THE REACTIVE HYPEREMIA RESPONSE OF THE UNINVOLVED SKIN OF PATIENTS WITH PSORIASIS[1]

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Previous studies have indicated that the uninvolved skin of persons with psoriasis is affected in this disease. Kortyanshev (1) and Madden (2), respectively, have shown that there are histological changes in the skin of uninvolved and healed areas of individuals suffering from psoriasis which are relatively constant. Their studies revealed a lengthening of the papillary bodies and rete pegs, capillary dilatation, and leucocyte infiltration in the areas not grossly affected. They concluded that, because of the generalized involvement, psoriasis was a blood-borne disease. In this study, the author, using the reactive hyperemia test, will show that the uninvolved skin of patients with psoriasis shows a different reaction from the skin of individuals having no dermatological lesions.

In 1942, a test was described by DiPalma, Reynolds, and Foster (3) which enabled one to measure quantitatively the response of the smallest cutaneous blood vessels to local ischemia. It was felt that this test measured the ability of these small blood vessels to respond to the 'H' substance released at the site of the ischemia. The normal range of responses was tabulated in a study made on normal individuals. The results showed a seasonal variation in the response of these blood vessels.

Further experimentation with this test revealed that various substances applied locally to the skin of normal individuals effected changes in the response of the small cutaneous blood vessels to the 'H' substance (4). It became apparent that it would be important to determine if the small cutaneous blood vessels of individuals with various dermatological conditions showed an abnormal response to this reactive hyperemia test. Thus, if it were found that the skin of such an individual showed an abnormal response, it would then be desirable to learn whether or not a substance which could change this abnormal reaction to 'H' substance in the direction of a normal response could also effect a clinical improvement.

METHOD AND PROCEDURES

The reactive hyperemia test, as described by DiPalma, Reynolds, and Foster (3), was used exclusively in this study. Approximately 260 readings were taken on 33 patients with psoriasis. The readings were taken at approximately one week intervals for varying lengths of time. All types of psoriasis were studied with the exception of pustular psoriasis. The patients ranged in age from 9 to 74 years. The duration of the disease varied from 4 weeks to 38 years. There was an approximately equal distribution of males and females. The diagnosis of psoriasis, in the majority of cases, was made by gross examination of the lesions. In all questionable cases, histological studies were made and the diagnosis then verified. All reactive hyperemia readings in this study were made on uninvolved skin, and

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TABLE I

Comparison of readings of reactive hyperemia thresholds taken on the same day of patients with psoriasis and control subjects

PATIENTS WITH PSORIASIS					CONTROLS			
Date	Patient	Age	Duration of Disease	Threshold in seconds	Subject	Age	Remarks	Threshold in seconds
2 Jul.	C. Mc.	24	6 months	60	C. F.	19	History of allergy to chocolate, no symptoms at present.	35
	I. M.	23	2 years	55	D. R.	17	Acne Vulgaris, mild, face.	30
					R. L.	28	Chronic urticaria, no symptoms at present.	20
					A. H.	27	Allergy to human hair, no symptoms at present.	20
13 Jul.	E. H.	31	7 months	100	L. A.	24	Acute urticaria one month ago, no symptoms at present.	20
	A. R.	21	4 years	85	A. H.	27	Same subject as above.	25
					A. P.	20	Recovered from contact dermatitis, no visible lesions.	30
					H. K.	16	Volunteer subject, no disease.	20
20 Jul.	D. R. M.	23	1 year	90	A. H.	27	Same subject as above.	25
					M. G.	18	Acne Vulgaris, mild, face.	20
23 Oct.	H. N.	36	16 years	110	J. V.	24	Medical student, no disease.	50
					A. R.	23	Medical student, hyperhidrosis, mild.	40
18 Dec.	M. S.	35	5 years	105	R. S.	28	English seaman, no disease.	45
					C. M. B.	40	Epistaxis 2 days ago, upper respiratory infection, mild.	70
20 Jan.	C. R. C.	18	4 months	75	S. M.	24	Medical student, no disease.	65
					R. D.	21	Volunteer subject, no disease.	45
7 Apr.	P. R.	18	1 year	115	V. M.	25	Medical student, no disease.	40
					F. M.	21	Medical student, no disease.	45

12 May	C. M.	28	4 years	75	B. G.	16	Chronic urticaria, no symptoms at present.	40
	S. P.	24	4 years	75	F. M.	21	Medical student, no disease.	35
					V. M.	25	Medical student, no disease.	40
					F. F.	21	Medical student, no disease.	45
26 May	A. S.	22	5 years	55	G. F.	22	Medical student, no disease.	35
					F. M.	21	Medical student, no disease.	35
Mean threshold for patients with psoriasis				83	Mean threshold for control subjects			36

in all cases they were taken on the ventral surface of either forearm. No subjects were accepted if there were psoriatic lesions on both the forearms.

The test used in this study has been adequately described.

Briefly, the method depends on the application of a weighted rubber ring (weight loading 100 grams/square centimeter) to the skin of the ventral surface of the forearm. The minimal time, expressed in seconds, required to elicit hyperemic rings of uniform width and coloration, and with discrete edges is noted as the stimulus time or *threshold*. The length of time required for the hyperemic rings to fade completely is noted as the *clearing time*. Sub-threshold and super-threshold reactions occur with stimulation times less or greater, respectively, than that necessary to produce the threshold response. It is particularly important to remember that there is a seasonal variation in this response. Thus, while the normal threshold may be approximately 20 seconds in mid-summer, it may increase gradually to approximately 70 seconds in mid-winter. The usual error in performing this test was estimated to be ± 3% when performed by a trained observer using proper precautions.

When the diagnosis of psoriasis was established, the patients were instructed to discontinue all external and internal medication and return in 2 weeks, at which time the initial reactive hyperemia test was performed. After the initial readings were recorded, 13 patients were given an ointment containing Aquaphor and starch, 6 patients were given a preparation of Mucilage of Acacia and Aquaphor, and as controls, 13 patients were given no medication at all. The patients receiving medication were instructed to use it extensively, even applying it to the uninvolved areas. They were told to follow as closely as possible a schedule of applying the ointment for 2 hours at a time, as many times a day as they could.

These substances were used because of their known measurable effects in causing a marked increase in the sensitivity of the smallest cutaneous blood vessels to the 'H' substance liberated at the site of the local ischemia. The starch and Aquaphor ointment was prepared by mixing a saturated aqueous starch solution with equal parts of Aquaphor. The acacia ointment was made of a 65% aqueous solution of powdered gum acacia U. S. P. mixed with an equal part of Aquaphor.

RESULTS

Table I

Mean Threshold for Patients with Psoriasis	83 seconds
Mean Thresholds for Controls taken on same day	36 seconds
Difference in seconds	47 seconds

All the patients with psoriasis lesions showed a higher reactive hyperemia threshold than any of the control readings taken on the same day. The cases selected in the control series were of individuals of approximately the same age as the patients with psoriasis.

Initial Readings—(Table II)

The initial readings on all the patients with psoriasis showed a marked positive deviation from the normal threshold. There was no correlation between the age of the individual or the duration of the disease and the amount of the deviation from the threshold of normal individuals. However it was noted that the more widespread the psoriatic lesions, the greater the deviation from the normal response. The clearing times also showed a corresponding deviation from the normal and were therefore not recorded on all patients.

TABLE II

Initial readings

PATIENT	AGE	DURATION OF DISEASE	MONTH	NORMAL THRESHOLD IN SECONDS	PATIENT'S THRESHOLD IN SECONDS	DIFFERENCE IN SECONDS	PERCENTAGE DIFFERENCE
Group A							
C.H.	17	2 years	Feb.	70	85	15	21
A.P.	9	4 weeks	Nov.	60	95	35	58
C.S.	11	2 years	Nov.	60	90	30	50
J.K.	65	20 years	Aug.	25	190	165	650
C.M.	28	4 years	May	40	75	35	88
J.T.	52	18 years	Nov.	60	80	20	33
H.A.	74	21 years	May	40	165	125	315
H.N.	36	16 years	Oct.	50	110	60	120
M.F.	12	4 months	July	20	100	80	400
M.W.	52	38 years	Oct.	50	135	85	170
M.T.	51	3 years	July	20	135	115	575
S.F.	40	32 years	Nov.	60	145	85	141
S.P.	24	4 years	May	40	75	35	88
Group A	Mean difference from normal thresholds in seconds					+68	
	Mean % difference over normal thresholds					+208 %	
Group B							
D.R.	16	3 years	May	40	50	10	20
C.Mc.	24	6 months	July	20	60	40	200
I.M.	23	2 years	July	20	55	35	175
M.J.	51	3 years	July	20	65	45	225
P.S.	53	6 years	July	20	95	75	375
E.H.	31	7 months	July	20	100	80	400
Group B	Mean difference from normal thresholds in seconds					+53	
	Mean % difference over normal thresholds					+235 %	
Group C							
M.S.	35	5 years	Dec.	70	105	35	50
M.V.	11	1 year	Aug.	25	55	30	120
C.R.C.	18	4 months	Jan.	70	75	5	7
A.R.	21	4 years	July	20	85	65	325
C.C.	14	6 years	July	20	50	30	150
D.R.M.	23	1 year	July	20	90	70	350
E.Mc.	46	14 years	May	40	65	25	85
F.C.	37	2 years	May	40	80	40	100
M.B.	12	1 year	May	40	85	45	128
S.S.	54	3 months	July	20	155	135	675
P.R.	18	1 year	Apr.	60	115	55	91
C.V.	52	2 months	July	20	95	75	375
A.S.	22	5 years	May	40	55	15	27
Group C	Mean difference from normal thresholds in seconds					+48	
	Mean % difference over normal thresholds					+190 %	

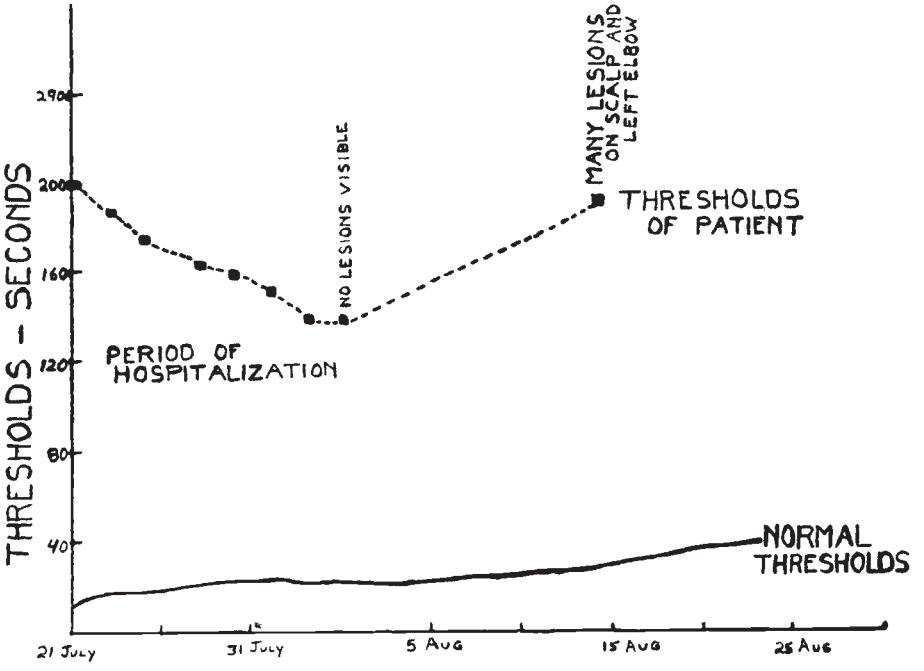
TABLE III

Final readings

PATIENT	DURATION OF TREATMENT	MONTH	NORMAL THRESHOLD IN SECONDS	PATIENT'S THRESHOLD IN SECONDS	DIFFERENCE IN SECONDS	PERCENTAGE DIFFERENCE	CLINICAL IMPRESSION
Group A—Patients receiving starch ointment							
C.H.	5 months	June	30	35	5	17	No lesions visible
A.P.	3 months	Jan.	70	85	15	22	Very much improved
C.S.	11 months	Oct.	50	60	10	20	No lesions visible
J.K.	8 months	Mar.	65	150	85	130	Slight improvement
C.M.	1 month	June	30	60	30	100	No noticeable change
J.T.	3 months	Jan.	70	80	10	14	Very much improved
H.A.	11 months	Apr.	60	150	90	150	Slight improvement
H.N.	3 months	Dec.	70	100	30	43	Slight improvement
M.F.	11 months	June	30	40	10	33	Very much improved
M.W.	10 months	July	20	45	25	125	Very much improved
M.T.	10 months	Apr.	60	65	5	8	No lesions visible
S.F.	2 months	Dec.	70	110	40	57	Slight improvement
S.P.	7 months	Nov.	60	75	15	25	Very much improved
Group A	Mean difference from normal thresholds in seconds.....					+28	
	Mean % difference over normal thresholds.....					+57 %	
Group B—Patients receiving acacia ointment							
D.R.	11 months	Apr.	60	65	5	8	Very much improved
C.Mc.	12 months	July	20	85	65	325	No noticeable change
I.M.	9 months	Apr.	60	65	5	8	Very much improved
M.J.	9 months	Apr.	60	80	20	33	Very much improved
P.S.	1 month	Aug.	25	80	55	220	Slight improvement
E.H.	2 months	Sep.	40	115	75	197	Slight improvement
Group B	Mean difference from normal thresholds in seconds.....					+39	
	Mean % difference over normal thresholds.....					+132 %	
Group C—Patients receiving no medication at all							
M.S.	4 months	Mar.	65	105	40	38	No noticeable change
M.V.	5 months	Dec.	70	85	15	21	Slight improvement
C.R.C.	5 months	May	40	90	55	125	Slightly worse
A.R.	6 months	Dec.	70	115	45	64	No noticeable change
C.C.	5 months	Nov.	60	75	15	25	Very much improved
D.R.M.	4 months	Oct.	50	115	65	130	Slight improvement
E.Mc.	3 months	July	20	90	70	350	Very much worse
F.C.	2 months	July	20	90	70	350	Slightly worse
M.B.	3 months	July	20	105	85	425	Slightly worse
S.S.	1 month	Aug.	25	155	130	520	No noticeable change
P.R.	1 month	May	40	115	75	185	Slightly worse
C.V.	3 months	Sep.	40	110	70	175	Slight improvement
A.S.	3 months	July	20	50	30	150	Slightly worse
Group C	Mean difference from normal thresholds in seconds.....					+58	
	Mean % difference over normal thresholds.....					+199 %	

Final Readings—(Table III)

In all the cases of psoriasis treated with the starch or acacia, it was clearly observed that, as the small cutaneous blood vessels became more sensitive to the 'H' substance at the site of the local ischemia, the psoriatic condition correspondingly improved. The control cases which received no medication showed no significant or appreciable changes in their responses to the reactive hyperemia test.



Graph I. Illustrates the case of a patient who received intensive starch paste therapy in the hospital over a two week period. Patient received a generalized application of starch paste four times daily for two hours at a time. Final reading was taken two weeks after discharge from hospital.

Graph 1

During the two week period of intensive starch paste treatment the threshold of this patient showed a marked trend towards that of the normal, and at the time of the patient's discharge from the hospital the skin, including the shaved scalp, showed no lesions grossly. All that remained were areas of pigmentation. However, two weeks later, during which time the patient received no medication, he returned to the clinic with a marked exacerbation of his psoriasis. At this time a reactive hyperemia test was performed and showed another marked positive deviation from normal.

DISCUSSION

The explanation of the generalized high thresholds in all the cases of psoriasis studied is not yet clear. However, the evidence is in favor of a substance which circulates throughout the body affecting these small cutaneous blood vessels in either one of three ways, or by a combination of any of these mechanisms. The first explanation may be that the ability of the body to produce 'H' substance is impaired by this circulatory substance. Second, there may be a refractory state to the 'H' substance produced at the site of the local ischemia, by the mechanism as explained by Lewis (5). Third, this substance may be the cause of an increase in the sympathetic tone of these small cutaneous blood vessels.

The action of the starch and acacia in combination with the Aquaphor in increasing the sensitivity of the small cutaneous blood vessels to the 'H' substance is apparently the reverse of the process involved in psoriasis. Thus, these substances may act in a way which either enables the body to produce more 'H' substance or they may cause a regression in any refractory state produced, or they may cause a decrease in the sympathetic tone of the small blood vessels. Other studies (6) have shown that if the normal sympathetic tone of the small cutaneous blood vessels is increased, there may be a transient rise in the threshold. Furthermore, it has been found by the use of the reactive hyperemia test, that normal individuals during periods of emotional strain have also shown an increase in their threshold (6). This mechanism might well be the reason for the fact that patients with psoriasis may have an exacerbation of their clinical condition when they are emotionally upset (7); and conversely may show an improvement clinically when their mental state is better.

In the control group of psoriasis patients not receiving therapy, approximately the same mean reaction was noted at the final readings as those initially taken. Clinically some patients in the control group showed some improvement, some remained about the same, and the others showed an exacerbation of their symptoms with a correlation to rises and depressions in their respective threshold curves. There was no definite trend noted in the controls, whereas those patients receiving the starch and acacia ointments showed a marked mean decrease in their thresholds accompanied by a general clinical improvement for that group. While starch and acacia have proven to be of therapeutic value in psoriasis, the author makes no claim that they are panaceas for this condition. However, further studies in this field should contribute much to the understanding of the abnormal physiological processes involved not only in psoriasis, but in other dermatological conditions as well.

SUMMARY

1. A study of 33 patients with psoriasis is presented. The reactive hyperemia test was performed on the uninvolved skin of these patients. Approximately 260 separate readings were done at weekly intervals.

2. Initial readings on all patients with psoriasis showed a marked positive deviation from the thresholds of normal individuals. This is further evidence that the etiology of psoriasis is blood-borne.

3. Thirteen patients were given starch ointment, 6 patients were given acacia ointment, and 13 patients received no medication, as controls.

4. Results of the final readings showed that the patients receiving the medication improved clinically and their mean threshold was correspondingly decreased in the direction of normal.

5. Results of the final readings on the control patients who received no medication showed neither significant trends in the reactive hyperemia thresholds, nor in their clinical condition.

6. The mechanism involved in these studies is not clear at this time, but further investigation should help a great deal in understanding the abnormal physiological conditions occurring in psoriasis and other dermatological conditions.

BIBLIOGRAPHY

1. KORTANYSHEV, A. I.: Histopathologic Character of Apparently Healthy Skin in Psoriatic Patients, Vestnik ven. i dermat., 1939 no. 1. p. 30; abstracted Arch. Dermat. & Syph. **40:** 813 (Nov) 1939.
2. MADDEN, J.: Studies of Uninvolved Skin of Patients with Psoriasis Arch. Dermat. & Syph. **44:** 655–664 Oct. 41.
3. DIPALMA, J. R., REYNOLDS, S. R. M., AND FOSTER, F. I.: Quantitative Measurement of Reactive Hyperemia in the Human Skin, Am. Heart J. **23:** 377, 1942.
4. MILBERG, I. L., DIPALMA, J. R.: The Effects of Hydrophilic Bases and Salt Solutions upon Reactive Hyperemia in the Skin: Application in a case of Lichen Ruber Planus., J. Invest. Dermat. **5:** 403–410, Dec. 1942.
5. LEWIS, THOMAS.: Blood Vessels of the Skin and Their Responses. London., Shaw 1927
6. Unpublished data.
7. ORMSBY, O. S., MONTGOMERY, H.: Diseases of the Skin, Lea and Febiger, Philadelphia. Sixth Edition.