Hyde - (J.N.)

A CONTRIBUTION TO THE STUDY OF THE BULLOUS ERUPTION INDUCED BY THE INGESTION OF THE IODIDE OF POTASSIUM.*

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ON the 23d of June, 1879, I was visited by a female patient with an infant at her breast, who delivered a note from a physician of Chicago, in which the latter requested me to give an opinion as to the skin disorder with which the child was affected. From the statements made by this mother, and from the information subsequently given by her attending physician, the following history was obtained:

The father was and had always been an entirely healthy man. The mother had occasionally suffered from head- and back-ache, and from an affection of the skin which had at times troubled her since childhood, but which had not manifested itself since her marriage. At one time, however, since that date, she had suffered from a small abscess on the inner face of the thigh, which, after discharging, had healed without untoward symptoms. Upon examination, this woman was found to be free from all evidences of syphilitic infection. She was well developed, had an abundant supply of milk for her infant, and only exhibited a moderate pallor of the exposed mucous surfaces. The cicatrix left by the abscess described above had no suspicious features.

Soon after her marriage she had been delivered of an infant which speedily displayed an eruption upon the surface of its skin. This was, according to the diagnosis of her physician, a simple eczema of the face and scalp, which, though somewhat rebellious, yielded to appropriate treatment. When convalescing from this attack the child was seized with cholera infantum, and died in its ninth month.

The second pregnancy terminated in the birth of the present fe-

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male infant, Amanda Gabrielle, now eight months old. As in the case of the child which was lost, she had, soon after birth, exhibited over the skin of the face and scalp an eruption which was recognized by the physician to be a typical eczema capitis. This cutaneous disease had also proved persistent under the treatment employed, but had gradually improved until about one month prior to the present examination, when an abundant crop of boils had appeared over the scalp. These increased in number until the physician estimated that he had opened hundreds with the lancet in the region described. They gave exit to an abundant, creamy, and laudable pus, when the process of repair speedily followed. During that time the eczematous condition had gradually ameliorated. In spite of these accidents the case was progressing fairly well, when the complication ensued with regard to which my opinion was asked. This complication was the development of certain cutaneous lesions, of formidable aspect, greatly different from those previously observed.

Upon examination the little patient was seen to be a fat and well-nourished baby, with the eruption of six teeth accomplished. It was exceedingly fretful and irritable, no doubt partly in consequence of the extent of the cutaneous disease with which it was affected, and which was pretty surely the source of disagreeable, if not painful, sensations.

The entire scalp was covered with an extensive yellowish crust of moderate thickness, evidently composed of the dried exudation of a preceding inflammation of pustular type, together with the sebaceous secretion usually seen in such cases. Sparse and light-colored hair-filaments were embedded in the crust. Similar, less bulky, and slightly-reddened crusts covered also the temples and the upper portions of the cheeks. Here it was evident that the surfaces had been irritated by scratching, as the marks of the fingers and nails were to be distinguished. No pus was confined beneath the crusts either of the scalp or face. The acuteness of the inflammatory process had evidently subsided. Here and there could be seen the sites of the abscesses whose history has been given. In short, the external appearances of the portions of the body described were those of an ordinary eczema capitis in the phase of retrogression.

But over the extremities and nates an eruption of a distinctly different type was visible. It consisted of variously-sized vesicles and bullæ, displayed upon the arms, forearms, hands, palms, interdigital spaces, backs of the hands, wrists, nates, thighs, legs, ankles, dorsum of the feet, and the spaces between the toes. The smaller lesions were dispersed between the others, but the larger were grouped about the wrists and ankles. They were displayed upon both sides of the body, and were limited to similar localities on each side, so that a certain degree of symmetry was thus demonstrable. Proceeding upward and downward from a circlet surrounding the wrists and ankles, where, as has been stated, was the region of most plentiful development for the upper and lower extremities, the bullæ became progressively fewer and smaller. Thus there were but a few

small, imperfectly-developed vesicles upon the extremities of the fingers and toes, and above the elbows and knees. Those upon the nates were not only ill developed, but surrounded by hyperæmic patches and sparse, delicate crusts, suggesting that in this locality the two disorders of the skin had coexisted and their phenomena become intermingled.

The vesicular and bullous lesions varied in size from that of a large pin-head to a pigeon's egg, those fully developed far outnumbering all others. Though they were for the most part discrete, it was clear that some of the largest had resulted from coalescence, the partition-septa showing after rupture. Some were elevated above the general surface of the integument to the extent of from 8 to 10 millimetres. The smaller were roundish in shape; the larger were either globoid or—and this was not rarely to be noted—elliptical in contour. Often they showed as merely irregular and bulging projections from the general surface.

These lesions had no disposition to rupture, but were remarkably firm and persistent. According to the statement made by the physician, they had originally contained a serous and in some cases a semi-purulent fluid, but at the time of the observation now detailed there were very few which could be made to exude a fluid sufficiently thin to drop from between the fingers after rupture of the wall of the bleb. Each contained a semi-gelatinous mass, suggesting the appearance of boiled sago. The smaller bodies contained a thickened serum of high specific gravity. Here and there among these smaller bodies were slightly larger lesions resembling pustules and containing inspissated pus.

The color of the skin affected with this eruption was unchanged, nor was the peripheral integument altered by inflammation-exudates or œdema. The bullæ were of a dark purplish shade when fully developed, this hue being most distinct about the sides of each. There was no areola of redness about the base of any. The smaller lesions were yellowish and reddish-yellow in color.

In many of the larger and a few of the smaller lesions, there was an appearance which suggested umbilication. This in some instances amounted merely to an apical flattening, and was without question in all cases due to the collapse of the roof-wall upon the shrunken contents of the enclosing chamber. This feature, especially when distinguishable in the lesions of a vesicular or pustular type, strongly suggested the similar eruptive symptoms of varicella and certain forms of variola. It was clear, however, that in the case of these smaller lesions they were no longer in process of development. As compared with those which were evidently more mature, all seemed alike to have been arrested in their course after each had attained its greater or less size.

On the 7th of July I enjoyed a final opportunity of examining this patient. At that date the lesions had naturally much changed in appearance. The eruption as a whole was much less prominent and its earlier characters much less pronounced. Still, here and there over

the originally affected surfaces were to be seen relics of large-sized bullæ, distinct in outline, though otherwise changed. For the most part the lesions remaining evident were dark brownish-colored scabs, made up of the desiccated roof-wall of the pre-existing pemphigoid lesions, without traces of desiccated or otherwise altered exudation. These crusts were firmly adherent to the surface beneath, which seemed to be a base constituted of a more or less solid tissue resembling the flattened syphilitic condyloma. When removed, they disclosed a granulating surface beneath, without the interposition of a purulent or other pathological fluid. The general condition of the little patient had also in the mean time greatly improved. There had been but little loss of flesh, which was the more noticeable as the temperature was unusually high, and the child, while dentition was in progress, had an extensive eczematous trouble upon the scalp.

At the conclusion of my first examination of this patient I recorded the case as one of eczema of the face and scalp, for the relief of which the iodide of potassium had probably been administered, with the result of producing a pemphigoid rash. In the present state of our knowledge, and especially since the publication of Dr. Duhring's similar case, I feel confident that such would have been the prompt diagnosis of all who have studied the literature of the subject. To this source only could I refer, as I had never before enjoyed the opportunity of studying this particular one of the several rashes which the potassium iodide is capable of producing. Soon after this date, in an interview with the attending physician, he admitted, in response to my questions, that for four weeks prior to the appearance of the intercurrent skin disease the child had taken daily 0.30 gm. of the iodide of potassium, which had been intended for the relief, not of the eczema, but of the numerous boils which succeeded to the former trouble. The remedy had been suspended at the time of the appearance of the bullæ, though the doctor had not suspected that the two stood in the relation of cause to effect.

The number of recorded cases in which this accident has occurred is sufficient to establish the origin and identity of this eruption, and to justify certain deductions respecting its natural history.

As far as known to me, the literature of the subject consists of papers by Bumstead, of New York (*Amer. Journ. of the Medical Sciences*, July, 1871, p. 99); the Boinet-Cazenave cases, cited by Bumstead (*Iodothérapie*, 2d, 1865, p. 68); a paper by Dr. Tilbury Fox, of London (reprint from "The Clinical Society's Transactions," vol. xi., 1877); the observations of an anonymous reviewer in the *Edinburgh Med. Journ.* for August, 1873, cited by Dr. Fox; reports from the practice of Mr. Hutchinson, of London (*vid.* "Clinical Society's Transactions," 1875, vol. viii., and also "Report of the Medical and Surgical Registrars of the London Hospital" for 1875); with a clinical lecture by Dr. Duhring, of Philadelphia (*The Med. and Surg. Reporter*, August 4, 1877, p. 89); a report of cases treated by Dr. R. W. Taylor, of New York (*Arch. of Dermatology*, April, 1877, p. 227); a case recorded in the service of Dr.

F. N. Otis, at the Charity Hospital, New York (*N. Y. Med. Record*, March 8, 1879, p. 225);* and a paper by Dr. J. M. Finny, of Dublin, read before the Dermatological Subsection of the British Medical Association (*Brit. Med. Jour.*, Aug. 23, 1879, p. 291.)†

Respecting the rarity of this eruption, it may be remarked that Dr. Fox, at the date of writing his paper, was in position to say that Mr. Lane, Mr. Berkely Hill, Mr. Alfred Cooper, Mr. Coulson, and Profs. Hardy, Bazin, Guibout, and Fournier had never seen a bullous or pemphigoid eruption which could be attributed to the drug. And Dr. Bumstead relates that, in the article written by H. E. Fischer, of Vienna (*vid. L'Union Médicale*, January 31, 1860, from the *Wien. Med. Wochensch.*), devoted especially to the eruptions produced by the iodide of potassium, no mention is made of the rash here considered.‡

A chromo-lithograph of about the size of an octavo page accompanies Dr. Fox's paper, and represents well in outline the lesion observed by me. Had a few more stones been used in the production of this plate, giving the purplish shades seen by me, more especially at the sides of the bullæ, the portrait would fairly represent also the colors of the larger lesions I have described. Plate numbered 33, in the Sydenham Society's series, entitled "Hydroa from the Iodide of Potassium," in no way suggests either the eruption figured by Dr. Fox or that described by me.

In the following table I have placed side by side (for the purpose of comparison) the salient features of the various cases detailed by the authors named above:

* I am indebted for my record of this case to the kindness of Dr. P. B. Porter, of New York.

† See *Archives of Dermatology*, Oct. 1879, page 404.

‡ In a note from Prof. White, of Boston, received since these lines were written, I am informed that he has never seen the eruption here described.

No. of Case.	Author.	Sex.	Age.	No. of Attack.	Total Amount of Iodide of Potassium Administered.	Disorder for which the Drug was Prescribed.	Interval between Administration and Appearance of Eruption.	Lesion.	Locality of Lesions.
			Years.						
1	Bumstead.	M.	28	4	ʒj (4 gm)	Syphilis	24 hrs.	Bullæ.	Back of neck, forehead, face, backs of hands.
2	Taylor, R. W.	F.	.....	..	Less than ʒj (4 gm)	.....	.....	Bullæ, followed by ulcers.	Face, forehead, arms, tongue, roof of mouth, gluteal region.
3	Taylor, R. W.	F.	.....	..	.....	.....	.....	Bullæ.	Arms, neck, and legs.
4	Duhring.	M.	20	1	Gr. v (0.30 gm).	Eczema.	4 hrs.	Vesicles, bullæ.	Backs of hands, backs and sides of fingers, one wrist (inner surface), flexor and extensor surfaces of forearms, groins, and pubis, thighs, backs of feet, ankles, toes.
5	Fox, T.	M.	27	..	ʒiij (12 gm).	Syphilis	24 hrs.	Large vesicles.	Forehead, eye lids, face, scalp, nape of neck.
6	Fox, T. (Broadbent).	F. 1 at.	39	..	ʒj (4 gm)	.....	5 days	Bullæ.	Forehead, backs of hands, under lip, side of nose, backs of arms, elbows.
		2 at.	39	2	ʒj (4 gm)	.....	5 days	Bullæ, followed by ulcers.	Sides of nose, cheeks, forehead, arms, hands, legs, tongue.
7	Hyde.	F.	8 mos.	1	ʒij (8 gm).	Eczema.	3 wks.	Bullæ and vesicles.	Arms, forearms, hands, palms, interdigital spaces, backs of hands, wrists, nates, thighs, legs, ankles, feet, and between the toes.
8	Hutchinson.	M.	26	..	.....	Syphilis	.....	Bullæ, pustules.	Face, arms, legs, body.
9	Hutchinson.	...	.....	..	.....	.....	.....	Vesicles.	.....
10	"								
11	"								
12	"								
13	Anon.	...	.....	..	.....	.....	.....	Bullæ, vesicles.	.....
14	Cazenave.	...	.....	..	.....	.....	....	Bullæ, followed by ulceration.	.....
15	Otis.	F.	Adv'd age.	1	.....	Syphilis	.....	Pustules and bullæ.	Forehead, face, hands.
16	Finny.	...	.....	..	Increasing doses for weeks.	.....	.....	Vesico-pustules and erythema.	Trunk.

Color of Lesion.	Contents of Lesion.	Size of Lesion.	General Condition of Patient and Concomitant Symptoms.	Interval after Discontinuance of Drug to Disappearance of Lesions.	Fatal Cases.	Remarks.
Reddish or purplish.	Clear to turbid serum, blood.	Very large.	Cachexia.	A few days.	.....	Skin about lesions red and œdematous.
.....	Sero-pus, blood.	.....	Sick, tongue swollen, fever.	.....	.....	Intense cephalalgia. Alarming symptoms, swelling of face, mouth, and pharynx.
.....	Blood.	Large.	Chills and itching of the skin.	A few days.	.....	Appearance of having been produced by burn.
Pale, yellowish-white, and glistening.	Clear serum, no pus.	Pin-point to large pea.	Good.	4 or 5 days.	.....	Septa, boiled sago-grain appearance. No œdema. One lesion in centre of palm.
.....	Milky fluid, thin pus, inodorous.	.....	Cachexia and feebleness.	3 to 4 days.		
Yellowish scab.	Turbid serum, grayish pus.	Threepenny piece.	Pleurisy, pericarditis, sore mouth.	5 to 6 days.	1. Chronic Bright's Disease.	Painful.
.....	Sanguinolent and purulent.	Large.	Sore mouth.	6 to 8 days.		
Dark-purple.	Serum, sero-pus, gelatinous mass.	Pin-head to pigeon's egg.	Fair general condition; eczema.	A few days.	.....	Quasi-umbilication.
Purple and red.	Thin, yellow, offensive.	¼ to ½ in. high.	.....	18 days.	1	Inflamed areola.
.....	.....	Shot, cherry.	.....	.....	.....	No umbilication; depressed centre.
.....	.....	.....	Fever, distress.	.....	.....	Umbilication.
.....	Serum, blood.	.....	.....	.....	.....	Lesions readily torn.
.....	.....	Large.	Marked cachexia; extensive superficial ulcerations of surface of extremities.	1 week.	.....	Some pustules, distinctly umbilicated.
.....	.....	Small shot to split pea.	.....	6 days.	.....	.....

A study of the cases tabulated above suffices to establish the following facts:

The eruption has been recorded by the authors named as occurring eighteen times in fourteen individuals. Of nine patients, whose sex is stated, four were males and five females. The youngest patient is she whose case I have described,—one which, for that reason, has an especial interest in this connection,—an infant at the breast, 8 months old. The age of the eldest of those whose age is given was 39 years. In two cases, the eruption recurred in each individual; once in a second, and once in a fourth attack. The quantity of the drug recorded to have been ingested, varied from 0.30 gramme to 12 grammes. In a few instances the medicament was continued after the production of its toxic effects, in consequence of a failure to recognize their import. Four times the remedy was administered for the relief of syphilis; twice in the treatment of eczema. The period which elapsed between the administration of the last dose and the explosion of the cutaneous symptoms varied between four hours and five days.

By ten writers the lesions are described as "bullous," five adding the term "vesicle;" two adding the word "pustule;" in one case only is the eruption said to be constituted only of "large vesicles;" once, of "vesico-pustules."

As regards the localities affected by the eruption, we find that it was observed twenty-one times upon the different portions of the head and neck; twenty times upon the upper extremities; twelve upon the lower; and but six times over the surface of the trunk. To enumerate these localities more precisely, we find six observations of the disease on the forehead; five on the face; two on the sides of the nose; two on the tongue; one on the cheeks; one on the eyelids; one on the under lip; and three on the back of the neck. Eight times it was noticed on the arms and forearms; once on the hands; six times on the backs of the hands; twice on the backs and sides of the fingers; twice over the wrists; and once only over the elbows. Twice the bullæ appeared over the general surface of the body; twice over the nates; and once over the groins and pubis. Four times the legs were affected, and twice each the thighs, ankles, feet, and toes.

The lesions, which were generally described as bullæ, began either as, from the first, pin-point-sized vesicles, or as shot-like papules, at the apices of which vesiculation subsequently occurred. These in color were pale yellowish-white, and glistening. In some instances, where only a small dose of the drug had been administered, or where it had been promptly discontinued on the appearance of toxic effects, the subsequent evolution of symptoms was not decided. Where, however, the dose had been large, or persistently continued, and especially when there had been coincident cachexia, subsequent changes were noticed in the eruptive phenomena. In color the bullæ became successively red, dark-red, purple, and dark-purple. Containing at first merely a clear and limpid serum, the

contents of the lesions changed to a thin sero-pus, inodorous, and sometimes almost creamy. To this succeeded a pure yellowish pus, which, in cases, degenerated to a sanguinolent ichor, of foul odor. In a few instances blood only was found in the pemphigoid lesions at an early stage.

The existence of the toxic phenomena is in cases compatible with the enjoyment of fair health. This, at least, was noted in two instances. In four there was a record of cachexia and prostration; in one the patient suffered from chills. Two fatal cases are recorded; one from chronic Bright's disease, with pleuritic and pericardial complications. In the case of the other patient the history is indefinite. It seems clear, however, that the result was due rather to the depraved general condition of the patient than to either the remedy or the eruption produced by it. It should be remembered in this connection that the greater number of patients displaying this form of cutaneous disease will always be those in whom the effects produced by the drug are partially masked by the disorder for which the drug is prescribed. There is no reason to believe that in those depressed states of the system where the bullæ have been noted, for example, upon the mucous surfaces of the roof of the mouth and the tongue, the cachexia is immediately and solely due to the action of the iodide of potassium.

Upon one point all the authors are agreed, viz., that in a few days after the drug is discontinued, the eruption disappears, even in cases where there is great cachexia. Eight days at the longest have sufficed to greatly improve the cutaneous symptoms, the patient in one case dying over two weeks after the eruption first appeared.

Upon two points there is a discrepancy between those who have reported cases. One of these concerns the inflammatory areola, which, in certain patients, has been seen surrounding the individual lesions, and in others has been absent. The other relates to the umbilication of the bullæ. This has not been observed by the greater number of authors; and I am inclined to believe that in those cases where it has been seen, the phenomenon was due to the shrinkage of the roof-wall of the lesion upon its contents.

The late lamented Dr. Tilbury Fox, from the observations to which he had access at the time his paper on this subject was read before the Clinical Society of London, draws some conclusions which can only be accepted with reserve in the light we can command at the present time. He states, for example, that the pemphigoid rash is excited only "under the influence of small and few doses," a conclusion certainly not warranted if the history of my case be accepted as typical of the infantile symptoms. He also declares that "the action of the drug in these cases is not limited to the skin, but produces great depression, with or without pyrexia, ulcerations of the mucous membranes, etc.," a deduction which is manifestly incorrect as applicable to all cases, and one which, as I have attempted to show, may be doubted in all those cases where a depressing disease has existed, for the relief of which the remedy was prescribed.

Lastly, Dr. Fox is of opinion that the eruption is one which originates in the sebaceous glands, and that the contents of the bullæ are altered secretions of the sebaceous glands. Investigation, chemical and microscopical, will of course be necessary to set at rest the problem which he thus presents, but the clinical reasons for dissenting from his opinion seem to me to be worthy of consideration. If the sebaceous glands were the seat of the disease, it would be reasonable to look for its most abundant development in those localities where we are accustomed to find the sites of election of such other sebaceous-gland disorders as milium, comedo, seborrhœa, acne, etc. These sites of election, it need not be said, are the face, the scalp, the back of the neck, the back of the trunk, and the genital region. But it has been pointed out above that the pemphigoid rash under discussion, though occurring most often upon the head, has never been reported upon the scalp, and that the region of next preference is the upper extremity, especially over the wrists and forearms, localities which, as Bumstead shows, are exposed to the air, and which, it need not be said, are not regions where we are accustomed to find the sebaceous-gland disorders mentioned above. I desire also to call special attention to the fact that, both by Dr. Duhring and myself, the lesions were observed upon the palms of the hands, where Biesiadecki and others have never been able to demonstrate the presence of either sebaceous glands or lanugo follicles.

Two other clinical considerations should be here mentioned. One is the chronicity which usually characterizes sebaceous-gland disorders, such as acne, comedo, etc., as opposed to the circumstance that the bullæ produced by the iodide of potassium have been seen within five hours after the administration of the drug. The other is the recorded occurrence of blood-contents in the lesions. The transformation of the secretion of a sebaceous gland into a thin odorless or offensively-smelling sero-pus cannot be viewed as beyond the possibility of occurrence; but a sanguineous seborrhœa could be regarded only as the symptom of a formidable constitutional dyscrasia. These and possibly other considerations which might be suggested lead me to the conclusion that, for the present, at least, we are not justified in accepting without reserve the statements relative to the sebaceous origin of the rash which we have been studying.

The most valuable of the practical conclusions to which such a study leads would seem to be: (*a*), that, in eczema, where a distinctively vesicular or bullous eruption becomes suddenly apparent, the lesions intermingled with those characteristic of the disorder named, in the person of patients who have been under the charge of inexperienced practitioners, the possibility that the iodide of potassium has been previously administered should be carefully estimated; (*b*), that it is not only possible but quite probable that the rare vesicular and bullous lesions recorded as occurring in acquired syphilis may be rashes induced by the administration of the iodide of potassium for the relief of the disease.