F. ARCAMONE (*)

Research and Orphan Drugs (**)

It is a generally accepted issue that, even where scientific and industrial feasibility exists for new drugs for the treatment of rare diseases, the too small number of patients renders return of investment for development and of production and distribution costs, not to say making a profit, quite unlikely. Therefore such therapeutically useful agents, also indicated as "orphan drugs", are of limited commercial value and not available to patients. A second problem is that represented by the development of drugs in cases in which a great medical need does exist, but mostly in geographic regions of less developed countries unable to represent an economically effective demand.

It should be noted that researchers may find the study of orphan drugs as attractive as that of other, profit making medicinal compounds. In fact medicinal chemists are not generally directly involved in preparing a sales budget. On the other hand, they can find the discovery and development of a drug for a rare disease a very rewarding accomplishment as normally the problem is of great scientific interest.

In my personal experience I have already encountered different cases amenable to this discussion. Lucensomycin, a polyene antifungal agent, was made available in the market as an ointment in 1965, but withdrawn in 1976 because of its limited field of application, notwithstanding its demonstrated usefulness in topical fungal infections (Charts 1 and 2). Distamycin A, an antiviral antibiotic, was registered in 1976 as a drug for the topical treatment of herpes cheratitis, herpes simplex, varicella and herpes zoster, but never launched because of production costs and distribution problems (Charts 3 and 4). On the other hand a third compound, the endecapeptide eledoisin, a takykinin originally isolated from the methanol extracts of the posterior salivary glands of the Mediterranean octopod *Eledone moschata*, has been on the market in Spain for years starting from 1976.

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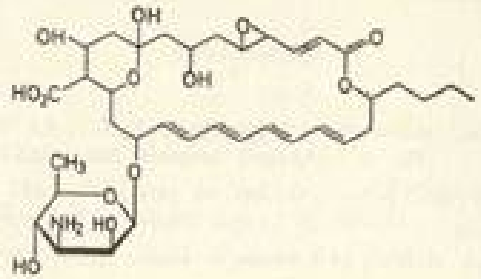
(**) Presented at the International Meeting « New Strategies for Orphan Drugs » (Rome, 8-9th March 1983).



Lucensomycin
From *Streptomyces lucensis*: US Patent 3, 170, 837 (1965)
Antifungal (topical)
Registration (Italy): 1965
Launch: 1965
Withdrawn: 1976

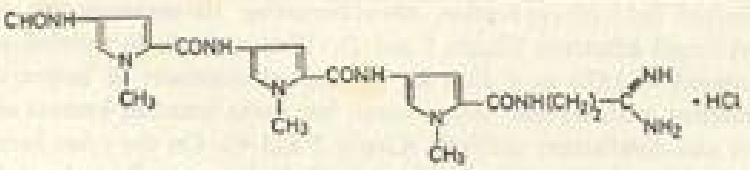
Chart 1

LUCENSOMYCIN HAS BEEN FOUND TO

— POTENTIATE CYTOTOXICITY OF ANTICANCER AGENTS:
F. Valeriote *et al.*, « JNCI », *72*, 435 (1984)

— REPRESENT A USEFUL TOOL FOR THE STUDY OF BEHAVIOUR OF BIOMEMBRANES:
R. Strocchi *et al.*, « Biochem. Pharmacol. », *28*, 2427 (1979).

Chart 2



Distamycin A (Stallimycin, Herperal ®)
From *S. distallicus* (« Nature », *203*, 1064, 1964)
Obtained by total synthesis
Antiviral
Registration as Herperal: 1976 (Italy)

Chart 3

DISTAMYCIN A IS CLINICALLY AFFECTIVE ON INFECTIONS DUE TO THE POLLOWING VIRUSES:

— HERPES SIMPLEX
— HERPES ZOSTER
— VARICELLA
— POXVIRUS VARIOLAE VAR. BOVIS

References: D. Bassetti, « Gior. Mal. Infett. Parassit. », *21*, 849 (1969);
G. Paschetta, Ibid., *24*, 795 (1972);
A. De Vriendt & L. Wehmars, Ibid., *24*, 63 (1972);
L. Muscardin, « Chron. Derm. », *3-4*, 3 (1971);
D. Bassetti, « Min. Med. », *64*, 2077 (1973);
E. Bertoglotti, « Min. Ped. », *28*, 538 (1976).

Chart 4

The peptide, now obtained by chemical synthesis, is a powerful stimulator of salivary and lachrymal secretions through a direct action on the secretory cells and a unique relief to the sufferers of keraticonjunctivitis sicca, Sjögren's syndrome, senile xerophthalmia and other hyposecretions that account for only a small proportion of the population. Further development, that is to say full exploitation of the therapeutic potential, is hampered by the limited commercial value. However, the ethical value of the drug greatly outweighs any profitability consideration (Charts 5 and 6).

A very recent case is that of the new semisynthetic ansamycin derivative, compound LM-427. This new drug exhibits outstanding activity against a variety of *Mycobacterium* species, including the agent of leprosy (also rifampicin resistant) and atypical species, such as those that are notoriously responsible for severe infections in AIDS patients. Both potential applications of the drug

pGlu — Pro — Ser — Lys — Asp — Ala — Phe — Ile — Gly — Leu — Met — NH_2

Eledoisin
From the octopod *Eledone moschata* (1962)
Obtained by total synthesis
Stimulator of lachrimal secretion
Registration as Eloisin (Spain): 1975
Launch: 1977

Chart 5

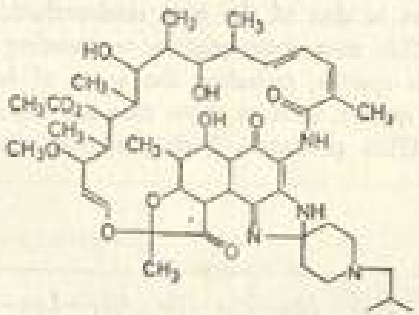
ELEDOISIN IS EFFECTIVE ON:

— KERATOCONJUNCTIVITIS SICCA
— SJOGREN'S SYNDROME
— SENILE XEROPHTHALMIA
— HYPOSECRETION DUE TO IRRADIATION OR ABLATION OF THE MAIN LACHRYMAL GLANDS
— INSUFFICIENT SALIVARY SECRETION

Chart 6

represent examples of the general cases described above for the orphan drugs. As regards the second application, LM-427 is currently investigated in AIDS patients at the Center for Disease Control (CDC) in Atlanta, USA, under an "emergency" IND (Chart 7).

What might we suggest for reasonable exploitation of these useful albeit commercially not appealing products? In the U.S. six orphan drugs were approved under a new incentive program in 1983, namely: sodium cellulose phosphate for prevention of kidney stones in certain patients, acetohydroxamic acid for kidney infections, injectable hematin for hepatic porphyries, chenodiol for dissolving gallstones, α-fetoprotein diagnostic kit for management of testicular



LM 427
Rifamycin S. derivative
Antituberculor, Antileprosy
Entered in clinical use under emergency IND
(CDC, Atlanta, USA): 1983
Autorizzazione Ministeriale (Italy): 1984

Chart 7

ORPHAN DRUGS APPROVED DURING 1984 BY FDA:

PIMOZIDE (McNeil) for Tourette's Syndrome
PENTAMIDINE (Lyphomed) for pneumonia in AIDS
HYDROMORPHONE high potency (Knoll) for chronic pain
NALTREXONE (Du Pont) as narcotic antagonist
DESMOPRESSIN (Armour) for haemophilia

(*Source*: « Scrip », Feb. 11, 1985)

Chart 8

cancer, and etoposide for refractory testicular cancer. In addition, seven orphan product grants have been awarded by the US FDA Orphan Products Board. The products are bacitracin tables (pseudomembranous colitis), topical capsaicin (post-herpetic neuralgia), live attenuated cytomegalovirus vaccine (kidney transplants), enzyme reagents (phenylketonuria), methotrexate (juvenile rheumatoid arthritis), suppressin A (histiocytosis X), teflon (palatal insufficiency). In fact, in the U.S. the legislators have prepared a bill (the Orphan Drugs Act) that includes tax credit, abbreviated approval process for new drugs, and marketing rights (Chart 8).

As regards the discovery of new medicines for the treatment of diseases typical of Third World countries, a contribution might also be insured by the Universities through State-funded research. This includes the "Progetto Finalizzato del CNR per la Chimica Fine e Secondaria", a part of which should be devoted to develop drugs falling into the above-mentioned category such as antimalarials and other antiparasitic agents for human and veterinary use. The drugs should clearly satisfy the criteria of western regulations in terms of safety of medicines, development being attributed to private firms on a contract basis. The pharmaceutical industry should be entitled to production and distribution, deriving the little benefit justifying the corresponding effort (Chart 9).

PROGRAMMED APPROACH

— RESEARCH AIMED AT THE DISCOVERY OF NEW DRUGS FOR RARE DISEASES OR FOR DISEASES TYPICAL OF THIRD WORLD COUNTRIES MIGHT BE FUNDED BY CNR (E.G. « PROGETTI FINALIZZATI »).

— DEVELOPMENT, PRODUCTION AND DISTRIBUTION MIGHT BE ATTRIBUTED TO PRIVATE FIRMS ON A CONTRACT BASIS.

Chart 9