than in the dizygotic group.

Table 9. *Studies on Twins with Prurigo Besnier.*

Monozygotic:

	Age	Sex	Prurigo Besnier	Asthma bronch.	Rhinitis atopica	Concordance: Onset	Course	i. c. tests	Vasofunctional test	Other	Discordance: Onset	Course	i. c. test	Vasofunctional test	Other
1.	23	male	+	+	+	+	+		+				+		
2.			+	−	−										
3.	31	male	+	−	−	+	+								
4.			+	−	−										
5.	10	male	+	−	−					ichthyosis				+	history of food-allergy
6.			−	−	−										
7.	49	fem.	+	−	+								+	+	chlorphenthiazin-derm., urticaria
8.			−	−	−										
9.	14	fem.	+	−	−								+	+	history of food-allergy
10.			−	−	+										

Dizygotic:

1.	22	fem.	+	−	−	+	+						+	+	patch test, history of food-allergy
2.			+	−	+										
3.	30	fem.	+	−	−				+			+	+		achylia, salpingitis, hormonal dysfunction
4.			+	+	+										
5.	8	fem.	+	−	+						+		+		localization of Prurigo Besnier
6.			+	+	+										
7.	25	fem.	+	−	−	+	+						+		patch test
8.			+	−	−										
9.	21	fem.	+	−	−							+			
10.		male	+	+	−										
11.	30	fem.	+	−	−										
12.		male	−	−	−										
13.	13	fem.	+	−	−										
14.		male	−	−	−										
15.	22	fem.	−	−	−			+						+	
16.		male	+	+	+										
17.	26	fem.	+	−	+								+	+	localization of Prurigo Besnier, urticaria
18.		male	+	+	+										

abbreviations: fem.: female
derm.: dermatitis

Combination with manifestations of respiratory allergy (Table 9 b) occurs fairly frequently, but it must be kept in mind that 2—2 twin couples were still below the age of 21 (although two of these had already had manifestations of respiratory allergy). It is also interesting to note the great divergence of various atopic symptoms; only with 3—4 uniovular, and 7—8 biovular twin pairs could convergence be observed. The onset and history of PB only were parallel in the material in cases of identical twins (Table 9 c), the dizygotic group showed divergence also in this respect.

Table 9 a. *Disposition to atopic diseases in twins with Prurigo Besnier.*

	Concordance	Discordance
Monozygotic	3	2
Dizygotic	6	3

Table 9 b. *Atopic manifestations in twins with Prurigo Besnier.*

	Prurigo Besnier	Prurigo Besnier+ Asthma bronch.	Prurigo Besnier+ Atopic Rhinitis	Prurigo Besnier+ Asthma+Rhinitis
Monozygotic	5	—	1	1
Dizygotic	7	1	3	4

Table 9 c. *Onset and course of Prurigo Besnier in twins.*

	Concordance	Discordance
2 Monozygotic	2	—
6 Dizygotic	2	4

Table 9 d. *Intracutaneous tests in twins with Prurigo Besnier.*

	Absolute concordance	Discordance	
		complete	only in some reactions
3 Monozygotic	—	1	2
6 Dizygotic	1	—	5

Table 9 e. *Vasofunctional tests in twins with Prurigo Besnier.*

	Concordance	Discordance
4 Monozygotic	1	3
4 Dizygotic	1	3

Table 9 f. *Familial atopic heredity in twins with Prurigo Besnier.*

	No heredity	Prurigo Besnier	Asthma bronch.	Rhinitis atopica	Prurigo B+ Asthma br.	Prurigo B+ Rhinitis atopica	Prurigo B+ Asthma+ Rhinitis	Asthma+ Rhinitis a.
Monozygotic	3	—	1	—	—	1	—	—
Dizygotic	4	2	1	1	1	—	—	—

Also from the point of view of the i. c. investigations described in Table 9 d divergences were surprisingly great. The only convergence in the group was when both showed negative i. c. test results (cases 15—16). Mayr had a similar case (47). From the point of view of divergences the author used strict criteria and included cases in that group even if there was divergence in one-two reactions only. On this basis, and in spite of certain similarities, all PB cases of Buffum-Feinberg (12) and Criep (20) must be considered divergent. The latter recorded convergence in his twins from the point of view of the i. c. test with respiratory allergy.

Also in regard to vasofunctional investigations (Table 9 e), the divergence seems noteworthy, considering that uniovularity is usually stated on the basis of "polysymptomatic similarity diagnosis" (Siemens, 76) which also comprises the condition of the skin vessels (dermographism). When investigating the trafuril reaction in his monozygotic twin pairs, Illig (34) obtained from both a response of erythematic character.

According to Table 9 f only about half of the twins showed atopic heredity factors amongst the ancestors. Granting that the anamnestic data are inexact, they nevertheless point to the frequent absence of the atopic heredity factor in such twin cases. Bowen (9) found a higher percentage in this respect, and 85 % had a family heredity (without closer definition) and heredity was positive in all the seven allergic identical twins of Criep (20), and three described by Buffum-Feinberg (12). There was no hereditary taint in the twins of Mayr (27) or Frain-Bell & Koblenzer (27). Thus, in summary, rather discordant values were obtained from identical twins regarding allergic disposition, occurrence of PB and a history of same, its combination with manifestations of respiratory allergy, i. c. and vasofunctional tests. Even family hereditary traits could only be demonstrated in about half of them.

SUMMARY

The results of investigations of 1200 Prurigo Besnier (PB) in-patients of the Dept. of Dermatology, Karolinska Sjukhuset in the years 1953—59 will be considered in detail in several communications to appear. Apart from a survey of the literature the present paper deals with combination of PB with respiratory manifestations, the onset of the PB and of respiratory manifestations and above all with the influence of atopic heredity. Atopic heredity could be demonstrated in about two-third of the patient material. It was found that there is a closer parallel between atopic combinations and the intracutaneous test than between the intracutaneous result and the hereditary factors, or atopic combinations and heredity respectively. In cases of infantile eczema which can be considered as Prurigo Besnier the disease did not occur earlier in families with hereditary traits.

Heredity had no influence on the vasofunctional tests (acetylcholine, trafuril, mechanical stroking) investigated in 100 PB patients. No diagnostic vasofunctional test uniformly applicable in all these exists, but their simultaneous application is of great diagnostic help. Yet with 10 % of the patients all tests were negative. Even on the basis of examinations of patients with allergic rhinitis and asthma the specific character of these investigations could be established only incompletely from the point of view of Prurigo Besnier. It is impossible to

evaluate diagnostically in Prurigo Besnier the non-appearance of the histamine flare.

The data of 5 monozygotic and 9 dizygotic twins with Prurigo Besnier were evaluated from the point of view of allergic disposition, combination with manifestations of respiratory allergy, heredity, history of PB and other characteristics. Where-ever possible the data were considered on the basis of intracutaneous and vasofunctional tests. Data grouped according to concordance and discordance show that in the case of identical twins there is considerable discordance in all respects, and atopic heredity could only be demonstrated in the ancestors of about half of the cases.

The influence of atopic hereditary factors on the combination of Prurigo Besnier with respiratory manifestations, on the onset of the Prurigo Besnier, on the result of intracutaneous tests and on the result of vasofunctional tests with Prurigo Besnier is very small, as is also shown by the twin investigations.

RÉSUMÉ

On publiera dans plusieurs communications les 1200 cas de prurigo de Besnier étudiés à la Clinique dermatologique de l'Hôpital Karolinska au cours des années 1953 à 1959. La présente communication donne un aperçu de la littérature et traite de la combinaison à des manifestations respiratoires, de la période de début et surtout de l'influence de l'hérédité. Un facteur héréditaire était présent dans environ deux tiers des cas. Il existe un parallélisme plus étroit entre les manifestations atopiques et les tests intracutanés qu'entre le résultat des tests et les facteurs héréditaires ou entre les manifestations atopiques et le passage à la descendance.

Dans les cas d'eczéma infantile qui purent être rattachés au groupe du prurigo de Besnier, l'affection ne se manifesta pas plus précocement dans les familles entachées d'allergie. L'hérédité est également sans influence sur le résultat des tests vaso-fonctionnels pratiqués chez 100 malades (acéthylcholine, trafuril, irritation mécanique). Aucun de ces tests ne possède de valeur diagnostique générale, mais leur emploi simultané peut aider au diagnostic. Tous les tests restèrent négatifs chez 10 % des malades. Leur caractère non spécifique dans le prurigo de Besnier se dégage de recherches dans la rhinite allergique et l'asthme. La suppression de l'érythème histaminique n'a pas de valeur diagnostique.

Après discussion de la littérature, on rassemble les résultats fournis par 5 paires de jumeaux monozygotes et 9 paires de jumeaux bizygotes du point de vue de la potentialité allergique, de la combinaison à des manifestations allergiques respiratoires, de l'hérédité, de l'anamnèse et d'autres caractéristiques comme les épreuves vaso-motrices et les tests intracutanés. A ce point de vue, les résultats classés par concordance et discordance montrent en partie une discordance significative chez les jumeaux vrais, qui ne révèlent d'hérédité atopique que dans la moitié des cas environ.

En résumé, l'influence des facteurs génétiques sur les combinations respiratoires du prurigo, sur le début du prurigo de Besnier et sur les résultats des épreuves fonctionnelles et des tests chez le prurigo Besnier est très réduite, ce qui se dégage également de l'étude poursuivie chez les jumeaux.

ZUSAMMENFASSUNG

Untersuchungen von 1200 Fällen von Prurigo Besnier, die an der Hautklinik des Karolinska Krankenhauses während der Jahre 1953—59 durchgeführt wurden, werden in mehreren Mitteilungen veröffentlicht. Die vorliegende Mitteilung

gibt eine Literaturübersicht und befasst sich darüberhinaus mit der Kombination mit Manifestationen am Respirationstrakt, mit dem Beginn der Prurigo Besnier bzw. der Manifestationen an den Atmungswegen und vor allem mit dem Einfluss der Vererbung von atopischen Krankheiten. Eine Vererbung war in etwa Zwei-Drittel unseres Materials vorhanden. Nach den Ergebnissen gibt es eine engere Parallelität zwischen atopischen Manifestationen und Intrakutantesten als zwischen dem Resultat der Intrakutantestungen und hereditären Faktoren oder zwischen atopischen Manifestationen und Vererbung.

In Fällen von Eczema infantile, die der Prurigo Besnier-Gruppe zugeteilt werden konnten, trat die Erkrankung in allergisch belasteten Familien nicht früher auf.

Die Vererbung hatte auch keinen Einfluss auf das Resultat der bei 100 Prurigo Besnier-Kranken durchgeführten vasofunktionellen Testungen (Acetylcholin, Trafuril, mechanischer Reiz). Keiner der vasofunktionellen Testungen besitzt einen allgemeinen diagnostischen Wert, die gleichzeitige Anwendung ist jedoch von bedeutender diagnostischer Hilfe. Bei zehn Prozent dieser Kranken verliefen jedoch all diese Proben negativ. Der für Prurigo Besnier allgemein unspezifische Charakter dieser Proben geht auch aus Untersuchungen an allergischen Rhinitis- und Asthmakranken hervor. Das Ausbleiben des roten Hofes nach Histamin kann bei der Prurigo Besnier diagnostisch nicht bewertet werden.

Nach Besprechung der diesbezüglichen Literatur werden die Ergebnisse von 5 monozygotischen und 9 dizygotischen Zwillingspaaren vom Gesichtspunkt der allergischen Empfänglichkeit, der Kombination mit allergischen Erscheinungen an den Respirationsorganen, der Vererbung, der Anamnese und anderer charakteristischer Zeichen sowie der vasofunktionellen Hautprüfungen und intrakutanen Testungen zusammengestellt. In dieser Hinsicht zeigen die nach Konkordanz und Diskordanz eingeteilten Ergebnisse teilweise eine bedeutende Diskordanz bei identischen Zwillingen, die atopische Heredität konnte nur bei etwa der Hälfte dieser Fälle nachgewiesen werden.

Zusammanfassend kann gesagt werden, dass der Einfluss der genetischen Verhältnisse auf die respiratorische Kombinationen der Prurigo Besnier, auf den Beginn der Prurigo Besnier und auf die Ergebnisse der vasofunktionellen und intrakutanen Testungen bei Prurigo Besnier sehr gering ist, was sich aus den Untersuchungen der Zwillinge ergibt.

RESUMEN

En una serie de comunicaciones se irán detallando los datos de investigaciones efectuadas en 1.200 enfermos de Prúrigo de Besnier del Karolinska Sjukhuset en los años 1953—59. Esta comunicación, además de una revisión de la literatura sobre el tema, trata de la combinación con manifestaciones respiratorias, los accesos de PB y los fenómenos respiratorios y, sobre todo, la influencia de la herencia atópica. La herencia atópica pudo demostrarse en dos tercios del material clínico. Según mi experiencia hay un paralelismo más estrecho entre las manifestaciones atópicas y el «test» intradérmico que entre la prueba intradérmica y los factores hereditarios, o las manifestaciones atópicas y la herencia. En los casos de eczema infantil catalogables como Prúrigo de Besnier la enfermedad no comienza más precozmente en familias con rasgos hereditarios.

La herencia tampoco ha influido en las pruebas funcionales vasculares (acetilcolina, trafuril, golpe mecánico) investigadas en 100 casos de Prúrigo de Besnier. No parece haber una prueba funcional, vascular diagnóstica universal para estos enfermos, pero su aplicación simultánea es de gran ayuda diagnóstica. Aun así

el 10 % de los enfermos dieron resultado negativo a todas ellas. Basándose en el examen incluso de pacientes de asma y rinitis alérgica, pudo establecerse el carácter no enteramente específico de estas investigaciones desde el punto de vista del Prúrigo de Besnier. Es imposible valorar la no aparición de la areola histamínica a los efectos diagnósticos en el Prúrigo de Besnier.

Después de discutir la literatura sobre el tema, siguieron los datos de 5 gemelos monocigóticos y 5 dicigóticos con Prúrigo de Besnier, desde el punto de vista de la susceptibilidad alérgica, herencia, historia de P. B. así como otras características, y considerado en lo posible sobre la base de las pruebas intradérmicas y vasofuncionales. Los datos agrupados según la concordancia y discordancia muestran que en el caso de gemelos idénticos existe una considerable discordancia en todos estos respectos y que la herencia atópica sólo pudo ser probada en los antecesores de la mitad de ellos.

Recapitulando: la influencia de los factores hereditarios atópicos en la combinación con manifestaciones respiratorias del Prúrigo de Besnier, el brote del prúrigo de Besnier, el resultado de las pruebas intradérmicas y el resultado de los «tests» vasofuncionales, es muy pequeña, como se ha visto por la investigación en gemelos.

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