

The investigation of quindoxin photosensitivity

S. ZAYNOUN, B. E. JOHNSON AND W. FRAIN-BELL

Department of Dermatology, University of Dundee, Dundee, Scotland

Quindoxin (quinoxaline di-N-oxide) is a photosensitizer capable of producing photocontact dermatitis. The study of a group of seven affected subjects has provided evidence of persistent light reaction and "photoallergy", most probably to the parent substance and not to any photoproduct or contaminant. Clinical and photobiological similarities to the photosensitivity dermatitis and actinic reticuloid syndrome were demonstrated.

Key words: Persistent light reaction – photo allergy – quindoxin photocontact sensitivity.

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In 1971 quinoxaline di-N-oxide (quindoxin) was marketed as a growth promoting factor and added to pig feed (Fig. 1, A and B). In 1972 Dawson & Scott reported having seen cases of photocontact dermatitis in agricultural workers exposed to a feeding mixture containing this substance and in whom they demonstrated positive photopatch test reactions to a 1 % concentration. Two years later they described their findings in a total of 17 cases (Scott & Dawson 1974). Sporadic similar cases have been seen throughout the U.K. during the period 1974-75. We have had the opportunity to study seven examples of this quindoxin-induced photosensitivity in whom a degree of light sensitivity reaction had developed and persisted for varying periods of time, after the pig feed had been removed from the market in the autumn of 1973.

The study was planned so as to observe the natural history of the persistent light reaction in each subject and the changes which occurred in the action spectrum with the passage of time and to associate this with responses of the skin on photopatch

testing to quindoxin; and lastly to determine whether the skin response could be attributed to specific photodegradation products of quindoxin.

Materials and Methods

The affected subjects (five male and two female) were agricultural workers, all of whom had been involved at one time or other with the feeding or day-to-day care of pigs. In each subject a series of routine biochemical and haematological tests were done, including estimations of porphyrin levels in blood, urine, and faeces.

The *action spectrum* was determined on the skin of the back using an irradiation monochromator; the technique was previously described by Mackenzie & Frain-Bell (1973).

Photopatch testing was carried out using a range of concentrations (0.5, 0.1, 0.05 and 0.01 %) of quindoxin in soft paraffin or where specifically mentioned in aqueous solution which were applied to the skin of the back and irradiated 24 h later with long

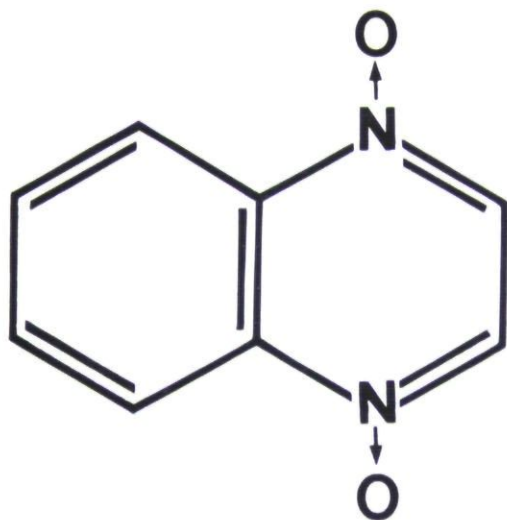


Fig. 1A. Structural formula of quinoxin (quinoxaline di-N-oxide).

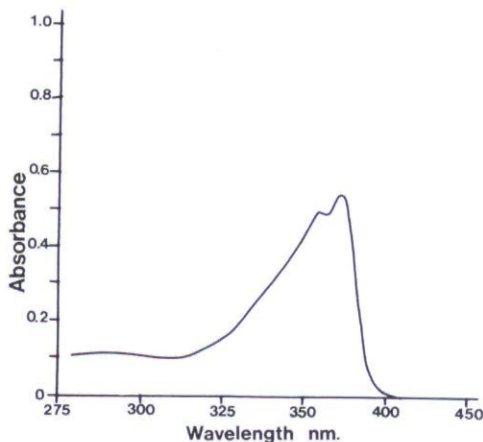


Fig. 1B. Ultraviolet absorption spectrum of quinoxin; 0.5 mg % (3.2 μ mol %) in barbitone buffered saline, pH 7.2.

wavelength ultraviolet radiation (long UVR) using a black light source (Philips, F20T, 12 BLB, fluorescent tube) with an emission spectrum ranging from 300 to 400 nm, peaking at 355 nm. A glass filter was used to screen off wavelengths < 320 nm. The amount of irradiation used was that of a previously determined sub-erythema dose

for each patient. Non-irradiated control patch tests were applied and read at 48 h. Similar patch and photopatch tests were carried out in subjects 2, 3, 4 and 5, using quinoxin which had previously been exposed to long UVR.

In cases 6 and 7 photoproducts of quinoxin were also used for patch and photopatch testing on normal and "stripped" skin. Purified photoproducts used were identified as 2-quinoxalinol-4-oxide (II), 2,3-dioxoquinoxaline (III), and 2-oxoquinoxaline (IV) as 0.1 % solutions or suspensions in water and PMF, and three freshly prepared chromatogram fractions from irradiated quinoxin. To obtain the latter, a 1 % solution of quinoxaline di-N-oxide (I) (quinoxin) in barbitone buffered saline, pH 7.4, was irradiated using a black light fluorescent tube for 3 h, total incident dose approximately 2400mJcm². A total of 0.1 ml each of irradiated and non-irradiated control solutions was subjected to thin-layer chromatography using Silica gel 60[®], precoated sheets (Merck) and ascending development with chloroform:methanol, 90:10. Under Wood's light illumination, three photoproducts were observed; these were marked and the silica containing them was scraped from the backing and suspended in 0.01 ml water for application. In addition, quinoxaline, mono-N-oxide (V), a contaminant of quinoxin present in different batches in amounts varying generally from 0.1 to 1 % and never more than 2 %, was used in patch and photopatch tests as 0.1 % solution in water and in PMF.

Lymphocyte transformation tests were performed in subjects 1, 3, 4, 5, 6 and 7, using a technique already described (Hutchinson et al. 1972, Raffle et al. 1975).

Results

Case 1 - H.B.

This 63-year-old male farm worker, a pa-

Table 1. Duration of the photocontact dermatitis in each case

Case No.	Name	Sex	Age	Duration of photocontact dermatitis	
				Onset	Cleared by
1	H.B.	M	63	July 1972	1976 (still affected)
2	L.D.	M	65	February 1972	1976
3	W.G.	M	62	August 1971	1976 (still affected)
4	N.L.	M	45	May 1972	1974 (still affected)
5	C.W.	M	54	Summer 1972	1975 (still affected)
6	M.A.	F	54	May 1973	December 1973
7	S.R.	F	55	November 1972	May 1974

tient of Dr. Adrian Ive of Newcastle, when first seen in July 1974 gave a history of not having suffered from any skin condition, nor had any member of his family prior to July 1972, at which time he developed an acute dermatitis of the exposed skin (face, scalp, ears, side and back of neck, forearms, and backs of hands). During the winter of 1973, the dermatitis improved although it did not entirely clear, becoming acute in the spring of 1973 and persisting throughout the summer, at which time the diagnosis of photosensitivity dermatitis was first made. Since then the dermatitis has persisted with spring and summer aggravation, but with a tendency towards slow, progressive improvement.

The contact with the feeding mixture preceded the eruption in 1972 by 3 months, though it was no longer being added to the

pig feed after the autumn of 1973, traces of the material presumably could have persisted for some time. He continued to work on a farm until April 1975, then retired on account of ill health. At the time of the first action spectrum studies in July 1974, he was found to have a mild dermatitis with a moderate degree of lichenification of the skin of the backs of hands and forearms and the back of the neck. When he was seen again in March 1975 for repeat action spectrum studies, there was a minimal dermatitis of the skin of the face and neck with chronic lichenified dermatitis of the elbows; the skin was otherwise clear. During an investigation in the spring of 1975, a relapse occurred on exposed skin sites in association with the positive reactions of the back skin to quindoxin patch and photopatch testing and to the irradiation as part of the action spectrum determination. He replied to a letter sent to him in February 1976 to say that since he was last seen in the spring of 1975, the dermatitis had improved but was persisting to some extent in the forearms.

When first investigated in July 1974, he showed an abnormal erythema action spectrum extending into the long wavelength ultraviolet. The threshold dose levels were below normal and abnormal papular reactions were obtained with both short and long wavelength ultraviolet (Table 2). When

Table 2. Action spectrum involved in the persistent light reaction

Case No.	Wavelengths		
	290-320 nm	300-400 nm	> 400 nm
1	+	+	+
2	+	-	-
3	+	+	-
4	+	-	-
5	+	-	-
6	-	-	-
7	-	-	-

Table 3. Results of patch and photopatch tests using A) quindoxin and B) pre-irradiated quindoxin

Case No.	A) Quindoxin		B) Pre-irradiated quindoxin	
	Photo-patch test	Patch test	Photo-patch test	Patch test
1	+ ve	- ve	N.D.	N.D.
2	+ ve	- ve	+ ve	- ve
3	+ ve	- ve	- ve	- ve
4	+ ve	- ve	+ ve	- ve
5	+ ve	- ve	+ ve	- ve
6	+ ve	- ve	N.D.	N.D.
7	+ ve	- ve	N.D.	N.D.

N.D. = Not Done.

these investigations were repeated in the spring of 1975, the action spectrum for both erythema and the papular reaction had spread into the visible as far as wavelength peak 430 nm (bandwidth, 400-460 nm).

On patch and photopatch testing to quindoxin using a range of concentrations and doses of irradiation, he demonstrated on both occasions (1974 and 1975) marked sensitivity, in that positive responses were produced with concentrations down to 0.01 % quindoxin and 1 min of black light irradiation (35-40 mJcm²). The closed patch test was negative (Table 3).

Case 2 - L.D.

This 65-year-old farmer, a patient of Dr. John Lyon of Ipswich, had not suffered from any skin condition prior to February 1972, at which time he developed fissuring and cracking of the skin of the tips of the fingers, soon to be followed by a dermatitis which affected the backs of the hands and forearms, later involving the skin of the face and becoming worse during the summer of 1972, continuing on through the winter of 1972 and throughout 1973, with some summertime aggravation, virtually clearing in the early spring of 1974, only to relapse

later. On examination in July 1974, he was found to have a lichenified dermatitis of the backs of hands and forearms, otherwise, the skin was clear. He replied to a letter sent to him in February 1976 to report a slight relapse in the summer of 1975; he had remained clear since then.

In July 1972, action spectrum studies showed abnormally high sensitivity to wavelengths between 290 and 320 nm (Table 2). Positive photopatch test reactions were obtained to quindoxin, down to a concentration of 0.01 % and a long UV irradiation dose of 1 min (35-40 mJcm²). In addition, there was a positive photopatch but a negative closed patch test reaction to quindoxin after the chemical had been irradiated for 30 min with black light, prior to application to the skin. Most probably some parent quindoxin was still present in the suspension used, which would account for this positive photopatch test reaction (Table 3).

Case 3 - W.G.

This 62-year-old lorry driver was a patient of Dr. Desmond Burrows of Belfast. He had been employed for a number of years delivering animal feeding stuffs to farms. Since 1957 he had suffered from an eruption during the months of sunshine which affected the exposed skin of the backs of the hands, the rim of the ears and round the neck and on the face. In 1971, he developed for the first time cracking and fissuring of the skin of the hands, which continued on into the winter of 1973, necessitating fairly long periods off work. Since November 1973 the dermatitis of the hands improved but he has continued to suffer from the original photosensitivity dermatitis response which had affected him since 1957. In November 1973 he changed his job from that of a lorry driver to a security officer, although remaining with the same firm. Examination of his skin in February 1975 showed the presence of a lichenified derma-

titis of the skin of the face, sides of the neck, ears, and backs of hands. In response to a letter in February 1976, he said that the dermatitis since last seen in February 1975 had continued to trouble him through 1975, with a significant improvement since using titanium dioxide-containing light-screening preparation.

In 1975 an abnormal action spectrum was demonstrated involving the short and long UV wavelengths (Table 2). In addition, a positive photopatch test to quindoxin was obtained, as well as a negative closed patch test and a negative photopatch and closed patch test to quindoxin which had been previously irradiated prior to application to the skin (Table 3).

This man would appear to have had an idiopathic photosensitivity dermatitis since 1957 and then developed a "photoallergic" reaction to quindoxin (1971) which altered the pattern of the response of the skin.

Case 4 - N.L.

This 45-year-old man, a patient of Dr. Desmond Burrows of Belfast, worked as a store keeper in a meal and animal foodstuff production firm, and prior to the summer of 1972 had not suffered from any skin condition, at which time however he developed an eruption on exposed skin (face, rim of the ears, scalp, and backs of hands). This eruption continued to trouble him so that he stopped work in November 1972. He returned to work with an electrical firm in May 1973. Throughout the summer of 1973 the dermatitis continued to trouble him but to a lesser extent. By the summer of 1974 he was able to go out in the sunshine, although he did get a mild relapse on the skin of the face and backs of the hands, suggesting that some degree of light sensitivity remained. Examination of the skin in February 1975 showed no evidence of dermatitis of exposed skin sites, although he was found to have a lichenified dermatitis of the dor-

sum and sides of the feet. He did not reply to a letter sent to him in February 1976.

In February 1975, action spectrum studies showed minimal abnormal increased sensitivity to wavelengths between 290 and 320 nm (Table 2). The photopatch test to quindoxin in a concentration reduced to 0.01 % was positive using an irradiation dose of long UV of only 2 min (70-80 mJcm²) (Fig. 2). In addition, a positive photopatch test reaction to quindoxin which had been irradiated with UV prior to application to the skin was obtained, most probably as in cases 2 and 5 due to some residual parent quindoxin being present; but closed patch tests to quindoxin, both with and without prior irradiation of the chemical, were negative (Table 3).

Case 5 - C.W.

This 54-year-old lorry driver, a patient of Dr. Desmond Burrows of Belfast, worked with an animal meal firm and had been employed for many years loading and delivering animal feed to farms round the country. He had not previously suffered from any skin condition until the summer of 1972, at which time he developed an acute reaction of the exposed skin of the face, neck, rims of the ears, and backs of hands. This continued to trouble him with lessening severity on into the winter of 1972, at which time he stopped work for approximately 6 months, and by the time the summer of 1973 arrived, he was still experiencing trouble on the exposed skin but to a less extent and involving mainly the face and the back of the hands. Since that time the condition has slowly improved, and during the summer of 1974, although he did develop minimal reactions of exposed skin on exposure to sunshine, this was probably slight. On returning to work in the summer of 1973, he changed his job and was no longer involved with animal feed or other agricultural pursuits. In reply to a letter

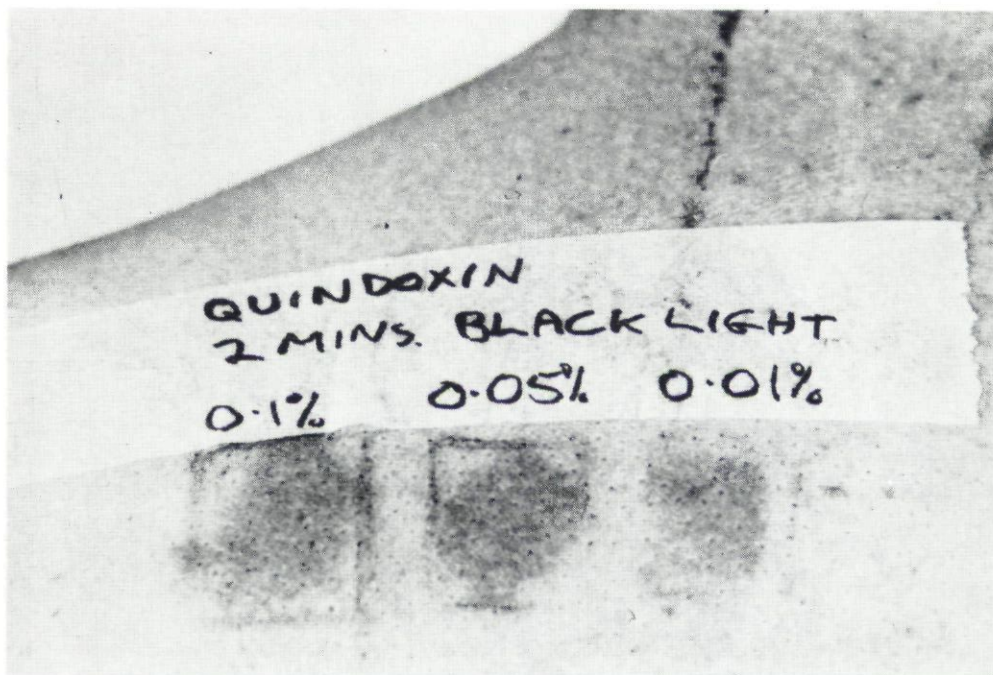


Fig. 2. Positive photopatch test reactions obtained.

written to him in February 1976, he mentioned that the skin of his hands and face had reacted to sunshine on occasions during the summer of 1975.

In February 1975, action spectrum studies showed minimal abnormal increased sensitivity to wavelengths between 290 and 320 nm (Table 2). However, on photopatch testing, a positive photopatch test to quindoxin was demonstrated in a concentration of 0.01 % and an irradiation dose of 2 min of long UV (70-80 mJcm²); the closed patch test was negative. Also a positive photopatch test reaction to quindoxin which had been previously irradiated with long UV was obtained, the closed patch test being negative (Table 3).

Case 6 - M. A.

This 54-year-old lady, a patient of Dr. Desmond Burrows of Belfast, had been breed-

ing and caring for pigs for a number of years, which entailed preparing and giving them their daily meal. She had not suffered from any skin condition prior to May 1973 at which time she developed a dermatitis on the skin of the backs of the hands and forearms with later swelling of the skin round the eyes, but otherwise no affection of the skin elsewhere. This skin reaction continued to trouble her with variable degrees of severity until December 1973 at which time it cleared and has not relapsed since. She has continued to look after the pigs.

The results of action spectrum studies in October 1975 showed a normal action spectrum for erythema (Table 2). However, a positive photopatch test reaction was demonstrated to small amounts of quindoxin down to a concentration of 0.01 % and an irradiation dose of only 1 min of long UV (35-40 mJcm²) (Table 3). In addition, a po-

Table 4. Results of patch and photopatch tests to chromatogram fractions (A) purified photo-products (B) impurity compound (C) quindoxin

Case No.	Chromatogram fractions (A)			Photoproduct (B)			Impurity (C)
	1	2	3	II	III	IV	V
6	- ve	- ve	- ve	- ve	- ve	- ve	+ ve
7	- ve	- ve	- ve	- ve	- ve	- ve	+ ve

sitive photopatch test reaction to compound V was obtained, although tests to all the other three purified photodegradation products and to the chromatogram fractions were negative (Table 4). The closed patch tests to quindoxin and the various fractions were also negative.

Case 7 - S.R.

This 55-year-old lady, a patient of Dr. Desmond Burrows of Belfast, looked after pigs. Prior to November 1972 she had not suffered from any skin condition at which time, however, she developed a reaction of the skin of the backs of the hands and forearms, spreading after a month or two to involve the skin of the face and the ears, the sides of the neck and the exposed 'V' of the neck. The condition continued to trouble her up until approximately May 1974 since when she has been virtually free of any skin reaction. In December 1974 she sold her pigs and became a traffic warden. Examination of the skin in September 1975 showed no abnormality. She did not reply to a letter written to her in February 1976.

On phototesting in 1975, a normal action spectrum for erythema was found (Table 2). However a positive photopatch test reaction was demonstrated to quindoxin down to a concentration of 0.01 % and with an irradiation dose of only 1 min of long UV (35-40 mJcm²) (Table 3). In addition, a positive photopatch test reaction was obtained to compound V, although negative to all the other four purified photodegradation pro-

duct fractions and to the chromatogram fraction (Table 4). The closed patch tests to quindoxin and the various fractions were negative.

Reference to Table 1 will show the duration of the photosensitivity dermatitis. Five of the subjects first developed the condition in 1972 (Nos. 1, 2, 4, 5, and 6), case 3 being a year earlier in 1971, and case 6 a year later in the summer of 1973. Cases 2, 6, and 7, eventually cleared after a duration varying from a minimum of 6 months (case 6) to a maximum of 4 years (case 2). However, cases 1, 3, 4 and 5 are still experiencing episodes of exposed skin site dermatitis particularly in the summer time, that is, up to 4 years after the onset of the photosensitivity reaction. Cases 4 and 5 were still affected after 2 and 3 years respectively, although the progress of case 4 in the summer of 1975 is not known, since he did not reply to the letter sent to him in February 1976. However, in no subjects except for case 3, who had suffered from photosensitivity dermatitis of persistent light reaction type since 1957, was any residual photosensitivity response severe.

Table 2 shows the responsible wavelengths involved in the persistent light reaction in each subject and it can be seen that in only case 3 (290-400 nm) and case 1 (290-> 400 nm) was photosensitivity demonstrated outside the short UV wavelengths (290-320 nm). In cases 6 and 7 the action spectrum was normal. Case 1, in whom the action spectrum was found to in-

volve wavelengths throughout the short and long UV and into the visible as well, demonstrated this involvement on two separate occasions (July 1974 and March 1975).

Table 3 shows the results of photopatch testing in which positive photopatch tests were obtained in all seven cases mainly with grade 3 (erythema and oedema) or grade 4 (+ vesicles) responses, even with concentrations as low as 0.01 % quinoxaline dioxide and the minute amounts of irradiation of 1 min of long UVR (35-40 mJcm²). All the closed patch tests were negative, showing that there was no evidence of abnormal skin test reactions in the absence of light, that is, a true photocontact response. Two additional subjects, one a 39-year-old male control and the other a 50-year-old male farmer with idiopathic photosensitivity dermatitis, gave negative photopatch test and closed patch test reactions to 1 % quinoxaline dioxide. The photosensitivity reaction in the seven subjects is therefore presumably not of phototoxic type.

Unfortunately, it was not possible to carry out tests with the three purified photoproduct compounds (II, II and IV) and the impurity compound (V), and the three chromatogram fractions except in the last two subjects, cases 6 and 7. In each instance positive photopatch test reactions were obtained with the impurity compound V only, these being negative with the closed patch tests (see Table 4).

Preliminary studies of these patients' lymphocyte transformation responses to long UV irradiated and non-irradiated quindoxin and to the three photoproducts, using a technique previously reported for investigations of chlorpromazine photosensitivity (Raffle et al. 1975) produced equivocal results. However, the experimental conditions required for successful studies of lymphocyte transformation vary for each and every compound used, especially where a photosensitivity element is present, and further

investigations of irradiation conditions and supposed antigen concentration are required before cell-mediated immunological mechanisms are incriminated, or excluded from consideration, in this form of photosensitivity reaction.

Discussion

There seems little doubt that quindoxin is capable of producing in certain predisposed individuals a state of continuing persistent light reaction responses of the skin for variable periods of time after contact with the responsible substance has been avoided; and that the potential to respond to contact with the chemical also continues, as demonstrated by positive photopatch test responses on skin testing, long after apparent clinical cure.

There would also appear to be a number of common clinical and photobiological features in this group of subjects with quindoxin photosensitivity and cases of the so-called idiopathic photosensitivity dermatitis and actinic reticuloid syndrome (Ive et al. 1969, Frain-Bell et al. 1974).

Burckhardt (1941) suggested that photosensitivity responses to sulphonamide resulted from an allergic reaction to a photoproduct of the drug. A similar mechanism for photosensitivity reactions to related sulphonamides was proposed by Schwarz & Speck (1957) and by Burckhardt & Schwarz-Speck (1957). This concept was brought forward by Willis & Kligman (1968) to explain the photosensitivity reactions to tetrachlorosalicylanilide (T₄CS): in their view the sole action of light was to change the parent compound into a potent allergen.

In all seven quindoxin-sensitive subjects a positive photopatch test was obtained with relatively minute amounts of quinoxaline dioxide (0.01 %) and low doses of long UVR (35-40 mJcm²), whereas in two control subjects negative photopatch tests were

obtained using 1 % of the chemical and 1000-1200 mJcm² long UVR. This would suggest a "photoallergic" response and not a phototoxic one. Also, in every case the closed patch test was negative and therefore there was no evidence of cell-mediated allergic sensitivity in the absence of exposure to light. Except for case 1, in which the results had to be discarded because of technical problems, the remaining six subjects failed to show any evidence on patch testing of positive reactions to quindoxin which had previously been exposed to long UVR. If the response of the skin in tetrachlorsalicylanilide and sulphonamide photosensitivity is in fact due to an allergic reaction to a photoproduct, this could not be the explanation in these quindoxin-sensitive subjects.

Quinoxaline di-N-oxide (I) is very sensitive to long wavelength UVR. The major photoproduct is 2-quinoxaline-4-oxide (II) and in chronological order this is the first compound produced; it is photolabile but only slightly. It is not clear whether the other photoproducts, 2,3-dioxoquinoxaline (III) and 2-oxoquinoxaline (IV) result from photochemical reactions of II or are direct products of the parent substance I.

Quinoxaline mono-N-oxide (V), a contaminant, is present in very low concentrations with the quindoxin, at most 2 %. However, in the two cases (6 and 7) in whom it was possible to patch and photopatch test to this contaminant (V) using a concentration of 0.1 %, a positive photopatch test consisting of erythema and oedema (grade 3) was obtained. With an 0.01 % solution of quindoxin, however, where grade 4 vesicular reactions were obtained on photopatch testing, we have calculated that there would be something in the region of only 0.0001 % of the contaminant. It is very unlikely therefore that the contaminant was the sole or main reason for the photosensitivity response, rather than the parent quindoxin.

Thus, the results obtained with both patch

and photopatch tests with the three chromatogram fractions and the purified photoproducts (II, III, and IV) either on normal or stripped skin are consistently negative. If therefore the photosensitivity reaction to quindoxin did represent an immunological reaction to an allergen formed simply by a photochemical reaction of the parent compound, a positive closed patch test result in one of these could be expected, and this we did not demonstrate. Similarly if the photosensitivity reaction resulted from a photochemical reaction of one of the photoproducts (II, III, and IV) rather than the parent quindoxin itself, a positive photopatch test result would have been expected and once again we failed to demonstrate such positive responses.

Recently Calnan (1975) has reported a case of contact dermatitis to quindoxin in which a positive closed patch test was demonstrated, indicating a routine cell-mediated allergic response occurring without the element of light.

The investigation of this small group of subjects has therefore demonstrated the ability of the chemical quindoxin to produce photocontact dermatitis followed by persistent light reaction and a state of "photoallergy", with similarities both clinical and photobiological to the photosensitivity dermatitis and actinic reticuloid syndrome.

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and help in investigating this problem of chemical-induced photosensitivity.

Postscript

Since this paper was completed, an opportunity arose to study an eighth case of quindoxin photosensitivity (patient of Dr. Burrows) which was that of a 50-year-old farmer's wife with a mild degree of persistent light reaction dating from 1971, with an abnormal erythema action spectrum involving the short and long UV wavelengths up to and including 400 nm peak (bandwidth 370-430 nm), and with photopatch test evidence of sensitivity to the chemical. This case was interesting in that it showed that the continuing abnormal action spectrum which had been demonstrated only in the five male cases could also occur in the female.

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Address:

Dr. S. Zaynoun
Department of Dermatology
University of Dundee
Dundee
Scotland

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