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## PHENOLPHTHALEIN ERUPTIONS \*

FRED WISE, M.D., AND E. W. ABRAMOWITZ, M.D.

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### INTRODUCTION

In susceptible persons the ingestion of phenolphthalein provokes a peculiar eruption of the skin. This eruption consists of a few widely scattered and numerous irregularly grouped polychromatic macular plaques, varying in diameter from that of a pinhead to several inches, varying in color from pink to bright red, dusky violaceous and deep purple; it is relapsing in course, chronic in nature and usually results in a protracted pigmentation of the affected areas of skin. Slight scaling may accompany the evolution of the lesions; a peculiar mottling is sometimes seen in the central zone of the macules; vesiculation, erosion and superficial ulceration may occur, more especially on the mucous membranes of the mouth and on the skin of the genitals; a burning sensation sometimes precedes and accompanies the appearance of the patches; moderate to severe itching may be a symptom during their evolution. The eruption, clinically, is a persistent multiform erythema, which, instead of vanishing without leaving a trace, persists more or less indefinitely and terminates in a yellowish-brown deposit of pigment in the affected sites. After the subsidence of the active lesions, relapses are apt to take place, following the ingestion of phenolphthalein. These relapses most frequently appear and reappear in the original sites of the primary eruption, but they may also occur elsewhere. Mild constitutional symptoms, such as headache, malaise, slight rise of temperature and pulse rate may accompany the relapses.

To the best of our knowledge only one other toxic agent is capable of provoking an identical eruption, namely, antipyrin. Eruptions having many points of resemblance to those caused by phenolphthalein and antipyrin, are sometimes encountered following the use of arsphenamin and neo-arsphenamin.

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\* From the service of Prof. John A. Fordyce, Vanderbilt Clinic, College of Physicians and Surgeons, Columbia University.

## FORMERLY UNRECOGNIZED EXAMPLES OF THE DERMATOSIS

The first article in which a phenolphthalein eruption is mentioned, was published by Abramowitz,<sup>1</sup> in January, 1918. He reported five cases of persistent erythema multiforme, associated with pigmentation (melanin). These patients were under our observation in Dr. Fordyce's services at the Vanderbilt Clinic.<sup>2</sup>

The differential diagnosis of dermatitis medicamentosa from a phenolphthalein eruption was definitely established, however, in only one of these five patients when the article was submitted to the publisher. Further study of these eruptions has convinced us that all these patients had an idiosyncrasy toward phenolphthalein, possibly also toward antipyrin. None of them had been given arsphenamin. The paper by Abramowitz contains a thorough description of the clinical and histopathologic findings in these patients. Photographs of most of his patients are reproduced in this paper. For a complete account of these early cases, the reader is referred to Abramowitz's publication.

In the past four or five years several examples of the dermatosis were presented before various local societies, the etiologic factor being unknown at the time, under such titles as erythema multiforme perstans, melanoderma from recurrent erythema multiforme, toxic erythema, and so forth.

Among these was a boy, M. C., aged 9, presented by MacKee and Wise<sup>3</sup> in April, 1916, before the Manhattan Dermatological Society, under the erroneous title of "erythema multiforme and iris." It was subsequently discovered that the eruption was directly due to the ingestion of phenolphthalein tablets.

This boy had an extensive eruption involving almost the whole body. It consisted of macules ranging from a half inch (1.27 cm.) to 5 or 6 inches (12.7 or 15.24 cm.) in diameter; the color of these was reddish-violet in the larger middle zone, gradually becoming red and then pink toward the peripheral zone. The central portions of some of these macules presented what looked like small cutaneous hemorrhages or contusions; the plaques appeared to be in various stages of involution, some of them having a yellowish, others a dark-brown tint, while still others were a bright pink. The lesions had been present in varying degrees of severity for seven months; the old lesions always flared up after the ingestion of phenolphthalein, and now and then new lesions would appear, persisting for months at a time, leaving a brown stain after involution. There were also evidences of broken blebs on the lips and in the mouth.

1. Abramowitz, E. W.: Erythema Multiforme Associated with Cutaneous Pigmentation (Melanin). Clinical and Pathological Report of Five Cases, *J. Cutan. Dis.* **36**:11 (Jan.) 1918. (This paper was received for publication, April 5, 1917.)

2. One of these patients was previously under the observation of Dr. Ludwig Weiss, the other had previously consulted Dr. Howard Fox.

3. MacKee, George H., and Wise, Fred: *J. Cutan. Dis.* **34**:846, 1916.

The second example was the case of Mrs. A. S., presented by MacKee and Wise<sup>4</sup> before the New York Academy of Medicine, November, 1916, as a case of erythema multiforme perstans. This patient was a married woman, aged 34, who gave a history of repeated attacks of an eruption which consisted of dime to palm-sized, smooth, round and oval violaceous and bluish-red macular patches, appearing on the trunk, buttocks and extremities. These patches did not itch, and some of them would persist without showing signs of involution for weeks and months at a time. Then they would gradually fade for awhile, only to reappear chiefly in exactly the same sites as before. The duration of the trouble was three years. In some of the lesions which showed evidences of retrogression, there was a peculiar mottling and reticulation of the surface, presenting yellowish and almost white areas in the midst

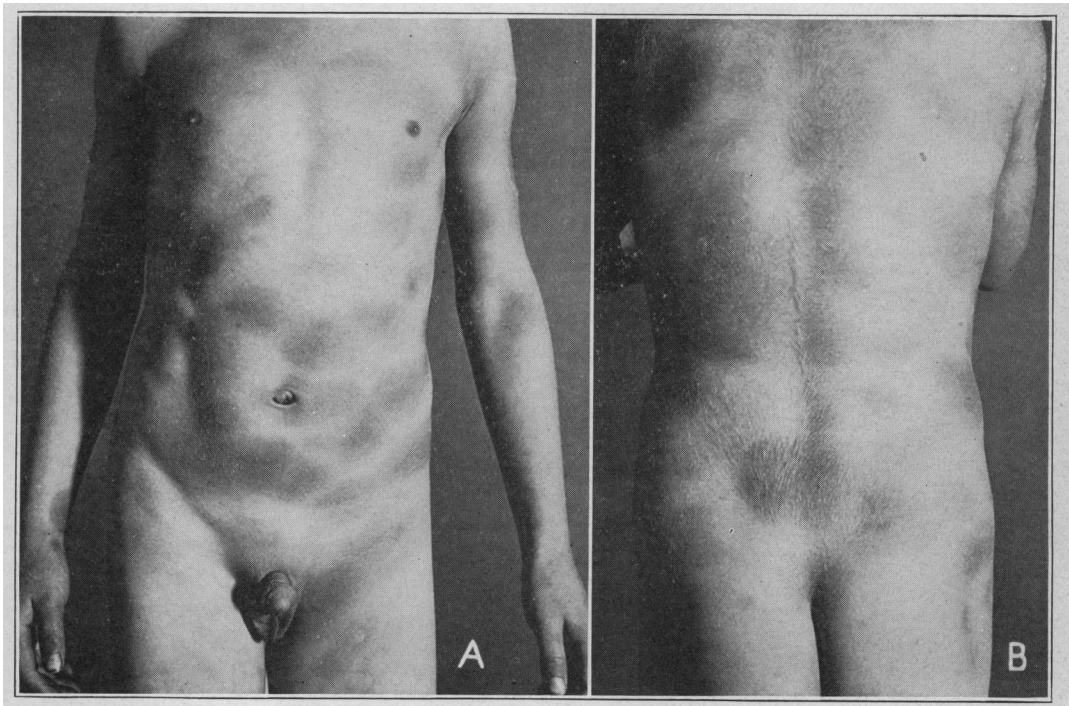


Fig. 1.—*A*, polychromatic macular eruption in a boy, aged 9, caused by ingestion of phenolphthalein. The lesions recurred in situ repeatedly, after the drug had been taken. Pigmentation persisted for about a year after stopping the remedy. (Vanderbilt Clinic.) *B*, rear view; the patch on the lumbosacral region shows the site of predilection.

of the violaceous plaque. The general appearance was that of an erythema multiforme in the stage of resolution, but instead of fading within a week or so, these plaques would persist without much change for long periods of time. The patient was suffering from obstinate constipation. Treatment had been of little avail.

4. MacKee, George H., and Wise, Fred: *J. Cutan. Dis.* **35**:554 (July-August) 1917.

Another example was the case of Mr. S. A., presented by MacKee and Wise<sup>5</sup> as a case of erythema maculatum perstans, before the New York Academy of Medicine, April, 1917. This man was single, aged 45, who said that the lesions began three years ago and persisted until December, 1916. They consisted of smooth, flat, reddish and violaceous macules, located on the arms, legs, buttocks and scrotum. On the scrotum, the surface of the lesions was somewhat moist and eczematous in appearance. In December, a fresh outbreak of reddish patches occurred, most of them reappearing in the same sites as on the previous eruption. These patches would persist for weeks or months, without showing signs of involution. They were uninfluenced by ordinary forms of treatment.

The patient presented by the late Dr. Harris before the Chicago Dermatological Society, June, 1918, undoubtedly belonged in the same category.<sup>5a</sup> The cases of Berk, Stelwagon, Hartzell, and McEwen (quoted by Abramowitz) were in all probability also members of the same group of eruptions, namely, either antipyrin or phenolphthalein exanthems.

#### REPORT OF CASES<sup>6</sup>

The following additional examples of phenolphthalein idiosyncrasy have recently been observed by us in dispensary and in private practice.

5. MacKee, George H., and Wise, Fred: J. Cutan. Dis. **36**:190 (March) 1918.

5a. Harris: J. Cutan. Dis. **37**:258, 1919.

6. For the sake of completeness, Abramowitz's Case 5, in which the cause of the eruption was readily demonstrated as being due to phenolphthalein, is included in this report:

**CASE 5.—History.**—Patient, J. T., was first seen by Dr. Howard Fox. Later she appeared at the Vanderbilt Clinic for treatment. She was 27 years old, born in Russia, and had been in the United States eleven years, always in New York City. She was married eight years and had one child, living and well, 7 years old. One year ago she had a premature delivery, the child living only two days; the cause of this was not known. The family history was negative, and there was no history of any skin disease in the family. She did not recall ever having had any illness and was always in good health. Her periods were regular.

**Physical Examination.**—The patient was a brunette, of average height and weight, and well built. She was not very intelligent and seemed to be somewhat neurotic. Detailed examination of her nose, mouth, throat, larynx, eyes and ears revealed nothing abnormal. Similar examination of the thorax, abdomen and extremities was also negative. Clinical examination of the urine and stools was also negative. The Wassermann test was negative. The examination of the blood showed 4,000,000 red blood corpuscles with a hemoglobin of 85 per cent. (Tallqvist's). The white cells and differential counts were normal.

**Dermatologic History.**—She said she had trouble with her skin for the past one and one-half years. No reliable description could be obtained from her as to how the eruption looked when it first appeared, or the manner of distribution. The relapses were quite frequent and were accompanied by itching.

According to her family physician, who saw her early in the last pregnancy, there were present pigmented stains on her body from previous attacks. She was free of relapses during the pregnancy and not until six months after confinement did she complain again. At this time she took some proprietary

CASE 1.—Mrs. E. A., aged 25, born in the United States, recently married; of dark complexion and rather frail, had been troubled with constipation for the past eleven years, for which she had been taking remedies, during the past four years especially. She presented herself at the clinic on Oct. 20, 1920; she said that her skin trouble began about three years ago, coming on in attacks, at first once a month, later as often as once a week, and accompanied by a good deal of itching. The eruption was confined to the forehead, around the mouth, axillary folds, shoulders, arms, sacrum and thighs, and consisted of violaceous and brown patches varying in size from that of a dime to that of a silver dollar. The patches were sharply outlined, oval and circular in shape, slightly infiltrated, with hardly any scaling.

Dr. J. L. Kantor of the gastro-intestinal department of the Vanderbilt Clinic reported that the patient had a general ptosis of her stomach and intestines; the stomach contents, feces, urine and full blood count were normal. There was no other organic disease detected on general physical examination. Her Wassermann reaction was negative.

She was closely questioned as to whether she took any of the widely advertised brands of laxatives containing phenolphthalein, and her answers led us to believe that this was the cause of her eruption; she favored this type of laxative as they were "very palatable and caused no cramps." Some of the brands she took were ex-lax, phenolax, partola and analax, but she used ex-lax chiefly.

Without waiting for the eruption to subside completely, she was given, five days after admission, two 5-grain tablets of phenolphthalein; these she took at home, reporting to us that a few hours later the itching became worse

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laxative to which she attributed the outbreak. This laxative contained a small amount of phenolphthalein ( $\frac{1}{2}$  to 1 grain). Five weeks ago she stated that she had another relapse immediately following the ingestion of this laxative. She denied taking any other drugs or headache powders.

*Description of the Eruption.*—The lesions were distributed around the mouth, over the chest, back, arms and thighs. They consisted of roughly oval and circular patches, varying in size from a quarter to a half dollar. The lesions were slightly elevated, the surfaces were smooth and free of scales and the margins somewhat thickened but ill defined. Their color was brown; some of the spots were of a red-violet tint. This latter appearance was due to the fact that the patient had just had a relapse. She said the old spots always flared up when that occurred.

*Histopathologic Examination.*—The section was taken from a purplish pink lesion on the skin of the postaxillary fold. Dr. Howard Fox had kindly sent the specimen to the Vanderbilt Clinic. The stains used were: hematoxylin-eosin, Weigert's elastic tissue, and Perles' stain for iron in pigment.

Excepting for considerable pigmentation, there were no notable changes in the tissue. There was a loosely laminated horny layer covering a moderately acanthotic rete. The rete pegs were somewhat increased in size and several were confluent. The rete also showed a moderate parenchymatous edema. There was very little vascular dilatation but some endothelial proliferation and hyperplasia. There was a moderate perivascular collection of round cells, mostly in the papillary and subpapillary bodies. The collagen and elastica were normal. There were many pigmented cells in the perivascular zones, irregularly pear-shaped and containing fair sized, dark brown granules which did not give a blue reaction with Perles' stain.

and that new spots had appeared on her skin. She visited the clinic the following day, and showed new erythematous, slightly infiltrated patches on her body; the old brown and violaceous plaques were now deeply violaceous in color with a definite pink areola. There still was considerable itching, and the patient did not feel well in general. She was advised against the further use of phenolphthalein remedies and to refrain from taking any other medicine. She was free of any further relapses except a mild attack of angioneurotic edema of the left eyelids about three months later, which was promptly relieved by a 5-minim subcutaneous injection of epinephrin. The eyelids showed no pigmentation after this nor was there any relapse on the body. She denied taking any other medicines.

About four months after admission there were still some yellowish brown stains at the site of her former eruption. At this time the patient submitted to having the skin of her arm scarified; phenolphthalein powder, dry and in suspension in sterile water was applied, also in decinormal sodium hydrate solution, and in alcoholic solution; all tests were negative. The percutaneous injection of 0.1 c.c. of a sterile alcoholic solution of phenolphthalein, caused a dime-sized wheal in one-half hour with an erythematous halo, the reaction subsiding seven days later. This was probably due to the alcohol, as we obtained the same reaction in another patient who showed no susceptibility to phenolphthalein. She further consented to take some ex-lax for the purpose of studying a fresh lesion through biopsy. Twenty minutes after taking four adult doses of ex-lax (about 8 grains of phenolphthalein in all), her face and body began to itch severely, with new lesions appearing and the old ones flaring up. At this time a test was made on her urine with some caustic soda added to it, but no reaction for phenolphthalein was obtained. Some of the biopsy material was macerated and caustic soda added, also with a negative result. The stool could not be obtained.

CASE 2.—Mr. E. C., aged 69, a Russian Jew, who had been in the United States nineteen years, who had no regular occupation, and who smoked and drank occasionally and otherwise led a normal life, about two years ago had gastric hyperacidity with eructations, for which he took various proprietary medicines; ex-lax and a prepared headache powder were his favorites.

When he first appeared at the clinic, the patient said that he had had three similar attacks during the past year. The present eruption had existed for about four days and was preceded and accompanied by a good deal of itching. The eruption was most marked on both lips, which were swollen and blue, with small red denudations and some scaling. There was slight infiltration and pain on palpation. The right side of the hard palate showed a pearly-gray plaque about one-half inch (1.27 cm.) in diameter. The forehead, right side of the neck, backs of the hands and the palms, and the corona penis, showed single bluish scaly plaques, slightly infiltrated and varying in size from that of a split pea to that of a twenty-five cent piece.

He was given one 5-grain powder of phenolphthalein one afternoon at the clinic; nothing happened for about one hour. He then began to complain of smarting in the mouth, with itching of the face, neck and hands, severe headache and general indisposition. He unfortunately took a headache powder for the relief of his headache, but he was positive that his rash was markedly aggravated before this. He was examined the following afternoon at the clinic when it was found that the entire hard palate was covered with numerous pearly plaques, his lips were more swollen and quite painful and the skin lesions had increased to twice their former size. His general appearance

was that of a sick man. Two days after taking the phenolphthalein powder, he was much more comfortable and all the lesions were subsiding.

His urine was examined at this time by adding a few drops of a strong caustic potash solution to about 10 c.c. of urine, with no change in the specimen except a slight clouding. Another specimen was then acidulated with a few drops of dilute hydrochloric acid, boiled and then cooled, and a few drops of alkali then added (according to the method of Kastle); this test also was negative. Dr. E. G. Miller, Jr., of the department of biochemistry, Columbia University School of Medicine, was given a sample of urine and feces for the determination of the presence of phenolphthalein. The results, however, were negative.

CASE 3.—Mr. E. W., aged 29, born in the United States, a salesman, married and the father of two healthy children, first noticed the eruption in

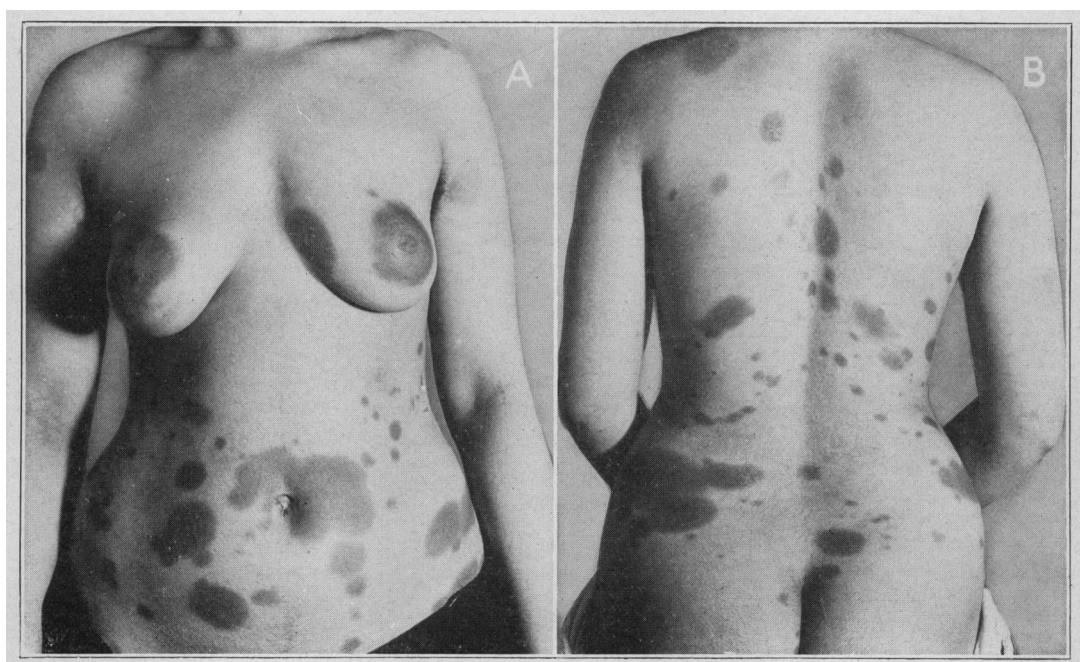


Fig. 2.—*A*, polychromatic macular eruption in a woman, aged 34, caused by ingestion of phenolphthalein. The eruption persisted for three years, with varying grades of severity. (Vanderbilt Clinic.) *B*, rear view. The patches near the sacrum show the site of predilection.

the mouth and on the genitals, twenty-four hours previously. On close questioning he admitted taking ex-lax for constipation the night before the appearance of the eruption. He had never taken it before. About the middle of the dorsum of the shaft of the penis, he presented a bluish plaque the size of a five-cent piece, sharply outlined and slightly infiltrated. Just back of the corona was another patch of the same size, but eroded. The left side of the hard palate presented a pearly-gray plaque about the size of a dime. A dark-field examination of fluid obtained from the erosive lesion on the penis was negative. There was no glandular enlargement and no other eruption. His

Wassermann reaction, two months later, was negative. The erosive lesions healed under mild antiseptic dressings.

About one week after he came under observation and while his eruption was subsiding, he was asked to take three adult doses of ex-lax. This he did, reporting the following day, when he showed a definite and distinct aggravation of his previous lesions on the penis. There were three erosions now instead of one, and the itching was again present. About three hours after taking the laxative, itching commenced. Strangely enough there were no new lesions in his mouth, in fact they had disappeared.

His urine was negative for albumin, and when caustic alkali was added to another sample, it gave no color reaction for phenolphthalein.

CASE 4.—Gussie T., from Dr. Thornley's service, Gouverneur Hospital, 18 years of age, American born, of Russian parentage, and a stenographer, with nothing of importance in her family or past history, experienced the first attack of skin disease about eight months ago; it was similar to the present eruption and left brown stains. The present attack occurred about three weeks ago, and when she appeared at the clinic she showed about two dozen spots, varying in size from that of a dime to that of a silver dollar, sharply outlined, brownish to violaceous in color. In addition, the breasts showed palm-sized livid and mottled patches. The eruption was distributed over the anterior and posterior surfaces of the trunk, sacral region, palms and flexor surfaces of the wrists. A special feature of the eruption was the peculiar streak-like depigmentations in the larger mottled and livid patches.

She had been using partola and ex-lax for constipation, but she was not quite sure for how long a period. Having satisfied ourselves that she had not been taking any other drug, such as antipyrin, and instructing her not to take any medicine for one week, we gave her 5 grains of pure phenolphthalein one afternoon about 4 o'clock. She reported at the clinic the following afternoon, when she showed a definite increase in the severity of the eruption, as evidenced by the presence of erythema, purpura-like coloration and even vesiculation, in the old lesions. She was a dull, phlegmatic type and did not notice any definite subjective sensations, as increase of itching, peculiar taste in her mouth or feeling ill. We succeeded in proving to the patient and to her father that the cause for the eruption was the ingestion of phenolphthalein, as not only did the eruption become worse after its administration, but since she had stopped taking this drug, the eruption had not recurred. We tried a percutaneous test with a watery suspension of phenolphthalein on this patient also, with a negative result as in the others.

She was a brunette, 5 feet 5 inches (1.66 meters) tall, and weighed about 122 pounds (55.5 kg.). There was no visceral abnormality. A single specimen of feces and a specimen of urine were collected after the phenolphthalein ingestion test. These were kindly examined by Dr. E. G. Miller, Jr., of the department of biochemistry, who reported: The urine examination was negative; but the feces showed a good trace of phenolphthalein. Unfortunately, neither the urine nor feces represented full twenty-four hour specimens.

#### CUTANEOUS AND MUCOUS MEMBRANE REACTIONS

The reactions in the skin and mucous membranes caused by phenolphthalein in patients having an idiosyncrasy for that drug, are apparently identical with those provoked by antipyrin. Some years ago Dr. Fordyce treated a patient who had an extensive antipyrin exanthem, of

which he obtained a photograph. This picture is almost identical in appearance with the illustrations shown in this paper.

The most frequent phenolphthalein eruption is the maculo-erythematous plaque; the interior of the plaque soon becomes markedly hyperemic; almost invariably a narrow pink peripheral zone surrounds the hyperemic area; the latter shows color changes due to the evolution of the lesion; it is at first bright red, soon assumes a dusky red hue,

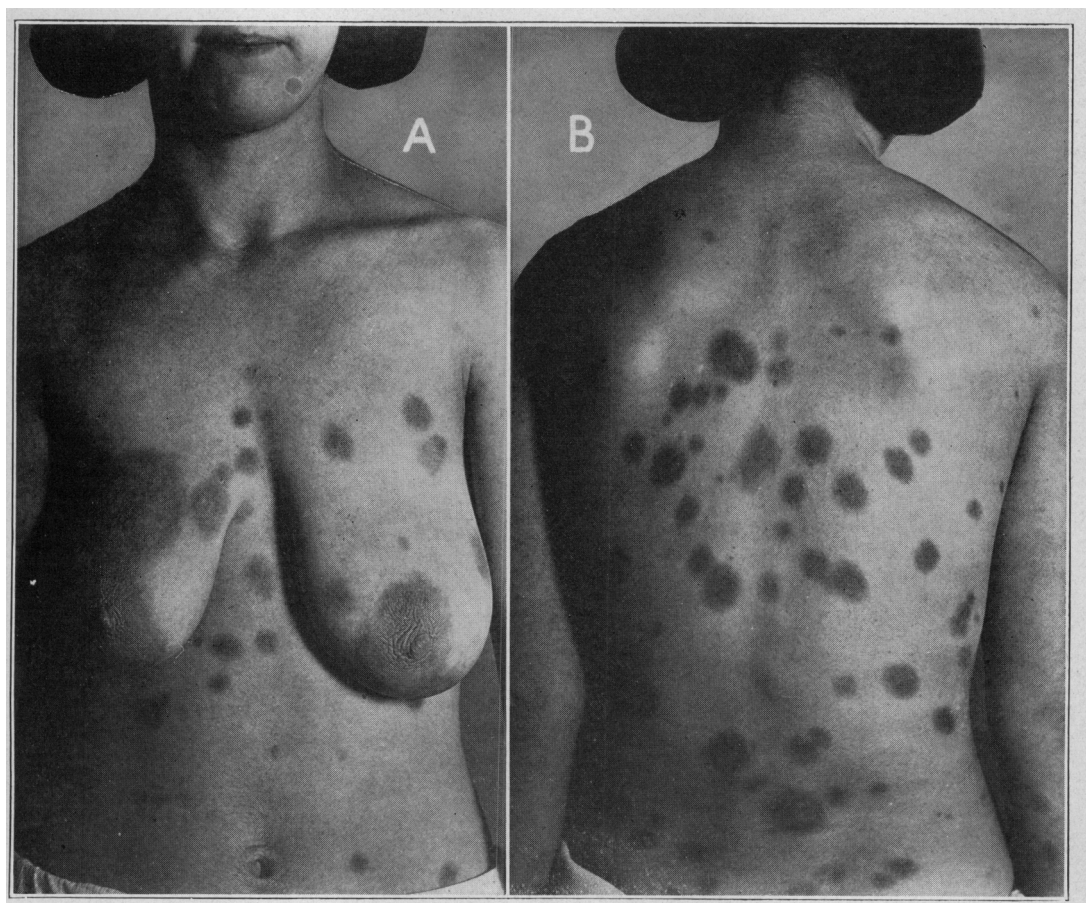


Fig. 3.—*A*, polychromatic macular eruption in a girl, aged 18, caused by the ingestion of phenolphthalein. The duration of the eruption was eight months; severe "flaring up" of pigmented macules, following ingestion of phenolphthalein. Note lesions with mottling in central zones. (Courtesy of Dr. Thornley, Gouverneur Hospital, New York.) *B*, rear view.

then becomes violaceous or deep purple (especially on the skin of the penis). Sometimes there is also a mottling. Finally, a dark brown pigmented patch occupies the site of the original lesion. During retrogression of the patch, faint scaling often occurs.

The next most frequent lesion is the erosive lesion of the lips, tongue and buccal mucosa. Here the resemblance to early syphilis and to pemphigus or erythema bullosum, is marked, and may even give rise to great difficulty in diagnosis. The buccal and lingual lesions are usually quite sensitive.

The eruption may appear on any part of the body, but the mouth, genitals and lumbosacral region are areas of predilection. One of our patients had large palmar and plantar lesions.

#### PHENOLPHTHALEIN AND ANTIPYRIN

Thus it is evident that the types of phenolphthalein eruptions which we have thus far seen, greatly resemble the better known common forms of antipyrin exanthems. Apolant's<sup>7</sup> classification of the antipyrin eruptions is interesting in this connection, because it may well be applied (at least in part) to phenolphthalein. Apolant describes a localized exanthem, a generalized disseminated exanthem and a congestive edema, the last being a manifestation of general toxemia. He describes the disseminated eruption as occurring in morbilliform, scarlatiniform, bullous and hemorrhagic exanthems, and also as an erythema nodosum. It is not improbable that future observations in patients having an idiosyncrasy for phenolphthalein may reveal analogous clinical manifestations.

Another interesting analogy between the two drugs is the well-known fact that an antipyrin eruption will, in certain patients, disappear, despite the fact that more antipyrin is being ingested.<sup>8</sup> In two of the patients mentioned by Abramowitz, retrogression of the lesions was noted during the ingestion of further doses of phenolphthalein. Such a varying susceptibility to antipyrin is interpreted by Apolant, for example, as being due to a fluctuating idiosyncrasy; he speaks of patients in whom the idiosyncrasy remains always the same; those in whom it gradually increases, and those in whom it gradually decreases as time goes on; and those in whom it varies at different times. It may be assumed that the same phenomena obtain with respect to phenolphthalein.

#### PHENOLPHTHALEIN AND ARSPHENAMIN

Are drugs other than antipyrin and phenolphthalein capable of provoking an identical eruption? Speaking from knowledge gained by personal observation, we would answer, "No." But whether or not this opinion is susceptible to corroboration by other, perhaps more expe-

7. Apolant, Hugo: Antipyrin Exanthems, *Arch. f. Dermat. u. Syph.* **46**: 345, 1898.

8. Stelwagon: *Diseases of the Skin*, 1907. In speaking of antipyrin, Stelwagon says that in some instances a tolerance is soon established, and the eruption may fade while the patient still continues to take the drug.

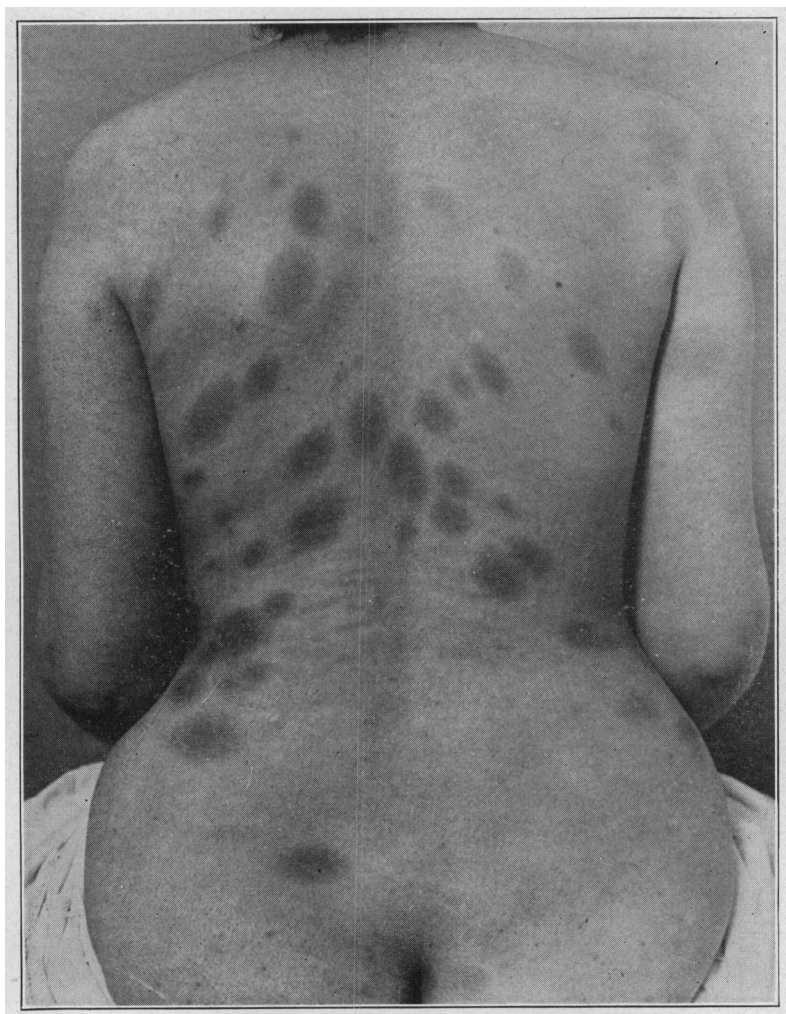


Fig. 4.—Recurrent polychromatic macular plaques in a woman, aged 27; "flaring up" in situ after taking phenolphthalein. Patient also presented lesions of the buccal mucosa. Duration of eruption, one and one-half years. (Courtesy of Dr. Howard Fox.)

rienced clinicians, is an open question. Thibierge and Mercier,<sup>9</sup> for example, reported a case of pigmented erythema following in a few hours, injections of neo-arsphenamin. The eruption resembled closely that produced by the ingestion of antipyrin. Chargin, in a verbal communication, said that he had seen a similar eruption following injections of arsphenamin. This brings up the interesting question: Do some of these patients take phenolphthalein to evacuate their bowels in preparing for arsphenamin treatment? In obtaining histories from the majority of our patients, we learned that it required reiterated and persistent questioning to elicit from them the truth with regard to habits as to the use of cathartics. They would wind up a long and tedious session by finally exclaiming: "Oh, yes, I take an ex-lax tablet now and then." Most of them being of foreign birth, they have a way of evading replies to questions which to them seem entirely irrelevant. This partly accounts for our failure to discover the etiologic factors in the earlier cases which came under our notice.

Several papers dealing with peculiar and unusual eruptions following arsphenamin injections have recently been published. Those which interest us here have been called "fixed" arsphenamin eruptions, in contradistinction to the evanescent forms. Among these publications are those of Naegeli,<sup>10</sup> Engwer and Josephson,<sup>11</sup> Dora Fuchs,<sup>12</sup> Bitterling,<sup>13</sup> Schoenfeld,<sup>14</sup> Edmund Hofmann,<sup>15</sup> Leibkind,<sup>16</sup> Mergelsberg,<sup>17</sup> Nathan,<sup>18</sup> Gruetz.<sup>19</sup>

Perusal of these articles demonstrates the fact that certain "fixed" arsphenamin eruptions sometimes resemble those provoked by phenol-

9. Thibierge and Mercier: Taches érythémato-pigmentées à répétition "in situ" a la suite d'injections de novarsénobenzol, Bull. soc. Franç. de dermat. et syph., 1919, p. 93.

10. Naegeli, O.: Fixes Neosalvarsanexanthem und Adrenalinwirkung, Korrespbl. f. Schweizer Aertzte, 1917, No. 39; Ref. Dermat. Zentralbl., 1918, p. 171.

11. Engwer and Josephson: Ueber Salvarsantherapie und Salvarsannatrium, München. med. Wchnschr., 1919, No. 9, p. 243.

12. Fuchs, Dora: Fixe Salvarsanexantheme, Deutsch. med. Wchnschr., 1919, No. 46.

13. Bitterling: Fixe Salvarsanexantheme, München. med. Wchnschr., 1919, No. 9, p. 342.

14. Schoenfeld, W.: Fixe Salvarsanexantheme, Deutsch. med. Wchnschr., 1920, No. 1.

15. Hofmann, E.: Ueber Salvarsanexantheme, Dermat. Ztschr. **31**:1 (July) 1920.

16. Leibkind, M.: Beitrag zur Kasuistik der Salvarsanexantheme (fixes exazerbierendes Erythem), Dermat. Ztschr. **31**:91 (Aug.) 1919.

17. Mergelsberg, O.: Ueber einen Fall von Ueberempfindlichkeit gegen Quecksilber und Silbersalvarsan, Dermat. Ztschr. **31**:129 (Sept.) 1920.

18. Nathan: Dermat. Ztschr. **29**: No. 3, 1920.

19. Gruetz, O.: Ueber fixe Exantheme nach Altsalvarsan, Dermat. Wchnschr. **70**:305 (May 15) 1920.

phthalein and antipyrin; but they are not alike. Dr. Chargin, at a recent meeting of the Section of Dermatology, New York Academy of Medicine, demonstrated his patient (mentioned in the foregoing), who had two or three well-defined nummular macules, with well marked borders, on the trunk and extremities. These would appear after the administration of arsphenamin and would fade between treatments.

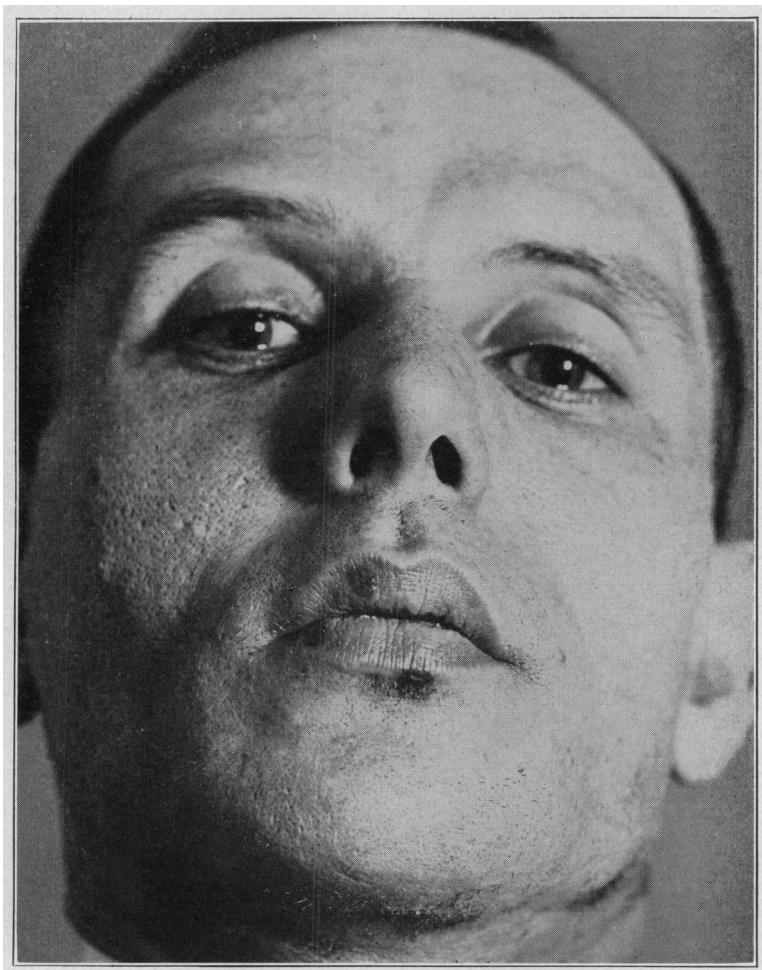


Fig. 5.—Recurrent vesicular lesions on both lips and adjacent skin of lower lip, with similar crusted patches on the neck, caused by ingestion of phenolphthalein. (Courtesy of Dr. Parounagian, Bellevue Hospital, New York.)

Their color was a uniform pink—there was no evidence of the characteristic play of colors seen in the phenolphthalein rashes; the borders were sharply defined; there was no mottling, nor was there evidence of pigmentation. However, the macules were indistinguishable from

those provoked by antipyrin, during a certain stage of evolution. Cases like that of Chargin are frequently described in the literature quoted.

In an article entitled "Der Phenolphthalein Unfug" (The Abuse of Phenolphthalein), Silberstein<sup>20</sup> describes the effect of phenolphthalein on himself. In 1911, he took an adult dose of the drug, following which he soon noticed many raised plaques on the tongue. At that time he was unable to account for the appearance of these lesions. Fearing epithelioma, he stopped smoking and was mentally quite perturbed. In 1912 he again took a very small dose. Shortly after, he had the impression of tasting phenol and then a bullous stomatitis developed, with a herpetic eruption of the skin and general constitutional symptoms. On July 12, 1919, he was called to see a woman who complained of general pains in the body and loss of appetite. Just below each eye she had narrow reddish streaks which consisted of small petechial hemorrhages, resembling bruises. She had taken seven candy laxatives (presumably phenolphthalein) in three days, and had frequency of urination, but the urine was free of albumin. On August 12, the red spots turned brown and two months later they disappeared. He concludes that phenolphthalein is not an indifferent remedy, and that the drug should be used with caution, as there are many widely advertised brands on the market.

Rosenstein<sup>21</sup> states that a woman called on him who had been taking Boxberger's Kissingen Pills for the past several weeks as an antifat preparation. She had lost weight, she said, but it was at the expense of her general health. She could not get rid of the diarrhea, and on examination it became evident that she was suffering from severe hemorrhagic nephritis. Urinalysis revealed 0.1 per cent. albumin in the urine, and in the sediment there were many granular and waxy casts. After a week's illness the patient recovered completely. The pills in question were found to contain phenolphthalein, although on the label only rhubarb and extract of cascara sagrada were mentioned as ingredients. Rosenstein expresses the wish that the authorities might take such action as would prevent the indiscriminate sale of such remedies.

#### HISTOPATHOLOGY

The histopathologic features have already been described in a study of the five biopsies obtained by Abramowitz. We have obtained several new sections since his findings were published. The sections were stained with hematoxylin-eosin, polychrome methylene blue, and Weigert's elastic tissue stain. All were stained with Perles' stain (ferrocyanid) for the detection of hemosiderin.

20. Silberstein, L.: *Der Phenolphthalein Unfug*, Therap. Halbmonatsh. **34**: 306 (June 1) 1920.

21. Rosenstein, P.: *The Abuse of Phenolphthalein*, München. med. Wchnschr. **67**:263 (Feb. 27) 1920; abstr., J. A. M. A. **75**:1168 (Oct. 23) 1920.

The microscopic changes were practically the same in all. To recapitulate: There was a moderate hyperkeratosis and lamination of the epidermis, due to edema; parakeratosis was absent. The rete showed a slight parenchymatous and interstitial edema; a few round cells and chromatophores were found in the basal layer. Slight acanthosis was present in some sections. The stratum lucidum was usually absent, and the granular layer presented a normal appearance.

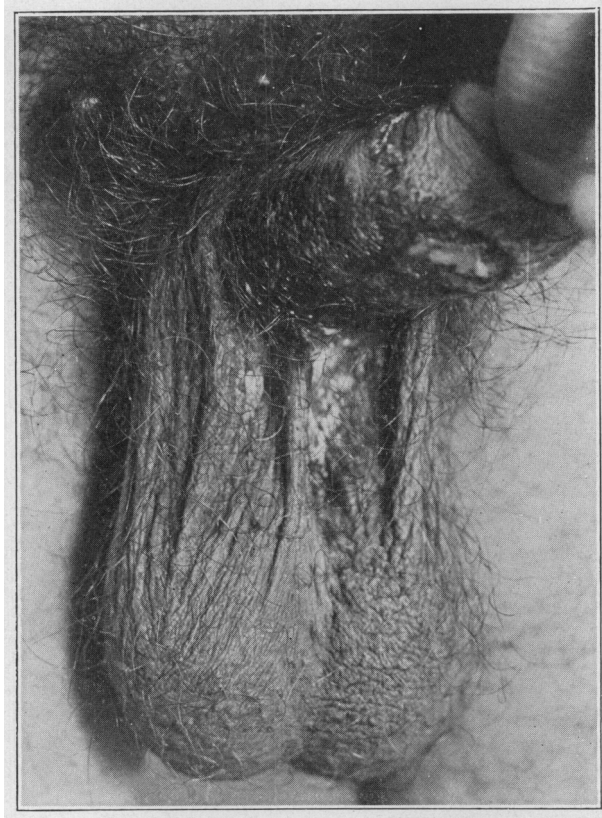


Fig. 6.—The same kind of erosive lesions on penis and scrotum following ingestion of phenolphthalein as in patient in Figure 8. The crusted penile lesion resembled a chancre. The other lesions resembled mucous patches. Note the large, dark patch covering the lower right side of the shaft of the penis. This was deep purple—the “black penis” of antipyrin. (Courtesy of Dr. Parounagian, Bellevue Hospital, New York.)

In some of the sections there was a dyskeratinization of the granular layer and of the upper layer of the rete cells. The papillary bodies were moderately thickened from an edema; there was moderate dilatation of the papillary and subpapillary vessels and a more pronounced

dilatation of the lymphatics and the perivascular lymph spaces. The collagen and elastic fibers of the papillary bodies were spread apart by the edema; the collagen in the subpapillary region was thickened and the striation somewhat dimmed. No degeneration of collagen or elastin was noted. There were no hemorrhages. The infiltration was chiefly perivascular and confined to the papillary and subpapillary regions, consisting mostly of round cells and proliferating connective tissue cells; an occasional polymorphonuclear, plasma and mast cell was noted.

These changes are similar to those seen in erythema multiforme.

In addition, many pigmented cells were found in the perivascular lymph spaces of the subpapillary region; a few were in the papillary bodies and occasionally in the epidermis. Little pigment was noted lying free in the collagen spaces. These pigmented cells were about two or three times the size of the round cell, spindle and pear-shaped, containing moderate sized, dark brown granules which did not react to Perles' ferrocyanid stain. The cells were chromatophores and the pigment melanin. According to Unna, pigment in the skin which does not react to Perles' stain with ferrocyanid, is melanin. Hemosiderin reacts with ferrocyanid, as it contains oxid of iron.

#### PROPRIETARY REMEDIES

On account of its mild action as a laxative and its nonirritating qualities on the intestinal mucosa, phenolphthalein has become a popular remedy and is used extensively by both laymen and physicians.

The following list<sup>22</sup> includes some of the better known proprietary brands and compounds containing phenolphthalein:

Analax	Phenolphthalein laxative
Aromatic laxative tablets	Probilin
Alophen	Prunoids
Cholelith pills	Purgatol
El Zernac	Purgen konfekt
Exurgine	Purgella
Ex-Lax	Purglets
Laxophen	Purgo
Laxine	Purgolade
Laxerconfect	Purgotin
Laxothalen tablets	Purgylum
Normalax	Rexall orderlies
Partola	Rhuphen
Paraphthalein	Taurocol tablets
Phenalin	Thalosen
Phenolax wafers	Veracolate
Phenolphthalein agar	Zam Zam

22. Part of this list is from an article on "Phenolphthalein," J. A. M. A. 74:29 (Jan. 23) 1920.

## CHEMISTRY

Phenolphthalein is a dihydroxyphthalophenone having the chemical formula,  $C_{20}H_{14}O_4$ . It is a white or yellowish-white crystalline powder, practically insoluble in water but soluble in thirteen parts of alcohol and in aqueous solutions of alkalis. With the alkalis it gives a pink coloration, hence its use as an indicator. It is also soluble in olive oil to about 2 per cent. It is a phenol compound belonging to a class of bodies known as triphenyl methane dyes, to which also fuchsin, eosin and fluorescein belong.

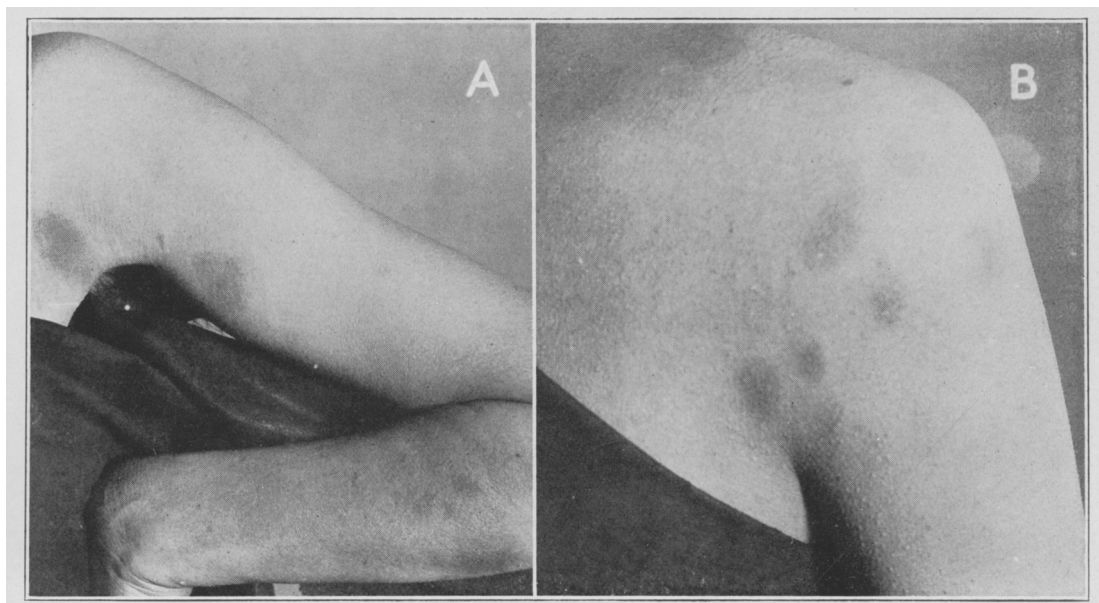


Fig. 7.—*A*, pigmented patches at sites of preceding recurrent phenolphthalein rash in a woman, aged 25. The eruption appeared at varying intervals for three years. Relapses occurred in situ after taking phenolphthalein preparations. (Vanderbilt Clinic.) *B*, rear view.

## TOXICOLOGY

*Physiologic Action, Pharmacology, Dosage.*—Hydrick<sup>23</sup> demonstrated the presence of albumin in the urine of twenty patients after the ingestion of from one to two grain doses of phenolphthalein. The amount of albumin varied from a trace to 0.25 per cent. The albuminuria lasted from one to three days; traces of phenolphthalein were demonstrable in the urine.

23. Hydrick, J. L.: Albuminuria Following the Ingestion of Phenolphthalein, *Proc. Am. Soc. Biol. Chem.*, 1914, p. 36.

He also administered large doses of phenolphthalein to two cats. No change was noted in the urine or in the viscera at necropsy. Animals are more resistant to the drug than man. His explanation of the action of the drug is that phenolphthalein forms a sodium salt which is an irritant, and thus induces purgation, either by the irritation of the intestinal mucosa by the unabsorbed portion, or by stimulation of the intestinal nerve plexuses which regulate peristalsis, by the absorbed portion.

Elmer,<sup>24</sup> after a series of experiments, said that he doubted that sodium salts played any part in the purgative action of the drug. He believed that the drug itself acted as an irritant.

With regard to toxicity, Elmer cites Best as reporting a case of poisoning caused by a 15 grain dose. No details are given. One grain per kilogram can be given to animals without danger. He reports four patients who took 30 grains or more daily, for at least two weeks, without ill effects. One patient took from 30 to 60 grains daily for fourteen months, without ill effects.

As to the fate of the drug in the body, 87.17 per cent. is recovered in the stools. A small quantity may be detected in the urine only after the ingestion of large doses. So far as can be determined, the drug is not broken down in the body. Elmer believes that Best's case of poisoning is a manifestation of idiosyncrasy, or that the symptoms were due to some other cause.

Kastle<sup>25</sup> quotes Ehrlich, who showed that powerful reduction of phenolphthalein was accomplished in the animal organism. Kastle injected 0.5 c. c. of a phenolphthalein suspension in water, into the peritoneal cavity of a guinea-pig weighing 325 gm., and observed no ill effects. He added caustic soda to the urine of the guinea-pig and obtained no reaction for phenolphthalein; but when he boiled the urine with dilute hydrochloric acid, allowed it to cool, and then added caustic soda, he obtained the purplish red color reaction of phenolphthalein. This means that phenolphthalein when injected into animals, forms, through a combination with the cells, some conjugated compound which of itself gives no color reaction with caustic soda, but which, when hydrolyzed with hydrochloric acid, yields phenolphthalein as one of the by-products of the hydrolysis. By this test he showed the presence of phenolphthalein in the urine for as long as thirty-five days after the intraperitoneal injection.

In addition to phenolphthalein, the following phthaleins were also injected intraperitoneally, and the urine also gave purplish-pink reac-

24. Elmer, W. P.: Action and Dosage of Phenolphthalein, *Med. Rec.* **74**:838 (Nov. 14) 1908.

25. Kastle, J. H.: Conduct of Phenolphthalein in the Animal Organism, *Hyg. Lab. Bu'l.* **21-29**:23, 1905-1906.

tions after boiling with dilute hydrochloric acid, allowing to cool, and then adding sodium hydroxid (this reaction, was, however, present to a much lesser extent): fluorescin, *o*-cresolsulphonephthalein, sulphone-fluorescin, and other phthaleins.

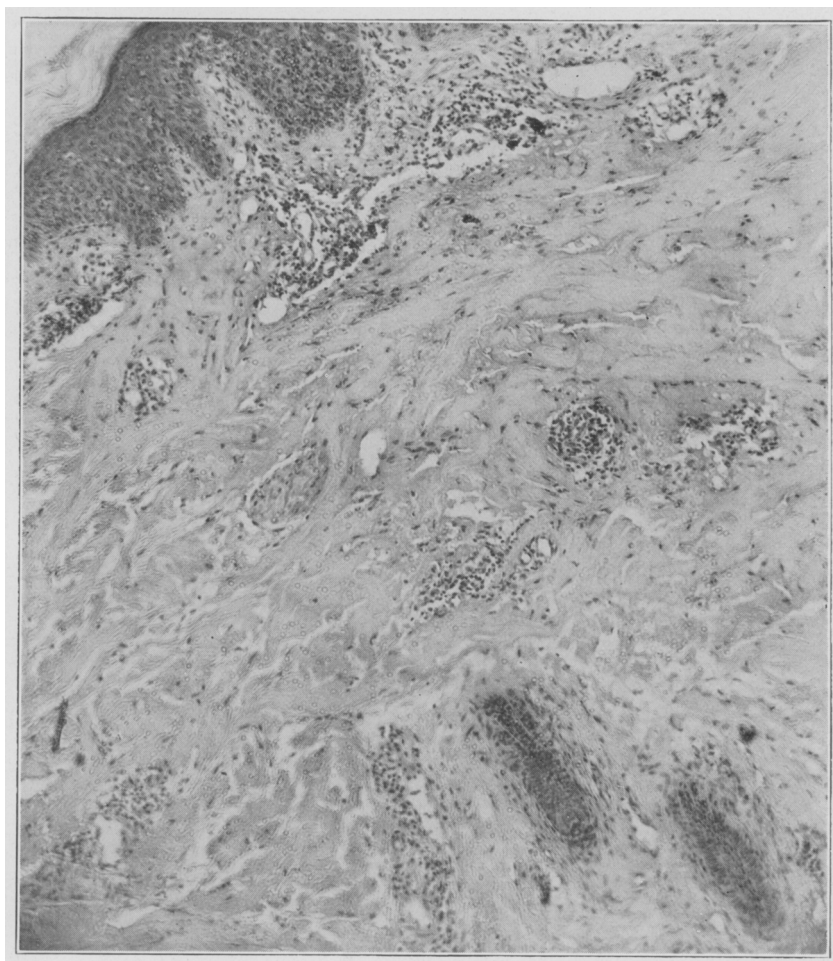


Fig. 8.—Section from an active macular lesion, showing edema throughout the skin, dilatation of lymphatics and lymph spaces, perivascular collection of round cells and connective tissue cells; chromatophores lying in the perivascular lymph spaces of the subpapillary region (low power).

Enormous doses of the drug were given by Abel and Rowntree<sup>26</sup> to animals intravenously and no toxic effects were noted.

26. Abel and Rowntree: Action of Some Phthaleins and Their Derivatives, *J. Pharmacol. & Exper. Therap.* **1**:262, 1909-1910.

The average dose for adults is 5 grains, for infants and children, from  $\frac{1}{2}$  to 1 grain. The symptoms of an overdose in a susceptible person are: purgation, colic, rapid pulse, palpitation, difficult breathing, uneasiness and even collapse. The drug is odorless and tasteless.

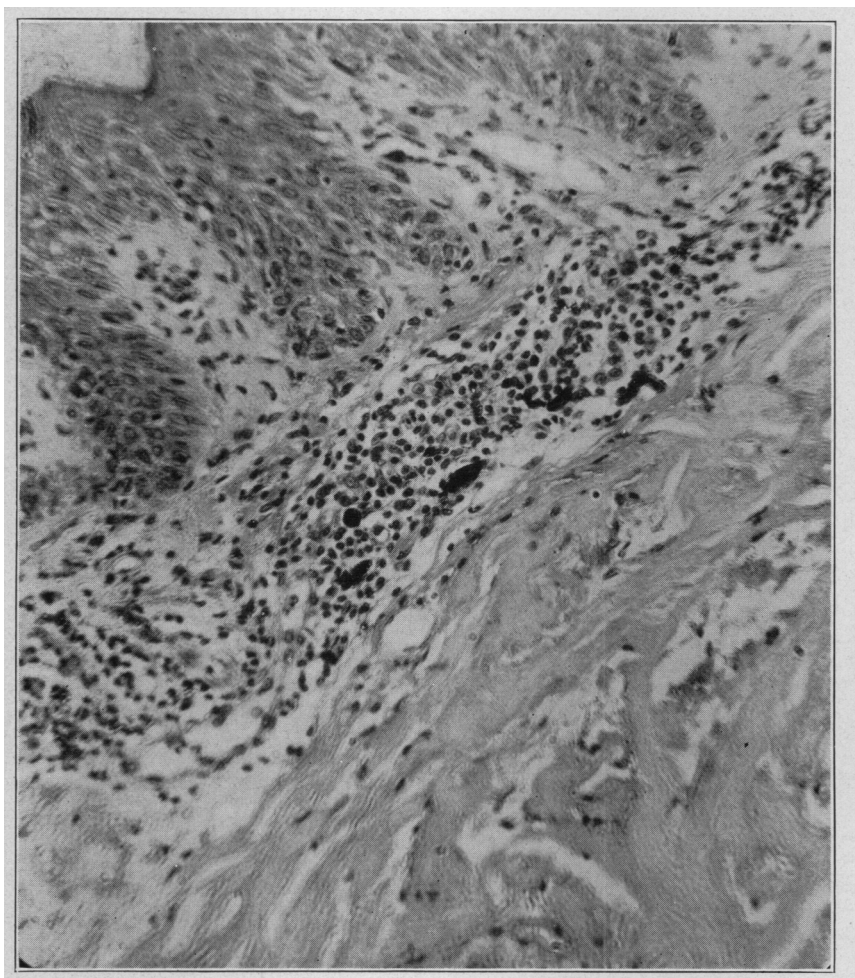


Fig. 9.—Same area as shown in Figure 8, showing chromatophore cells lying in the perivascular lymph spaces (high power).

#### COMMENT

Our failure to obtain positive skin reactions in these patients is probably not due to the phenolphthalein itself, but to some split product, perhaps allied to the antipyrin or arsphenamin split product, a similar eruption occurring with these drugs. The nature of this split prod-

uct should be the object of further study. Brunettes seem to be more susceptible, and the normally hyperpigmented areas of the skin seem to be favorite sites of the eruption. The sections of lesions show an excess of melanoblasts. These cells are said to be related to the chromaffin cells of the suprarenals, and are said to be increased in suprarenal insufficiency. Furthermore, the beneficial use of epinephrin in persons who react to arsphenamin points to the possibility that the patients susceptible to these drugs and exhibiting these peculiar skin reactions have hypo-adrenalism. Most of the patients become ill after taking phenolphthalein; they feel weak and depressed and have a slight rise of temperature and a weak pulse; this points to a general metabolic disturbance and to a possible splitting up of the drug in the body, and not in the skin itself. Possibly the hypertrophy of the melanoblastic elements in the skin is caused by hypo-adrenalism. The administration of epinephrin to these patients, however, does not seem to prevent or retard the eruption.

We have not as yet given these patients experimental doses of antipyrin and arsphenamin to determine their susceptibility to these drugs. This we intend to do in the future. Should they prove susceptible, the value of epinephrin as a deterrent to the various reactions, will be demonstrable.

Another phase of future investigation will bear on the question whether these patients show a diminished secretion of phenolphthalein as compared to those not susceptible to the drug.

#### CONCLUSIONS

In susceptible persons, the ingestion of phenolphthalein provokes a peculiar polychromatic eruption on the skin, with bullous, vesicular and eroded lesions of the mucosae and genitals.

The cutaneous lesions leave pigmented areas which persist for months and even years.

The lesions "flare up" after the ingestion of the drug, usually affecting the same sites as in the preceding eruption.

The pigment in the skin does not react to Perles' ferrocyanid test; the cells in the corium are chromatophores and the pigment melanin.

The eruption exhibits many points of similarity to those resulting from antipyrin and arsphenamin.

24 West Fifty-Ninth Street—235 West Seventy-First Street.

#### ABSTRACT OF DISCUSSION

DR. HERMAN GOLDENBERG, New York: The subject so splendidly pictured by Drs. Wise and Abramowitz has interested me for many years. It has been my fortune to see two cases of so-called "fixed" arsphenamin eruption. The three drugs, arsphenamin, phenolphthalein and antipyrin cause the same type of erup-

tion, which is always fixed at the same place; the question arises, Have they anything in common to explain this peculiar feature? In 1914, Schumacher of Berlin published an article entitled, "Arsphenamin, a True Arsenical Dyestuff." He stated that if you take the urine of a patient who has received an arsphenamin injection, if you shake this urine with a certain reagent and filter it, a filtrate is removed and does not give any more arsphenamin reaction. This is a specific which Schumacher claims is a dyestuff. In a conversation with Dr. Schamberg, this view was not upheld by him. I am not sufficiently versed in chemistry to decide one way or the other, but the fact remains that these three drugs are aromatic compounds which contain dyestuffs in solution, and that in my opinion is the explanation of the eruption. The experiments that Dr. Wise speaks about taking up we have already made. In a patient with pigmented erythema we have given phenolphthalein for one week, and the patient passed phenolphthalein. We have injected a patient with arsphenamin, with negative results.

DR. JOHN A. FORDYCE, New York: There is a hair dye, extensively used, which goes under the trade name of Goutte à Goutte and this is not infrequently added to henna. In itself henna does not produce an eruption but when Goutte à Goutte is added to it it does. I recently saw a woman who had used this for years without any ill effect, but who suddenly developed an eruption all over the body. It lasted for two months and left a marked pigmentation of the skin. At the time of the eruption there was a leukocytosis of 20,000 or more, and a rise of temperature with a marked systemic disturbance. Dr. Wise might add this to the compounds he has already mentioned.

DR. HOWARD FOX, New York: In addition to my own case of phenolphthalein eruption I have lately had the opportunity of seeing others of this kind and feel that they present a rather striking clinical picture. The eruption consists of various coin sized or larger, fairly sharply demarcated plaques which are erythematous at first and later are followed by persistent pigmentation.

DR. GROVER W. WENDE, Buffalo: I wish to express my appreciation of Dr. Wise's contribution to drug pigmentation. I can hardly agree to the confining of this type of pigmentation to the ingestion of phenolphthalein. For a considerable period I have had under my care a patient with circumscribed erythematous eruption, ultimately becoming pigmented spots, following the administration of arsphenamin, which corresponds clinically to the case shown by the essayist. I have given this patient from ten to fifteen injections of arsphenamin; following each injection these patches light up, last for a time and then subside. The spots are now almost black and correspond very well to the last case thrown on the screen.

DR. WALTER J. HIGHMAN, New York: I was very much interested in Dr. Wise's excellent presentation of this subject. So far as New York is concerned, these eruptions are quite common. I have seen three cases in the last six weeks. The lesions were somewhat larger than any shown by Dr. Wise's patients, and the lesions had become confluent so that they formed an extensive outline, possibly in consequence of something the patient had applied to relieve the pruritus and the scaling. This looked like parapsoriasis. I think an eruption of this sort should be emphasized in general medical literature, for on one occasion I saw a woman put on a very restricted diet in order to control an eruption which her physician thought due to food, but which was actually due to phenolphthalein. She was taking phenolax to move bowels

that had nothing in them to move. It is simply because we do not seem to be able to present dermatologic facts in a way that induces the general practitioner to read them that so many mistakes in diagnosis occur. I wonder whether the reason the results were negative in Dr. Wise's cases was not because he used pure phenolphthalein in his tests. I wonder whether it would not be possible to use the serum of patients who had ingested phenolphthalein to obtain the reactions.

DR. JOHN H. STOKES, Rochester, Minn.: All too little is known about this eruption by the profession at large. I wish to know whether Dr. Wise has made any experiments as to how small an amount of phenolphthalein may be necessary, instead of how large an amount, to produce the eruption. I have had under observation a patient with the typical blue-black penis who had acquired urticaria while a dairy worker when he was using phenolphthalein while testing milk. I wonder whether the limited exposure to the drug under such conditions could have brought about the eruption. The patient admitted, however, that he had acquired the habit of using phenolphthalein while in the dairy because it was so accessible, and had just fortified himself with a two weeks' supply with the intention of getting rid of his eruption.

DR. SIGMUND POLLITZER, New York: I am of the opinion that while the phenolphthalein and antipyrin eruptions are similar to, they are not identical with, that of arsphenamin. The last has a decided resemblance but, in my limited experience, the lesions are never so dark, although we have heard today of a case from Dr. Wende in which injections of arsphenamin had produced a very dark lesion; ordinarily they never become so dark as those we see resulting from antipyrin or phenolphthalein. This difference, however, may be due to the circumstance that while the noxious laxatives are usually taken daily, the administration of arsphenamin would be discontinued as soon as an eruption was apparent. As to the cause, of course we can only speculate, but I think it is not the phenolphthalein itself which produces it. The work of Dr. Wise rather definitely establishes this. There is some split-product of the phenolphthalein produced either in the digestive tract or in the blood which causes the eruption, and there is one group which is common to phenolphthalein, antipyrin and arsphenamin. I do not refer to the benzol ring which is the chemical basis of an unlimited number of organic compounds, but rather to the phenol group. The possibility that phenol is responsible for this eruption might be submitted. I would suggest to Dr. Wise an experimental test in suitable subjects. The practical importance of this subject rests on the fact that the use of laxatives containing phenolphthalein is increasing.

DR. JAMES HERBERT MITCHELL, Chicago: Dr. Ormsby and I have recently seen three cases of this type, and in his absence I saw another case of the same sort. There is much difficulty in obtaining from these patients a history concerning the drug. One of the first cases that appeared was demonstrated before the Chicago Dermatological Society, but the other two have not been. One was a woman with an eruption of this type and although she was quizzed intensively it was impossible to get any history of the drug. Finally, after some time she admitted taking a remedy which she procured from a friend. She sent for the prescription and it was found to contain antipyrin. Another patient was seen recently with an eruption on the hands. This man denied taking any drug. I suspected phenolphthalein, and as a warning told him to take no drugs at all. He said he would not, but that he might take phenolax once in a while. He then admitted having taken

phenolax the day before the eruption appeared. I saw one case of this eruption in a woman who said it appeared each time she was given an injection of arsphenamin. She came through Chicago on her way to a distant city and stopped off to ask advice about taking further injections. I quizzed her about medicine, but she denied taking any. So far as I could make out, the eruption was of the same type as that of phenolphthalein or antipyrin, but I saw her only once.

DR. GROVER W. WENDE, Buffalo: The patient of whom I spoke had not taken phenolphthalein. I think, however, castor oil had been taken. I think we are likely to discontinue arsphenamin if we obtain a skin reaction, but this case, one of grave cerebrospinal syphilis, demanded its continuance and gave me an opportunity for extended observation. As we had full drug control, I do not think the patient took any preparation for headache.

DR. POLLITZER, New York: Was there any effect from atropin?

DR. WENDE, Buffalo: After the injection of  $\frac{1}{50}$  grain of atropin, a delay in the appearance of the eruption followed the administration of the arsphenamin. Instead of coming on while the patient was on the table receiving his injection, the erythematous-urticarial eruption appeared about half an hour thereafter. Furthermore, the eruption appears regularly in this patient whether receiving arsphenamin or neo-arsphenamin; the eruptions in my case are indistinguishable from those shown by the essayist.

DR. HERMAN GOLDENBERG, New York: I have seen two cases that were identical with those pictured here. If the essayist has seen one case, he has seen a case in which the day after the injection the pigmentation was not so pronounced as a day or two afterward. Neither of these two patients had taken any phenolphthalein.

DR. FRED WISE, New York (closing): Dr. Goldenberg spoke of his patients' not taking any phenolphthalein while receiving the arsphenamin injections, but unless the physician tells his patients what to take for a laxative they may take phenolphthalein, which may account for the eruption after the arsphenamin is given. Dr. Highman's constructive criticism was very well worth while. If patients are told that their eruption is due to phenolphthalein they refuse to take any more. In the future we will not tell them, but will try to do our experiments before they discover the cause of the rash. I was surprised to hear Dr. Wendt tell us that he saw a similar type of eruption caused by arsphenamin, because I expected to have the members agree that it was another type of eruption. In regard to the eruption described by the Germans and Austrians, not one eruption has been identical with those described by me. I am inclined to think you can make a diagnosis of either phenolphthalein or antipyrin eruption but not arsphenamin, on the strength of those pictures. Since arsphenamin has been used for eleven years, it seems strange that so few pigmented eruptions should occur. The same might be said of phenolphthalein. In regard to Dr. Stokes' question, I regret to say that we have made no experiments to show how small a dose will produce the eruption.