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A Cutaneous Test for Rheumatic Activity in Children. (20734)

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(Introduced by Robert C. Batterman.)

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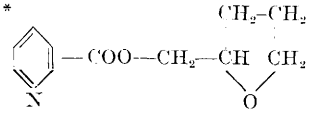
The evaluation of activity of rheumatic fever is made clinically on the basis of Jones'(1) criteria and the combined results of such tests as antistreptolysin-O, antistreptokinase, antihyaluronidase, and C-reactive protein determinations(2-6). No single test permits estimation of rheumatic status. Our studies directed toward finding more adequate diagnostic aids led us to the work of Nassim and Banner(7), who described the absence of a cutaneous hyperemic and/or edematous response to the topical application of a 5% water-miscible cream containing the rubefacient(8-11), tetrahydrofurfuryl ester of nicotinic acid, in 5 patients with active rheumatoid arthritis. It appeared to us that the skin response to this drug might be of diagnostic value in rheumatic fever.

Materials and methods. The skin response to topical application of a vaseline-lanolin ointment containing 5% tetrahydrofurfuryl ester of nicotinic acid* was determined in 337 white and Negro children, several months to 18 years of age.† All skin tests were performed and interpreted by the authors without knowledge of the clinical diagnoses and estimates of rheumatic activity, which were made independently by the clinical or medical director of each institution. Thus the tests were done "blindly", those observing and interpreting the responses being completely unaware of the probable diagnosis, and the clinicians being unaware of the test results. Seventy mg of the nicotinic acid ester ointment was gently rubbed, by means of the examiner's finger (covered by finger cot), with 35 circular strokes into an area 1½ inches in diameter on the volar aspect of the forearm about an inch above the wrist. A control ointment was applied in the same manner, either on the forearm above the test area or



* Supplied by Ciba Pharmaceutical Products, Summit, N. J., under trade name Trafuril.

† These studies were carried out at our hospital, Children's Heart Hospital (Philadelphia, Pa.), Gallinger Municipal Hospital (Washington, D.C.), Irvington House (Irvington-on-Hudson, N. Y.), Jackson Memorial Hospital (Miami, Fla.), and King's County Hospital (Brooklyn, N. Y.). The authors acknowledge with thanks the co-operation of Drs. Francisco A. Hernandez, Gene H. Stollerman, Ella Roberts, Joseph Fazekas, Richard S. Gubner, Franz H. Stewart, Scheffel H. Wright and Warren W. Quillian, and the medical and nursing staffs of these institutions.

TABLE I. Diagnoses and Responses to Tetrahydrofurfuryl Ester of Nicotinic Acid of 337 Patients.

	Total cases	Typical							Atypical		
Hyperemia in ointment zone		+ or >	±			0 to —		Total	± within 10 min. fading to — in 30 min.	0 to —	Total
Edema " " "		+ or —	+		—	+	—		—	—	
Hyperemia in spread zone: >⅛" +, or >¼" ±		+ or —	+	—	+	—	+	+	—	—	
Active rheumatics	22	2	—	—	—	—	—	—	2	7	13	20
Inactive "	187*	179	3	—	1	—	1	—	184§	1	—	1
Rheumatic activity suppressed by cortisone or aminopyrine	5	5	—	—	—	—	—	—	5	—	—	—
Rheumatic activity clinically indeterminate	20	10	—	—	—	1	—	—	11	2	7	9
Normal	51†	41	2	—	2	1	—	2	48	—	2	2
Congenital heart disease	39‡	25	1	1	3	2	1	2	35	1	2	3
Misc. (a) Glomerulonephritis (subacute)	2	2	—	—	—	—	—	—	2	—	—	—
(b) Tonsillitis (including 1 case later diagnosed as scarlet fever)	3	—	—	—	—	—	—	—	—	2	1	3
(c) Others (1 case each of: hyperthyroidism, pneumonia, Riley's syndrome, psychic vomiting, bronchiectasis, pyelonephritis, skull fracture, and idiopathic endothelial fibroelastosis)	8	7	—	—	—	—	—	—	7	—	1‖	1
Total non-rheumatics	103	75	3	1	5	3	1	4	92	3	6	9
Totals	337	271	6	1	6	4	2	4	294	13	26	39

* Including 2 cases not tabulated: one, which faded from + to — and at the same time developed edema +, and was interpreted as typical; and the other, which had a borderline reaction consisting of ± hyperemia, no edema, ± spread of ¼ inch, and was impossible to interpret.

† Including 1 untabulated case which was not readable because hyperemia was indeterminate.

‡ Including 1 untabulated case which faded from + to — and at the same time developed edema, and was interpreted as typical.

§ Includes 20 patients with elevated sedimentation rates: 11 were unexplained and 9 were attributable to other conditions, as follows: 3 diphtheria toxoid inoculation, 2 tonsillitis, 1 menstruation, 1 cystitis, 1 pyelitis and 1 dental caries.

‖ Skull fracture.

on the corresponding site of the other forearm. The *test and control ointment* areas and the *surrounding "spread zones"* were observed for hyperemia and edema, and classified as "typical" or "atypical" according to the presence or absence of the skin changes described below. In the first 75 patients, readings were made over a 3-hour period. It was found that during the first 30 minutes following inunction, the difference between the 2 types of responses was most apparent. Readings were therefore made 10, 20, and 30 minutes after application. After 30 minutes, the ointments were removed by repeated gentle wipings with alcohol pledgets, and a final reading made by comparing the test and control. If intense hyperemia developed before 30 minutes, the ointments were removed at once, and the reactions read. This rapid hyperemic response was noted particularly in infants under 2 years of age. Generally, the younger the child, the more rapid and intense was the hyperemia. No attempt was made in this study to evaluate responses in adults. Responses were best read by daylight. *Skin color changes* observed within 30 minutes were graded as: 0, blanching without edema; —, no visible color change; ±, barely perceptible hyperemia; + to ++, hyperemia of increasing intensity. The width of the spread zone reaction also was recorded. In no case was any skin reaction observed with the control ointment. Any questionable edema was disregarded. In grading the hyperemia in the spread zone, it was considered present if it was more than ¼ inch and ± in intensity, or ⅛ inch and + in intensity. Table I shows the criteria used for classifying typical and atypical responses. Generally, a *"typical"* response consisted of the development of hyperemia within 30 minutes: + to ++ in the ointment area, and — to ++ in the spread zone, extending in some cases as much as an inch beyond the site of application. Edema, with or without hyperemia, also occurred; as edema developed, hyperemia often faded, resulting in blanching. An *"atypical"* response was characterized by blanching or failure of the skin to become hyperemic at the ointment site by the end of the 30-minute period, or the development of barely perceptible (±) hyperemia within 10 minutes, fading out completely after 30 minutes. *Edema was never present in an atypical reaction.* The first 31 patients in the convalescent or active stages of rheumatic fever were followed for the effects of inunction with the nicotinic acid ester on blood count, sedimentation rate, electrocardiogram and body temperature, determined immediately before, 24 hours after, and one week following the skin test. Temperature was also recorded 3 hours after inunction. Subjective responses of the patients were noted.

Results. The types of skin response encountered in patients with and without rheumatic activity is presented in Table I. Twenty of 22 rheumatically active patients gave atypical responses, while 189 of 192 inactive patients gave typical reactions. Of the 25 patients in whom the test was performed 2 to 5 times each, the results obtained remained constant in 22 whose clinical status remained unchanged. In 3 patients whose activity status changed while under observation, the skin responses to the nicotinic acid ester reflected the changes as they occurred. One patient gave a typical response during a period of inactivity and an atypical response when she was later considered questionably active. Another child, who was originally inactive, gave a typical normal response to his first test; an atypical response to his second, when clinically active; and a typical response to his third test, when his status had reverted to inactivity. The third child presented an atypical response while active, a typical response when activity was suppressed by cortisone, and an atypical response again when the cortisone was discontinued.

No significant changes in blood count, sedimentation rate, electrocardiogram or body temperature were observed in the 31 patients in whom such determinations were made. Subjectively, patients frequently experienced mild itching and/or a feeling of warmth of short duration at the site of the test.

Discussion. The high correlation observed between the type of skin response to the tetrahydrofurfuryl ester of nicotinic acid and the presence or absence of rheumatic activity indicates that this drug may be useful in evalu-

ating and following changes in the activity status of rheumatic patients. The present study has been limited to children, and the criteria set forth may not be applicable to adults. There are indications that readings in adults may require more than the 30 minutes we have established for final readings in children. Concentration of the ointment may be a factor.

Many more subjects will have to be studied before final evaluation can be made as to the diagnostic value of skin testing with the tetrahydrofurfuryl ester of nicotinic acid in rheumatic fever. Studies in rheumatoid arthritis and collagen vascular diseases are also indicated. The mechanism of this reaction, as well as the possible role of beta hemolytic streptococcal infection, are under investigation.

Summary. 1. Inunction with an ointment containing 5% tetrahydrofurfuryl ester of nicotinic acid (Trafuril) in 337 children caused localized cutaneous hyperemia and/or edema ("typical" reaction) in normal subjects and those with congenital heart disease or non-rheumatic conditions. 2. Twenty of 22 patients with active rheumatic disease failed to show this typical hyperemia or edema. Their response ("atypical") consisted of either blanching, failure to react, or barely perceptible hyperemia. 3. Inactive rheumatics and patients whose activity was suppressed by cortisone or aminopyrine gave typical reactions. 4. The atypical response was observed in tonsillitis and streptococcal sore throat, as well as rheumatic activity.

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Influence of Diet on Serum Alkaline Phosphatase in Rats and Men. (20735)

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The determination of serum alkaline phosphatase has proved to be valuable in the diagnosis of certain diseases of the bones and liver. There is no satisfactory explanation for the phenomena on which these tests are based. Kay(1) suggested that bone was the major source of the enzyme. Gould and Schwachman(2) came to similar conclusions from their experiments on scorbutic guinea pigs. Armstrong and Banting(3) found that removal of viscera in animals did not affect the serum phosphatase level and therefore, concluded that most of the serum phosphatase came from bone. The work of Bodansky(4) on serum phosphatase of dogs under various dietetic conditions is significant. He found that prolonged fasting greatly reduced the serum phosphatase activity of young dogs and that an increase of this enzyme was obtained only after ingestion of carbohydrates. Ingestion of cream or meat did not have any effect. Weil and Russel(5) studied the same phenomena in albino rats. They found that the plasma phosphatase in albino rats was greatly reduced by fasting. Only the ingestion of the alcohol-soluble fraction of the rat diet increased the plasma phosphatase level. The ingestion of carbohydrates and proteins did not increase the low phosphatase activity

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