

Meyer (W.)

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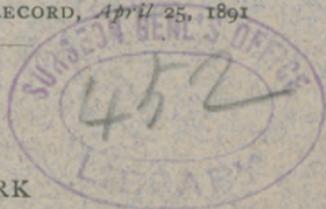
*ESPECIALLY THE BLUE PYOKTANIN,
IN THE TREATMENT OF INOPERA-
BLE MALIGNANT GROWTHS*

BY

WILLY MEYER, M.D.

ATTENDING SURGEON TO THE GERMAN AND NEW YORK SKIN AND CANCER HOS-
PITALS

Reprinted from the MEDICAL RECORD, April 25, 1891



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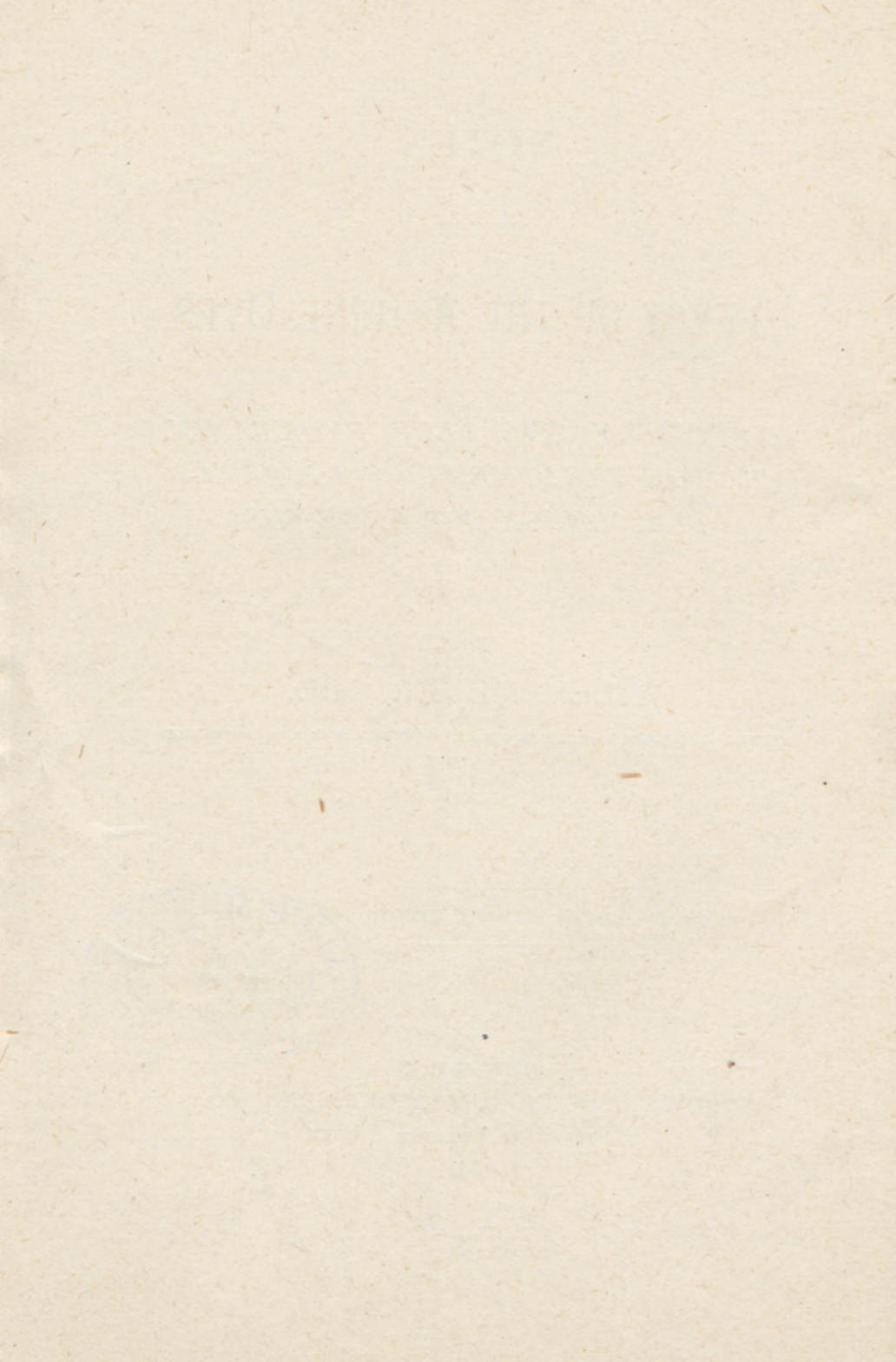


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NOTES ON THE EFFECT OF THE ANILINE
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IN, IN THE TREATMENT OF INOPERABLE
MALIGNANT GROWTHS.

At a time when tuberculin and cantharidate of potash are injected for the cure or the improvement of tuberculous troubles, and our medical journals and periodicals are constantly full of reports which are the result of a comparatively short time of observation of the individual medical man, it seems rather queer to join this interesting and at the same time necessary rapidity of publication with new remedies applied for the cure or improvement of another chronic and malignant disease. If I nevertheless give a preliminary report of an eight weeks' use of the aniline dyes, especially of pyoktanin (blue), in the treatment of inoperable malignant growths, I do so because this my rather short experience with the aniline dyes made me believe that they will most probably play an important rôle in the treatment of such patients as suffer from cancerous (and sarcomatous) new growths, where neither knife nor cautery can bring any more help; and because I think that if many colleagues try the aniline dyes for this unhappily so common disease, important facts in regard to use and effects will be gained so much quicker, mistakes in dose and application found out meanwhile by experience can be avoided, and many poor creatures may perhaps be benefited so much sooner, if only in regard to alleviating the pains which so frequently accompany exulcerated facial neoplasms.

The literature on the effects and on the value of external as well as internal application of the aniline dyes, es-

pecially pyoktanin (blue), in general surgery is comparatively small yet. Notes in this respect will be best found in the second treatise of J. Stilling,¹ Professor of Ophthalmology at the University of Strasbourg, Germany, who, together with Dr. Wortmann, made careful bacteriological and chemical researches with the different aniline dyes. He baptized one of the methyl-violets, which showed the greatest antiseptic power, pyoktanin, and introduced two different kinds of the drug, the blue and the yellow (pyoktanin cæruleum and pyoktanin aureum). The latter is also called auramin.² Its antiseptic power is far less than that of the former one; it is mostly used in superficial wounds and on the face, as it dyes the tissues yellow.

In regard to this special subject, viz., the use of the aniline dyes, especially pyoktanin,³ in the treatment of inoperable malignant growths, only a few gentlemen have so far reported. Stilling mentions in his second paper⁴ that he succeeded in curing with pyoktanin an extensive exulcerated epithelioma of the face (ulcus rodens) which, beginning in the middle of the dorsum of the nose, involved the entire wall of the lachrymal sac and half of the upper eyelid. He first sterilized the surface with a large pyoktanin stick and then powdered the pure substance on the formed eschar. This procedure was repeated a number of times. A hard cover was thus formed, which could not be pulled off. It came off by itself after a number of weeks, and underneath a smooth cicatrix presented itself. The eyelid, of course, was contracted. He states this case to show how effective the aniline dyes can be even

¹ Anilin-Farbstoffe als Antiseptica und ihre Anwendung in der Praxis. Zweite Mittheilung. Strassburg. 1890.

² The drug is manufactured by Merck & Co., Darmstadt, Germany (71 and 73 William Street, New York City). Their preparation is reliable and chemically pure. In ordering "Pyoktanin" "Merck" should be marked on the prescription.

³ In mentioning "pyoktanin" in the following notes always the "blue" one is alluded to.

⁴ Loc. cit., p. 96.

in such cases under special favorable circumstances, and not to claim to have found a remedy for cancer. In another case, which seemed to be much more favorable, this kind of application had no success whatever.

On January 30, 1891, Professor v. Mosetig-Moorhof read a very interesting paper before the Vienna Society of Physicians, "A Contribution to the Treatment of Inoperable Malignant Growths,"¹ in which he reported on his experience with pyoktanin in such cases. He stated that on November 20, 1885, he had presented to the same society two patients with very extensive inoperable epithelioma of face, in which he had succeeded in removing all the diseased tissue with the help of a drug (lactic acid). But as early as 1883 he had treated an inoperable round-cell sarcoma of the right groin of a man, aged fifty, with parenchymatous injections of a one per cent. solution of an aniline dye (anilinum trichloratum). Eight weeks later the œdema of the lower extremity had disappeared, the large tumor was reduced to a nodule of the size of a walnut, and the ulceration had healed. The patient left the hospital cured and attended to his business. He died one year later of pneumonia; the neoplasm had not recurred. As in the course of the treatment he had nearly lost his patient by using one drachm of the one per cent. solution in one sitting, most probably on account of poisonous impurities in the drug,² and as he later saw in three other cases, treated in the same way, very annoying and dangerous general effects, he stopped these researches and only started them again after having read Professor Stilling's discovery of pyoktanin, a powerful antiseptic drug, which is perfectly harmless and chemically not poisonous to the organism. In the treatise referred to, a number of cases are reported which demonstrate that in pyoktanin a remedy seems to have been found which can possibly bring help in cases of inoperable malignant growths, where

¹ Wiener klinische Wochenschrift, 1891, No. 6, p. 101.

² These impurities are arsenic, sulphate of copper, and chlorate of zinc.

formerly the patient and doctor likewise seemed to be absolutely helpless.

At the same meeting Dr. Neudoerfer reported¹ that in the spring of 1890 a woman, more than seventy years of age, came under his treatment, who suffered from an inoperable cancer of the right breast. The whole breast and surrounding tissues were densely infiltrated by a cancerous growth and partially exulcerated. The ulcerations were first dressed with pyoktanin solution, later on spread with a powder, which consisted of one to two parts pyoktanin to one hundred parts talcum venetum. The patient seemed to be very satisfied with this treatment. She still complained of pain during the night, but the neoplasm, although not diminished in size, stopped growing.

In November, 1890, he treated a second similar case in a woman more than sixty years of age in the same way. In this case also the ulceration did not spread: the infiltrated glands in the axillary cavity became continuously smaller and movable.

Stilling² proposes to make use of such aniline dyes for parenchymatous injections of inoperable neoplasms, which slowly, and for a small percentage only, dissolve in a 0.6 per cent. solution of chloride of soda—viz., blood. The injected fluid will then not as quickly leave the tissues, into which it has been injected, by diffusion, and therewith enter the blood. In the latter respect he advises great care, as the dye enters the red blood-corpuscles, and, if entering in too large an amount, may endanger their function, possibly destroy life. He believes that ethyl-violet will best answer this purpose. Only 0.7 to 0.8 part are soluble in 1,000 water; it has besides the strongest antiseptic power of all the drugs belonging to this class. Stilling called it ethyl-pyoktanin; it is also manufactured by Merck. In regard to its practical application in in-

¹ Wiener klinische Wochenschrift, 1891, No. 6, p. 113.

² Ueber die Therapeutische, Verwerthung der Anilin-Farbstoffe. Wiener klin. Wochenschr., 1891, No. ii., p. 201.

operable cancer cases, he thinks it best "to make use of the well known method of Von Nussbaum, who tied the arteries which fed the neoplasm, in order to stop its growth. The tissue, thus having been made bloodless first, should then be thoroughly dyed in all its parts, and that as rapidly as possible."

Von Moseitig presented four of his cases, previously referred to, at a recent meeting of the Vienna Society of Physicians¹ (March 13th). The patients had all been materially improved, but were not yet cured. He also stated that a woman with papilloma of the bladder, who had been treated with injections of pyoktanin, 1 to 1,000,² had had no more vesical hemorrhage and was able to attend to her work; she had also got rid of the troublesome stranguria. He assumed that the papilloma had materially shrunk. A gentleman with an immense inoperable adeno-sarcoma of the pelvis, which had made him an entire invalid, was so far improved by the color-cure that he again entered society and left for the South. The rest of the tumor presented about the fifth of its original size. Sixteen more cases of this kind were submitted to the same treatment. Fourteen of them were materially improved; two died. In none of the cases did the neoplasm spread during the treatment. One of the deaths was due to a sudden compression of the trachea by a large sarcoma of the thyroid gland; the other was caused by an uncontrollable venous hemorrhage occurring in the course of the treatment, in a man with a sarcoma of two fists' size, which was seated in the parotid region and the right side of the neck. The post-mortem revealed that the superficially ulcerating neoplasm had undergone fatty degeneration in the deeper region, which was attributed by the author to the use of the pyoktanin. The tumor

¹ Wiener klin. Wochenschr., No. 12, p. 224, and Wiener Med. Presse, No. ii., p. 429.

² According to my experience with irrigating irritable bladders with pyoktanin solution, 1 to 1,000 was found to be too strong. One should rather begin with 1 to 5,000 or even 10,000, and then slowly increase the percentage.

had infiltrated the wall of the internal jugular vein and then, by its breaking down, given free exit to the venous blood. Von Mosetig concludes that we had better be careful with this treatment in cases of malignant growths which have developed in the neighborhood and around large blood-vessels. He is inclined to avoid injection into the tumors which involve large veins and also into those which cannot easily be reached by the needle of the syringe. He now prefers a solution of 1 to 500 as a standard solution, which is filtered through heated asbestos to remove undissolved crystals, which might plug the needle, and makes the injections in a concentric manner, letting his needle enter into the surrounding healthy tissues. Von Mosetig does not share Stilling's fear that too large an amount of the dye could enter the blood and thus do harm by staining the red blood-corpuscles. In several hundreds of these injections neither he nor his assistants had ever seen any untoward accident. Microscopical examination of extirpated pieces of three different new growths, which had been injected, made by Riehl, of Vienna, demonstrated that the nerves, muscles, connective tissues and young epithelial cells were diffusely dyed, but the nuclei only slightly, or not at all. To explain this phenomenon and at the same time the necrobiosis or fatty degeneration and reabsorption of the growths after the injections (which in his opinion can only take place if the cells and the cell-nuclei of the neoplasm themselves have really been affected by the pyoktanin), Von Mosetig advances the hypothesis that the pathological cells or their nuclei contain a specific chemical substance, which is able to reduce the aniline dyes in such a way that the latter lose their blue color; in other words, that this at present unknown substance reduces the blue aniline dyes to white, that is leukaniline. When the tumor has been extirpated and sections have been prepared from it for microscopical examination the leukaniline in them, being exposed to the oxygen of the air, turns blue again. Now a poisonous chemical product has lately been found in

carcinomata by Adamkiewicz, which, inoculated in rabbits, kills them by p̄alysis of the brain in a few hours. Perhaps this poisonous product reduces the aniline dye and therewith becomes neutralized itself. This again might then explain the following regressive fatty metamorphosis and arrest of further growth. It is, however, necessary to state that this poison has only been found in cancers and not in sarcomata, which also react upon the aniline dyes.

Billroth¹ is rather sceptical in regard to the value of pyoktanin injections in cases of malignant growths. Three patients, having far advanced sarcoma (posterior aspect of thigh, sternum, popliteal space) got worse; one of them died of sepsis. The tumors were softened and the covering skin was perforated. This occurrence can only be looked upon, according to Billroth, as unfortunate to the patient. The exulcerated growth troubles the patients much more and will render their condition more dangerous. Patients afflicted with exulcerated cancerous growths also did not improve. Billroth does not believe that pyoktanin, when injected, has any specific influence whatsoever, but that it is merely the water, which, forcibly pressed into the tissues, makes them swell and later unable to live.² The researches are continued in his clinic.

The aniline dyes were first externally applied in two of my patients at the Country Branch of the New York Skin and Cancer Hospital. The treatment was started on January 2d, this year.³ We used fuchsin, first in solu-

¹ Wiener klin. Wochenschr., No. 12, p. 236.

² Stilling is strongly opposed to this explanation (Wien. klin. Wochenschr., April 2d, p. 263). He maintains that it has been clearly shown "that the living protoplasm of plants, as well as animals, is colored and at last destroyed by the aniline dyes. The latter takes place as soon as the dye is introduced into the cell in so large a quantity that the cell cannot get rid of it any more by diffusion." Stilling advises at the same time to make up the solution with a 0.6 per cent. solution of chloride of soda, in order to avoid embolies of the capillaries with undissolved pyoktanin-crystals (Neudoerfer).

³ In my first communication to the New York MEDICAL RECORD (March 7, 1891, Correspondence), the date of commencing this treatment was erroneously put as January 6th.

tion, then in ointment. Since February 20th, after having read Von Mosetig's original communication, I substituted pyoktanin for fuchsin, as it is chemically pure, especially free from arsenic, and also more soluble in water.

Since that time nine patients of the New York Skin and Cancer Hospital, all suffering from cancer, have been treated with local applications of pyoktanin in ointment, powder, or substance, and with parenchymatous injections of pyoktanin solution, 1 to 300. Their cases have been very carefully observed and treated by Dr. F. Torek, Assistant-Surgeon to the Skin and Cancer Hospital, the house-staff of the City Hospital and the Country Branch, and myself. Two patients of my private practice, one of whom has a recurring cancer of the breast, the other an inoperable cancer of the rectum, which necessitated anterior colotomy three months ago, have also been subjected to this treatment (in the first ethyl-pyoktanin was first used). They have been, however, only for a short time under observation. Their histories can therefore not be used for this communication. In two of the nine hospital patients the treatment was begun when both were very low already. One of them died from cachexia, the other from a chronic nephritis of long standing. I am sure that, in both, the very short use of pyoktanin had nothing to do with their death. I nevertheless regret that a post-mortem could not be made. The other seven are still under treatment, three of them only for a rather short period. Their histories will appear in a later paper.

The histories of the remaining four cases, as far as they may perhaps be of interest, are in a condensed form as follows :

CASE I.—Mrs. E. M——, aged seventy-three; German. Large ulcerated epithelioma (rodent ulcer) of scalp, forehead, nose, and eyes of twenty years' standing. Left eye entirely destroyed; also a part of both lids of right eye. Patient is still able to see indistinctly with the latter to a distance of about one to two feet. Excruciating pains, especially during the night, for a long time.

January 2, 1891.—Application of fuchsin, 1 to 250 (equal parts of alcohol and water), on a portion of wound. (Dr. A. C. Lewis.)

January 6th.—No discharge from this spot ; surface of a more healthy appearance.

January 10th.—There is a little discharge. The sore presents “a fairly healthy granulating surface.”

February 14th.—Condition unchanged ; there seems to be no tendency to spread.

February 20th.—Patient states that the former pain has entirely disappeared. “This is the best treatment she has so far undergone.” Application of pyoktanin 1 to 200 talcum.

March 24th.—Wound continues to present a more healthy, rather granulating base, and has perceptibly decreased in size around border on top of head ; a small area has cicatrized there ; at several other points, notably at the middle of the forehead, there is a tendency to heal. The hard borders have softened. Discharge scanty, but not as much as under the original fuchsin-treatment. A number of grooves seem to be more excavated than formerly (this is most probably due to necrobiosis of the cancerous tissue). Patient has but little pain. The borders of wound touched with large pyoktanin stick, likewise the right upper eyelid ; powder, strengthened to 1 to 50 talcum.

CASE II.—G. B——, aged seventy-one ; German. Defect of nose, recurrent exulcerated epithelioma of neighboring parts of both cheeks and of glabella, of inner third of the left lower and both right eyelids, cancerous infiltration of the upper lip.¹ Since 1886 rhinoplasty twice performed at the German Hospital ; recurrence ; amputation of the second nose, which had been made by plasty, in 1889, at the New York Skin and Cancer Hos-

¹ Patient was presented to the New York Surgical Society on February 25th, and to the Scientific Society of German Physicians on February 27th. Cf. Report of the New York Surgical Society of February 25th, in New York Medical Journal, April 11th.

pital. A number of further attempts during this year to check the continuous spread by operative interference, also applications of different chemicals without result.

January 6, 1891.—External application of fuchsin solution, 1 to 200 alcohol, started; on account of pain lanolin was soon substituted for alcohol.

February 25th.—The former frequently excruciating pains, which disturbed the sleep, have entirely disappeared; the secretion has stopped. The base, formerly showing all the characteristics of an exulcerated epithelioma, has become smooth and rather resembling a granulating surface. The grooves are more shallow, the hard and thickened borders nearly all around soft and sunken in. During the seven weeks that the fuchsin has been in use the growth has not spread, except on the left cheek, where a small nodule, still surrounded by healthy tissue, has made its appearance near the border. A perforation through the upper lip into the mouth has also not extended.

March 4th.—The whole surface was painted with the large pyoktanin pencil, and then powdered with pyoktanin in substance. Parenchymatous injections, 15 minims each, of pyoktanin solution, 1 to 300,¹ were made underneath small, hard nodule in left cheek, both sides of upper lip, and into recurring exulcerated cancer of the size of a small cherry in the left submaxillary region (a large secondary growth had been removed there eighteen months ago); injections in the face very painful. In the following days patient complained of a great deal of pain.

March 6th.—Pyoktanin, $1\frac{2}{3}$ grain in capsule, administered internally, was not retained by the stomach.

March 11th.—Second injection, 15 minims at different points of upper lip; 8 minims in the submaxillary growth.

March 13th.—Parenchymatous injection of 20 minims

¹ Blue stains on the operator's fingers, got in making the injection, will be best removed by using the liquid green soap, or a solution of Castile soap in alcohol, 1 to 10.

into lower half of right border of the ulcer ; the border is still swollen.

March 16th.—Patient complains of continued pain. The perforation through the upper lip into the mouth has extended (rapid breaking down of former infiltration). The wound appears to be deeper. The left eye is injected, its lids swollen (paralysis of vasomotor nerves?). Patient states he has by far more pain than under the fuchsin treatment.

March 17th.—Fuchsin ointment reapplied.

March 25th.—Patient complains of no pain. The sore appears rather healthy, but has extended in its lower part, the hard border which was especially injected with the pyoktanin solution having broken down on many spots. Nodule on left cheek and in submaxillary region partially necrosed, giving exit to a very scanty dark-bluish secretion. No œdema. So far no tendency to cicatrization.¹

CASE III.—Mrs. C. M.—, aged fifty-nine ; German. Recurrent cancer of right breast. Amputatio mammæ and extirpation of cancerous axillary glands at the German Hospital. Double ligature and excision of a piece about one inch long of vena axillaris. Diffuse cancerous infiltration surrounding the subclavian vein and reaching under and above the clavicle had to be left behind. Primary union of the wound. Admission to the Skin and Cancer Hospital, January 9, 1891.

February 20th.—œdema of right arm, which can only be very little abducted from the chest-wall. Infiltration in right infra-clavicular groove and quite markedly also below the broad scar, which is the result of the operation. Above the latter, especially toward the axillary region, disseminated small cancerous nodules. Injection of 1 drachm of the pyoktanin solution into different spots above the scar. Massage for one-half hour with the intention to press the fluid upward into the axillary cavity.

¹ At time of correcting proof (April 21st) cicatrization has started at different spots.

During the following night patient complained of a great deal of pain in axillary region. Temperature normal.

February 23d.—Injection of the same amount; immediate marked bluish discoloration of the skin. It is evident that the small nodules are not injected. Evening temperature, 100.5° F., rectum.

February 26th.—Injection of 1 drachm into the growth, and 15 minims underneath and into a number of cutaneous nodules. Massage.

February 27th.—The mucous membrane of the gums along the border of the teeth appears bluish.

March 3d.—Cicatrix perforated in length of one inch; blue-colored, œdematous tissue making its appearance. Pain on pressure above this spot. The whole infra-clavicular region pinkish-red and œdematous. No rise of temperature. The nodule, injected five days ago, has flattened, and is decidedly indistinct in its contours. Injection of four small cutaneous nodules at their base with 15 minims of the pyoktanin solution each. One more drachm into different spots of the diffused swelling, 2 drachms in all. The newly opened spot is powdered with pyoktanin in substance, and then covered with a piece of iodoform gauze.

March 6th.—One pill of pyoktanin, 1 $\frac{2}{3}$ grain, in capsule, administered internally, was soon rejected. The small nodules have softened and are almost imperceptible to the touch. The infiltrated area also softer and œdematous. Patient can move the right arm much better than before the injections. Wound again dressed with pyoktanin in substance.

March 8th.—Slight hemorrhage from the broken spot.

March 11th.—The infra-clavicular region gives the sense of fluctuation; by pressing upon it a quantity of a thick, dirty bluish fluid, intermingled with shreds of broken-down tissue, and a great deal of fat escapes through the fistulous opening in the cicatrix.¹ Small fluct-

¹ Careful microscopical examination of this fluid was kindly performed by Dr. I. Adler, of this city. The doctor's report reads as

uating spot at the outer angle of the latter is incised. It contains blood mixed with the same grayish-blue material. Injection of 1 drachm of the pyoktanin solution.

March 13th.—Patient complains of pain in the region of injections. There is a continuous colored discharge from the opening.

March 16th.—The spot immediately above the cicatrix decidedly flattened, up to three fingers' breadth below the lower border of the clavicle. Pain on pressure, fluctuation, continuous discharge. A number of the small nodules, which formerly seemed to have entirely disappeared, again perceptible to the touch. I think that the disappearance was partially an illusion, owing to the occurrence of œdema, which temporarily concealed the nodules, but, which subsiding, left them again distinct. (A few of them certainly were reabsorbed.)

March 17th, 20th, and 24th.—Injection of 1 to 1½ drachm of the pyoktanin solution each time.

March 26th.—The fistulous tracks in the injected area were split under ether. It was found that a thick ramified mass, dyed deep blue, was lying in the midst of nor-

follows: The fluid, of pale-violet color and containing small scraps of a solid matter, which formed an uneven and irregular sediment, was submitted to microscopical examination, and showed the following:

1. A colorless, serous, slightly viscid fluid. In this fluid were suspended globules of free fat in great profusion and of all sizes; fat-crystals; innumerable leucocytes of all kinds, principally, however, of the large polynuclear species; a comparatively small number of red blood-corpuscles, all these of natural appearance and entirely unstained. Furthermore, large masses of granular amorphous detritus, either suspended loosely throughout the fluid or else gathered together into more compact masses. These latter were sometimes diffusely stained of a very pale, grayish-violet tint.

2. The solid particles, which consisted of portions of fatty tissue and of patches of epithelial cells. The fatty tissue showed the regular polygonal fat-cells, sometimes emptied of their contents, sometimes filled with them. In either case a distinct and diffused bright violet-staining of the membrane could be made out, while the fat itself never showed any color. The epithelial cells were of the large, irregular, flat pavement species, either singly or in groups. Wherever an epithelial cell was found, it was at once recognized by its deep saturated stain. The coloring was entirely diffuse, and no nucleus could be made out without the aid of acids.

mal uncolored fatty tissue. This mass evidently was necrosed tissue, which could be easily shelled out with the finger or the sharp spoon; in many spots it was still adherent to its surroundings. The underlying muscles and neighboring tissues appeared to be normal in color, but rather indurated. Dr. I. Adler kindly consented to make a microscopical examination of the necrosed mass.

The wound was loosely packed with iodoform gauze, which was freely dusted with pyoktanin in substance. Pyoktanin gauze, as manufactured by Merck & Co., was not just at hand.

March 30th.—First change of dressing; gauze removed. Very little secretion. Wound in perfect condition.¹

CASE IV.—Mrs. W——, aged forty-six; English. Admission to the City Hospital, February 24, 1891. Large ulcerated inoperable cancer of left breast, which involves both inner quadrants. Disease present for two years. Left breast is about three or four times larger than the right healthy one, and hangs down three inches lower. Nipple retracted and ulcerated. In inner, upper quadrant a large deep ulceration with thick everted borders; in left axilla and in the pectoral region a great number of small, cancerous, cutaneous nodules of various sizes. Superficial cancerous sore in left axilla. No œdema of left arm as yet.

February 28th.—Parenchymatous injection of pyoktanin solution, 1 to 300 (1 drachm), into both lower quadrants under the ulceration. Needle entered at different points and was gradually pushed forward from the healthy surrounding tissues. In the afternoon patient felt chilly and rather uncomfortable, complained of dizziness and a burning sensation over a certain portion of scalp. No

¹ April 21st, when correcting proof: Wound without secretion, closing, cicatrizing. Still some infiltration at inner end of former scar, also near the axillary cavity. Growth checked in its spreading. No parenchymatous injection since March 17th.

rise of temperature. Ulceration powdered with pyoktanin in substance.

March 2d.—General condition good. Discharge of ulcer less offensive. Injection of 2 drachms of pyoktanin solution at different spots.

March 3d.—No dizziness at this time after yesterday's injections. One capsule of pyoktanin, $1\frac{2}{3}$ grain, taken internally, thrown up within two hours. At the same time patient's bowels move quite freely.

March 4th.—Evening temperature, $101\frac{2}{3}^{\circ}$ F.; no appetite; patient feels uneasy; capsules discontinued.

March 5th.—Three small cutaneous nodules in upper, outer quadrant injected; turned blue soon after; surface, when touched with a needle, was found to be anæsthetic; local anæsthesia confined to the bluish surface only, lasted over half an hour; extirpation of one nodule (for microscopical examination) thirty minutes after injection, was pronounced to be painless. Wound stitched with catgut and painted with pyoktanin collodion, three per cent.; parenchymatous injection into growth, 1 drachm.

March 6th.—Pyoktanin, $1\frac{2}{3}$ grain, given internally as before, again badly borne; patient vomits and feels very weak; temperature, 103° F.

March 7th.—The nodules injected two days ago are noticeably smaller and less infiltrated; they were, with a number of others, reinjected, as also was the large tumor. Total amount, $1\frac{1}{4}$ drachm. A cyst, which had formed under the ulcer, was aspirated; it contained unstained blood.

March 9th.—The small nodules, mentioned before, considerably smaller and softer, but still perceptible. Parenchymatous injection of $1\frac{1}{2}$ drachm into tumor and nodules.

March 11th.—Injected with same amount.

March 12th.—Patient dizzy and faint; no appetite; vomiting.

March 20th.—Tumor much softer, and in both inner quadrants markedly smaller. The often-mentioned hard

nodule in inner upper quadrant has softened somewhat, but is still hard at its base. It was injected with 20 minims pyoktanin solution, 1 to 200; the larger growth with 1 drachm of same strength.

March 22d.—Since last injection stomach irritable; food frequently vomited; the skin, especially on the inner side of the tumor, is wrinkled; the formerly raised and everted edges of ulcer have flattened, and are much softer than before; the powdered pyoktanin on the ulcer always forms a dry eschar, which can be removed with the forceps, and is evidently necrosed tissue. On removing the eschar a dyed surface appears, which bleeds slightly; no discharge, but still some smell; below the ulcer two new perforations have formed.

March 25th.—Small nodule in the inner upper quadrant has broken down, giving exit to the thick, bluish-dyed fluid; on pressure, a small mass of necrosed bluish tissue appears, and is easily extracted with the forceps. The surrounding shell still hard, but less so than before.¹

In reviewing these four histories and also considering my experience with pyoktanin as well as ethyl pyoktanin in my private patients, I should like to state the following facts in regard to the treatment of inoperable malignant growths with these aniline dyes, as far as they have been exhibited up to date (April 8th):

1. The aniline dyes, applied on the surface of exulcerated growths in ointment or powder (about 1 to 200), or in substance, have a strong analgesic effect.²

2. Parenchymatous injections of pyoktanin solution, 1 to 300, repeated every second day till fifth day, the dose not exceeding one and one-half drachm, have in my cases proved to be innocuous to the general system.³

¹ April 21st: The last mentioned spot nearly closed; no infiltrated shell. Whole growth greatly reduced in size ($\frac{1}{2}$ to $\frac{1}{8}$); no spread.

² I have seen the same effect in other painful sores, as ulcer of leg, and especially in fissura ani.

³ The injections have to be made under careful antiseptic precautions. The only necessary instrument is a well-working tapping-

3. The symptoms following the injections are either general or local.

The general symptoms, which can also follow the internal use of methyl-blue (as recommended for inoperable malignant neoplasms by Dr. Max Einhorn of this city),¹ are nausea or vomiting, weak and slow pulse, headaches, general malaise. These symptoms may come on the same day or the day following the injection; as a rule, they do not come at all; now and then there is a slight rise of temperature, usually subsiding within twenty-four to forty-eight hours.

The local symptoms are :

a. Pain following the injection. It may be of long or short duration, slight or severe. It is more severe where the cancerous infiltration affected by the injection is dense (epithelioma of face, disseminated cancer of breast, etc.). It seems that local anæsthesia may follow the injection.

b. Œdema, coming on either acutely, and then accompanied with slight redness (non-inflammatory) and pain on pressure, or rather in a subacute form. This serous transudation of the growth may be the first step to reabsorption. The slight fever, observed in a number of patients, soon following the injection, had then to be looked at as being an aseptic one, possibly due to this reabsorption.

syringe, which holds two drachms, with long and short needles. The needle must be boiled before use and then kept in alcohol. The skin of the area where the injection is going to be made must be cleansed with ether. The solution must be kept in a dark bottle, otherwise it is decomposed; 0.6 per cent. solution of chloride of soda should be used instead of water.

¹ Methyl-blue was first used internally by Ehrlich (Ueber schmerzstillende Wirkung des Methylen-blau, Deutsche Med. Wochenschr., 1880, No. 23). Lang saw good effect of its internal administration in cases of cystitis and pyelitis (Wiener klin. Wochenschr., 1891, No. 6, p. 112). Methodical internal application of methyl-blue as a help in hopeless cancer cases was first tried and recommended by Drs. J. Rudisch and M. Einhorn, of this city (New York MEDICAL RECORD, March 21, 1891, Correspondence). The proper maximum dose pro die seems to be about five grains. It is best given in capsules, each containing $1\frac{1}{8}$ gr.

c. Breaking down of the injected tissue, with perforation of the skin or scar, which latter is the result of the operation (aseptic necrosis). By using a stronger solution, 1 to 200, the necrobiosis seems to be more rapid in smaller nodules. How far the surrounding infiltrated shell which is left behind is apt to spread farther can only be determined by continuous observation. It may be advisable to use a weaker solution, 1 to 500, instead of 1 to 300, as we can thus dye a larger portion of the growth in one sitting, without increasing the dose of pyoktanin. We then inject a larger quantity of solution and still need not apprehend general symptoms. Perhaps the weaker solution will not destroy the tissue so rapidly and thus rather induce reabsorption than necrosis. The sinus or sinuses established by the breaking down of the tissues give exit to a thick, dark-blue fluid, which, by microscopical examination, proves to be not colored pus, but débris of the injected neoplasm. It is generally intermingled with shreds of necrosed tissue. In splitting these sinuses one may find necrosed, deeply dyed, ramified tissue, surrounded by normal undyed fat and muscles,¹ which is easily shelled out. Whether it will be necessary and possible to remove the necrosed tissue by operation or whether this tissue will be extruded by means of a slow disintegration and longer secretion cannot yet be determined. We also have to prove yet, whether operative interference in this stage will really benefit our patients. Perhaps nature gets slowly rid of the necrosed tissue without help. As it seems, the carcinoma tends more to necrobiosis and perforation during this treatment than the sarcoma. I personally could so far only subject cancer cases to the color cure. (V. Mosetig had his most striking results in patients suffering from sarcoma (see above).

¹ This observation coincides with the remark of Stilling, that a normal, living cell will retain the fluid only for a short while (it is well known that the fat-cells are never stained by aniline) getting rid of it by rapid diffusion. Only diseased or dead cells will retain the dye permanently.

He maintains that the injections, made under antiseptic precautions into neoplasms, which are still covered by healthy skin, produce necrobiosis and fatty degeneration, which is not followed by perforation, but by reabsorption.¹ Billroth, on the other hand, saw rapid softening and perforation in two out of three patients who suffered from sarcoma and were treated with the injections.)²

d. Breaking down of the injected tissue (necrobiosis) with subsequent reabsorption (Cf. 3). This will probably be oftener seen, if we stop the injections for some time as soon as spots in the growth have softened, and only start them again after these spots have shrunk (provided, of course, that they did not perforate). Small, hard nodules in the skin, as seen especially in the disseminated cancer (recurring cancer of breast), can entirely disappear in a very few days, even if the pyoktanin solution was injected into their base.³ Perhaps the rapid disappearance is not reabsorption but only an illusion, which is caused by the œdema of the immediate surrounding tissue. A number of the nodules reappear after a few weeks, sometimes rather multiplied. The attempt at dyeing these small nodules directly, by pushing the needle right into them, is frequently unsuccessful, even in regard to the microscopical appearance, and causes severe pain.⁴

4. An infiltration of hitherto healthy tissue with the neoplasm, in consequence of this treatment, has not been observed in a single case.

5. In no case did the growth spread during the treatment.

¹ Wiener klin. Wochenschr. 1891, No. 12, p. 224. ² Ibid., p. 236.

³ Confer v. Moseitig, Wiener klin. Wochenschr., 1891, No. 6, p. 102.

⁴ Microscopical examination found the cells and nuclei of the new growth, small or large, unstained (Riehl). To explain this v. Moseitig advanced a special and interesting hypothesis (see above). It must, however, be stated in regard to the examination made by Riehl, that the neoplasm from which the specimen was taken had been injected only once. Perhaps another result had been obtained, were the injections repeatedly made into the same spot before extirpation.

6. Applications of pyoktanin in substance on exulcerated tumors slowly removes the diseased tissue in the shape of dry gangrene. There is no suppuration under the eschar, on account of the strong antiseptic qualities of the dye, and consequently no cachexia. Pyoktanin is, however, no deodorizer. It also is no stypticum.

7. It may be advisable to combine the parenchymatous injections and local application of pyoktanin with giving aniline dyes internally. Pyoktanin is, in my cases at least, not borne by the stomach. Methyl-blue seems at present to be the most preferable.

8. If it could be proved by further observations that continued injections determine the necrobiosis of "all" the diseased tissue, the use of the aniline dyes, especially pyoktanin in its different ways of application and methyl-blue, will have a permanent place in operative surgery, no matter how much time the cure demands, no matter whether it is accompanied by pain, inconvenience, and dangers to the patient.¹

It might then be advisable in patients who can still stand some loss of blood to remove as much of the new growth as can be reached with the knife or cautery, and then to inject. The size of the consequent granulating surface, as long as it is only healthy, would be immaterial. Skin-grafting would determine cicatrization.

9. If, on the other hand, continuous observations should demonstrate that necrobiosis with perforation or with

¹ Proper care can do away with or avoid a great deal of the latter. The pains after injections into densely infiltrated spots may, I hope, be overcome by paying special attention that the dye is properly distributed through the growth. A larger amount of fluid deposited in one spot must of course greatly increase the local intra-parenchymatous pressure and immediate pains. It will also produce rapid local necrobiosis. The addition of a few drops of a five per cent. solution of cocaine to the fluid, where it is to be injected into infiltrated spots, did also help to reduce the pain. By keeping one's self with the amount inside of proper limits ($\frac{1}{2}$ grain) no poisonous effect need be feared from the use of this salt. A careful antiseptic management of the case will fight all dangers possibly arising from the presence of an open wound.

fatty degeneration and reabsorption does only affect a portion of the neoplasm, and diseased tissue is left behind in spite of a long and careful treatment, we will certainly do much better not to begin any such treatment at all, at least not as long as the tumor is still covered by healthy skin. Billroth¹ has already emphasized this fact.

10. But suppose, that future observations should really demonstrate that the aniline dyes do not specifically attack carcinoma and sarcoma, as Billroth seems to apprehend, their administration will nevertheless be of great value to the poor hopeless patients. We will be able, by using them, to check the "exulcerated" growth from further spreading and thus lengthen life for some time at least; we will prevent cachexia; we will alleviate the sometimes so excruciating pains in such cases of ulcerating neoplasms where neither morphine nor cocaine can bring any benefit.

¹ Loc. cit.

