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THE ETIOLOGY OF ECZEMA

WITH A PRELIMINARY REPORT OF EXPERIMENTAL STUDIES*

FREDERICK G. HARRIS, M.D.

CHICAGO

It has been the custom of the Chicago Dermatological Society to penalize the retiring president to the extent that his "swan song" shall consist of a paper on some subject of dermatologic interest. Conforming to that custom, I offer the following remarks on the etiology of eczema. It might be well here to ask the indulgence of the Society and its friends for taking up their time with a discussion on such a commonplace subject. My only excuse for so doing is that since the selection of the subject is left to the victim I can say that I know of no other dermatosis that plays such a large part in the life of the dermatologist nor one an adequate explanation of which would have a greater influence on his conceptions of many cutaneous diseases.

With the controversy over the relative merits of the terms dermatitis and eczema I shall have nothing to do. In my mind that question will be settled when we find the etiology of the latter.

The various theories as to the causation of eczema may grossly be divided into three classes: external irritation, bacterial irritation, and

* This paper, published posthumously under an improvised title, is a fragment which I believe all who cherish the memory of Frederick G. Harris will be glad to see in print. The address was delivered in January, 1916, as that of the retiring president of the Chicago Dermatological Association. I was so much impressed with the point of view of the thesis itself and with the originality of approach and the promise of the experimental work that I repeatedly urged publication on its author while he lived, and after his untimely passing, could not rest content until I had, through Mrs. Harris' cooperation, unearthed the manuscript. The bibliography alone, of which unhappily only a remnant was found, represents, so Mrs. Harris informs me, many months of intensive reading. No evidence of any collaborative assistance could be found in the available papers. My personal hand in the matter extends to the improvising of a title, the checking of as many bibliographic references as possible, the correction of a few obvious stenographic errors in what must have been a first draft, the interchanging of one or two paragraphs, the insertion of subtitles, and the summarizing of one chart (b-imidazolethylamin determinations).

JOHN H. STOKES, Rochester, Minn.

humeral irritation, according as their adherents, while admitting other factors, place the most weight on the one or the other.

The external irritation theory is fathered by the Vienna school beginning with Hebra; to this school, external irritation, mechanical, chemical or thermal, is the important factor in the production of the disease.

The infectious theory is represented by the Hamburg school. Here the all important cause is held to be the various pyogenic cocci. It would seem that this view has the least to recommend it, for it has been shown repeatedly that the fresh eczema vesicle is sterile. Bruck and Hidaka¹ studied the subject biologically and were unable to demonstrate an increase in agglutinin or hemolysin. Bering and Enomoto² showed that the scales of eczema contained no increase of opsinin over those of other dermatoses. Their results with agglutinin were similar to those of Bruck and Hidaka. We must admit that after an eczema is once established, bacteria may play an important part as an irritant and serve to prolong the disease, but as for their being the exciting factor, except in rare cases the theory would seem to have little to recommend it.

The internal or humeral theory is represented by the French school.

The writer has long felt that the important factor in the production of an eczema was an increased irritability of the skin or of some structure in it, this abnormal irritability resulting in a reaction of the skin to irritants of varying degrees of intensity. Thus a skin in this state of unstable equilibrium would react to an irritant of any type, be it ever so mild. A skin in a state of normal equilibrium would require an irritant of great intensity, the reaction in this case being called an artificial dermatitis. A skin in a highly irritable state could react to a stimulant so mild as to be considered physiologic.

There are many facts, clinical and experimental, which serve to substantiate this view of the etiology of eczema. The treatment of the disease would be greatly simplified if we knew the factor or factors which are capable of upsetting the normal equilibrium. With that object in view this study was undertaken, and it is to be considered in the nature of a preliminary report.

REVIEW OF THE LITERATURE

In 1892, Samuel³ showed that after a rabbit's ear had recovered from a croton oil dermatitis, the skin of that area was relatively immune

1. Bruck, C., and Hidaka, S.: *Biologische Untersuchungen über die Rolle der Staphylokokken bei Ekzemen*, Arch. f. Dermat. u. Syph. **100**:165-176, 1910.

2. Bering and Enomoto: *Zur Aetiologie des Ekzems*, Arch. f. Dermat. u. Syph. **119**:365-367, 1914.

3. Samuel, S.: *Ueber eine Art von Immunität nach überstandener Croton-Entzündung*, Arch. f. path. Anat. u. Physiol. u. f. klin. Med. **127**:467-476, 1892.

to a second application. This immunity lasted from four to five weeks and could be kept up indefinitely by continued intermittent applications. He showed that the inflammatory reaction in the immunized ear was less and of shorter duration than was the case in a normal ear. He was able to prevent inflammation of one ear by dipping the other ear in cold water, showing the influence of the nervous system on the production of inflammation.

Schaer⁴ produced a similar immunity with croton oil too weak to cause more than the mildest grades of dermatitis.

Fuerst⁵ studied the changes of the epithelium caused by heat and cold in men and animals. He was able by repeated freezing or burning to so change the skin that the same exposures caused no inflammatory reaction.

Stein,⁶ using applications of croton oil, ethyl chlorid and carbon dioxid snow, of increasing strength, but short of those required to produce a visible dermatitis, was able to produce an immunity which was not specific, but which was of longer duration, and more marked for the specific agent. He says that this immunity is not due to anatomic changes, but is due to changes in the cells of the affected tissues (cellular umstimmung). It is a common occurrence to see patients with pediculosis whose skin seems to have an immunity to the traumatism of scratching. The result of scratching in this disease is usually a pus infection, not an eczema. It is difficult to correlate these observations with the numerous cases of acute eczema of sudden onset, seemingly due to an irritant to which the patient has been exposed often for years.

Schultz,⁷ in a series of careful experiments on patients suffering with various diseases, has studied the reaction of the normal skin of these patients to decreasing strengths of phenol. Some of his findings are interesting and significant. He showed that there was no constant difference in the reaction of the skin in different parts of the body of the same person. The age of the person, moreover, had no influence on the reaction. The skin of forty-one syphilitic patients reacted in about the same way as that of normal persons. One syphilitic patient showed an increased reaction, but it is interesting to note that this was in a fat man with a tendency to intertriginous eczema.

4. Unable to trace.

5. Fuerst, E.: Ueber die Veränderungen des Epithels durch leichte Wärme- und Kälteeinwirkungen beim Menschen und Säugethier, *Beitr. z. path. Anat. u. allg. Path.* **24**:415-457, 1898.

6. Stein, R.: Experimentelle und histologische Untersuchungen über Hautgewöhnung, *Arch. f. Dermat. u. Syph.* **97**:27-54, 1909.

7. Schultz, J. H.: Die Prüfung der Hautreaktion auf chemische Reize, *Jahrb. f. Kinderh., N. S.* **78**:347-349, 1913.

Normal areas of skin in psoriatic patients showed less reaction than the skin of persons free from psoriasis. One psoriatic patient showed an increased reaction. It is noted, however, that this patient was so susceptible to chrysarobin that it was necessary to stop the treatment from time to time. Patients with ichthyosis and dermatitis herpetiformis gave a decreased reaction. Normal skin of eczema patients showed a remarkably increased reaction.

Weidenfeld⁸ made an extensive study of the reaction of the skin of eczema patients to irritants, using decreasing strengths of croton oil. Although his results run parallel to those of Schultz, we believe it worth while to give some of his findings in detail. He found that the skin of eczema patients shows a greater reaction than normal skin, and the more acute the disease the stronger is the reaction. As a rule, the more extensive the disease is, the greater is the reaction. The strength of the reaction, as a rule, decreases as the disease disappears. The increased sensitiveness lasts for some time after recovery, but is, however, transitory. The normal skin near the eczematous patch shows a greater reaction than that at a distance. The skin of a healed patch is more sensitive than the skin that has not been affected. The serum of eczema patches, applied to intact skin or to skin which had been scarified, does not cause eczema. Scarification and application of croton oil showed eczema patients to be much more sensitive than normal persons. Ichthyotic skins showed a lessened reaction.

Kaposi,⁴ Kreibich⁹ and others hold that under the influence of the primary patch of eczema the vasomotor system of the whole skin is irritated.

Weidenfeld thinks that the irritability of the whole skin runs so parallel to that of the primary patch that no other conclusion is permissible than that in the primary patch, toxic substances are formed which pass into the blood and cause those changes in the skin which predispose it to eczema.

Rachmilewitsch¹⁰ has shown that the skin of children with exudative diatheses is more sensitive to mechanical and chemical irritation than that of normal children.

All these experiments would seem to indicate that the skin in eczema is in an unstable condition, ready to respond to the slightest irritant by the production of an inflammatory reaction which we call eczema.

8. Weidenfeld, S.: Beiträge zur Pathogenese des Ekzems, Arch. f. Dermat. u. Syph. **111**:891-984, 1912.

9. Kreibich, C.: Ueber nervöse Ueberempfindlichkeit der Haut, Arch. f. Dermat. u. Syph. **93**:59-64, 1908.

10. Rachmilewitsch, E.: Hautreaktionen von Kindern mit exudativer Diathese, Jahrb. f. Kinderh., N. S. **77**: 176-180, 1913.

That this irritability does not reside in the epithelial cells is shown by the fact that it is not specific, and it varies too rapidly. Weidenfeld showed, moreover, that subepidermal injection of croton oil in eczema gave an increased reaction. The source of the irritability could reside in the blood vessels or nerves. There are many reasons for believing that the blood vessels are only secondarily involved. Therefore it might be well to investigate the possibility that the nervous system is at fault.

INFLUENCE OF THE NERVOUS SYSTEM ON DERMATOSES

There are a number of dermatoses, in the etiology of which the nervous system is supposed to play a greater or less rôle. Cassirer,¹¹ who is probably the best authority on the question of neurotropism, has pointed out that the skin is especially well suited for the demonstration of neurotrophic changes.

Königstein¹² has called attention to the sensory changes present in vitiligo patches, the center being hypesthetic, while the border is hyperesthetic.

Kreibich had previously shown that the border of a patch of vitiligo reacts much more strongly to irritation than does the center. Schultz, in the phenol experiments referred to in the foregoing, found in three vitiligo cases with sensory changes, that the reaction was increased at the periphery and decreased in the center. Two cases without sensory changes gave normal reactions. Vörner⁴ has verified these observations.

It is interesting to learn that Moro⁴ believes that his tuberculin reaction, which clinically simulates eczema rather closely, is an inflammatory reaction due to the irritation of nerves sensitized to tuberculin.

In 1906, Spiess¹³ reported some observations and experiments which have not received the attention they would seem to deserve. He noticed that after tonsillectomy, if the denuded area was anesthetized, the inflammatory reaction and swelling was distinctly less or absent, and the wound healed more quickly. He found that various drugs, such as morphin, antipyrin, salicylic acid and quinin given internally had a similar action.

Spiess here calls attention to an every-day occurrence as showing the influence of the nervous system on the manifestations of inflammation. He cites the fact that a rhinitis, the secretion of which is profuse during the day, stops during sleep. He mentions also that wounds in

11. Cassirer, R.: Die trophischen Störungen, *Handb. d. Neurol.* **1**:1135-1156, 1910.

12. Königstein, H.: Sensibilitätsstörungen bei Vitiligo, *Wien. klin. Wchnschr.* **23**:1745-1748, 1910.

13. Spiess, G.: Die Bedeutung der Anästhesie in der Entzündungstherapie, *München. med. Wchnschr.* **53**:345-351, 1906.

hysterical and insane patients heal readily with few inflammatory signs. Strümpel¹⁴ reports the case of an hysterical woman who could pick eggs out of boiling water without showing burns. From his experiments Spiess concludes that an inflammation will not occur when one succeeds in anesthetizing the reflex fibers passing from the area in the sensory nerve.

In Samuel's experiments, he showed that when the sensory nerves supplying the ears of rabbits were cut, scalding did not cause inflammation. There are many other clinical observations showing the influence of the nervous system on inflammation (lepra, syringomyelia). The observations of Samuels and Spiess have been abundantly confirmed by the experiments of Bruce,¹⁵ Januschke,¹⁶ and Luithlen.¹⁷

Bruce showed that when the conjunctiva was anesthetized with alypin or by cutting its sensory nerves, the instillation of oil of mustard into the conjunctival sac was not followed by inflammation.

Januschke found that magnesium sulphate narcosis, also narcosis with chloral hydrate or ether, delayed or prevented inflammatory reactions. Morphin, antipyrin, sodium salicylate and quinin exhibited the same effect, but to a less extent. He also found, and this I wish especially to emphasize, that epinephrin subcutaneously administered also prevented the usual inflammatory reaction, and this in spite of the fact that there was no appreciable influence on the blood vessels.

Weidenfeld¹⁸ has shown that in cases of dermatographism, the skin did not react over an area anesthetized with cocain, and that epinephrin influenced the skin in such a way that it did not react to mechanical irritation. He also showed that epinephrin applied either externally or subcutaneously, would prevent the inflammatory reaction to mustard

14. Strümpel: Quoted by Spiess.

15. Bruce, A. N.: Ueber die Beziehung der sensiblen Nervenendigungen zum Entzündungsvorgang, *Arch. f. exper. Path. u. Pharmakol.* **63**:424-433, 1910; abstr. *Arch. f. Dermat. u. Syph.* **107**:508-509, 1911.

16. Januschke, H.: Ueber Entzündungshemmung, *Wien. klin. Wchnschr.* **26**: 869-874, 1913.

17. Luithlen, F.: Tierversuche über Hautreaktion, *Wien. klin. Wchnschr.* **24**:703-705, 1911. Ueber Chemie der Haut, *Wien. klin. Wchnschr.* **25**:658, 1912. Ueber die Einwirkung parenteral eingeführter Kolloide und wiederholter Aderlässe auf die Durchlässigkeit der Gefässe, *Med. Klin.* **2**:1713-1714, 1913. Ueber Veränderungen der Hautreaktion, *Wien. klin. Wchnschr.* **26**:1836-1837, 1913. The Etiology and Etiologic Therapy of Eczema from a Chemical Basis, *Urol. & Cutan. Rev., Tech. Suppl.* **1**:97-101, 1913. Veränderungen der Hautreaktion bei Injektion von Serum und kolloidalen Substanzen, *Wien. klin. Wchnschr.* **26**:653-658, 1913. Ueber Allgemeinbehandlung der Hautkrankheiten, *Wien. med. Wchnschr.* **64**:1821, 1887, 1914.

18. Weidenfeld, S.: Ueber mechanische Reizbarkeit der Haut (Dermographismus), zugleich eine Studie über Adrenalinwirkung auf die Haut, *Archiv. f. Dermat. u. Syph.* **99**:229-272, 1910.

plaster, although when the inflammation had reached a certain grade the subsequent application of epinephrin did not affect the process.

Since itching is such an important symptom of eczema, it is interesting to review Winkler's¹⁹ work on that subject. We are apt to explain the presence of eczema as the result of itching and subsequent scratching, but, as Kreibich has pointed out, eczema is uncommon as a complication of some of the worst of the itching dermatoses, such as lichen planus, dermatitis herpetiformis and winter pruritus.

Winkler was able to dissociate the sensations of the skin and to show that the sensation of itching was a physiologic perception and distinct from the perception of pain. He showed, too, that the sensation of itching is closely associated with the vasomotor system. He found that the anesthetic zones in hysteria were insensitive to itching, as shown by the absence of the usual rise of blood pressure. Cocain prevented the perception of itching. Skin into which epinephrin had been cataphoretically applied was insensitive to itching, and an itching area could be relieved in the same way. Winkler also showed that an area denuded of epidermis did not itch. He concludes that the perception requires the presence of the intra-epithelial nerve endings.

INFLUENCES TENDING TO SENSITIZE THE SKIN

We are prone to explain a given eczema as the result of chemical or other irritation, blaming anything with which the patient comes in contact, be it ever so mild. Even though the patient may have been exposed to the same agent for years, and in spite of the fact that the skin has the ability to a marked degree to develop an immunity to irritating substances, the patient nevertheless develops a dermatitis. We are apt in these connections to speak of the skin as being sensitized and of eczema as being an anaphylactic phenomenon. If we are to continue to hold these views it behooves us to inquire why the skin should, from time to time, become sensitive to external influences, which at other times and often for years have caused no reaction. The important factor would seem not to be the irritating influences, since they are legion both in kind and degree of irritating power, but rather some factor or factors which change some structure in the skin, so that it is more susceptible to external influences.

It has been shown that the epidermis is not at fault. The blood vessels lie too deep to be reached by the external irritant, so we are compelled to fall back on the nervous system. The intra-epithelial nerve fibrils, situated superficially as they are, could be the structure irritated. Remembering Winkler's work and the part played by these structures

19. Winkler, F.: Studien über das Zustandekommen der Juckempfindung, *Arch. f. Dermat. u. Syph.* **99**:273-334, 1910.

in the sensation of itching and their close connection with the vasomotor system, we can well understand that irritation of these endings might be followed by itching and by vasomotor changes.

It is not difficult to imagine that the irritability of these nerves could be increased or decreased. As an example of the latter could be mentioned the experiments with hysterical patients, quoted in the foregoing, with cocain, etc. Especially do I wish to call attention to the action of epinephrin in diminishing irritability. If the irritability of these nerves can be diminished, naturally we must conclude that it can also be increased.

At this point I should like to correlative the various experimental and clinical observations detailed.

1. It is conceded that eczema is an inflammatory reaction of the skin.
2. The normal skin of eczema patients is especially sensitive to external irritation, be it mechanical, chemical or thermal.
3. The sensation of itching is inherent in the epidermis, is a prominent symptom of eczema and can be prevented and counteracted by epinephrin.
4. Inflammation of the conjunctiva and skin, usually resulting from the use of strong irritants, can be prevented by paralyzing the reflex arc in various ways, among which is ²⁰ the local or subcutaneous use of epinephrin.
5. Since the vasomotor changes in eczema are so intimately associated with itching, and it has been shown that epinephrin prevents them both and is a normal constituent of the blood, it requires no great imagination to suppose that a deficiency of the active epinephrin in the blood could account for the increased sensitiveness of the skin on the one hand and the itching on the other. Might not the epinephrin act on the cutaneous reflex arc? ²¹
6. The rather frequent association of eczema, low blood pressure and asthma, all conditions counteracted by epinephrin, is suggestive, to say the least.

In the experimental investigation of this theory it remains, then, to ascertain whether in cases of eczema the epinephrin in the blood is diminished or not. Unfortunately, at present this is impossible, the amount normally present being so small that with the known tests it is impossible to show a decrease.

Another possibility, however, suggests itself. Might there not be some toxic substance, or substances, which, entering the blood from

²⁰. The passage seems more comprehensible when "or by" is used in place of "among which is."

²¹. This question is inserted in the author's handwriting in the manuscript.

time to time would, in spite of a normal epinephrin content, act as an irritant to the vasomotor system and especially to the cutaneous reflex arc or neutralize the normal epinephrin action at this point? The rather intimate association between eczema on the one hand and various metabolic and nervous disturbances on the other hand suggested such a possibility.

THE INFLUENCE OF DIET AND THE GASTRO-INTESTINAL TRACT

Especially susceptible of interpretation from this point of view is Jadassohn's ⁴ third group as described in his work on "Hautkrankheiten bei Stoffwechsel Anomalien." This group includes diseases of those organs which have to do with the reception, preparation, distribution and excretion of food materials. Of these, the one which seemed to present the greatest likelihood of being at fault was the gastro-intestinal tract.

Dermatologists have long recognized the fact that various dermatoses are dependent, to a greater or less degree, on abnormal conditions in the gastro-intestinal tract. Especially is this true of eczema. It is not necessary here to call attention to the frequency with which eczema is accompanied by disturbances in the gastro-intestinal tract. You have all considered the subject and arrived at your own conclusions; and yet, as justifying my own point of view, I would like to call attention to the fact that Spiethoff ²² has shown that gastro-intestinal disturbances were found in the following conditions in the percentages given:

TABLE 1.—PERCENTAGE OF CASES IN VARIOUS CONDITIONS IN WHICH GASTRO-INTESTINAL DISTURBANCES WERE FOUND

Pruritus	70
Urticaria and symptomatic erythema.....	58
Strophulus	82
Rosacea	75
Eczema	54
Infantile eczema	52

In this connection, we believe a consideration of the cutaneous diseases of animals would help us to an adequate realization of the close connection between the gastro-intestinal tract and cutaneous diseases. Whereas eczema forms from 30 to 50 per cent. of all skin diseases in human beings, in animals it is found in about the percentages given in Table 2.

The disease has not been described in wild animals or those in captivity. It seems to be confined to the domestic animals, and among these the carnivora appear to be especially predisposed.

22. Spiethoff: Magendarmstörungen bei Haut- und Schleimhauerkkrankungen, München. med. Wchnschr. 59:991-992, 1912.

With the exception of ergotism, urticaria and pellagra, we can recall no cutaneous disease which is known to be due directly to food. In animals there are a number described, and veterinarians call especial attention to the close association between food intoxication and cutaneous eruptions. It is possible that the diet of animals is so limited that in any deviation followed by a skin disease the association is obvious. Be that as it may, the fact remains that if the limited diet of animals is so important a factor in the production of skin diseases among them, the varied diet of human beings, while making the problem more difficult, also makes it more important.

TABLE 2.—ECZEMA IN ANIMALS

	Percentage of All Skin Diseases
Dogs	7
Cats	4
Birds	3
Horses	0.5
Cattle	Uncommon

I think we shall have to admit that the gastro-intestinal tract has an influence on the skin, far greater than that of any other organ. The writer has been impressed in particular with the frequency with which constipation, high protein diet and alcoholism have occurred in these cases of eczema.

Luithlen has shown that in animals the reaction of the skin to irritants is modified by diet, particularly in that a vegetarian diet diminishes the reaction. Bulkley has frequently called attention to the advantages of such a diet in the treatment of eczema. Recently Lier and Porges²³ have called attention to the frequency with which subacidity and anacidity is found in cases of subacute and chronic eczema. Block⁴ has shown that dogs from which the pancreas has been removed develop an artificial dermatitis much easier than before removal.

THE ACTION AND FORMATION OF HISTAMIN

All these facts, and many more, could be cited tending to prove that the protein of the food is commonly the deleterious part of the diet. This suggestion, taken in connection with the considerations mentioned before regarding the action of epinephrin, would support the possibility that some substance might be formed in the gastro-intestinal tract which, when absorbed, would neutralize or counteract the action of epinephrin at various points in the body.

23. Lier, W., and Porges, O.: *Dermatosen und Anazidität*, Wien. klin. Wchnschr. **26**:1974-1976, 1913.

In considering this possibility my attention was directed to beta-imidazolethylamin, a toxic amin formed from histidin, the latter being a product of pancreatic digestion. Beta-imidazolethylamin or histamin counteracts (is an antagonist to) epinephrin at almost all points.

Berthelot and Bertrand ²⁴ showed that this substance was produced in the intestine by the *Bacillus aminophilus intestinalis*. Mellanby and Twort ²⁵ isolated from the ilium a strain of colon bacilli, which was able to form it from histidin, and they were able to demonstrate its presence in the wall of the intestine. Mutch ²⁶ has studied the question of the formation of histamin and other poisons in the ileum of constipated subjects. He shows that 14 per cent. of the protein intake can be recovered at the lower end of the ileum in the form of the simple products of digestion. Eyre ²⁷ has examined the bacterial flora of the ileum of sixteen constipated subjects at operation, and in only one case did he fail to find pathogenic organisms. In a series of constipated subjects operated on by Lane, in those with a blood pressure below 110, Mutch found organisms which produced histamin.

Thus it is seen that conditions which would result in an increase of the unutilized protein or in constipation, could result in an increased formation of toxins. Might not this be the reason for Block's finding of an increased susceptibility to dermatitis in depancreatized dogs instead of a lack of the internal secretion of that organ, as he thought?

Since the lower end of the ileum is especially adapted for absorption, it is readily seen that toxic substances formed there can be absorbed and enter the circulation. It is not necessary that the substances so absorbed be themselves deleterious to the skin, for they may act on some other organ in the nature of a stimulant or depressor. Lane ⁴ has shown the effect of intestinal toxins on the thyroid in the production of exophthalmic goiter, and he has also called attention to the pigmentation of the skin due to intestinal toxemia.

24. Berthelot, A., and Bertrand, D. M.: Recherches sur la flore intestinale; isolement d'un microbe capable de produire de la B-imidazolethylamine aux depens de l'histide, Compt. rend. Acad. d. sc. Par. **154**:1643-1645, 1912. Recherches sur la flore intestinale; sur la production possible de ptomaines en milieu acide, *ibid.* **156**:1027-1030, 1913.

25. Mellanby, E., and Twort, F. W.: On the Presence of B-imidazolethylamine in the Intestinal Wall; with a Method of Isolating a Bacillus from the Alimentary Canal Which Converts Histidine Into This Substance, Jour. Physiol. **45**:53-60, 1912-1913.

26. Mutch, N.: The Formation of B-iminozolyethylamine in the Ileum of Certain Constipated Subjects; With Note on the Urine in Constipation, Quart. J. Med. **7**:427-443, 1913-1914.

27. Eyre: Quoted by Mutch.

EXPERIMENTAL STUDIES: HISTAMIN

With these ideas in mind the writer undertook some investigations to determine the frequency with which histamin is found in cases of eczema. The method used was as follows:

The stools were heated with an excess of 5 per cent. of hydrochloric acid to hydrolize the fats, then filtered while hot, and to the filtrate phosphotungstic acid was added and allowed to stand twenty-four hours. The precipitate formed was collected and washed with 1 per cent. of hydrochloric acid. This was then suspended in water and treated with a saturated solution of barium hydroxid. After filtering, the filtrate was shaken with ether, which dissolves the amins. To this ethereal solution was added 1 c.c. of ether which had been shaken with hydrochloric acid. This changed the amin to the chlorid. The ether was evaporated and the residue was dissolved in 1 c.c. of distilled water.

Unfortunately, on account of the war, the prohibitive cost of phosphotungstic acid compelled us to limit our examination to one stool. When one considers that Eppinger²⁸ advises the use of a total stool for ten days, the fact that we failed to find histamin in so many of our cases is not at all significant. The test used to determine its presence was to scarify lightly an area on the forearm into which the solution was rubbed. If histamin is present in a concentration of as much as 1:1000, a wheal will form within five minutes.²⁸

The author realizes the fact that the intestine is not the only place in which this or other toxins may be found, and he would call attention to the possibility of these substances being formed in any infected focus accompanied by destruction of tissue. The results obtained were:

[The results were never summarized by the author, possibly because of his dissatisfaction with their incompleteness. At one time he expressed to me the feeling that the cutaneous test used for identifying the histamin was not wholly trustworthy since he had noticed an increasing tendency to reaction in his own skin after performing a number of tests on it. From a table among his papers relating to this work it appears that sixteen analyses for histamin were performed. Of these, three were definitely or strongly positive (one, acute eczema; one, psoriasis and one chronic eczema in a child). Two were rated as $\pm$ (one, chronic eczema; one, exfoliative dermatitis), and eleven were negative as follows: erythema multiforme 1, pellagra 1, dermatitis herpetiformis 1, psoriasis 2, acute eczema 1, chronic eczema 3, pityriasis rosea 1, urticaria 1 and urticaria pigmentosa 1. If it is recalled that Harris was obliged to limit himself to a single stool analysis, when the stools for ten days were called for, the results seem more suggestive.—JOHN H. STOKES.]

28. Eppinger, H., and Gutmann, J.; Zur Frage der vom Darm ausgehenden Intoxikationen, *Ztschr. f. klin. Med.* **78**:399-412, 1913.

EXPERIMENTS ON INDICAN

The presence or increase of indican in the urine has long been thought to be of significance in various skin diseases, but the mistake has often been made of considering the indoxyl as the offending agent. It is generally admitted that the amount of indican in the urine is a good index of the degree of intestinal toxemia, although the indican itself is innocuous. Therefore, since we were interested in toxins found in, and absorbed from, the intestine, it was thought it might be of advantage to study the question of indican. Since the question of indicanuria in skin diseases had previously been gone into extensively, it was decided to investigate the question of its presence in the blood.

TABLE 3.—INDICAN *

25 cases of eczema, 21 cases examined:
9 were + + +, all chronic cases.
2 were + +.
4 were +.
6 were trace.
6 psoriasis cases: 4, + + +; 2, +.
In one of these cases the diagnosis was doubtful.
2 cases of dermatitis herpetiformis: 1, +; 1, + +, pink.
2 cases of erythema multiforme: 1, + + +; 1, + +.
2 pellagra: 2, + + +.
1 generalized exfoliative dermatitis, trace.
1 pityriasis rosea, trace.
1 diabetes with ecthyma, + +.
1 uremia, + + +.
2 chronic interstitial nephritis, trace.
1 urticaria pigmentosa, + +.
2 urticaria, + + +.
1 angioneurotic edema, +.

* This table is reproduced exactly as it was found in the manuscript.

Obermayer and Popper²⁹ showed it was constantly present in cases of uremia and absent in normal individuals. Tschertkoff³⁰ found that these observers had overestimated its significance, for he found it absent in certain cases of nephritis. He concludes, however, that in normal or sick patients without kidney insufficiency, and irrespective of diet, indican is never found in the blood serum. Patients with marked indicanuria never showed indicanemia. Tschertkoff thinks that the presence of indican in the blood is a more reliable sign of kidney trouble than nitrogen retention.

The indican was extracted from the blood by the method of Obermayer and Popper: Ten c.c. of blood serum were precipitated with 50 c.c. of 95 per cent. alcohol. This was filtered and the filtrate evaporated

29. Obermayer, F., and Popper, H.: Ueber Urämie, Ztschr. f. klin. Med. **72**:332-372, 1911.

30. Tschertkoff, J.: Indikämie und Urämie (Azotämie), Deutsch. med. Wchnschr. **40**:1713-1715, 1914.

on a water bath. The residue was dissolved in 10 c.c. of water. Two to three minims of a 10 per cent. solution of sugar of lead was added to precipitate the animal ³¹ acids. Any excess of lead was precipitated with one minim of a 10 per cent. solution of sodium phosphate. This was filtered and the filtrate contained the indican in 10 c.c. of serum. To determine its presence we made use of a delicate test, originated by Jolles.³² It might be added that this test is not only simple, but is ten times more delicate than Obermayer's. To the filtrate containing the indican was added 1 c.c. of a 5 per cent. alcoholic solution of thymol. To this mixture was added an equal amount of Obermayer's reagent. After standing for fifteen minutes the indican was shaken out with chloroform.

ANTITRYPSIN DETERMINATIONS

One hears so much these days concerning the skin reactions due to the trypsin-antitrypsin balance, that it was thought possible a study of the antitrypsin control of these cases would be interesting. One can imagine that chemical irritants penetrating to the rete mucosum could adsorb antitrypsin, resulting in a solution of the epithelial cells and vesicle formation. The method used was that of Puillet and Morel.³³

TABLE 4.—RESULTS OF EXPERIMENTS WITH ANTITRYPSIN *

Of 12 cases of eczema examined:
8 were below normal
2 were above normal
Of 5 cases of psoriasis examined:
4 were below normal
1 was above normal—gave slight indican
Of 6 control cases of various diseases:
4 were normal or above
2 below normal. One of these was a possible parapsoriasis

* The normal finding is 60.

ABDERHALDEN REACTIONS

While the primary pathologic change in eczema is in the corium, there is secondarily a destruction of epithelial cells of the rete mucosum. Therefore it was thought that a study of the Abderhalden reaction might reveal something of interest. A substrate was prepared of the epidermis of a child 11 days old. At the same time substrates of various organs were used. The results are not at all conclusive, and until we have a satisfactory explanation of this reaction no conclusions can be drawn from them.

31. This is presumably a stenographic error for "amino."

32. Jolles, A.: Ueber eine neue Methode zur quantitativen Bestimmung des Indikans im Harne, *Ztschr. f. physiol. Chem.* **44**:79-103, 1915.

33. Puillet, P., and Morel, L.: L'index antitryptique dans les maladies mentales, *Rev. de psychiat.* **18**:249-259, 1914.