diffuse, usually precedes the other signs. Lewis (1936) has pointed out that this pain does not arise in the artery at the site of the obstruction but much lower in the limb in the muscles deprived suddenly thereby of their blood supply, and that its onset even when abrupt is delayed. It is relative in severity to the size of the occluded artery only because a greater territory of tissue is rendered ischaemic, and it is relieved instantly when the blood supply is restored by removal of the clot, or it is reduced in degree if the plug passes on. Thus embolism of the brain or spleen is painless, because those organs contain no muscle. There is no evidence that arterial spasm alone directly produces pain.

The clinical associations of embolic catastrophes are well illustrated by the following case.

A man aged 38, who eight years previously was found to have mitral stenosis, developed auricular fibrillation and at the same time a sudden (painless) right hemiplegia due to cerebral embolus. Two years later his digitalis was inadvertently stopped for a while and his heart began to race. Ten days after redigitalization he woke with a violent pain in the hemiplegic leg and the foot went cold. The agony of his pain lasted twenty-four hours and was relieved only by hanging the foot down. From 4 in. (10 cm.) below the knee his leg was found to be cyanosed, oedematous, and icy cold. The diagnosis of popliteal embolus was made and he was treated conservatively. Within ten months he could walk unaided for 200 yards without pain, but four months later he suffered another stroke and died.

Tragic examples of this nature are only too common where embolic incidents have accompanied the onset of fibrillation or have followed mistakes in treatment. Because the pulse rate is slow or the symptoms have abated, digitalis maintenance therapy is stopped; the insidious acceleration of the ventricular rate which ensues is fraught with dangerous consequences. Such accidents would happen less often if we always remembered to warn each patient with auricular fibrillation that digitalis was his life-line, to be depended upon perpetually for the rest of his days.

Conclusions

In those circulatory conditions where a prevailing symptom is extrathoracic pain (in the head, limbs, or body) the degenerative arterial disorders play an important part with their attendant thrombotic and embolic incidents. Hence the symptom of extrathoracic pain in cardiovascular disease for the most part is rare in childhood, unusual in youth, but commoner as age advances. The pain usually conforms to some distinctive clinical picture. Examples are considered in this paper with the object of promoting familiarity with their qualities.

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VIOFORM IN THE TREATMENT OF SKIN DISEASES

BY

I. MARTIN-SCOTT, M.D.

The quinoline derivative known as "vioform" (5-chloro-7-iodo-8-hydroxyquinoline) is a stable, almost odourless, greyish-yellow powder which is only slightly soluble in water. It contains 41% iodine and 12% chlorine, and its use in the treatment of amoebiasis is world-wide (Cameron, 1947). For several decades it has been used as an antiseptic dusting powder and as the active ingredient of Alexander's ointment on the Continent (Perutz *et al.*, 1933). Only within recent years has its value in dermatology been appreciated in America (Wise and Sulzberger, 1942; Sulzberger and Wolf, 1942; Pillsbury *et al.*, 1943), and the external therapeutic uses were recorded by the American Medical Association in 1944. In Great Britain its value in dermatology has not yet been estimated.

Early in 1948 I obtained a small quantity of vioform powder and, in a 3% strength in a water-miscible cream, found it to be most useful in the treatment of pyococcal skin infections. The importing chemists then kindly offered to manufacture two types of preparation for trial, and a clinical investigation was started in June, 1948.*

Preparations Used.—Guided by the experience of Sulzberger and Baer (1946), it was decided to use only the following two preparations: (1) vioform cream (V.C.), which consists of 3% vioform in a water-soluble base composed of sodium lauryl, stearyl alcohol, spermaceti, glycerin, yellow soft paraffin, and water; (2) vioform ointment (V.O.), consisting of 3% vioform in a simple petroleum-jelly base.

Selection of Cases.—The majority of the cases were treated as out-patients. The greater number and variety of such cases outweighed the uncertainty of proper application by the patient. Patients of any age or sex were treated, but in view of the limited supplies of vioform no cases of widespread dermatoses were included. With the knowledge that other hydroxyquinoline ointments were useful in the management of pyodermias, it is not surprising that many cases of this type were chosen.

Control of Results.—It was considered that the number of cases would be too small to compare this remedy against a standard topical treatment by the method of treating alternate cases suffering from the same skin disease. Likewise, the better method of comparing the results of two similarly affected and symmetrically situated lesions in the one person treated by two different methods was thought impracticable in dealing with out-patients. Where it is considered to be of interest, however, reference will be made to previous treatments which had failed.

Classification of Cases.—A total of 115 consecutive cases of various skin diseases were treated. These have been grouped thus:

Group A	..	Sycosis barbae	..	..	15 cases
" B	..	Folliculitis of other areas	..	..	17 "
" C	..	Impetigo contagiosa	..	..	14 "
" D	..	Acne vulgaris	..	..	10 "
" E	..	Impetiginized eczema	..	..	14 "
" F	..	Post-auricular dermatitis	..	..	10 "
" G	..	Miscellaneous group	..	..	35 "

Where more than one type of infection was present the case was listed under the more prominent condition.

*I am indebted to Messrs. Ciba Laboratories, Ltd., Horsham, Sussex, for kindly supplying the applications used in this study.

Results of Treatment

Group A. Sycosis Barbae

The patients were instructed to use V.C. for shaving, and to leave a film on the face thereafter. A second application was advised at midday, and V.O. was used at bedtime. They were told that this was a treatment under trial, and all promised to report any relapse which might occur.

TABLE I

Case No.	Duration of Disease	Type and Severity	Previous Treatment	Bacteriology	Treatment Time Using Vioform	Follow-up
6	7 months	Average	Pen., Hg	—	3 weeks	Relapse 3 mths. later
8	12 years	"	Quin.	—	4 "	No relapse
11	6 "	Superficial	Pen., Hg	—	3 "	2 mths. later
16	2 "	Average	Pen.	Pen.-sensit. S.P.A.	6 "	No relapse
18	2 weeks	Superficial	Pen., Hg	Pen.-sensit. S.P.A.	3 "	3 mths. later
33	4 "	"	Pen. cream	S.P.A.	1 week	No relapse
37	3 years	Deep-seated	Pen., Quin., X rays	Staph. albus	12 weeks	3 mths. later
39	3 "	"	Pen., Hg, Sulpha., Quin.	S.P.A.++	8 "	Improving
41	2 weeks	Superficial	Pen., Hg, Sulpha., Quin.	Pen.-sensit. S.P.A.++	1 week	No relapse
44	2 "	"	Quin., Sulpha.	—	1 "	1 mth. later
74	15 months	Deep-seated	Pen., Hg	S.P.A.+	6 weeks	No relapse reported
84	6 weeks	Superficial	Pen. ung. and cream	Pen.-sensit. S.P.A.	2 "	Improved
89	18 months	Average	Pen. cream, Hg	—	1 week	No relapse
90	5 years	"	Pen., Quin., X rays, Vaccine	—	2 weeks	6 mths. later
93	2 weeks	Superficial	Not known	—	2 "	No relapse

Hg = A mercury ointment. Pen. = Penicillin preparation. Sulpha. = Sulphonamide cream. Quin. = Ung. Quinolol Co. S.P.A. = *Staphylococcus pyogenes aureus*.

Table I shows that 13 out of the 15 cases had no signs of active disease after treatment with vioform alone. Only two of these 13 cases had slight relapses, which quickly responded to further treatment. The average treatment time of the 11 cases which were apparently cured after one course was three weeks, and the average duration of the disease before treatment was over 2½ years.

With such a short follow-up period it cannot be claimed that 87% of the cases were "cured." It will be noted that four of the cases failed to report back after apparent cure. These cases may be considered to have remained free from symptoms for the following reasons: (1) three of them had suffered for several years and had been "cured" in a few weeks; (2) vioform preparations could not be renewed without further consultation and were not yet on sale to the public; and (3) three of the cases lived in a country district served by one local hospital.

The only two failures were Cases 37 and 74. The former patient volunteered that it was "easily the best stuff" he had used in his three years of treatment. In both cases the lesions were indurated and deep-seated, and the pus was caseous. Case 74 was eventually cleared up by cauterizing the four remaining pustules with pure phenol, and Case 37 is at present having fractional doses of x rays in conjunction with vioform treatment.

It is of interest to note that twelve of these cases had previously been treated unsuccessfully with local penicillin, and that in four of these the causative staphylococcus was found to be penicillin-sensitive.

Table II shows that all 17 cases responded well to treatment. The average duration of treatment was just under three weeks, but this includes two cases which required six weeks; these two cases were infections of the forearms

Group B: Folliculitis of Other Areas

TABLE II

Case No.	Site	Duration of Disease	Previous Treatment	Vioform Prep. Used	Bacteriology	Time to Cure
2	Hand	3 weeks	Pen. cream	V.O.	—	10 days
14	Legs	3 months	Sulpha., Pen.	V.O.	Pen.-sensit. S.P.A.	4 weeks
24	Thighs	Few days	Nil	V.O.	S.P.A.	10 days
36	Pubis	2 weeks	G.V.	V.O.	S.P.A.	7 "
38	"	4 "	Hg	V.O.	S.P.A. and Str. haem. C	7 "
40	Arms	4 "	Pen. syst. and local	V.C.	S.P.A.++	2 weeks
45	Scalp	18 months	Quin., G.V., Hg	V.C.	Sterile	4 "
55	Pubis	6 weeks	Pen. ung.	V.C.	S.P.A.	3 "
77	Arms, neck, Groin	8 days	Nil	V.O.	S.P.A.	Relapse 3 mths. later
86	"	4 months	Not known	V.O.	—	6 weeks
94	Pubis, axillae	5 years	Pen. syst. and local	V.O.	S.P.A.++	2 "
97	Back	8 months	Hg	V.O.	Pen.-resist. Sterile (2)	4 "
101	Forearms	4 weeks	Pen. syst. and local	V.O.	Pen.-sensit. S.P.A.+	Improved 2 weeks
105	Nape of neck	2 "	Hg, AgNO ₃ , B.G., Pen.	V.C.	—	6 "
110	Temples	2 months	Hg	V.C., V.O.	Pen.-sensit. S.P.A.	7 days
111	Groin	5 "	Hg, Pen.	V.O.	—	2 weeks
114	"	2 "	Pen. local	V.O.	—	4 "

Pen. = Penicillin preparation. AgNO₃ = Silver nitrate lotion 1%. Hg = A mercury preparation. G.V. = 1% Gentian violet lotion. S.P.A. = *Staph. pyogenes aureus*. B.G. = 1% Brilliant green. Str. haem. C = *Str. haemolyticus* Group C.

in manual workers, and it was thought that the mode of application was unsatisfactory: both cleared up quickly when V.O. was applied under a "viscopaste" bandage. All patients continued their normal activities whilst under treatment.

Group C: Impetigo Contagiosa

TABLE III

Case No.	Site	Duration of Disease	Previous Treatment	Vioform Prep. Used	Bacteriology	Time to Cure
24	Nose	4 months	Pen., Hg, Quin.	V.C.	S.P.A.	1 week
64	Ears, face	1 month	Pen. cream	V.C.	Pen.-resist. S.P.A.	2 weeks
73	"	5 days	"	V.C.	—	3 "
79	Pubis	9 months	Pen. local	V.C.	Pen.-sensit. Str. haem. C	4 "
85	Scalp	8 weeks	Not known	V.C.	S.P.A.	2 "
92	Ears	3 "	"	V.C.	—	1 week
96	Face	3 months	"	V.C.	Sterile	1 "
98	"	2 weeks	Pen. cream	V.C.	Pen.-sensit. S.P.A.++	1 "
99	Ears, face	4 months	Pen., Sulpha., Quin.	V.C.	Pen.-sensit. S.P.A.	1 "
100	Scalp	4 "	Not known	V.O.	—	2 weeks
102	Neck, ears	6 weeks	Pen., Resorcin	V.C., V.O.	Pen.-sensit. S.P.A.	2 "
103	Face	3 "	Pen.	V.C.	Pen.-sensit. S.P.A.++	1 week
107	Face, neck	2 "	Sulpha., Ung. S. & S.	V.C.	Pen.-sensit. S.P.A.	1 "
109	Temples	4 "	Pen. local	V.C.	Pen.-resist. S.P.A.	2 weeks

Pen. = Penicillin preparation. S.P.A. = *Staph. pyogenes aureus*. Sulpha. = Sulphonamide cream. Str. haem. C = *Str. haemolyticus* Group C. Quin. = Ung. Quinolol Co. Ung. S. & S. = Ung. sulphur and salicylic acid B.P.

The results in all cases were good, and no relapses have been reported (Table III). In no case was any additional application used to remove infected crusts. Six cases in which the organism cultured was reported to be penicillin-sensitive failed to respond to local penicillin therapy. In many cases the patients claimed to be cured in two to three days, and the duration shown in Table III was the time interval till the patient was actually seen to be cured. Even with this possible overestimation the average treatment time for all types was only 10 days.

Group D: Acne Vulgaris

Ten cases of pustular acne were treated, and only five showed some slight improvement after four weeks of V.C.

twice daily. The results were not impressive, as it must be remembered that, while vioform was the only local application, the patients were advised regarding general hygiene and diet, and in several cases oestrogens and/or vitamins were given simultaneously.

I formerly used "ung. quinolor co." (Squibb) in cases of pustular acne with decidedly better results, possibly due to the benzoyl peroxide content in this preparation.

Group E: Impetiginized Eczema

There were 14 cases of eczema (mostly exogenous) which had become secondarily infected, and all presented crusted discoid lesions. In two-thirds of the cases the hands and fingers were affected. The more exudative cases were treated with V.C. thrice daily, while the other half applied V.O. twice daily. In the four cases investigated *Staph. pyogenes aureus* was cultured. The average duration of treatment was just over two weeks, and during this time the patient was sheltering the affected area from external irritants. The underlying eczema was cured in only two cases, but in all cases the crusting and inflammation subsided satisfactorily.

Group F: Post-auricular Dermatitis

TABLE IV

Case No.	Sex	Age	Duration of Disease	Previous Treatment	Bacteriology	Prep. Used	Time to Effect Cure
28	F	44	6 weeks	G.V., Pen.	S.P.A., Str. haem. A.	V.C.	2 weeks
51	F	41	4 years	Hg, Pen., AgNO ₃	—	V.O.	2 "
49	M	30	Not known	AgNO ₃ , Pen., Ung. S. & S.	S.P.A. + +	V.O.	3 "
52	F	72	1 year	Ung. S. & S.	S.P.A. + +	V.O.	2 "
53	F	68	8 months	Ung. S. & S.	S.P.A. + +	V.O.	1 week
59	M	37	5 weeks	Lot. calamin.	—	V.O.	2 weeks
61	F	24	2 years	Pen. syst. and local	—	V.O.	10 days
67	F	50	3 months	Not known	—	V.O.	6 weeks
71	F	32	3 weeks	Hg	S.P.A.	V.O.	1 week
117	M	45	2 months	Ung. S. & S.	Str. haem.	V.O.	1 "

Pen. = Penicillin preparation. S.P.A. = *Staph. pyogenes aureus*. Str. haem. A. = *Str. haemolyticus* Group A. Hg = A mercury preparation. AgNO₃ = Silver nitrate lotion 1%. G.V. = Gentian violet lotion. Ung. S. & S. = Ung. sulphur and salicylic acid B.P.

Every case had associated seborrhoeic eczema, and two had menopausal symptoms. Clinically the skin behind the ears was found to be reddened, glazed, and often exuding serum. The response to treatment was very good, and the average treatment time was just over two weeks. No relapses have been reported (Table IV).

Group G: Miscellaneous

This group comprises a miscellaneous collection of dermatoses which are often rather resistant to treatment. There were 35 such cases.

Angular Stomatitis.—Four of the five cases treated with V.C. twice daily cleared up after an average treatment time of 10 days; no other therapy was given simultaneously. In two of the cases there was associated naso-labial fissuring, which also responded well. The one failure is discussed later when dealing with toxicity.

Intertrigo.—There were five cases, which occurred in elderly patients. Clinically they did not suggest a fungous infection. The apposing skin surfaces were red and denuded, and in the midline there was often some superficial fissuring. Three of the five cases were considerably improved after four weeks' treatment with V.O.

Furunculosis.—Three of the four cases had suffered from recurrent boils for many years. In all four the septic conditions were cured within two weeks, but fresh boils occurred in two. These cases were found to have high fasting-blood-sugar levels, and when suitably dieted had no further furunculosis.

Chronic Paronychia.—Two of the four cases treated showed the typical chronic bolstering of the nail-folds, with dystrophy

of the nails but no purulent discharge. Staphylococci were cultured in both cases, and after four weeks' treatment they showed considerable improvement. The other two cases had purulent lesions of the nail-folds from which *Staph. pyogenes aureus* was cultured; there were no whitlows. Both cleared up after applying V.O. for an average treatment time of three weeks, though they had been resistant to local penicillin treatment.

Septic Excoriations.—Two cases of generalized pruritus and one of excoriated acne were treated. V.O. cleared up the crusted lesions in a short time but did not lessen the pruritus.

Chronic Lichen Simplex.—Two cases of localized lichenified skin without any associated infection were not improved by the use of V.O., nor was the irritation lessened.

Pruritus Ani.—One case, in which no changes in the skin could be seen, failed to be relieved after four weeks on V.O.

Pustular Psoriasis.—Three cases of the toxic bacteride type, with small intra-epidermic lakes of pus and light-brown punctate scabs affecting the soles and palms, were not improved after several weeks' local treatment with V.O.

Pustular Epidermophytosis.—Two cases of secondarily infected epidermophytosis interdigitalis in which *Staph. pyogenes aureus* was cultured from the pus, but in which there was no acute pain or lymphangitis, were treated. All evidence of sepsis had gone when seen 14 days later.

Ulcers.—Two simple chronic ulcers of obscure origin, one of the chin and one of the thigh, were slightly improved after dressings with V.O. twice daily.

Acne Necrotica.—One case showed improvement after treatment with V.O., but was not cured.

Furfuraceous Impetigo.—One case of four years' duration showed no significant improvement after four weeks' treatment on V.O.

Herpes Zoster.—This patient was an elderly man who was feeble and had a large crusted plaque over the frontal region. *Staph. pyogenes aureus* was cultured. He was treated with V.C. thrice daily, and within one week all evidence of infection had gone.

Pemphigus Vulgaris.—In one case V.O. was found to be a useful antiseptic dressing which assisted the healing of the raw areas after rupture of the bullae.

Mode of Action; Toxicity

Animal experiments in the past (Ciba, Ltd., 1948) and also the following observation on a patient have failed to support the theory that the disinfecting action of vioform is due to the liberation of free iodine. A patient who had a severe contact dermatitis due to tincture of iodine and who reacted with an extensive vesicular eruption to painting 1 sq. in. (6.45 cm.²) of her arm with liquor iodi mitis had no reaction after 48 hours' contact with 3% V.O.

About 5% of the patients treated admitted that there was a mild initial stinging of short duration, but in none of these cases was treatment discontinued.

In only one of the 115 cases was there severe primary irritation when V.O. was applied to the diseased skin. This patient was a nervous man who had had a long history of sycosis barbae, and his clinical record indicated that he was sensitive to sulphathiazole and "elastoplast." He reported with a slight angular stomatitis and erythema, scaling, and fissuring of the naso-labial folds. He was advised to apply V.O. twice daily to the affected areas, and when he reported two weeks later the condition was unchanged and he complained of intense irritation on each application of the ointment—he had stopped using it after only ten days. V.C. was applied in the consulting-room and he complained of irritation, though no inflammation was noted after 40 minutes. A patch test of V.O. applied to the healthy skin of the arm was negative after 48 hours. This is similar to the case of irritation reported by Reque (1947) in which true epidermal sensitivity was also absent. It seems probable that in my case the irritation was due to the vioform and not to the

paraffin base, as he subsequently improved on ung. hydrarg. ammon. dil.

Saunders (1946), who used vioform 1% in petrolatum in a mixed series of 14 cases, did not attempt any further study of the medication, because the incidence of irritation was too high and the beneficial results too poor.

No systemic toxic effects due to absorption from the skin were encountered. In view of the internal use of "enterovioform," this was not surprising.

Comment

In a study of a comparatively small number of cases in which the results of treatment were not controlled it is not possible to evaluate the efficiency of vioform scientifically. The clinical impression, however, in the management of several dermatological problems was extremely good. The ability to confront the chronic case of sycosis barbae and persistent post-auricular dermatitis without foreboding signifies at least the possession of a therapeutic agent of prowess. A safe and relatively non-irritant antiseptic or antibiotic is always welcome in dermatology; thus penicillin became the practitioner's friend. Later many pyococci were found to be resistant to it. It is probable that since the introduction of penicillin the number of skin infections referred to hospital has diminished—e.g., no cases of impetigo of children's faces have been seen in the last six months for inclusion in this series. No doubt the proportion of penicillin-resistant cases seen in hospital has increased. Whether vioform is superior to penicillin in the treatment of pyoderms cannot be assessed from this report, but it is a fact that in at least 37 cases in which penicillin had failed vioform produced the desired result. In the 16 cases in which penicillin sensitivity was estimated four were resistant and 12 were sensitive to penicillin. In 11 of these 12 cases penicillin had previously been used and had failed to improve the skin infection.

Summary and Conclusions

The value of 3% vioform in an ointment and in a cream base has been studied in 115 dermatological cases.

The results indicate that vioform is a valuable therapeutic agent in dermatological practice, and particularly in the treatment of pyococcal skin infections such as impetigo, folliculitis (especially sycosis barbae), impetiginized eczema, angular stomatitis, and post-auricular dermatitis. The cases of acne vulgaris in this series were not greatly improved.

It is relatively non-irritating, and the occurrence of epidermal sensitization is rare.

While it relieves the prickling of infected eczemas, it does not seem to have any antipruritic effect on non-infected dermatoses.

The only slight disadvantage revealed was the yellowish-grey colour. The cream is easily washed out of cotton fabrics, but stains from the use of the ointment are more difficult to remove.

Further study is required to estimate its value in other vehicles in dermatology, and also in other branches of medicine where antiseptic applications are required.

It is concluded that 3% vioform is a valuable addition to the medicaments at present used in this country for pyococcal dermatoses.

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THE TOPICAL USE OF VIOFORM IN DERMATOLOGY

BY

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The present investigations have been prompted by the shadow of Nemesis which now looms on the dermatological horizon, threatening retribution, in the forms of drug sensitization and drug-resistant organisms, for the indiscriminate topical use of sulphonamides and antibiotics. A spate of literature has indicated that drug sensitization may follow the external application of sulphonamides (*Army Med. Dept. Bull.*, 1943; Barber, 1944; MacKenna, 1945; Phillips, 1946; Tzanck *et al.*, 1947; Council on Pharmacy and Chemistry, 1947) and penicillin (Canizares, 1945; Friedlaender *et al.*, 1946; Chu and Cutting, 1946; O'Donovan and Klorfajn, 1946; Goldman *et al.*, 1946; Hellier, 1947; Templeton *et al.*, 1947; Phillips, 1948) and so seriously interfere with their later use in lethal disorders. Drug resistance, a sequel of sulphonamide therapy and the use of many antibiotics, has been shown by Barber (1947) and Barber and Rozwadowska-Dowzenko (1948) to occur when penicillin is used; their work foreshadows many more strains of penicillin-resistant *Staphylococcus aureus*.

My attention was directed by the work of Ingram (1938) and of Sulzberger and Wolf (1942) to an entirely different group of drugs—namely, the halogen-substituted quinolines. An attempt has been made to assess whether these drugs may be used to replace the sulphonamides and penicillin in external applications so that the aforementioned undesirable sequel may be avoided. The two members of this group under investigation are "vioform" and "sterosan." This paper deals with the former drug only.

Quinoline derivatives have been used for topical application in dermatology for a number of years. "Ung. quinolor co." (Squibb) contains a mixture of 5-chlor-8-hydroxyquinoline, 7-chlor-8-hydroxyquinoline, 5:7-dichlor-8-hydroxyquinoline, together with 10% of benzoyl peroxide in a paraffin-lanolin base. It is useful in the treatment of sycosis barbae, impetigo contagiosa, eczematized psoriasis, and psoriasiform or lichenoid neurodermite (Peck, 1934; Carpenter, 1938; Ingram, 1938).

Vioform has the chemical formula: 5-chloro-7-iodo-8-hydroxyquinoline.

It is an amorphous, greyish-yellow, voluminous powder containing 41% of combined iodine. Tasteless and colourless, it is insoluble in water and only slightly soluble in alcohol. It has a melting-point of 156° C. and can be sterilized at 100–110° C. Light and moisture cause a darkening in its colour. Oxidizing agents are chemically incompatible.