NIFURATEL IN URINARY INFECTIONS

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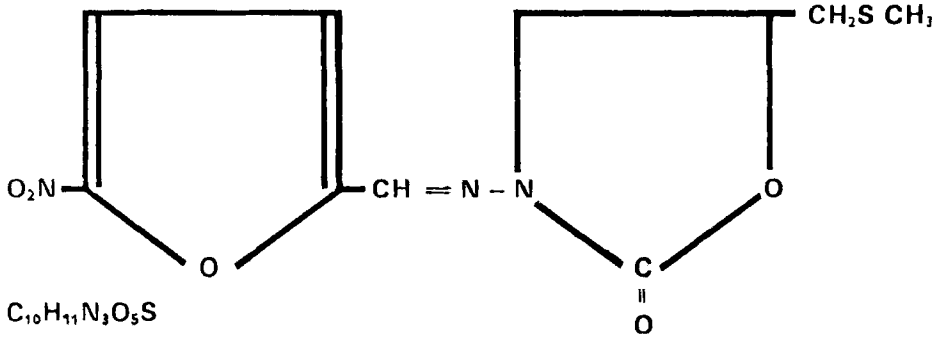
NIFURATEL (Magmilor—Calmic) is a new furan derivative with antibacterial properties. The chemical name is N-(5-nitro-2 Furfurylidene)-3-Amino-5-Methylmercaptomethyl-2-Oxazolidinone and has the structural formula shown below.



$C_{10}H_{11}N_3O_5S$

It has an antibacterial spectrum somewhat similar to that of nitrofurantoin and is more effective against Gram-negative than Gram-positive organisms. It is also very active against Candida and Trichomonas.

This compound has been in use on the Continent under the trade names of Methylmercadone and Macmiror since 1965. It has been used mainly in the treatment of vaginal discharge and vulvovaginitis due to pathogenic micro-organisms, including bacteria, Trichomonas and Candida (Sagone, 1965; Sarnella, 1966). It has been available for this purpose in the United Kingdom from 1968 (Murphy, 1968). Male partners have also been successfully cleared with oral therapy. Nifuratel has also been successful in the treatment of non-gonococcal urethritis in males (Longhi, 1967).

Cosciani-Cunico (1965), Coppi and Bertagnolli (1965) and Lotti (1968) in Italy have carried out clinical trials in urinary infections. The present paper describes a preliminary trial of this compound in the Mansfield hospitals. The results of treatment in 90 patients with acute or chronic urinary infection are assessed.

Metabolic and Physiological Data.—Nifuratel is one of the furan derivatives which are known to inhibit a variety of Gram-positive and Gram-negative organisms. The mechanism of the antibacterial action of these derivatives is unknown, but it is presumed that the compounds interfere with the enzymatic processes essential to bacterial growth. Bacteria develop only a limited resistance, and cross-resistance between these compounds and sulphonamides or antibiotics does not occur. The active principle of nifuratel is a breakdown product in the urine.

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In the recommended dosage, sufficient nifuratel is absorbed from the gastro-intestinal tract to give plasma levels capable of exerting a systemic trichomonacidal activity (plasma levels sufficient to exert a bactericidal and trichomonacidal activity are represented by fractions of a mcg./ml.). Nifuratel is excreted in the urine as a metabolite which has no trichomonacidal activity, but is still active as a bactericide.

Determination of blood, urine and genital tissue levels from homogenised uterus, tubes and vagina has been carried out in the rat after an oral dose of 50 mg./kg. and the following results were obtained:

Urinary levels	30 to 50 mcg./ml.
Plasma levels	1 to 2·5 mcg./ml.
Genital tissue levels	0·8 to 3·6 mcg./ml.

The plasma of rats treated orally with 100 mg./kg. of nifuratel possesses a trichomonacidal activity at a dilution to 1:4 to 1:10 in serum yeast extract media.

TABLE I

In vitro Antibacterial Activity of Nifuratel and Nitrofurantoin

Strains	M.I.C. (mcg./ml.)			
	Nifuratel		Nitrofurantoin	
	Average	Range	Average	Range
Esch. coli (27 varieties) .	10·1	1·6–50	20	5–50
Klebsiella (5 varieties) .	25	13·5–50	25	12·5–50
Proteus (5 varieties) .	75	25–100	75	25–100
Ps. aeruginosa (3 varieties)	83	50–100	83	50–100
Staph. aureus (14 varieties)	6	2·5–12·5	15	5–25
Shigella (9 varieties) .	7	3·1–25	15	5–25
Str. pyogenes (4 varieties)	10	1–25	5	0·25–10
Str. fæcalis (6 varieties) .	45	10–100	50	10–100

Teratology.—Teratogenicity tests have been carried out on three different species of animals and in three different European countries.

The tests have been carried out in the United Kingdom on pregnant mice, rats and rabbits and the results have been accepted as satisfactory by the Committee on Safety of Drugs. In addition to tests carried out in the United Kingdom, similar tests have been carried out in Italy and France.

The animals were divided into negative (untreated) control groups, groups treated with nifuratel, and positive control groups treated with thalidomide. The groups treated with nifuratel were further subdivided and dosage was administered at varying levels.

These animal experiments produced no malformations which could be attributed to nifuratel although characteristic malformations of the fœtus were observed in the thalidomide-treated group. It was concluded that nifuratel does not present any teratogenic hazards in these species.

In addition to laboratory tests, there have been clinical trials in Italy, France, Switzerland and Spain where the drug has been available since 1965. In all, 6,500 cases of vaginitis were treated. Candela and Romano (1968) found no teratogenic effect in 232 pregnant patients, confirming the experiences of other workers. However, as a routine precaution, it is recommended that treatment with nifuratel should be limited to the use of vaginal pessaries during the first 12 weeks of pregnancy.

Antibacterial Activity in vitro.—The antibacterial activity of nifuratel *in vitro* is summarised in Table I (Imperato, 1963; Scuri and Failla, 1964). It compares very favourably with that of nitrofurantoin for the more common urinary organisms. However, its activity is slightly reduced against *Streptococcus pyogenes* and increased against Shigellas and Salmonellas.

CLINICAL TRIAL

Methods.—*Collection.*—Mid-stream specimens of urine were collected from both sexes except when a specimen was taken from an indwelling catheter or at the time of cystoscopy. The urine was refrigerated and cultured within an hour of arrival in the laboratory. Mid-stream urines were also collected at the end of 14 days treatment and again 14 days after completion of the course.

Sensitivities.—A simple disc technique was used to assess sensitivity to nifuratel, using discs impregnated with 200 mg. of nitrofurantoin. This was necessary since nifuratel is not sufficiently soluble to diffuse into the agar plate in the time required.

TABLE II

Diagnosis in 84 Patients in the Chronic Group
(Patients receiving 16·8 g. course in brackets)

Recurrent pyelocystitis	26 (9)
Bladder neck obstruction	11 (2)
Post-prostatectomy	10 (6)
Renal stones	10 (3)
Carcinoma of bladder	6 (3)
Indwelling catheter	4
Incontinence due to cerebrovascular causes	4
Multiple disseminated sclerosis	4 (2)
Hydronephrosis	4 (1)
Prolapse	2 (2)
Urethral caruncle	1
Renal cyst	1 (1)
Urethral stricture	1 (1)

Dosage.—In the first part of the trial, involving 57 patients, a loading dose of 400 mg. (2 tablets) three times a day for 4 days was followed by a reduced dosage of 200 mg. (1 tablet) four times a day for 10 days, giving a total of 12·8 g. nifuratel over 14 days. In the second part 33 patients were given the loading dose of 400 mg. three times a day for the whole 14 days, a total of 16·8 g. nifuratel.

Classification.—Patients were divided into two main groups of acute and chronic urinary infections. There were 90 patients in all, with 6 acute and 84 chronic infections. The acute group had not been previously treated with antibacterial agents, while the chronic group had received previous treatment, but none with nifuratel. The chronic group was further subdivided into a recurrent group of patients who had responded to previous treatment, and a second group of patients whose manifestations, due to some underlying cause, persisted in spite of treatment. A few patients had mixed infections in which some organisms were resistant. Otherwise, only patients with sensitive organisms were treated, including the acute group where treatment had been started before sensitivities were known. All the patients had bacteriological evidence of infection, with over 10 leucocytes per high-power field, and a positive culture, and most of them had relevant symptoms. In the second part of the trial bacterial counts were done on the urine, a count of over 100,000 per ml. being required before an infection was diagnosed. Patients with acute clinical evidence of infection, but without pyuria and bacteriuria, were excluded from the trial, but it was noticed that their symptoms were often relieved after the treatment.

In this preliminary trial cure was defined as a sterile urine at 28 days, *i.e.* 14 days after the completion of the course of the drug.

The diagnoses in the 84 chronic patients are summarised in Table II. The largest group (26) in both parts of the trial is of recurrent pyelocystitis. Unrelieved bladder-neck obstruction (11), early post-prostatectomy convalescence and renal stones (10 each) follow. Over half the post-prostatectomy group were in the second part of the trial. Carcinoma of the bladder (6) and an indwelling catheter, hydronephrosis, multiple sclerosis and senile incontinence follow (4 each). The great majority of the patients were from urological wards, but some were from geriatric and young chronic sick wards, and a few from other departments.

Overall Results.—At the end of the 14-day course 61 of the 90 (68 per cent.) patients had sterile urine, but 15 had relapsed 14 days later. Seven of those who relapsed had had the 16·8 g. course, but in all of these the underlying cause had persisted. At 28 days, 46 of the 90 (51 per cent.) patients remained cured.

Results in the Acute Group.—This small group of six patients with acute pyelocystitis were all cured with the 14-day course of the drug, both clinically and bacteriologically. There were three females and three males, one of the females being a 9-year-old child, who received half the adult dose of nifuratel. The organisms involved were three *Escherichia coli*, two Proteus species and one Klebsiella species.

TABLE III

Species of 73 Organisms in 54 Patients with Chronic Urinary Infections who had the 12·8 g. Course

	Whole Group		Persistent Underlying Cause	
	Total	Cures	Total	Cures
Coliform group . .	32	22	10	7
Proteus species . .	15	4	9	1
Klebsiella group . .	3	1	1	0
Str. fæcalis . . .	17	6	7	1
Ps. aeruginosa . .	3	2	1	1
Staph. pyogenes . .	3	1	1	0
Total . . .	73	36	29	10

Results in the Chronic Group receiving 12·8 g.—All these 54 patients (21 male and 33 female) had previous antibacterial treatment. Symptoms were relieved in nearly all patients, but in only 25 of the 54 was there bacteriological evidence of cure. Table III shows the infecting organisms. The distribution is approximately the same in both chronic groups except for relatively more Proteus in the 29 patients with a persistent underlying cause—only one of the nine Proteus, one of the seven *Streptococcus fæcalis*. None of the five mixed infections in this group was cured, compared with five out of 14 mixed infections in the group without an underlying cause.

Results in the Chronic Group receiving the Full Course of 16·8 g.—In this smaller group of 30 chronic patients (Table IV), there were 17 males and 13 females. Again symptoms were relieved, and in 15 of the 30 patients there was bacteriological evidence of cure. Although this group is small these results suggest that the full course of 16·8 g. may be preferable, particularly

TABLE IV

Species of 33 Organisms in 30 Patients with Chronic Urinary Infections who had the 16·8 g. Course

	Total	Cures
E. coli	14	10
Proteus species	3	1
K. aerogenes	10	4
Str. fæcalis	4	1
Staph. aureus	2	1
Total	33	17

TABLE V

Analysis of 53 Bacteriological Failures of Treatment in 112 Organisms in 90 Patients

	12·8 g. Course	16·8 g. Course
Persistent sensitive organism	13	14
Persistent partially sensitive organism	4	1
Same organism becoming resistant	1	..
Replaced by other sensitive organism	6	1
Persistent insensitive organism (mixed infection)	6	1
Replaced by other insensitive organism	5	1
Total	35	18

as some underlying cause was considered to persist in all but three. These three were *E. coli* infections. There was a relatively large number of Klebsiella infections in post-prostatectomy patients in early convalescence. The three patients with mixed infections and underlying causes were not cured.

Analysis of Failures.—Fifty-nine (53 per cent.) of the 112 infecting organisms in 90 patients were eradicated; the reasons for failure in the remaining 53 are shown in Table V. The 27 persistent sensitive organisms were largely in the group of patients with an underlying cause.

Only one organism appeared to become resistant, an *E. coli*, but five appeared to become partially resistant. It is, of course, impossible to state with certainty that the resistant and partially resistant organisms were not due to re-infection. Only one of these, a Proteus, was in a patient having the 16·8 g. course. The other four (two Klebsiella, one *E. coli* and one Proteus) were in patients having the 12·8 g. course. Of the 23 organisms in mixed infections, 10 were resistant to begin with, but three of these were eradicated.

DISCUSSION

Range of Activity in vitro.—Nifuratel is active *in vitro* against fungi, Candida and Trichomonas. Its trichomonacidal activity *in vitro* is five to six times greater than that of metronidazole.

The *in vitro* activity of nifuratel in liquid medium has almost always been proved to be as high as that of nitrofurantoin except against *Str. pyogenes* (Table I). In the present trial, nitrofurantoin had to be used as a basis for *in vitro* disc sensitivities because of the sparing solubility of nifuratel and its poor diffusion on agar plates. *In vitro* studies of nitrofurantoin have already been done by Mintzer *et al.* (1953), Stewart and Rowe (1956) and many others since. There is no evidence yet of the development of cross resistance to nifuratel after treatment with nitrofurantoin.

Lotti (1968) compared minimum M.I.C.'s of nifuratel and nalidixic acid and found nifuratel almost as effective against *E. coli* and Klebsiella, less so against Proteus, but more effective against Pseudomonas, *Str. fæcalis* and Staphylococcus.

Nitrofurantoin is a valuable drug in spite of some resistant hospital strains. The most recent Mansfield Group Laboratory figures (Macis and Ward-McQuaid, 1968) show 98 per cent. of *E. coli* and coliforms to be sensitive to both nitrofurantoin and nalidixic acid and 95 per cent. to ampicillin. Eighty per cent. of Proteus organisms are sensitive to nalidixic acid, 60·5 per cent. to ampicillin, and 55 per cent. to nitrofurantoin, while 84 per cent. of Klebsiellas are sensitive to nalidixic acid and 75 per cent. to nitrofurantoin. There has been an increasing proportion of Proteus organisms in hospital so that our Coli/Proteus ratio is now less than 2:1. These two organisms account for 82 per cent. of our Gram-negative organisms. Walkey *et al.* (1967) in geriatric practice found Proteus infections to be the most common in the male, but *E. coli* most common in the female. In infections arising in general practice, however, Robertson (1968) found five *E. coli* to one Proteus, these two organisms accounting for over 90 per cent. of the infections. Ninety-nine per cent. of these *E. coli* and Proteus organisms were sensitive to nalidixic acid, 96 per cent. to ampicillin and 95 per cent. to nitrofurantoin. Most *Str. fæcalis* are also sensitive to both nitrofurantoin and ampicillin.

Side-effects.—Of the 90 patients in the trial, seven thought the nifuratel had upset them. Four complained of nausea, two of breathlessness, and one of weakness. (An eighth patient developed a mild rash and pruritus which was not considered of significance because it cleared up in spite of continued treatment.)

On direct questioning, a further four thought they might possibly have been upset by the drug—two complained of nausea and two of breathlessness.

The prolongation of the increased loading dose for the whole two weeks' course seemed well tolerated. Two of the 35 patients are included in the four who complained of nausea.

Dosage.—In the first part of this trial of nifuratel in urinary infections, the loading dose was 400 mg. three times a day for four days, followed by 200 mg. four times a day for 10 days, a total of 12·8 g. This was a similar schedule to that used by Coppi and Bertagnolli (1965) and Cosciani-Cunico (1965), their courses varying between 7 and 15 days. Lotti (1968) gave 400 mg. three times a day for between 5 and 20 days, and we followed this routine for the second part of this trial, a total of 16·8 g. in two weeks. Longhi (1967) used a similar dose for non-specific urethritis.

A larger dose was not used routinely for Proteus infections although an increased dosage of nitrofurantoin (up to 10 mg./kg.) is recommended for these infections. When the infection is chronic, a prolonged course of at least a month is suggested and a reduction of the dose for the second half. Both these points may well apply to nifuratel, but in the first part of this trial neither was the dosage increased nor was the course prolonged in either part of the trial. It seems reasonable to increase the dose in Proteus, Klebsiella and *Str. fæcalis* infections.

No attempt was made to alter the urine reaction, although nitrofurantoin theoretically works better in acid urine, as a lower *p*H tends to concentrate it in the urine (Woodruff *et al.*, 1961). Nor were special precautions taken with fluid intake. Washing out of bacteria by increased fluid intake is probably more important than drug concentration by fluid restriction (O'Grady and Brumfitt, 1968).

Toxicity.—Minimal side-effects are reported in the literature both in the smaller dose in gynæcological practice, and in comparable doses of 1,200 mg. a day used in the three previous trials in the treatment of urinary infection by Coppi and Bertagnolli (1965), Cosciani-Cunico (1965) and Lotti (1968).

Reported side-effects have included gastric symptoms, such as heaviness in the epigastrium (Leoni, 1964) especially after drinking wine (Chappaz and Bertrand, 1966), " gastralgia " (Longhi, 1967) and nausea (Sagone, 1965); and also flushing of the skin, a skin rash and possible allergic œdema (Chappaz and Bertrand, 1966; Kostic, 1968; von Helfenbein and Eisenhut, 1968).

In addition to occasional gastric symptoms, one of our patients had flushing of the face after drinking beer and whisky, and another a skin rash. We have also encountered the previously unreported symptom of breathlessness. We have now used the drug in 200 patients, and in only two cases has it been necessary to stop treatment. The first patient developed a severe rash on the third day of treatment. It would have been instructive to know if there was any cross-sensitisation with nitrofurantoin. Intradermal patch and other tests were not done. The second patient, an elderly man, developed severe breathlessness after each dose of the tablets and eventually stopped taking them. Investigation of cardio-respiratory function after this appeared within normal limits. Muir and Stanton (1963) and Israel and Diamond (1962) reported allergic pneumonitis with nitrofurantoin. Their patients developed acute dyspnœic attacks, associated with eosinophilia, after having a previous course of the drug. Our patient and four others in the trial who had slight breathlessness were all having the first treatment course of nifuratel. No patients with similar breathlessness have been found in over 40 reports on the use of nifuratel covering over 7,000 patients, in long-term toxicity tests, or in widespread clinical use of nifuratel on the Continent (data in the files of Polichimica).

We also had a further patient with a known skin sensitivity to nitrofurantoin who did not develop toxic effects on a course of nifuratel.

Nausea and vomiting and skin sensitisation are not uncommon toxic effects of nitrofurantoin. Other toxic effects of nitrofurantoin have not been repeated with nifuratel. These include the rare polyneuropathies, and even rarer hæmolytic and megaloblastic anæmias, and central nervous stimulation. Nitrofurantoin is also thought to stain deciduous teeth yellow if given to infants in high dosage for any length of time.

We have given nifuratel to only one patient with a raised blood urea, but without ill effect. It is our impression that toxic effects, particularly gastric disturbances, are less common than with nitrofurantoin.

We hope to have further information both as to comparative toxicity and therapeutic efficiency of nifuratel when we have completed a comparative trial of nifuratel and nitrofurantoin.

Results.—Assessment of urinary antibacterial drugs is notoriously difficult because of the many variable factors involved, and especially the wide variety of underlying causes. Chronic urinary infections frequently relapse after temporary cure, and infection may resolve spontaneously after the removal of its underlying cause. Even definition of a chronic underlying cause may be difficult. In this series chronic urological patients predominated. The results resemble broadly those of an early trial done in this hospital five years ago with nalidixic acid (Ward-McQuaid *et al.*, 1963). In both trials, about half the patients with chronic infections are bacteriologically cured at 28 days (nalidixic acid 14 out of 26, nifuratel 40 out of 84, but 15 out of 30 receiving 16·8 g.). Nearly all acute uncomplicated cases are cured.

At least two weeks' treatment should be given in chronic cases. Cosciani-Cunico (1965) sometimes prolonged treatment for 30 days. Our results, both in the whole series and by individual organisms, resemble broadly those of the three previous trials in urological patients. Coppi and Bertagnolli (1965) treated some 40 patients with a cure in 21. Cosciani-Cunico (1965), with a higher proportion of acute cases, had a bacteriological cure in 57 out of 95 patients. Lotti (1968) had a cure in 9 out of 23 chronic cases, and 10 out of 13 acute cases.

In the present trial nifuratel was most effective against *E. coli* (32 cures out of 47 infections), but less so against Proteus (5 cures out of 18), *Str. fæcalis* (3 cures out of 12) and Klebsiella (4 cures out of 11). Our results seemed more promising with the bigger dose in the second part of the trial. Lotti (1968) had no successes in six Proteus infections, and there are no specific references to successful Proteus treatment in other papers. On the other hand, nitrofurantoin is often successful against sensitive Proteus organisms, although Proteus organisms are less sensitive to both nitrofurantoin and nifuratel *in vitro* than they are to nalidixic acid. A small unpublished random trial of nitrofurantoin and nalidixic acid in the usual doses against Proteus organisms which were sensitive to the drug concerned was done in the Mansfield Group of Hospitals, using the same criteria as in the present trial. Nitrofurantoin cleared the urine in all 8 acute patients and in 10 of 25 chronic patients, compared with 8 of 9 acute and 12 of 27 chronic patients under nalidixic acid. Better results are expected from the use of nifuratel in Proteus and Klebsiella infections with a course of 400 mg. three times a day for two weeks (total 16·8 g.). If there is an underlying cause, then the course might well be prolonged with a reduced dosage.

Development of resistance during treatment in the present trial appeared to occur in only one of the 47 coliforms, and in none of the 18 Proteus organisms. Partial resistance appeared to develop in five organisms. Only one of these, a Proteus, was in a patient having the 16·8 g. course.

In the group of mixed infections, three insensitive organisms were also eradicated. Therapy had been commenced because the accompanying organism was sensitive.

Therapeutic Uses of Nifuratel.—Nifuratel seems likely to prove as effective as nitrofurantoin and possibly less toxic. It should prove a useful alternative to nitrofurantoin, nalidixic acid and ampicillin in the treatment of acute and chronic urinary infections. There is as yet no evidence of cross-resistance or cross-sensitisation with nitrofurantoin. Results with *E. coli* are more promising than those with Proteus, Klebsiella and *Str. fæcalis*.

Nifuratel should prove useful in acute infections because of its wide range and low toxicity, especially so if there is a vaginal discharge. Sulphonamides have long been used for uncomplicated acute infections, as a first-line drug, provided there is no sulphonamide sensitisation (Garrod and O'Grady, 1968). In the Mansfield Group Laboratory (Macis and Ward-McQuaid, 1968), 42 per cent. of the Coli/Proteus organisms as a group are resistant to sulphonamides. Robertson (1968*b*) finds an increase in sulphonamide resistance over the years, so that 61 per cent. of Coli/Proteus infections arising outside hospitals are now resistant. In the trial organised by the Bacteriology Committee of the Association of Clinical Pathologists many laboratories erroneously reported some sensitive *E. coli* as resistant. This difficulty in testing for sulphonamides is well known (Brown *et al.*, 1968). Nevertheless, there is a growing tendency to use what were previously regarded as second-line drugs such as nalidixic acid and nitrofurantoin empirically for acute infections as well as for acute relapses of chronic infections. A preliminary urine specimen should, of course, first be taken. In chronic cases it is usual to await results of sensitivity studies. Nifuratel should find a place here also, and the larger dose and a more prolonged course seem indicated for the less sensitive organisms and chronic infections.

There is not at present sufficient information about the use of this drug prophylactically, for long-term use, or in patients with renal failure, nor has it been used intravenously or as a bladder wash. Nifuratel is certainly promising enough to warrant further investigation. At this stage it must obviously not be given in early pregnancy, and only after serious consideration to patients with renal failure.

SUMMARY

A new furan derivative, known chemically as nifuratel (Magmilor) N-(5 nitro-2-Furfurylidene) -3-Amino-5-Methylmercaptomethyl-2-Oxazolidinone) was evaluated for activity in urinary infections. Nifuratel is known to inhibit both Gram-negative and Gram-positive organisms.

It also has good therapeutic action against Candida and Trichomonas. The trial involved 90 patients. In six there was an acute urinary infection and in 84 the infection was chronic. All the acute infections and 40 out of 84 (47 per cent.) of the chronic infections responded to nifuratel. Total resistance appeared to develop in one organism and partial resistance in five. The drug was most effective against *E. coli* (32 out of 47 infections cured). Side-effects were minimal.

We are indebted to those of our colleagues who allowed us to treat their cases, especially to Dr A. Fairley; and to Professor C. P. Beattie, in whose laboratory the tests were done, for his advice. We are also indebted to Calmic Limited and Polichimica Sap for the supply of nifuratel and for the data from their Research Files in the section on Pharmacology and Toxicology.

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