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Moroxydine: The Story of a Mislaid Antiviral

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A review is presented which began as a literature survey listing verbatim over fifty abstracts and references to the use of moroxydine in the treatment of a number of viral disorders throughout Europe and Scandinavia between 1960 and 1985. The list was first circulated in 1990 and was revised six times as new information became available. The sources are unusual in their diversity and originally appeared in several other languages besides English. Moroxydine may be effective against a number of DNA and RNA viruses, influenza being the original application of the substance when it emerged in the late 1950's. The drug received some attention around 1960, and the introduction of thalidomide at around the same time (1961) is one likely explanation for its current obscurity. Side-effects are reported to be mild and infrequent, and evidence exists that the substance possesses other characteristics which plead for further investigation. ***Key words: Adenovirus infections, human; Antiviral agents; Dengue; Drug therapy; Hepatitis; Herpes simplex; Herpes zoster; Influenza; Measles; Molluscum contagiosum; Mumps; Papilloma; Pityriasis.***

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The story begins in 1957 with a patent claiming that "The compounds especially salts of N^1, N^1-anhydrobis-(β-oxiethyl) biguanide, combine activity against several viruses of such different types as influenza, herpes zoster, smallpox, Newcastle disease, and canine distemper with an unusually low toxicity, resulting in a high security factor in clinical use" (1). When one considers the paucity of antiviral compounds currently available to physicians and the evidence which is to be detailed in this review, it quite defies belief that moroxydine has not found its way into the catalogue of substances available for the treatment of viral disorders.

The drug seems to have originated from the work of Melander and possibly also Nilsson at the Research Department of AB Kabi in Stockholm, and the date of its patent would now appear to place the substance firmly into the domain of generic medicine. Moroxydine was created in an era of scientific optimism, when popular newspapers proclaimed that nuclear energy would make electricity so cheap that metering would be unnecessary and scientists, it was reported, were working on a cure for the common cold. Moroxydine was probably one of these efforts, since the original research had reference to influenza. Regardless of its relative efficacy in any particular application, however, the drug may be unique in possessing activity against a wide range of DNA and RNA viruses. One of the earliest reports of the therapeutic use of moroxydine concerned varicella zoster virus (VZV): "The new drug moroxydine was given orally or intramuscularly to 26 cases with Herpes Zoster, tablet medication is preferred since equally good therapeutic results are obtained as on parenteral administration. After two days' adequate treatment the pains usually disappear, the temperature normalizes and propagation ceases" (2). Of the 26 patients treated, 13 excellent and 8 good results were reported. This pattern is to be consistently repeated as the story of moroxydine unfolds.

1960–1965

Hardly any references to moroxydine in serious, mainstream, English-language medical journals have been found; one was at the end of 1960. It took the form of a rather opinionated "Preliminary Communication" which appeared in the British Medical Journal. It might be surmised from the article that a good deal of publicity was being given to moroxydine around this time as an anti-influenza agent and, as Watson remarked somewhat cynically, a "surprisingly large number of other virus diseases" (3). The article condemned the substance as useless but the author's conclusions that the substance was ineffective against adenovirus and influenza infections were invalidated by the use of multiple drugs and inadequate controls. This report may have overshadowed a contemporary English-language account by Melander himself in a rather more specialized journal, which presented an important summary of the earlier work on moroxydine (4).

Only one published account was traced for 1961, and this provides a toxicological overview of ten different biguanides (5). The year after this account appeared moroxydine was mentioned in another mainstream medical periodical, in this case the German journal Der Hautarzt. Almost certainly one of the underlying reasons for the obscurity of moroxydine is the fact that it became available at about the same time as thalidomide in 1961. At this time drug licences were granted rapidly and virtually on purity considerations alone, a situation which changed suddenly when the side-effects of thalidomide became apparent. In the study, Theodor Nasemann of the University of Munich casually remarked that "We tried moroxydine clinically in several forms of HSV infection before deciding to experiment in vitro" (6), which might give an indication of the carefree attitude towards new drugs at the time. Since the original investigations involving moroxydine concerned influenza, it may have been concluded in the aftermath of the introduction of thalidomide that the risks of such a substance outweighed the benefits. Moroxydine may not have been the only promising new compound to be abandoned after the introduction of thalidomide, but it may have been the best. The peculiar combination of circumstances which has allowed potentially as fine a prize as moroxydine to be lost and found again is unlikely to be repeated.

Commenting on patients again, Nasemann continued: "We did not see a definite effect in all cases but undoubtably there

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was repeatedly an improvement so rapid that it could be attributed to moroxydine. In vitro, 3 mg/cm^3 of the substance inhibited the development of HSV infection in HeLa cells; at this concentration there were some minor signs of cellular toxicity but no cell death". He finally concluded that the "substance is virustatic and not virucidal", and this remark is especially telling in its naïvety; the possibility that a chemotherapeutic substance might actually eradicate virus, rather than merely inhibit replication, is unlikely to be entertained for long today in the pessimistic atmosphere which has come to pervade, particularly since the advent of HIV. In this instance it might even be possible that Nasemann was wrong; some of the accounts which follow imply that moroxydine might be capable of inhibiting the re-establishment of viral latency in some cases. Subsequent in vitro investigations give a degree of credibility to this claim.

In 1963 a Japanese patent was granted bearing the claim that moroxydine was useful as a remedy for diabetes mellitus (7). The nearest drug to moroxydine which is widely available at present is metformin, and this substance is effective in diabetics with some residual functioning pancreatic islet cells. The biguanide drug family also appears to have received attention as potential antimalarial agents. In another report in the same year, moroxydine was used in the treatment of a range of viral conditions including acute meningitis and pneumonia (8). A total of 26 patients were treated, often successfully, and in the 3 cases of meningitis a rapid return to normal temperature was consistently observed. This early French trial also contains the sole account to date of the use of the drug in hepatitis.

At this point there appeared a series of accounts, starting in 1964 and each by a different commentator, in the monthly journal Semaine Thérapeutique, a supplement to Semaine des Hôpitaux de Paris. The first was by Durandeau and concerned a group of patients with urethritis for whom all other treatment methods had failed: "Of 10 male patients who were carriers of viral urethritis, 8 have become cured; in 3 the laboratory has confirmed the disappearance of enclosing, the five others were not verified. The tolerance of the drug was always excellent" (9). This was quickly followed by the first report of the use of moroxydine at higher doses. "A 29 year old man with mouth ulcers recurrent over many years was treated with various medications without success. Treatment with moroxydine at 3×600 mg per day was given for six days and a recurrence with diminished intensity occurred after one month which was similarly treated. Over two years three outbreaks occurred much reduced in severity and duration which were easily treated with 3×300 mg per day. It is possible that moroxydine at elevated doses offers a therapy with long-lasting results" (10). Similarly, later that same year, the same pages carried the report that "A young woman, a six year old infant and an aged woman were treated for manifestations of varicella zoster virus at a dose of 500 mg or 900 mg per day for 6–10 days. There was no recurrence in at least two of the cases and although the number of patients is small in this report, there may be a secondary action of moroxydine which merits further study" (11).

These accounts, written in the style of their day, undoubtedly fail to be convincing when measured against the modern objective standard of the double-blind, randomized, controlled trial which has evolved over the last few decades. However, this is to take each of these reports in isolation; it is argued in this review that the cumulation of them is otherwise and that the independent accounts from so many different sources of the successful application of moroxydine testify to its usefulness. In any event, there can be no doubt about the general safety of moroxydine following early large-scale trials using the substance in the prevention and treatment of influenza. A Norwegian review documented a collection of trials involving 1,780, 596, 1,545, 4,358, 1,542 and 427 subjects with favourable, if inconsistent, results (12). This account, which appeared in 1965, is in fact the first in the present survey to use the term "double blind", and the concerns which were the legacy of thalidomide are also apparent. The trials took place during epidemics of influenza and non-bacterial respiratory tract infections among military and industrial personnel at doses of up to 1,500 mg per day. Moroxydine is evidently thought to be safe by the authorities in France and Belgium, where it is currently available from pharmacies without a prescription.

1966–1970

The next report from Semaine Thérapeutique is an account of the apparently successful use of moroxydine against mumps virus. "The preventive administration of moroxydine in a creche group of 18 infants of around 2 years old at risk of contracting mumps achieved more than 83% protection from infection. This level could probably be improved if treatment was started earlier and for a longer duration, continued for a week after the expiration of the probable period of incubation. The total inoffensiveness of moroxydine authorizes a recommendation for its large scale use for the prevention of epidemics in creches and, more generally, for groups of children and infants" (13). The general safety of moroxydine has evidently been apparent to the worker in this study and was subsequently objectively confirmed in the following account by Privat, again in Thérapeutique. This study involved 8 cases of pityriasis rosea and a further 12 patients with different herpes-like manifestations and ended with the conclusion: "The detailed analysis of the results obtained by this therapy reveals 17 satisfactory results and 3 doubtful. Pending clarification, we report the results of a preliminary study and will later announce our definitive conclusions" (14). No trace of a subsequent report by Privat has been found. "In the meantime, we are able to give a general impression which has progressively developed during the course of this study: it is known that certain therapeutic successes are, without any doubt, the result of the use of high doses of moroxydine. The excellent clinical tolerance of this medicament does not appear to be dependent on the dose and various blood, liver and renal examinations which we regularly practice with our patients have never revealed any perturbations".

Further evidence of what is perhaps the particular activity of moroxydine against VZV is provided by another French account, this time by Chevalier & Medioni. "The sudden arrival of a child with varicella in a children's home was followed by two simultaneous cases. A treatment of 600–900 mg per day for 10 days of moroxydine, 20–27mg/Kg/day, was instituted among the 30 children, 4–15 years old, who were presumed to be susceptible. A single case of varicella appeared 13 days later.

The authors underline the excellent tolerance of the medicament at this strong dose, and the likelihood of a remarkable effect of moroxydine in stopping the epidemic" (15). In an addendum to this report, the authors remarked that a similar trial 6 months later had confirmed the result of their first study.

The only recorded suspension of treatment with moroxydine due to side-effects was documented by Rivoire following a large-scale but uncontrolled study which was published in Lyon Médical in 1967. "The general tolerance of moroxydine is excellently demonstrated despite the elevated doses we have used. In effect, more than 100 patients have followed one or more cures of 10 days with a daily dosage of 2000 mg. We have noticed only some minor digestive trouble in the adult. We note, however, in 4 children struck by varicella, we have interrupted the treatment after the appearance of hepato-intestinal trouble. Moroxydine plays a valuable role in the treatment of certain dermatological affections due to herpes, zoster, aphthae and pityriasis rosea. The action of moroxydine is more rapid, more strong and more lasting when using a dose of 2000 mg/day and in the same way its tolerance is generally excellent" (16). The highest ever recorded dosage of 5,600 mg per day was reported in a similar trial by Ellena, this time on a smaller scale. Moroxydine was given to 38 patients and 18 good, 11 average and 9 neutral results were recorded. "The results obtained with 2400 mg are comparable with those obtained at double the dose" (17).

A year later, Ayih commented on the relatively low doses used in earlier studies and detailed the use of moroxydine in Togo, West Africa. A daily adult dose of 2,000 mg was quoted. The treatment, he said, was "given often and for prolonged duration at the start of a recurrence with remarkable clinical results. There is a rapid clearing of lesions while a certain weak euphoric effect of the drug has been noticed. The good general tolerance of the drug has been verified. One case of particular note may suggest that the dosage of moroxydine be individually tailored. An 18 month infant presented with a recurrent stomatitis accompanied with sores and the general phenomena of elevated fever, stomach problems and malaise. All the treatments tried still resulted in remissions of 2-4 months with relapses. At the age of 6 years the child received moroxydine at 300 mg per day for 7 days in two successive cures separated by 15 days. Notwithstanding the weak dose, the remission appears total more than 18 months since treatment with moroxydine" (18).

The mildly euphoric effect of moroxydine, first reported here, clearly raises the possibility of a psychological component in the action of this drug. The author of the present study took the drug at 3×600 mg per day for 14 weeks without interruption and can testify to the occasional incidence of euphoria. This effect was considered neither strong nor consistent, but only further modern trials will determine whether moroxydine is to be regarded as an aspirin or a penicillin for the 21st century or a mere psychological "pick-me-up". The likelihood of course is that the truth lies somewhere in between. At the very least, it appears that moroxydine is capable of counteracting the viremia and malaise which can be characteristic of infection by certain viruses.

After this period, up to 1968, the centre of interest in moroxydine moved from France (or, as in the latter case, a French colony) to Eastern Europe with three reports from Hungarian journals. The first again commented on the safety of moroxydine: "Its absorption is rapid, regardless of the route of administration. Its elimination is also rapid and it does not cumulate in the organism" (19). The report also stated that "Moroxydine has definite virustatic properties". It went on to detail a controlled study giving the result that moroxydine possessed greater effectiveness in preventing influenza than an inactivated vaccine based on several different influenza strains: "The attack-rate was 10.7% in a group of 5,036 subjects having had no prophylaxis, 5.1% in 1,419 having had an influenza vaccine and 3.9% in 737 having been subjected to moroxydine chemoprophylaxis". The subjects in this trial were railway workers, and the report also commented on a Swedish study published several years earlier involving 1,280 workers at the Volvo factories.

A subsequent 1969 account concerned primary herpetic gingivostomatitis, recurrent herpes labialis and aphthosis involving 58 patients and is an early example of the topical use of moroxydine: "A daily dose of 800 mg of moroxydine and painting with concentrated moroxydine solution shortens the healing time to 5 days. Local painting with moroxydine solution in recurrent herpes labialis stops the infection around the blisters within 24 hours, the process will be encompassed and completed within 2–3 days. A local treatment with moroxydine also seems to be effective in the case of aphthosis, but because of the small number of cases no definitive conclusion can yet be made" (20).

Yet more promising indicators of the activity of moroxydine are given in the abstract from the last of this trio of Hungarian reports: "Moroxydine has been tried out in 46 patients suffering from skin diseases of viral origin. In herpes zoster the pain subsided or disappeared completely; the time of recovery was reduced. In patients with herpes simplex the subjective symptoms disappeared; the time of recovery was shorter. Either no relapses occurred, or their form was milder and they appeared later than was usual. All of the patients with Stevens-Johnson syndrome, except one, recovered. In 2 cases mild relapses occurred" (21).

1970–1974

At this stage appeared the first of two reports of the in vitro activity of moroxydine by Galabov & Vilaginès of the Department of Virology, ISUL, Sofia and the Institut Pasteur, Paris. This is the first of two reports to suggest that moroxydine may possess a two-part mechanism of action in HSV-infected cell culture, with moroxydine at a concentration of 500 μg/ml. "Its weak action on the viral DNA synthesis and the strong inhibition it provokes on the viral development from the 10th hour after inoculation suggests that it could lead to the formation of non-functional structural proteins" (22).

The second report by Galabov & Vilaginès, published in 1971 and this time in English, confirmed the earlier observations of the dual action of moroxydine. In this exciting report the authors stated that the "compound's effect on the synthesis of the viral DNA is very slight in comparison with its effect on the production of mature virions at the same moment – an almost 100-fold decrease (when the compound is added immediately after the virus inoculation)" (23). It appears that moroxydine has an

Table I. *Quoted applications of moroxydine HCl (ABOB)*

Quoted applications	References
Adenovirus	3,12,25,28,36
Dengue fever virus	25
Hepatitis	8
Herpes simplex virus	6,8,14,16,17,18,20,21,25,27,30,34,41,42
Influenza virus	3,4,12,19,40
Molluscum contagiosum	16,32
Papillomavirus	39
Paramyxoviruses	13,25,40
Pityriasis rosea	14,16,38
Varicella zoster virus	2,8,11,14,15,16,17,18,21,24,25,30,35
Viral meningitis	8,26
Viral pneumonia	8

effect at two different phases in the viral replicative cycle, although one is 100 times weaker than the other, at least when measured according to virus growth in primate cell cultures. "Applied during the eclipse phase (2nd-4th hour), moroxydine leads to an ensuing delay of virus reproduction in the course of six hours, the difference with the control attaining approximately 2 log at the 10th hour, after which the production of mature virions gradually comes up to that of the non-treated cells (on the 20th hour: 0.5 log), i.e. the effect is reversible. The presence of moroxydine between the 4th and 10th hour does not appreciably modify the normal course of the growth curve. It may be deduced from these data that moroxydine seems to cause the formation of a certain quantity of nonfunctional early proteins, which results in the noted decrease in the synthesis of viral DNA".

This secondary action of moroxydine provides a putative explanation for the number of accounts detailed here of the long-term, curative properties of moroxydine in treating normally recurrent viral disorders. However weak or inconsistent this secondary mechanism may be, it would, if confirmed, be an extremely worthwhile topic for further investigation.

It is the view of the writer that in recurrent or persistent viral infection the commonly-held notion of a constant pool of latent virus is as unlikely a scenario as an inexhaustible desert spring; it must be fed from somewhere. Latency must be re-established in a cyclic fashion, and it is the possible interference in this process which is of particular note in this instance.

If the history of moroxydine and the manner in which it has been neglected turns out in retrospect to be describable as a catalogue of errors, the following trial might be considered to be the prize of the collection, by virtue of having been so frustratingly close. The experiment took place late in 1970. A sorry picture is described of the inability to eradicate the varicella which had become endemic over 3 years in a Cape Town convalescent home for coloured infants. The researcher gave moroxydine at approximately one tenth of the correct dose, yet nontheless claimed to have followed the manufacturers' recommendations. To compound matters, the treatment was discontinued as soon as the disease appeared. "All 23 patients in a Home for convalescent infants received 25 mg moroxydine 3 times a day (75 mg/day) until the disease appeared or until discharge. No side effects were observed but the attempt to eradicate chicken pox was unsuccessful. The staff consider that the disease may have occurred in milder form, but this is not certain nor is it good enough. Estimations of the number of crops of pocks show no difference between the control and treatment months" (24). It is possible to detect a certain arrogance in some of these reports (specifically, the latter and that of Watson (3)), as if the inclusion of a control group suddenly made the researchers' results infallible. It may be symptomatic of the same phenomenon to dismiss a feasible result solely because the modern protocol has not been used.

The following account, also in 1972, concerned moroxydine in the form of Vironil, one of three examples in this survey of the use of the substance as the main constituent of a proprietary drug combination (Table II). Presumably this was done as a marketing device, a fashion of the period to further distinguish one branded product from another. In this case it appears to have backfired dramatically. A doctor wrote: "During the past two months I have made the clinical diagnosis of dengue fever in 16 patients in this practice in Suva, Fiji. In every case, the patients had sudden relief of virtually all symptoms within 12 to 48 hours of instituting treatment with the Winthrop preparation, Vironil, and apparent cure of the condition after eight to ten days' treatment with Vironil" (25). The author of this letter to The Medical Journal of Australia went on to add himself to the number of people who had been successfully treated and who could now refer to "The day I had dengue". He also claimed good results in controlling other viruses (including two cases of mumps virus encephalitis) and said that moroxydine was

Table II. *Known preparations of moroxydine HCl (ABOB)*

Name	Form	References
1022 J. D.	100 mg tablet	8
Abitylguanide	1% eye drops	28
Albaton		
Biguamor		
Biguan		
Bioxine		
Cronoformin		
Diabenide		
Flumadon		
Flumidin/1[1]	100 mg tablet	2,4
Flumidin/2	100 mg tablet	3,12,30,42
Flumidin/3	400 mg tablet	38
Influcol[2]	10% eye drops	
Influmin[1]	10% eye drops	29
Morgalin[1]	100 mg tablet	19,20,21,27,32
Morgaline		
Spenitol	100 mg tablet	6
Virobis	25 mg tablet	24
Vironil[1]	100 mg tablet	25
Virugon	100 mg tablet	3
Virustat/1	100 mg tablet	10,11,13,14,15,16,17,18,31,33,34,40
Virustat/2[2]	400 mg tablet	41

[1] Flumidin/1 and Vironil were 100 mg moroxydine + 0.1 mg methatropine nitrate + 0.1 mg methscopolamine nitrate. Morgalin was 100 mg moroxydine + 100 mg ascorbic acid + 1 mg methylhomatropine bromide. Influmin eye drops were a 10% (formerly 20%) concentration in a 2% methylcellulose solution.

[2] Influcol (Poland) and Virustat/2 (France, Belgium) are currently available forms of moroxydine.

"Highly effective in the virus infections mentioned above, invariably effective in these clinically-diagnosed dengue cases, and free of any side effects in all cases in my care". This account is especially interesting because in two young dengue patients, treatment with moroxydine was interrupted due to a shortage of supply and was later resumed, with entirely consistent results. However, what might become to the reader a familiar syndrome in the history of moroxydine is once more in evidence: "Vironil almost certainly was overlooked by many medical practitioners when it was first promoted by the company, due to the fact that another product of a very similar name, produced by a different pharmaceutical firm, was promoted at the same time. The latter product was of the usual 'cold tablet' variety giving symptomatic relief only, so that the manufacturers' claims and the possibilities regarding the specific antivirus activity of Vironil were apparently overlooked by many doctors. Both of these preparations were promoted during winter in Australia, and with the emphasis, by the respective representatives, on their value in treating colds and influenza, hence the confusion between the two products, except in those doctors who noted the different and unusual structure of Vironil".

In 1973 a recommendation again appeared for the use of moroxydine in acute viral meningitis (26). In such urgent circumstances it would seem prudent to give rapid treatment with a substance which, according to the postulate, has a broad spectrum of antiviral activity until a precise aetiology can be determined and a more specific, potentially more effective, substance used. The writer has become aware that there is a school of thought which maintains that a broad-spectrum antiviral substance cannot exist, and so a counter-argument had better be given. In fact this argument can be reformulated as "We cannot do anything about HIV because the virus is continually mutating". Clearly this latter virus cannot be changing so extensively or it would not be distinguishable as HIV; stable characteristics do exist. At the risk of sounding trite, viruses in general must share common properties or they would not be recognizable as such, and a substance which interferes with or exploits some mechanism common to viruses would be generally effective against them. Perhaps a substance fulfilling this criterion should be described not as a "magic bullet" but as a "magic blanket".

The Czechoslovaks made a contribution in 1974 with a trial of 32 HSV patients aged 4–41. The paper provides a refreshingly humane outlook, and the following may be a good general summary of moroxydine. Here "aura" almost certainly refers to the prodromal phase of recurrent HSV infection: "We want to explain that enlightening on the pharmacodynamic effects of biguanides, previously not well known, was not intended to be the subject of this paper. We wanted to analyze results about the suffering caused by HSV. Best results have been obtained with HSV on the face and lips. Not so good results have been obtained with inflammation of the mucous membrane of the oral cavity (stomatitis). The patients have confirmed that the best results are obtained if treatment is begun during 'aura', but experience has shown that children cannot easily detect the feeling of tension at this stage of virus seeding. The medicament is licensed by the Health Office but nontheless was difficult to obtain. We think this biguanide derivative is a big success in the field of HSV prevention. It has a high efficiency although it doesn't enable full elimination of the smallest seeding in the case of each treated patient. The advantages are simple dosage methods, non-toxic and low price. An important goal is to use the drug sufficiently early i.e. during 'aura' of recurrency" (27).

1975–1980

Moroxydine has also been used in eye disease, and the Bulgarian worker Galabov appears once more as the co-author of another paper, this time using moroxydine with patients and topically. The trial might be regarded as typical of the Eastern European style, of a compassionate design intended to provide the most effective mixture of therapies for the majority of patients while attempting to gather useful information at the same time. The subjects were divided into 3 groups: 31 patients, the so-called placebo group, were treated with a combination of therapies excluding moroxydine; 104 patients were treated with a combination including moroxydine and only the remaining 16 patients used moroxydine alone. Still better results might have been obtained had a stronger concentration than 1% been used, however. "In an epidemic of viral keratoconjunctivitis in Bulgaria in 1972, caused by adenovirus 9, we applied moroxydine in 1% solution topically in 120 of all 151 observed patients. When the treatment could be begun in the first 3–5 days of the disease, a very favourable curing effect was noted. In most of the patients occurred a significant subjective improvement. The effect was most pronounced upon the course of the keratitis stage. When moroxydine was applied early, the observed keratitis was lighter, with slight visual impairment (with a duration of more than one month in 14.4% of the patients, as opposed to 57.3% in a placebo group), with quicker epithelialization of corneal erosions and, as a result, with fewer residual corneal opacities" (28).

The Poles have probably accumulated the greatest experience of treating eye disease in this way, and here once again the trial involved moroxydine alone. The following quotation is taken from a study involving 37 cases: "Prompt improvement and healing was achieved, mainly in early superficial keratitis cases. The compound also appeared very effective in keratopathies of probable virus etiology when other therapeutic methods failed. No complications or relapses were observed during the treatment" (29).

Haneke has completed two German studies of moroxydine, one in 1972 and the following one in 1976 which, excepting the present one, constitutes the most comprehensive commentary on moroxydine to appear to date, with around a dozen references relating to moroxydine. It is more measured than the earlier French reports, but again there are encouraging pointers to the usefulness of moroxydine, especially in the treatment of VZV. "20 patients with herpes zoster and 20 with recurrent herpes simplex were treated with moroxydine. With zoster the feeling of sickness disappears rapidly and the skin heals quickly. Taken early, the eruption of blisters in recurrent herpes simplex is mostly suppressed, or there is a rapid healing of damage to the skin. Recurrences will not be prevented, however moroxydine will still work with each recurrence. No side effects at all could be observed" (30).

Also in 1976 the Journal Français d'Oto-Rhino-Laryngologie

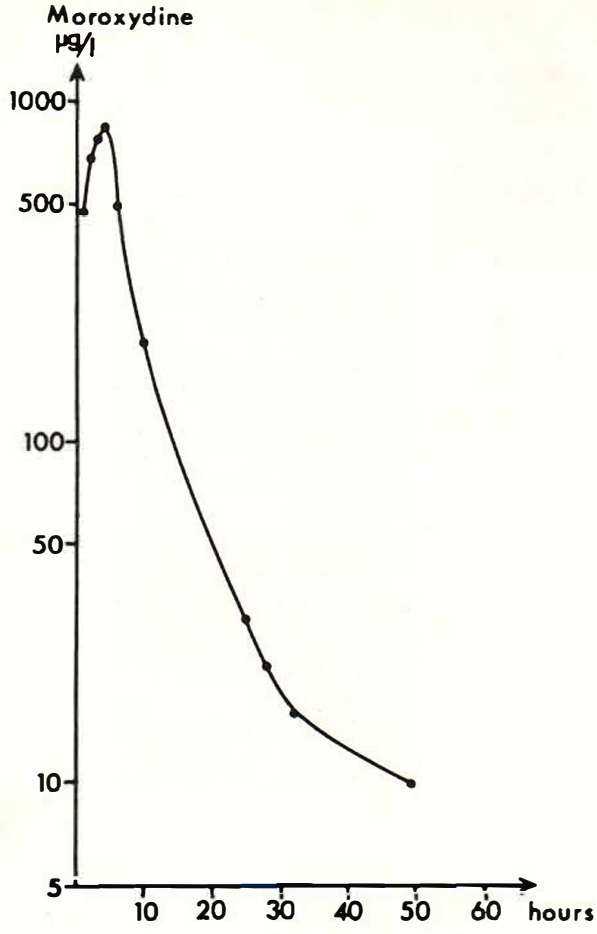

Fig. 1. "Serum levels of moroxydine in a human volunteer after oral administration of 800 mg of moroxydine hydrochloride" (37). Reproduced with permission.

reported an unusual application of moroxydine in preventing viral deafness. "The author reports some observations of patients presenting with recurrent deafness of viral origin and associated with slight fever, reduced sense of smell and taste and with a herpetic eruption. He insists on the value of an antiviral treatment and of cochlear support in stopping its evolution" (31). Regrettably the author omitted to state the dosage used.

The next reference, to another paper in Hungarian, is of even greater interest. Translation from Hungarian posed the greatest difficulties for the writer and his co-workers, and it is perhaps fortunate that an English abstract was available in this case. If this and another earlier report are confirmed, molluscum contagiosum would join dengue in the group of viruses which seem at present to be uniquely treatable by moroxydine. Treatment for molluscum contagiosum currently appears to consist of lancing the skin eruptions with iodine. "The great majority (97.7%) of 87 African patients suffering from molluscum contagiosum healed after the oral administration for several weeks of great doses of moroxydine. The frequency, clinical forms and epidemiological data of molluscum contagiosum in Black Africa are discussed" (32). This latter practitioner, Marton, also commented that at the "normal" adult dose of 600 mg/day, no results were seen; only when the dosage was increased did healing begin, after between 2 and 20 days of treatment.

A French report found that moroxydine, among a number of other substances (some of which are still regularly used), can induce perturbation of colour vision. A written enquiry to the authors as to whether the disturbance attributed to moroxydine was temporary or permanent remained unanswered. To quote from the report: "The molecules carrying one non-ionised atom of chlorine considerably disturb colour vision, it seems that the disturbance increases with the number of atoms carried" (33).

At this point the interest in moroxydine swings eastward again in the first of a collection of reports from Romania. If ever evidence is needed of the value of diverse scientific approaches, the value inherent in being different, it is here. The writer first encountered moroxydine as he was investigating the obscure subject of herpesvirus superinfection, encouraged by the British virologist G. R. B. Skinner. So rare are attempts to inoculate into a host a second, potentially less pathogenic virus to displace the first that a Romanian report was included in the literature search. It was at this point that the writer first came across claims that a combination treatment which included moroxydine could arrest long-term recurrent HSV disease.

The Romanians, almost uniquely, had been making serious and determined efforts to find a permanent treatment for HSV-induced disease for several years. The following was published in 1979: "The inefficiency or limited efficiency of some treatments may be due to the capacity of HSV to induce persistent infection, overcoming the host's immune defence mechanisms" (34). They went on to claim a 22.7% cure rate following the repeated administration of specific immunoglobulin plus moroxydine in a controlled study involving 110 cases of recurrent mucocutaneous herpes. Even better results were claimed in a second account which appeared three years later, but their use of gamma-globulin (IgG) in combination with moroxydine places some of their efforts outside the scope of this survey.

By this time, at the end of the 1970's, there were two more German contributions, the first of which is so unlikely that it might be considered absurd. At least these sources are consistent in demonstrating the extreme lack of knowledge which prevailed about the drug. "A report on a 64-year old woman with extensive herpes zoster of the trunk. The patient presented with urinary retention which stopped after 4 tablets of the chemotherapeutic agent moroxydine. This effect of moroxydine was unknown to the manufacturer and reports on this effect in the literature were not located" (35). In this case of varicella zoster neither the doctor nor the manufacturing pharmaceutical company attributed the outcome to the antiviral action of moroxydine, and the doctor (somewhat improbably) concluded that the drug was directly affecting the bladder sphincter.

The last German account of this period took the form of a letter by Mertens and the well-known virologist Eggers, but it was uninformed and inconclusive: "On one side, a marginal effect against adenovirus cannot be excluded, but on the other side not even close to enough is known which would appear to make it meaningful to use the drug in normal clinical practice, especially against influenza" (36). Eggers and especially Mertens were among the authors of a handful of subsequent reviews of antiviral treatments which appeared over the next few years, but nothing of significance was added about moroxydine.

After this, reports of the therapeutic use of moroxydine con-

Table III. *Languages, if not English, of papers quoted*

Language	Reference
Czech	27
French	8,9,10,11,13,14,15,16,17,18,22,26,31,33,40,41,42
German	6,28,30,35,36,38
Hungarian	20,21,32
Japanese	7
Norwegian	12
Polish	29
Romanian	39
Swedish	2

tinued at the slow rate of one or two per year. By way of an illustrative comparison, a modern search for references to the antiviral compounds in current use will typically reveal between 50 and 250 published studies involving each substance each year. A final check of three frequently used databases (EMBASE, MEDLINE and BIOSIS) during the last stages of this study produced 93 references to moroxydine. The actual search was for moroxydine or moroxydin or moroxidine or moroxidin, discounting duplicates. A similar search for citations of acyclovir or aciclovir, which was introduced in 1981, yielded 8,125 references.

1982 TO DATE

A modern analysis of serum levels following ingestion of 800 mg of moroxydine was documented in the following study. Moroxydine was described as "rather hydrophilic" (37). The report confirmed the earlier observations of the Hungarians (19) that the absorption and elimination of the drug is rapid. Its plasma half-life would appear to be around 8 h.

Perhaps the most convincing single study yet of the effectiveness of moroxydine appeared in 1984. The trial was controlled but not double-blind and yet another intriguing question was left as to whether moroxydine is virucidal or virustatic. The results of a study with 123 patients suffering from pityriasis rosea irritata were detailed. "During 1981 63 patients were treated with alb. aqu. lotion and anti-histamine. During 1982 60 patients were given immediate treatment with moroxydine-HCl at doses of 400 mg three times daily for adults and 400 mg twice daily for schoolchildren. In the largest and worst affected group of patients, those with skin eruptions appearing on the trunk and extremities, moroxydine-HCl shortened the therapy period by 50% compared with the same group in the control year. Overall, the shortening of unavailability for work of patients treated with moroxydine was around 50% as compared with the control groups. Even though moroxydine works not virucidally but virustatically, only one relapse was observed which occurred 12 days after return to work, possibly triggered by returning to work prematurely" (38).

There are two entries for 1985, both with details of unique applications of moroxydine. The first is a reference to the use of moroxydine against papillomavirus. Only 10 children with laryngeal papillomatitis were involved and so: "In spite of the very good results we obtained the number of subjects studied by us are relatively small and we cannot have a final conclusion regarding this treatment" (39). As previously mentioned, there have been a handful of reviews of antiviral treatments which make passing, almost cursory references to moroxydine, acknowledging its existence but quoting little or no literature because, presumably, hardly any could be located. The following excerpt is included here only because it raises the possibility of activity against another paramyxovirus: "It appears to have a preventive effect in man in respect of influenza A and possibly measles" (40).

Finally in 1986 there were two further reports worthy of inclusion and again they are from the French and the Romanians, which is perhaps appropriate. Here the French seem imprecise but unequivocal and the Romanians are quite specific. Firstly the French, in a review dedicated to moroxydine: "Some frequent herpes virus diseases can be treated with moroxydine hydrochloride. The author reports studies which verified its effectiveness and good level of tolerance" (41). In the Romanian report, the encouraging results of a study of 77 cases of HSV-induced eye disease are presented: "The treatment with moroxydine hydrochloride led to a reduction of 63% and 92%, respectively, of the incidence of herpes virus type 1 and 2 antigens in the conjunctival cells, coincident with the improvement of clinical symptoms or persistent recovery" (42).

At the conclusion of this review it should be stated that it

Table IV. *Recorded treatment strategies using moroxydine HCl*

Ref.[1]	Daily dose[2]	Days	Remarks/topical moroxydine
2	25–400 mg	3–7	In intramuscular or tablet form
3	300–600 mg		
4	300–900 mg	7–10	8 weeks of medication recorded
6	150–600 mg	7	
8	600–800 mg	6–24	
9	900 mg	10	Repeated after 8 days' cessation
10	900–1800 mg	5–6	
11	500–900 mg	6–10	
12	300–1500 mg		
13	400 mg	10	
14	1200–2000 mg	5–10	
15	600–900 mg	10	
16	2000–2400 mg	10	
17	2400–5600 mg	8–28	
18	400–2000 mg		
19	600 mg	8	
20	800 mg	5–8	+ local solution
21	300–600 mg	3–9	
24	75 mg	7–10	
25	600 mg	8–10	
27	300–600 mg	2–4	
28	400 mg	2–30	+ 1% solution + 1% creme
29	–	6–14	10% solution only
30	600–1200 mg	10	
32	300–2400 mg	14–42	No effect at "normal" dose
34	600 mg	10	+ intramuscular IgG[3]
38	800–1200 mg	8–15	
39	300 mg	10	
42	600 mg	7	Repeated 2, 4 or 6 times

[1] Where absent the dosages were either not stated or are not applicable (e.g. in vitro studies).
[2] Taken in two or three doses. Both infant and adult dosages are included in the range.
[3] Repeated three times at intervals of at least one month.

covers the most significant proportion of the entire recorded therapeutic use of moroxydine in the 36 years since its discovery was made public. Further, any search of the contemporary CD-ROM compilations for references to moroxydine will result in failure; nothing of note has been documented about the substance since 1986. Many of the journals quoted in this study are not included in Index Medicus, although it is thought that a greater number appear in Excerpta Medica. Records prior to 1966 were more difficult to trace, so that two important references, (4) and (8), were only discovered at the very closing stages of the study. There is still more to find, including some early Japanese studies which can be located using the chemical name for moroxydine hydrochloride, ABOB, as a search key; the designation by WHO of the generic name of moroxydine may have been delayed. The Chemical Abstracts number for moroxydine hydrochloride is [3160-91-6]. A separate acetylsalicylic acid derivative, bearing the proprietary name Assur, has also been used.

For the collation of this survey the following computer databases were used: BIOSIS, CHEMABS, EMBASE, International Pharmaceutical Abstracts, Martindale Online, MEDLINE and PASCAL; they were accessed in the first instance by modem from the main Amsterdam Public Library, for the most part at their expense. The search was made especially difficult because moroxydine has appeared under a great number of proprietary names (Table II), and thus many separate searches had to be made during the process of recovery. All the papers referred to were ultimately obtained save for the Japanese patent (7). At no point during the study was evidence found or any suggestion made that moroxydine could be acting as an immunomodulator.

Possibly the most optimistic of the reports included here are some of the early reports in Thérapeutique, these being among the papers which were obtained by two special visits to Paris during the study. Contemporary practitioners may have a still more hopeful attitude towards the activity of moroxydine. The reports contained in this survey carry varying degrees of authority but nontheless, considering the cumulation of them and the undoubted safety of the substance, the rapid adoption of moroxydine to current use would seem to warrant recommendation.

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