FIXED DRUG ERUPTION CAUSED BY 8-CHLOROTHEOPHYLLINE IN DRAMAMINE® WITH CLINICAL AND HISTOLOGIC STUDIES†

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The designation "fixed drug eruption" was probably first used by Brocq (1), whose description may be briefly summarized as follows:

Dusky red, later brownish plaques, with well-defined borders, and edematous or bullous centers, tending to recur at precisely the same site, leaving brown pigmented patches on healing.

The following drugs have been found to produce this type of reaction (2, 3):

Acetanilid	Iodides
Acetophenetidin	Ipecac
Aminopyrine	Para-aminosalicylic acid
Antimony salts	Penicillin
Arsenicals	Phenolphthalein*
Chlorotetracycline	Quinacrine
Barbiturates*	Quinidine
Bismuth	Quinine
Cinchophen	Salicylates
Emetine	Sulfonamides
Gold salts	Oxytetracycline

Antihistamine drugs have been reported to cause a large variety of cutaneous manifestations (4), but none have hitherto been reported as the cause of a fixed eruption. For the past three years we have been studying a patient with a fixed eruption caused by Dramamine®.

CASE REPORT

F.E., 57, female, married, owner of a telephone answering service, complained of recurrent, brownish areas on the right thigh, leg and foot for several years. At irregular periods, precisely the same areas would become itchy, occasionally blistered; and this would slowly subside to leave round, brownish patches of varying intensity (Figs. 1 and 2). She had frequent headaches, for which she took a large number of medications containing salicylates, caffeine, and acetophenetidin. She denied taking barbiturates, phenolphthalein-containing medications or sulfonamides, or any of the remainder of the drugs listed above as causing fixed eruptions. There apparently was no relation between the flares in the fixed eruption and the headache remedies, since these were taken frequently, in large quantities, but the flares were few and far between.

In April 1955 she developed herpes zoster ophthalmicus of the left eye. This healed in six weeks. On May 2, 1955 she took an aspirin tablet. There was no effect on the eruption. On May 5th she took two tablets containing caffeine, acetophenetidin and aspirin, with no change in the eruption. Barbiturates, sulfonamides, amphetamine containing reducing remedies, phenolphthalein, and quinine containing drinks all failed to influence the brown patches. Finally she had a flare of the eruption shortly after returning from a trip to Florida. The possibility that it was caused by Dramamine® taken to prevent motion sickness was considered, and as soon as the acute process subsided she was asked to take one Dramamine® tablet. The next morning each pigmented area flared (Figs. 3 & 4) with increased swelling and inflammatory halo, followed by deepened pigmentation. The reaction subsided in two weeks, leaving brown, well-defined, discoid patches on the thigh and foot. These faded slowly, but did not disappear.

Several blood counts revealed a red cell count varying between 3.5 and 4.2 million, with hemoglobin ranging between 11 and 13 grams. The white cell count was normal, with a normal differential. Other laboratory studies, including serologic tests for syphilis, total protein and A/G ratio, urea nitrogen, uric acid, and liver function tests, were all within normal limits.

CLINICAL STUDIES TO DETERMINE REACTIVE CHEMICAL GROUP

Dramamine® is a combination of diphenhydramine (Benadryl®) and 8-chlorotheophylline (hereon designated 8-CT), which have the chemical structures shown in Fig. 5.

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* Most frequently induce fixed eruptions.

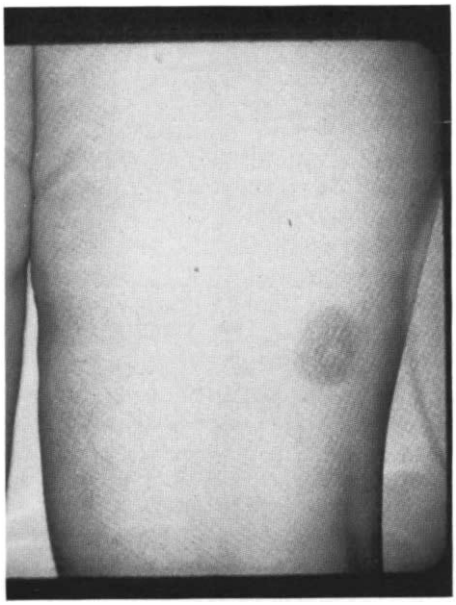


FIG. 1: Pigmented area on posterior aspects of thigh during quiescent phase. Note variation in intensity of pigmentation, and absence of inflammatory halo.

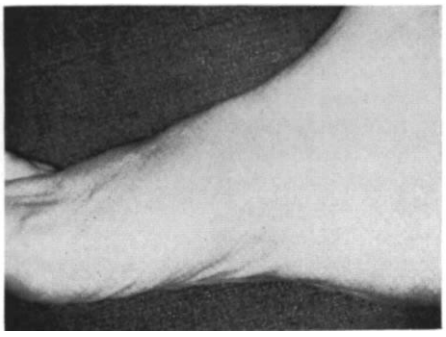


FIG. 2: Barely perceptible, slightly scaly and pigmented area on inner aspect of right foot, during quiescent phase.

Since there was no cutaneous reaction to Benadryl®, the patient was given 10 mg. of 8-CT; there was a prompt and striking flare (Fig. 4).

The evolution of the fixed drug eruption occurred as follows: Fifteen hours after ingestion of 10 mg. of 8-CT there was itching at the fixed reaction sites; at 16 hours a ring of erythema was noted around the pigmented patch; by 20 hours edema appeared, and in 22 hours a flat, superficial bulla developed. The bulla slowly increased in size, and pigmentation deepened.

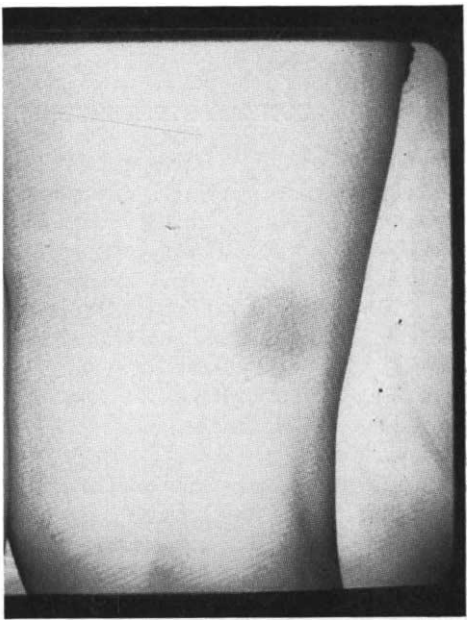


FIG. 3: Inflammatory halo about pigmented site on thigh, 48 hours following ingestion of 25 mg. of Dramamine®. An identical flare occurred following the ingestion of 10 mg. of 8-chlorotheophylline, but not when diphenhydramine was taken.

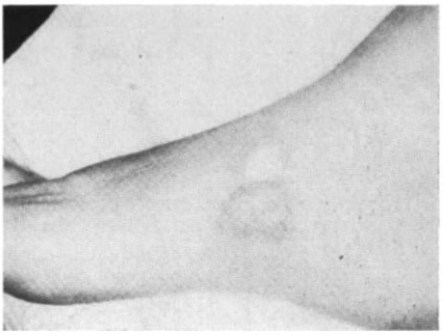


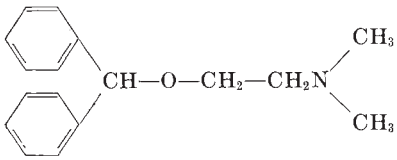
FIG. 4: Increased pigmentation, scaling, and inflammatory halo about pigmented site on right foot, following ingestion of Dramamine® or 8-chlorotheophylline.

Crusting slowly appeared and then disappeared over a period of 2 to 3 weeks, leaving the usual hyperpigmentation at the site.

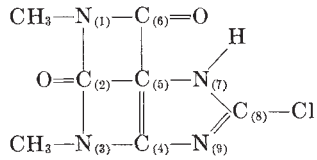
8-Chlorotheophylline is a xanthine derivative. The interrelationship between certain xanthines is illustrated in Fig. 6.

There was no reaction to unmodified theophylline, theobromine or caffeine, so that evidently the chlorine atom was necessary to provoke the reaction.

Diphenhydramine (Benadryl®)



8—chlorotheophylline*



* B-dimethylaminoethyl-benzohydryl ether-8-chlorotheophyllinate.

FIG. 5

Could theophylline substituted with other halogens produce the fixed reaction? Iodine and fluorine compounds were not available, but 8-bromotheophylline in a dose of 10 mg. caused precisely the same reaction as 8-CT.

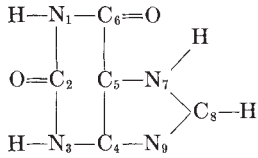
Was it essential that the halogen be in the 8 position? It seems that the only atom available for substitution in theophylline is carbon 8. Carbon 2 and 6 contain the keto group, and nitrogen atoms 1 and 3 a methyl group, leaving one nitrogen atom and carbon 8. Since the haloamines are not stable, the halogen cannot be substituted in any position other than carbon 8. Other halogenated xanthines were not available, so we do not know if a halogenated theobromine or caffeine would be reactive.

The question then arose whether she was sensitive to other antihistamine drugs. She was given commonly prescribed doses of the following drugs:

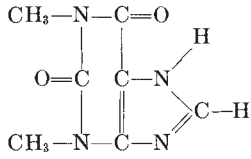
Benadryl® (Parke, Davis)
Bonamine (Pfizer)
Chlor-Trimeton® (Schering)
Clistin® (McNeil)
Co-Pyronil® (Lilly)
Histadyl® (Lilly)
Marezine® (Burroughs-Wellcome)
Neo-Antergan® (Merck, Sharp & Dohme)
Perazil® (Burroughs-Wellcome)
Phenergan® (Wyeth)
Pyribenzamine® (Ciba)
Thephorin® (Hoffmann-La Roche)

None of these had any effect on the eruption. Following the ingestion of 25 mg. of Benadryl,® she became dizzy and developed twitching of the face and extremities, but this subsided promptly. The other medications produced no effect other than drowsiness and dryness of the mouth.

Xanthine

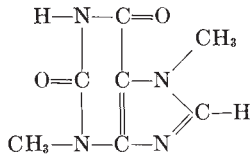


Theophylline



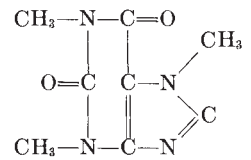
1,3 dimethylxanthine

Theobromine



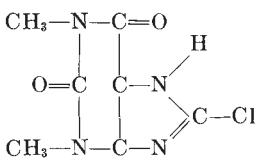
3,7 dimethylxanthine

Caffeine



1,3,7 trimethylxanthine

8—chlorotheophylline



1,3 dimethyl 8-chloroxanthine

FIG. 6

ATTEMPTS TO SUPPRESS REACTION

Since this remarkably cooperative patient made many air trips for which she required an anti-motion-sickness remedy, an attempt was made to suppress the fixed reaction. As noted above the patient had a systemic, probably

central nervous system, reaction to the diphenhydramine portion of the Dramamine® molecule, but this was suppressed, or prevented, by the complete compound. However, the antihistamine Benadryl® did not prevent the 8-CT from producing a fixed drug eruption. The possibility arose that the fixed reaction could be suppressed or prevented by other antihistamine drugs. Accordingly, over a six month period, all 12 of the drugs listed in the case report were given in full doses for one day before taking 10 mg. of 8-CT, the day it was taken, and for 5 days afterwards. There was no effect on the time of onset, the severity of reaction or its duration.

In the attempt to suppress the drug eruption, 80 mg. of hydrocortisone or its equivalent as prednisone or prednisolone were given. Here the intensity of the reaction was somewhat diminished but, time of onset and duration unchanged. The result was practically identical when ACTH, in a gelatin vehicle, was given in a dose of 80 units the day of administration, and 40 units daily thereafter, for 5 days.

It must be noted that this patient was deliberately exposed to the causative antigen at least 20 times, over a period of three years, yet she reacted just as vigorously at the end of this long period as she did at the beginning. This indicates quite clearly that there is little or no tendency for a patient to lose his sensitivity to a fixed drug antigen following repeated exposures over a long period of time; at least this is true in the case of this patient and this antigen, 8-chlorotheophylline. During a six month period this patient was re-exposed to this antigen 12 times at two week intervals, with not the slightest evidence of any tendency toward local or general desensitization or exhaustion of the reaction. The reaction remained exquisitely specific throughout the long period of study (21).

ATTEMPTS AT LOCALIZING THE SHOCK TISSUE

Attempts to determine the shock tissue in the fixed reaction have been made by others chiefly by transplantation experiments. Results have been inconclusive, but the current tendency is to localize the reaction in the deeper blood vessels, and to consider that it is then reflected like a cone toward the surface, to appear as a discoid plaque.

An attempt was made to study the vascular pattern at the reaction site by intravenous injection of sodium fluorescein followed by visualization under Wood's light. A quiescent patch shows no fluorescence. An activated patch, however, shows an intense ring of greenish fluorescence with a dark, central zone. The fluorescent ring marks the site of the inflammatory halo. The central edematous or bullous area develops fluorescence somewhat later, a fluorescence partly masked by the pigmentation. This fluorescence fades gradually over a 10–14 day period and then disappears; while its onset coincides with, or slightly precedes, the clinical flare. Based on other observations, this vascular ring, in all probability, consists chiefly of capillaries in the papillary zone, and may represent at least a portion of the shock tissue.

If the superficial capillary loops are the shock tissue, they may be accessible via the epicutaneous route, and a fixed reaction may then be obtainable by patch testing the previously reactive site. Accordingly, a patch test with powdered 8-CT was applied to the pigmented area on the right thigh for 48 hours. A control patch test was applied with plain, i.e., non-halogenated theophyllin powder to the pigmented lesion on the right foot. When the patches were removed in 48 hours, there was a moderate, fixed drug reaction with itching, edema, erythema and increased pigmentation on the thigh (Figs. 7 & 8) with no reaction on the foot. This same phenomenon was noted by Loveman (5) in his work on a fixed reaction caused by a barbiturate. Peck (6), in discussing Loveman's paper, suggested that this might best be called a Moro patch test, analogous to the Moro tuberculin test. It suggests that the shock tissue is readily accessible to the antigen via the epicutaneous route, and fits in with the concept that the superficial dermal vessels are at least part of the shock tissue. It also suggests that the antigen becomes complete in its passage through the epidermis and/or the adnexae, and does not require passage through the gastrointestinal tract before being able to unite with its antibody.

Derbes (7) has also obtained positive patch test reactions limited to the fixed reaction site with aminopyrine. We believe the patch test with the suspected material at a quiescent fixed eruption site is a useful diagnostic procedure for this type of drug eruption, without the potentially dangerous sequelae inherent in testing the suspected drug by mouth or by injection. As with

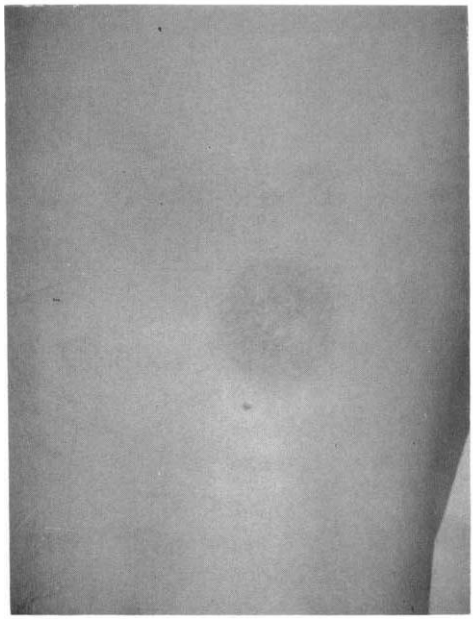


FIG. 7: Pigmented area, right thigh, just before application of patch test with 8-chlorotheophylline.

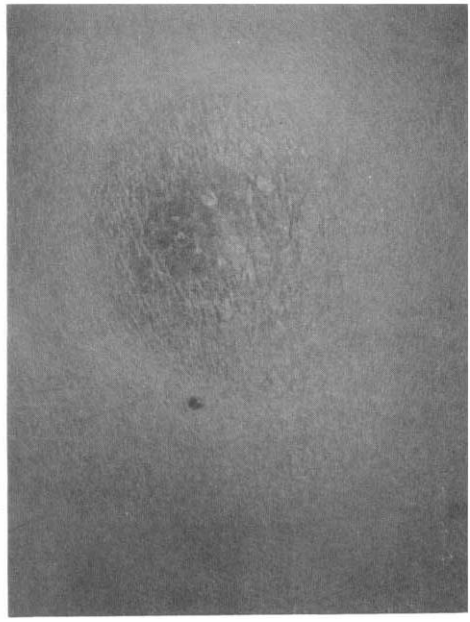


FIG. 8: Same area following removal of patch test with crystals of 8-chlorotheophylline applied to pigmented area for 48 hours. Note the bulla in the center, the increased pigmentation and inflammatory halo—a *fixed drug reaction*, not an eczematous reaction, to the patch test.

so many other tests, a negative reaction has little significance. It must be emphasized, however, that a positive reaction must reproduce the fixed drug reaction to be considered diagnostic. An eczematous or follicular response must be considered lacking diagnostic significance.

This is in contrast to results with patch testing in fixed reactions due to phenolphthalein, which, according to Baer (8) and the experience of the senior author, are negative. It is possible that phenolphthalein requires modification by passage through the gastro-intestinal tract and/or liver before it can become a complete antigen and unite with antibody to provoke a fixed drug reaction.

ADDITIONAL STUDIES

Following the intracutaneous injection of 0.1 cc of parenteral solution of Dramamine® into the center of the fixed reaction site on the right thigh, there was a sharp local flare with a peripheral zone of erythema and edema and deepening of the pigmentation within twelve hours, followed by a flare at previously involved sites on the foot and leg during the ensuing 12 hours. A control injection on the opposite thigh caused no local reaction other than a small slough, but did cause a moderate flare at all previously affected areas within 24 hours.

When this reaction subsided, 0.1 cc of a 0.5% suspension of 8-CT in water was injected into the fixed reaction site on the right foot. A mild local flare appeared, but other previously affected areas did not react. A similar injection on the other foot caused no reaction. Evidently there was little or no systemic absorption, probably because 8-CT is extremely insoluble in water.

HISTOLOGIC AND HISTOCHEMICAL STUDIES

Technic:

Under local xylocaine anesthesia biopsy specimens were removed (1) from the central bulla of the fixed drug eruption, (2) from the periphery of the lesion which clinically showed only erythema, and (3) from a normal skin site nearby. All three biopsies were performed at the same sitting, 48 hours after the administration of the allergen and 26 hours after the appearance of the bulla (see page 4).

The biopsy specimens were fixed in 95% alcohol (24 hours), absolute alcohol (24 hours), chloroform (2 hours); embedded under vacuum in paraffin; and serially sectioned at 4 microns.

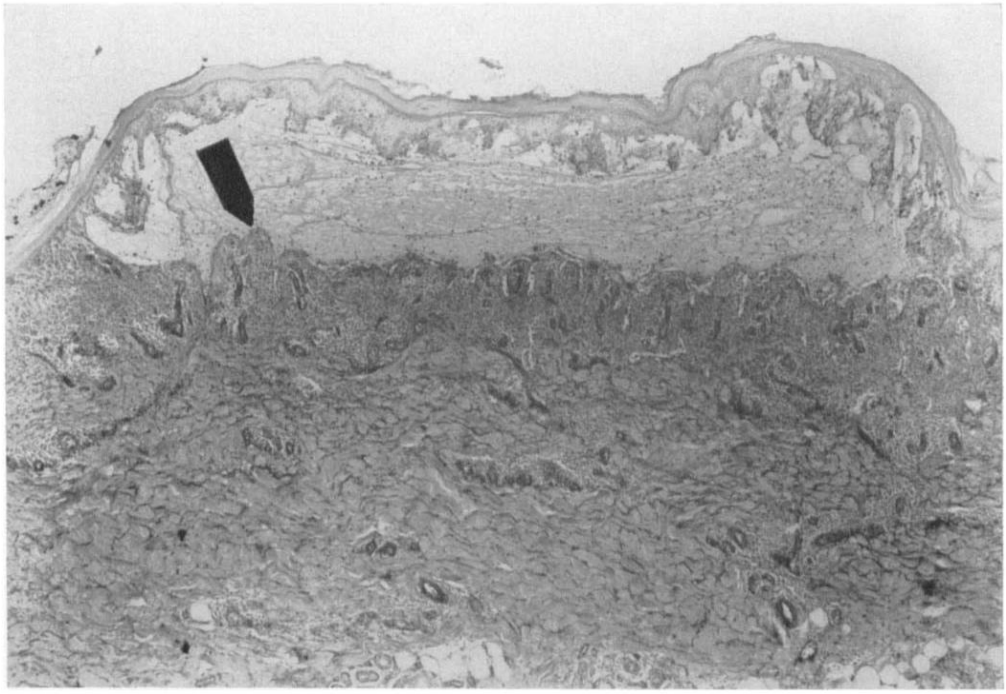


FIG. 9: Specimen from central bulla of the fixed drug eruption showing exocytosis, spongiosis, exoserosis, and reticular degeneration of epidermal cells in the sides and roof of the subepidermal bulla. Note denuded papillae at left (arrow) and perivascular inflammatory infiltrate in cutis. Hematoxylin-eosin stain. ×66.

The following stains were employed:

1. Hematoxylin and Eosin (aqueous, at ph. 6.0)
2. Toluidine Blue (at ph. 3.7)
3. Giemsa
4. Carmine
5. Hotchkiss-McManus including diastase digested controls for glycogen
6. Masson Trichrome
7. Orcein
8. Fontana (silver)
9. Alkaline Phosphatase (Gomori)
10. Alcian Blue—Periodic Acid Schiff
11. Perl

Findings: The essential histologic findings were:

A) *Changes in the Epidermis*
   1) *bulla formation* associated with reticular degeneration of the epidermal cells in the wall of the bulla.
   2) a process of *premature keratinization* of epidermal cells both of scattered individual cells and of groups of cells.

B) *Changes in the Cutis*
   1) a primarily *perivascular banal inflammatory infiltrate* in the upper cutis associated with pronounced *edema*.

A. Epidermal changes:

1. *Subepidermal bulla formation*—In the biopsy specimen taken from the central area of the lesion, the epidermis showed exocytosis, exoserosis and the formation of a subepidermal bulla (Fig. 9). The contents of the bulla was composed of mostly serum, a few leukocytes (polymorphonuclear leukocytes, lymphocytes, but no eosinophiles) and the remnants of necrotic epidermal cells. The epidermal cells of the walls of the bulla had undergone reticular degeneration (so that only their cell membranes remained in web-like networks). The dermal papillae which projected into the floor of the bulla were either completely denuded or were covered only by a few clusters of epidermal cells. There was no acantholysis or segregation of isolated epidermal cells. In some denuded areas on the floor of the bulla the basement membrane lining the papillae had been destroyed. The roof of the bulla consisted of epidermal cells with marked intracellular edema and nuclear abnormalities (pyknosis, crenation, condensation). In the bulla roof parakeratosis was apparent only in the lowermost horny layer. The

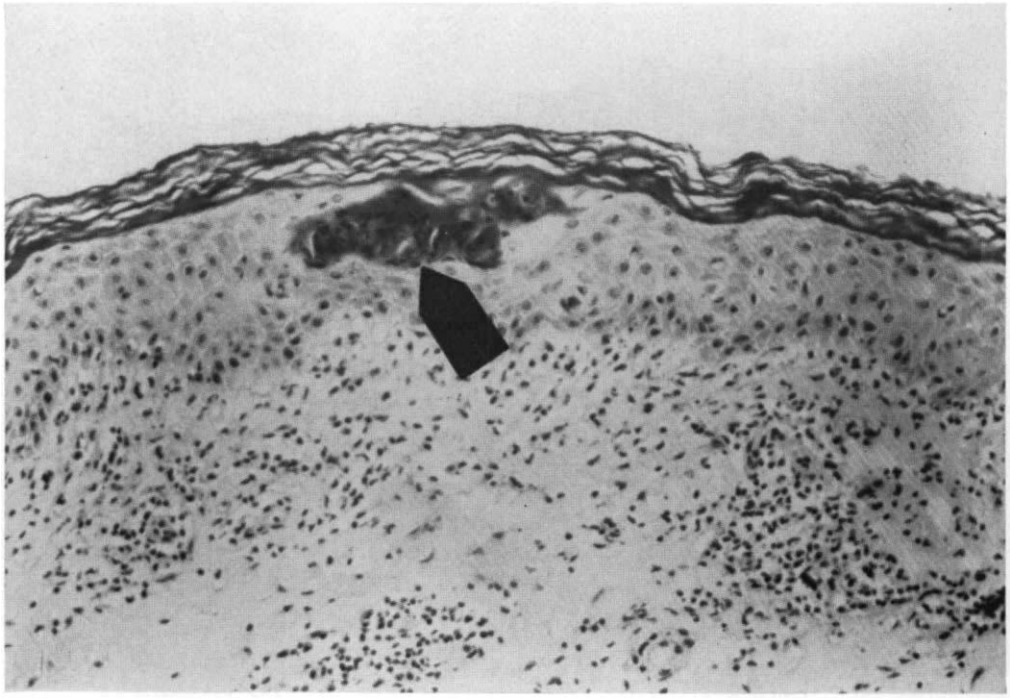


FIG. 10: Specimen from periphery of lesion showing prematurely keratinized epidermal cells (arrow) in continuity with overlying stratum corneum. Some nuclei have been retained in this keratin pearl. Giemsa stain. ×186.

absence of parakeratotic cells in the more superficial portions of the stratum corneum is indicative of the abruptness of the process so that parakeratosis has not yet reached the surface.

The epidermal cells neighboring the bulla have an accumulation of intracytoplasmic glycogen as might be anticipated in such damaged cells.

2. *Premature keratinization*—A striking feature which was most evident in the specimen taken from the periphery of the lesion (and absent in the normal skin specimen) was that of a process of *premature keratinization* of the epidermal cells. Although this process was found occasionally in an isolated epidermal cell it more commonly was seen in well localized groups of epidermal cells which resulted in formation of keratin pearls. These cell-nests of prematurely keratinized cells were seen predominantly in the upper one-half of the epidermis and on serial sections usually were found to be in direct continuity with the overlying stratum corneum so that they gave the appearance of horny invaginations of the stratum corneum into the epidermis (Fig. 10). The process of premature keratinization was also found in deep seated isolated epidermal "keratin pearls" not attached to the overlying horny layer (Fig. 11). Many "keratin pearls" were composed of a central refringent amorphous material which had all the special staining characteristics of the horny layer. At times nuclei were retained in this refringent material. A flattened layer of cells filled with keratohyalin granules surrounded this central horny material.

With the special stains employed the *staining characteristics of the keratin pearls resembled those of the normal stratum corneum and "stratum lucidium". Hematoxylin and eosin* stained the normal horny layer and the keratin pearls a brilliant refractile homogeneous pinkish-red. However, other elements in the epidermis such as the necrotic cells in the bulla wall and lakes of serum stained similarly. It was only after other stains were employed that it became obvious that the staining characteristics of the keratin pearls were consistently identical to those of the normal horny layer and differed from the necrotic epidermal cells which lined the bulla. Therefore, the two processes, i.e., spongiosis with bulla formation and premature keratinization, ap-

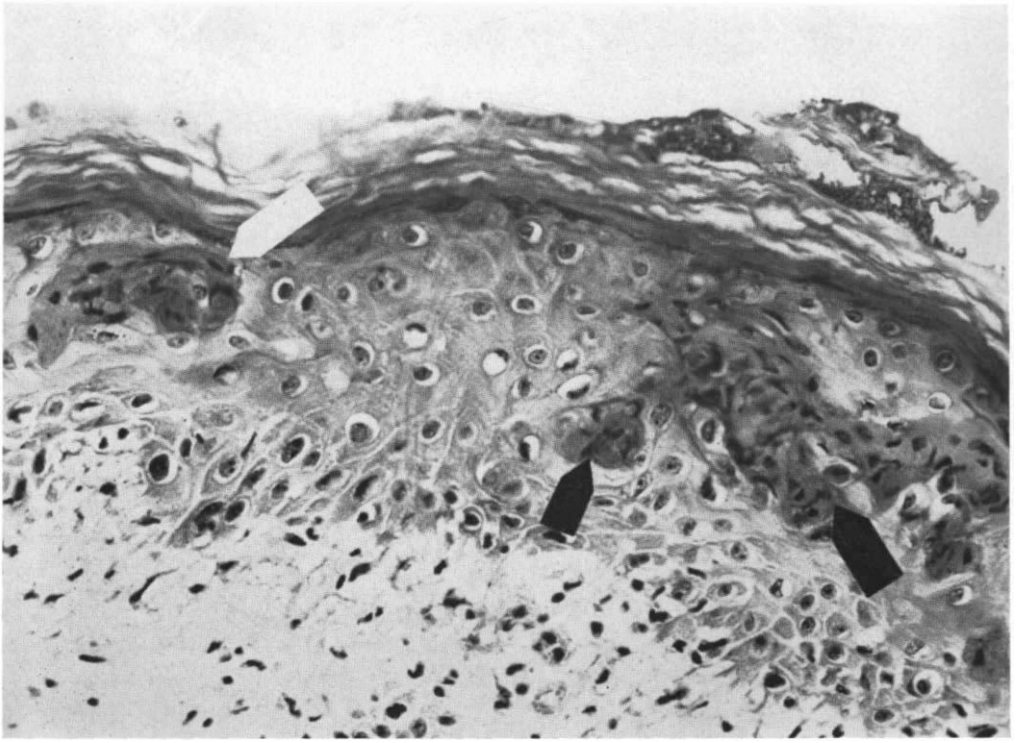


FIG. 11: Specimen from periphery of lesion with several groups (arrows) of nucleated prekeratinized epidermal cells. Hematoxylin-eosin stain. ×375.

peared to occur simultaneously in different areas of the epidermis.

With *toluidine blue* the normal stratum corneum was stained greenish-blue whereas the normal "stratum lucidum" remained unstained. Similarly the keratin pearls had greenish-blue centers surrounded by an unstained halo. *Giemsa* colored the normal stratum corneum and the central portions of the keratin pearls bright blue. With *lithium carmine* one again found all the elements of the normal epidermis reconstructed in the pearls since on the one hand the upper horny layer of the normal skin specimen and centers of the prematurely keratinized pearls were light pink, whereas on the other hand, the lower horny layer ("stratum lucidum") of the normal specimen and the peripheral portions of the keratin pearls stained dark pink.

A remarkable feature of these groups of prematurely keratinized cells was that they contained large quantities of melanin (Fig. 12) whereas it was present in relatively small quantity in the surrounding epidermis (Fontana stain).

B. Changes in the cutis in the specimen taken from the central bulla:

The most prominent changes were seen in the uppermost cutis and progressively lessened in its depth. In the papillary bodies and upper one-half of the cutis there was amassive essentially perivascular inflammatory infiltrate composed principally of small round cells and histocytes. Very few polymorphonuclear leukocytes were seen in this infiltrate. There appeared to be a slight increase in the number of mast cells in comparison with the normal control specimen. Remarkably, only a rare eosinophile was seen in the dermal cellular infiltrate.

The adnexae which consisted of a few hair follicles and eccrine sweat glands appeared relatively unaffected by the intense reaction higher in the cutis. However, some eccrine sweat glands showed vacuolization of the cells lining the acini while others had dilated lumens. These findings were presumably the result of back pressure on the sweat glands caused by mechanical obstruc-

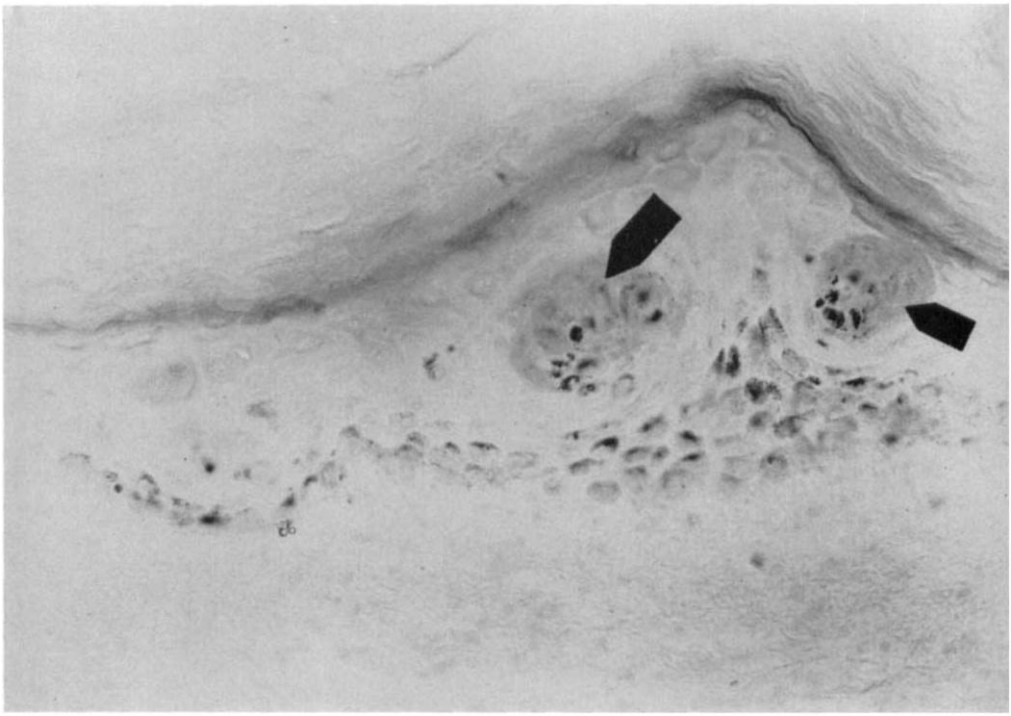


FIG. 12: Specimen from periphery of lesion stained with Fontana silver stain illustrating numerou melanin granules within the keratin pearls (arrows) in contrast to the relative sparsity of granules in the nearby epidermal cells. ×375.

tion of their ducts by the pathologic processes which had taken place in the upper cutis and epidermis.

Other stains of sections taken from the specimen removed from the central bulla included:

1. *Masson Trichrome*—the collagen fibers in the upper cutis were separated and pushed aside by the edema and inflammatory cellular infiltrate but were otherwise unaltered.

2. *Alkaline Phosphatase*—many of the fine capillaries in the upper and mid-cutis were easily identified in the massive inflammatory reaction by their strong alkaline phosphatase activity permitting one to establish the dilatation of the capillaries and primarily perivascular localization of the inflammatory infiltrate. Some inflammatory cells nearest the vascular walls had alkaline phosphatase activity although those farther away showed none. Those findings are probably due to diffusion of the enzyme. An abnormal feature was the presence of a number of dilated thin walled vessels in the upper cutis (dilated capillaries or lymphatic channels) *with absence of alkaline phosphatase activity*. Well below the massive inflammatory infiltrate of the upper cutis, there was a wide band-like zone of alkaline phosphatase activity in the cutis and subcutis which was found in relation to: the small blood vessel walls, the sparse perivascular inflammatory infiltrate, the eccrine sweat glands and the "ground substance" interspersed between the collagen bundles.

3. *Orcein*—the elastic fibers were dissociated in areas of marked edema and inflammatory infiltrate.

4. *Toluidine Blue*—a deposit of fine filaments of metachromatic material was seen between the connective tissue fibers throughout the cutis. This material stained purplish with Giemsa, magenta with Hotchkiss-McManus (both digested and undigested), and light greenish-blue with PAS-Alcian Blue. All these stains suggest that the metachromatic material between the collagen bundles is mucin or a mucoid material. No similar mucoid material was evident in the normal skin specimen.

DISCUSSION

It is apparent that this patient has a fixed drug eruption due to the 8-chlorotheophylline fraction of Dramamine®, and that a halogen must be present in the molecule to evoke the reaction.

The fluorescence of the erythematous halo following intravenous administration of sodium fluorescein beginning with the onset of the clinical reaction to the drug may be interpreted as indicating injury and increased permeability of the capillaries at that site (9), and suggests the capillary wall as being at least part of the shock tissue. The occurrence of a fixed drug reaction to patch tests with 8-CT at a reactive site suggests that the shock tissue is available to the antigen via the epicutaneous route, and also fits in with the superficial vessels as possible shock tissue sites. It is clear, too, that 8-CT is, or can become, a complete antigen via the epicutaneous route as well as via the gastro-intestinal tract. This is not true of some other drugs causing fixed drug eruptions. Specifically, phenolphthalein, according to Baer, and in the experience of one of us (C.S.) does not produce a reaction on patch testing over the site of the fixed eruption.

There have been a number of transplantation experiments designed to clarify the site of the shock tissue, some of which show that the fixed area of sensitivity can be moved from one area to another by transplantation of full-thickness grafts (10, 11), while others show that the skin of fixed eruption areas when transplanted to normal areas react at first, but later fail to react; while the normal skin transplanted to the fixed eruption site later becomes reactive (12, 13, 14). The first group of experiments fit in with the concept that the superficial blood vessels are the shock tissue (or part of it). The second group of experiments suggests that the shock tissue resides in the deeper vessels. It may also be interpreted, however, to mean that the newly transplanted capillaries require time for them to develop the characteristics necessary to become reactive, or that new formed capillaries, later developing at this site, become reactive, somehow, from the surrounding milieu.

Failure to inhibit the reaction with most of the available antihistamine drugs suggests that histamine does not play an important role in the mechanism of the reaction. The slight suppression with ACTH or steroids is probably merely a manifestation of local inhibition of full inflammatory response to the antigen-antibody reaction.

The histologic findings demonstrate that two distinct processes were taking place in the *epidermis* at the time that the biopsy specimens were obtained. The first was a massive intra- and intercellular edema, necrosis of epidermal cells and the formation of a primarily subepidermal bulla. The second process was one of premature keratinization of individual or groups of epidermal cells (pearls) in the stratum spinosum. Hematoxylin and eosin stains revealed the presence of a refractile bright pink-red substance within the cytoplasm of the cells composing these pearls which had all the special staining characteristics of keratin. There is no apparent relationship between the formation of the bulla and these peculiar prematurely keratinized cells and serial sections did not suggest that one gave rise to the other. The occasional presence of such prematurely keratinized cells adjacent to the bulla appears to be a chance finding (Fig. 13).

It is debatable whether the histologic findings of premature keratinization in the specimens taken from our patient can be called dyskeratosis. Civatte (18) mentions in antipyrine fixed drug eruptions the finding of scattered bizarre and mitotic Malpighian cells which suggested certain precancerous dyskeratoses. Although these precise features were not seen in the patient herein reported, it is nonetheless interesting to note that Civatte likened his findings to the dyskeratoses. If one understands dyskeratosis to mean a process in which epidermal cells undergo keratinization to form special types of cells (grains and corps ronds) which become segregated from the surrounding epidermal cells, the process occurring in our patient with fixed drug eruption is not one of dyskeratosis since none of these features were found. On the other hand, if one considers dyskeratosis to include all pathologic processes in which epidermal cells keratinize at the wrong time and in the wrong place while still in the epidermis (14), then the term dyskeratosis would apply to the events which have taken place. From these studies, the only apparent feature of the keratin pearls seen in these specimens which is abnormal is the fact that the cells were undergoing keratinization in an accelerated fashion at a site deeper in the epidermis than one finds in normal skin. However, as far as one could tell the process of keratinization which resulted in the formation of the keratin pearls appears to include all the successive stages which are found in normal keratinization (stratum spinosum—stratum granulosum—"stratum lucidum"—stra-

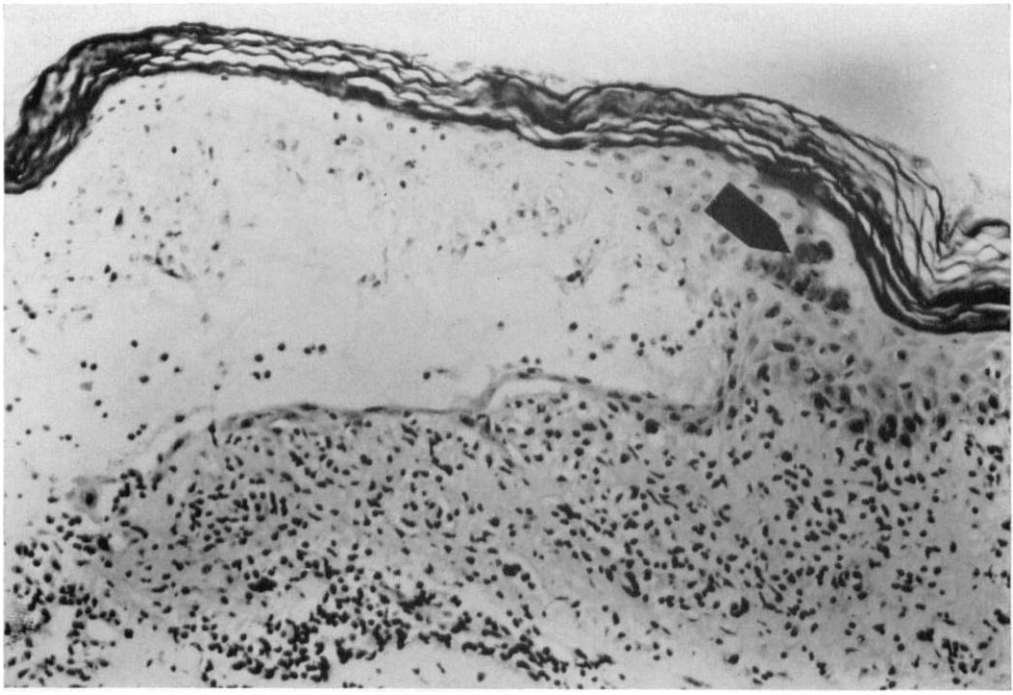


FIG. 13: This specimen from the bulla periphery has a small group of prekeratinized epidermal cells near its edge (arrow). Giemsa stain. ×186.

tum corneum). Because of the controversy we prefer to call the changes occurring in this specimen *premature keratinization.*

We have not come across other reports of similar observations which may mean that this process of premature keratinization is unique in our patient or that it had escaped the attention of others since in our case special stains were required to clarify the findings on routine hematoxylin-eosin stain. It is suggested that selected stains be employed on biopsy material from other patients with fixed drug eruptions, to determine if similar events take place.

Another possibility which exists is that this peculiar process of premature keratinization existed at the site of the fixed reaction *prior* to the administration of the allergen. This may be of more than academic interest since such a preexisting alteration may be a factor in the fixation of the eruption to a site. Although not confirmed by others (14, 15) some workers (10, 12) have shown that sites susceptible to fixed drug eruptions when transplanted to other areas in the same person retain their sensitivity at least for some period of time. Furthermore, Naegeli *et al* (10) have shown that skin removed from the site of a recently healed antipyrine fixed drug eruption when immersed in a 10% solution of antipyrine *in vitro* underwent marked epidermal (vesicular) and dermal (vascular dilatation, edema) changes, whereas normal skin taken from the same patient failed to show any such changes when immersed in the same solution for a similar length of time. These previous observations as well as our own suggest that detailed study of areas susceptible to fixed drug eruptions compared with neighboring normal skin should be carried out in the attempt to uncover chemical, anatomical, histochemical, or other differences which may explain the peculiarity of such fixed localizations.

A striking feature of the prematurely keratinized groups of epidermal cells was the findings of numerous melanin granules scattered throughout the keratin pearls when compared with the relatively few melanin granules visible in the surrounding unaffected epidermal cells. It remains to be determined what role, if any, melanin concentrated within these prematurely keratinized cells plays in the hyperpigmentation which so characteristically follows fixed drug eruptions. Previous workers (10, 12) have reported that in fixed drug eruptions manifesting hyperpigmentation melanin is found in excess in the basal layer

and in the upper cutis (predominantly within melanophages). The biopsy specimens from the lesion site in our patient did not show increased melanin in these sites when compared with the specimen taken from normal skin. However, the accumulation of melanin in the basal layer and upper cutis reported by others may not make its appearance until a later stage in the evolution of such lesions.

The findings within the dermis consisting of vascular dilation, marked edema and primarily perivascular cellular infiltration is consistent with the observations of others (10, 11, 14). The lack of alkaline phosphatase activity of some of the superficial capillaries is distinctly abnormal and an unusual finding in skin disease (15). The presence of a mucoid substance in the cutis can be seen in other inflammatory conditions involving the cutis.

SUMMARY AND CONCLUSIONS

1. A patient with a fixed drug eruption caused by 8-chlorotheophylline in Dramamine® is reported. This is believed to be the first such case recorded in the literature.

2. The identical reaction occurred with 8-bromotheophylline, but no reaction occurred to theophylline *per se* or to related xanthine derivatives, such as theobromine or caffeine.

3. There was no suppression of the reaction by the conjoint use of many different antihistamine drugs, and only minimal suppression from ACTH or corticosteroids.

4. Evidence is presented suggesting that at least part of the shock tissue resides in the superficial dermal blood vessels.

5. The histologic findings included a massive edema and primarily perivascular inflammatory infiltrate in the cutis. Epidermal changes consisted of 1) spongiosis, exoserosis and exocktosis with bulla formation and 2) an unusual process of premature keratinization in which single or groups of epidermal cells underwent keratinization in the form of keratin pearls within the stratum spinosum.

6. A fixed drug reaction limited to the pigmented site was produced by a 48-hour occlusive patch test with the suspected drug. It is suggested that this constitutes a useful and harmless diagnostic procedure for determining the causative agent in fixed drug eruptions.)

We wish to express our sincere thanks to Dr. Sonia D. Morrill for her valuable suggestions and review of the pathological and histochemical material.

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