EXCESSIVE THICKENING OF THIERSCH GRAFTS CAUSED BY A COMPONENT OF SCARLET RED (AMIDOAZOTOLUOL).[1]

BY JOHN STAIGE DAVIS, M.D.,

OF BALTIMORE, MD.

Instructor in Surgery, Johns Hopkins University.

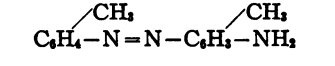
INTRODUCTION.

THERE has been some skepticism expressed at one time or another in regard to the power of epithelial stimulation claimed for certain of the organic coloring matters (scarlet red; soudan III; azodolen; pellidol, etc.), when applied locally to granulating wounds.

To my mind this matter has been settled beyond a doubt, as, during the last four years a number of enthusiastic articles have been published by well known investigators on the satisfactory use of these substances. These papers almost uniformly report splendid clinical results in hastening the healing of sluggish granulating wounds of varying etiology, and in every situation.

As is usual when a promising new therapeutic agent of this type is brought to the attention of the medical profession, it has been used by many who are not familiar with the prin-

[1] Amidoazotoluol is an amidoazo compound employed as an intermediate product, which, when combined with Beta naphthol, forms the scarlet red originally used, experimentally, by Fischer,[a] for the production of atypical epithelial proliferations; and first used, clinically, by Schmieden.[b] Amidoazotoluol was first used clinically by Hayward.[c] It has the formula—



[a] Münch. med. Wochenschr. Nr. 42, October 16, 1906, S. 2041.

[b] Zentralbl. f. Chir., Nr. 6, February 8, 1908, S. 153.

[c] Münch. med. Wochenschr. Nr. 36, September 7, 1909, S. 1836, and Deutsche Zeitschr. f. Chir. Bd. 112, 1911, S. 467.

ciples of wound healing, and who have little knowledge of surgical dressings. If unfavorable results have been obtained by such individuals, I do not believe it is entirely due to the dyestuff.

I have found that these substances will not heal every wound, but, in the majority of instances, when applied with the proper technic, they will cause epithelial stimulation in the edges of the most sluggish wounds, and give a rapid, stable healing.[2]

The use of these coloring matters has also been objected to, by some who admit their power of epithelial stimulation, on the ground that there might be the possibility of producing epithelial overgrowths having malignant characteristics. It is a well known fact that malignant degeneration may occur in any chronic ulcer, even though only the blandest dressings be used. The consensus of opinion, deduced from experimental and clinical work, is that there is no more danger of producing malignant growths by the clinical use of these substances, than with any other dressing. My own experience in the treatment of a large number of cases has convinced me of this, and I feel no hesitancy in using the organic coloring matters on proper wounds.

I take this opportunity of warning against the indiscriminate use of these substances by inexperienced persons, as considerable harm may be done with them by improperly applied, and too long continued, dressings. There is, occasionally an overgrowth of epithelium following the use of these dyestuffs, even when the greatest care is exercised, but after discontinuing the stimulating dressing, this overgrowth soon assumes the level of the normal skin.

The following case shows the epithelial stimulating power of amidoazotoluol to a remarkable degree, and may be of interest.

---

[2] Johns Hopkins Hospital Bulletin, vol. xx, No. 219, p. 176; ANNALS OF SURGERY, May, 1911, p. 702; Boston Med. and Surg. Jour., June 6-13, 1912.

Clinical History.—White man, aged thirty years. Engineer. Six months before admission was severely burned in an oil explosion. The head, neck, both upper extremities and portions of the back and chest were involved, and his condition was serious. He was admitted to the Johns Hopkins Hospital in a critical condition and remained there for five months. While in the hospital skin grafting was resorted to a number of times, and considerable progress was made toward healing. He was discharged at his own request before healing was complete, and was referred to the Out-Patient Department for dressings. After several weeks his condition was unimproved, and, as the hospital was crowded, he was sent to the Union Protestant Infirmary, where he came under my care.

Physical Examination.—The patient was anæmic and emaciated. There were large unhealed areas on the scalp and on both arms and forearms. I will describe only the ulcer on the right arm, as this is the particular wound to be considered in this report (Fig. 1).

An extensive granulating wound occupied the entire circumference of the lower two-thirds of the arm, including the elbow and upper two inches of the forearm. The wound extended three inches higher on the outer than on the inner side of the arm. On the inner side an area of skin previously grafted extended up from the forearm to the bend of the elbow. The granulations were exuberant, œdematous and unhealthy. Practically all the skin of the forearm adjacent to the ulcer had been grafted before the patient came under my care. During the interval between admission to the Union Protestant Infirmary and operation on the right arm, the other unhealed areas were grafted.

The granulations of this wound were brought into healthy condition by irrigations, free use of nitrate of silver, balsam of Peru, curved scissors, etc. At the same time very marked progress was also made toward healing by stimulating the wound edges with 4 per cent. amidoazotoluol ointment, alternating every 24–48 hours with zinc oxide, or boric ointment. The newly formed skin edges were thick and stable, but showed no tendency to overgrowth. As the granulations were flat, firm and rose pink in color, in spite of the rapid stimulation of the wound edges, it seemed advisable to hasten the healing by grafting.

Operation (June 28, 1910).—Nitrous oxide-oxygen anæsthesia. A number of large thin Thiersch grafts were obtained from the left thigh by the method used at the Johns Hopkins Hospital,[3] and the grafts were spread on protective and put aside. The thigh was dressed with boric ointment on protective, and the patient was allowed to regain consciousness. The granulating area on the arm was irrigated with salt solution and then dried carefully without causing bleeding. The grafts were button-holed and applied over a large part of the unhealed area. Rubber impregnated mesh was placed snugly over the grafts, and over this overlapping strips of protective, dry gauze and a bandage.

June 30. The dressings were removed down to the rubber mesh, which was not disturbed. The grafted area was irrigated with normal salt solution and dressed with 4 per cent. amidoazotoluol ointment on old linen, over the rubber mesh. This dressing was alternated with boric ointment every 24 hours.

July 12 (after six dressings with 4 per cent. amidoazotoluol ointment). The greater portion of the grafts had taken. Since the last note there had been a remarkable gradual thickening of all the grafts. The surface was smooth but rather uneven, and of a bluish grey color. The appearance was that of an œdematous epithelial mass. The thickness varied between ⅛ and ⅜ of an inch. I felt convinced from my experience with occasional overgrowths of wound edges and other grafts caused by the organic coloring matters, that this thickening would begin to subside as soon as the stimulant should be removed. The thickened grafts were dressed with stearate of zinc powder and exposed to the air, in order to promote drying. The amidoazotoluol was discontinued. There was no excessive thickening of the wound edges.

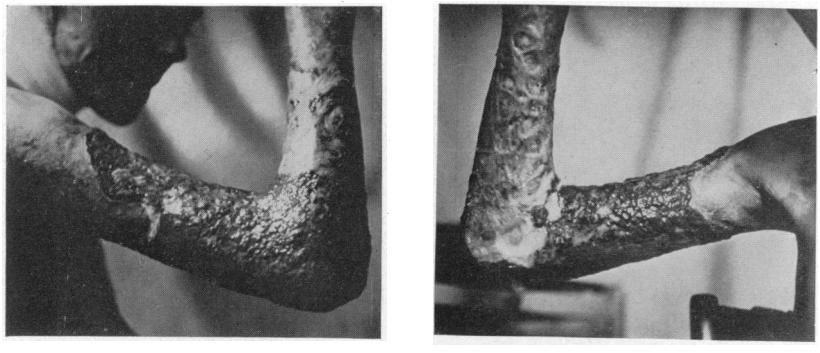
July 20. The thickening of the grafts was still very marked, but the overgrowth had begun to separate into irregular-shaped fungating masses. When a section was removed for microscopic examination, there was little pain but profuse bleeding (Fig. 2).

July 22. Thiersch grafts from the left thigh were placed on the remaining undisturbed granulations and dressed with moist salt gauze over the rubberized mesh.

---

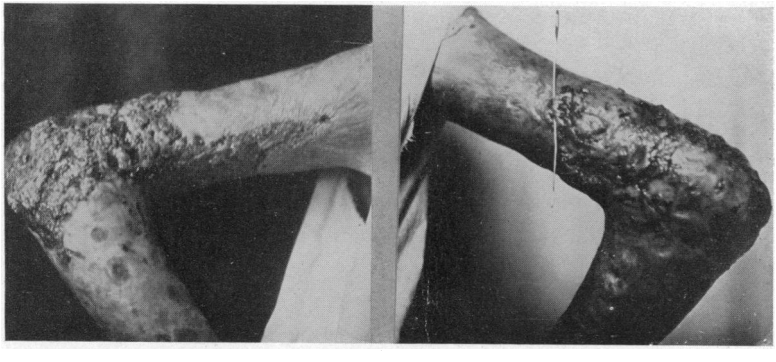
[3] ANNALS OF SURGERY, September, 1909, p. 543.

FIG. 1.



Appearance on admission. Ulcer of right arm due to burn six months previously. Note exuberant, unhealthy granulations. Grafted skin can be seen on the forearm.

FIG. 2.



(*a*) Taken July 20, 1910. Note the marked thickening of the Thiersch grafts. The thickened grafts have begun to separate into irregular fungating masses which can be plainly seen.

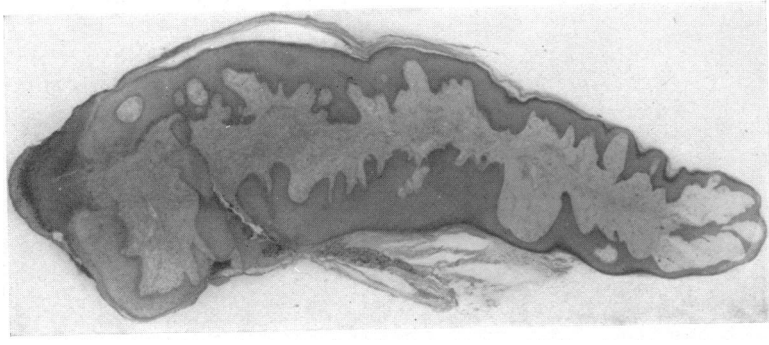
(*b*) Taken August 1, 1910. Portions of the thickened grafts have assumed the level of the normal skin. Over-growth can still be seen in other areas. Note the overgrowth which is attached only by its edges, beneath which a probe is passed. There are a number of similar areas scattered over the arm.

FIG. 3.

(*a*) Taken January 7, 1911. Five months after discharge. The skin is movable and, for the most part, smooth, although several thickened areas can be found. There is considerable pigmentation.

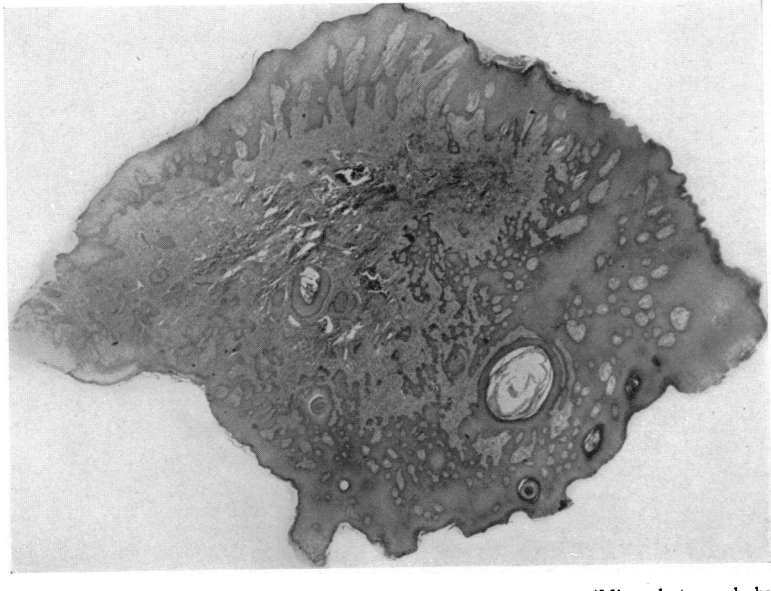
(*b*) Taken January 4, 1912. Seventeen months after discharge. There is marked blotchy pigmentation of the grafted area. On careful examination of this skin one or two small flat thickened areas can be found. There are also a few minute depressions in the skin which are filled with comedon-like masses. Otherwise the skin is normal.

FIG. 4.



Section of small papillomatous overgrowth. For description see text. (Microphotograph by Schapiro, Zeiss. Obj. AA. Oc. 3.)

FIG. 5.



Section of papillomatous overgrowth. For description see text. (Microphotograph by Schapiro. Zeiss. Obj. AA. Oc. 3.)

July 29. All the grafts last applied had taken, and *were of normal thickness,* no amidoazotoluol having been used. The first grafts had resumed, in some places, the appearance of normal grafted skin. In others, several areas had assumed a papillomatous formation. Some of these were of the size of a pea, and were adherent to the underlying clear skin by a small pedicle. Others were flattened mushroom-like masses, with overhanging edges, while other areas were adherent here and there along their edges, and not elsewhere, so that an instrument could be passed freely underneath them. Some of the thickened areas were 1½ inches in diameter, a single portion comprising about one-half of this, and the rest being made up of closely set papillæ, which extended above the surface of the skin from ⅛ to ⅜ of an inch.

Several of these areas were cut off, and normal looking skin was found beneath, except for bleeding at the points of attachment. Here and there masses of cheesy secretion could be pressed from under the overgrown areas, and this had the typical odor of the contents of an atheromatous cyst. Microscopic examination showed this to be made up of epithelial debris.

August 13. Some of the papillary overgrowths had been removed, and many others had dried out and fallen off, as the blood supply of the pedicles was gradually occluded. Those which remained were much less prominent than at the last note. A large part of the thickened grafts had assumed the level of the normal skin, which was of a pinkish color. These level areas gave no evidence of having undergone excessive epithelial stimulation.

The patient was discharged in excellent physical condition, and with practically complete healing of all his lesions.

October 15. The greater part of the grafted skin on the right arm was smooth, but here and there were scattered a few small, flat, dry, papillomatous overgrowths. These growths received their nourishment through very small pedicles, between which the formation was bridged. The patient was working at his usual occupation.

January 7, 1911. Practically all of the papillomatous growths had disappeared, and the area was covered with smooth, solid skin (Fig. 3).

January 14, 1912. The arm was covered with a stable, movable skin, which was heavily pigmentated. On careful examination one or two very small thickened areas could be found on the inner side of the arm. There were also several comedon-like masses which filled minute pockets in the skin.

January 5, 1913. The condition of the skin had not changed since the last note.

Histology.—(Microscopic examination by Dr. Joseph C. Bloodgood.[4]) (Fig. 4.) There was an oblong piece of tissue with a central zone of œdematous connective tissue surrounded by epidermis. The papillary bodies of the epidermis were present. These papillary bodies varied in size and shape; they were larger and more irregular than in the normal epidermis. In some places the hornified epithelium on the surface was more marked than normal. Corresponding to these areas the epidermis was thicker than in areas in which the hornification was less. The epidermis differed from normal in the fact that the basal cell was not so distinct in its morphology, and in places the downgrowth of epidermal epithelium was more irregular than normal. We would speak of it as atypical. In one end of the section the central connective tissue looked myxomatous or œdematous. In the faintly stained intercellular substance there were a few round and stellate connective tissue cells, resembling, therefore, myxomatous tissue. Here and there there was a lymph vessel filled with leucocytes. At the other end of the section there was a defect in the epidermal covering, and this was filled with lymphoid-cell granulation tissue. This granulation tissue grew out from a narrow isthmus in the epidermis, and projected over the surface of the epidermis, like a fungous ulcer. On each side of the granulation tissue in the defect in the epidermis, the epithelial cells were extending irregularly into the granulation tissue. The cell proliferation in the granulating tissue was of the type of the transitional and squamous cell. This histological picture was somewhat similar to that seen in the beginning of carcinoma.

The other piece of tissue (Fig. 5) had the appearance of having been cut on the bias. The central zone of connective

[4] I take this opportunity of thanking Dr. Bloodgood for the microscopic study.

tissue was smaller, the epidermis much thicker, and the section seemed to be horizontal through the papillæ rather than vertical. There were also a few cavity formations in the epidermis, filled with hornified epithelium, which had the appearance of the so-called inclusion dermoid cysts. In the connective tissue of this section, there were numerous endothelium-lined canals filled with blood, probably young capillaries, and some more dilated similarly lined spaces filled with blood which may have been veins. There were also some dilated endothelium-lined spaces which suggest lymphatics.

The entire picture, therefore, suggests unusual epithelial activity. That is, the healing process of epidermization was going on very actively; one would naturally conclude, perhaps too actively, or, as Adami would express it, "over-sufficient." The possibility of producing a definite malignant epithelial growth from such stimulation, as has been observed in X-ray and radium keratosis, should be borne in mind. This possibility is illustrated in the character of the epithelial overgrowth into the granulation tissue filling a defect in the epidermis as noted above. Here the cells were not growing as in normal epidermization in which the downgrowth was always composed first of a basal-cell layer, but, instead, the transitional and squamous cells were proliferating irregularly into the granulation tissue, as in carcinoma. But these cells as yet have not assumed the abnormal morphology seen in cancer.

REMARKS.

The microphotographs, especially Fig. 5, show a condition which resembles very closely sections of the atypical epithelial proliferations produced by injecting scarlet red oil, subcutaneously, under pressure into a rabbit's ear.[5] These experimental tumors never show a tendency to independent aftergrowth, and persist only as long as the injections are continued and the scarlet red remains in the tissues.

The epithelium of this patient seemed to be particularly responsive to the stimulation of amidoazotoluol, and these thickened grafts present the most remarkable condition of overgrowth which has come under my observation.

[5] F. H. Helmholz: J. H. H. Bull., Sept., 1907, p. 365, Fig. 2, Exp. Ia.

It is interesting to note that Thiersch grafts which were subsequently applied to unhealed portions of the same wound, under exactly the same conditions, but without being dressed with amidoazotoluol were not thickened.

There was also great thickening of the deep pinch grafts placed on the undisturbed granulations of the ulcer on the scalp, which had been treated with amidoazotoluol before and after the application of the grafts. There was no such thickening, however, of similar grafts placed on undisturbed granulations, when not dressed with amidoazotoluol. There was distinct overgrowth of epithelium, "pebbly formation," on the thigh, when the area from which the Thiersch grafts were removed was dressed with amidoazotoluol ointment. Another area on the thigh from which Thiersch grafts were taken, but which was dressed with boric ointment, showed no "pebbly formation."

The patient has been under observation for over two years and a half since his discharge from the hospital, and there is no sign of malignant degeneration anywhere.

This condition is unique, and I can find no report in the literature of a similar case. It demonstrates beyond a doubt the epithelial stimulating power of amidoazotoluol. It also seems to show that although this stimulation is excessive, there is no tendency to subsequent malignant degeneration.