Orphan Diseases and Orphan Drugs

Some pharmaceutical products that are commercially available in other countries, but not in the United States, are called "orphan drugs" [1].

They are "orphans" because they have not been "adopted" by any of the U.S.A. pharmaceutical companies.

In some cases an orphan drug may lack a home because it is needed to treat a rare or obscure disease, in which case the medical problem is labelled an "orphan disease". The number of patients requiring the drug is so small that a drug manufacturer cannot make a profit by developing and marketing the drug.

An example of an orphan disease is amyotrophic lateral sclerosis, also known as ALS and "Lou Gehrig's Disease", from the New York Yankees' baseball star.

The USA Dept. of Health & Human Services (DHHS) has estimated that 9,000 Americans are afflicted with ALS [1].

Another one is Epidermolysis bullosa or EB, a group of rare hereditary diseases causing severe painful and recurring blisters [2]. Some 25,000-50,000 people in the United States suffer from EB. The precise cause of EB is still unknown, but recent evidence indicates that an increase in collagenase activity is involved in the formation of the blisters.

One of the drugs that prevent collagenase from breaking down collagen is bufexamac, a topical non-steroidal anti-inflammatory agent, not yet approved in the U.S.A. but used in Europe to treat general inflammatory dermatoses. Patients with a second type of EB, dystrophic epidermolysis bullosa, can get substantial relief of their symptoms with bufexamac.

An example of orphan drugs is Alpha-l-Antitrypsin useful in genetically deficient cases of emphysema [2]. Alpha-l-antitrypsin, now produced in large quantities by a recombinant DNA-modified yeast, occurs as a natural human protein that is synthetized in the liver and then circulates in the blood. Its functions include inhibition of elastase, an enzyme that helps destroy bacteria in the lungs. Without inhibition by antitrypsin, elastase will begin to dissolve

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elastic tissues in the lung itself, thereby compromising the natural elasticity necessary for breathing and eventually causing significant emphysema. Almost 50,000 Americans have a genetic defect that results in low circulating levels of \( \alpha \)-antitrypsin [2].

An orphan drug may also be a common natural substance and in the U.S.A. a natural medicine cannot be strongly patented. If a natural is found to have previously unknown health benefits — and it can be weakly patented — most pharmaceutical companies still will not adopt the product. A substance that cannot be strongly patented also cannot be protected against exploitation by competing drug firms after a pioneering company has invested millions in the necessary research and development of the medication.

Such an orphan drug is 5-L-hydroxy-tryptophan or 5-HTP, which is a precursor of serotonin, a neurotransmitter which is involved in abnormal movements of animals and in the mechanism of action of many drugs acting on CNS or on Autonomic NS [3].

5-HTP was tested on a variety of diseases, including Down's syndrome, and found ineffective; then it was discovered to have a dramatic effect on many sufferers of myoclonus, a central nervous system condition that causes involuntary and sometimes disabling jerky muscle movements. 5-HTP represents a new change of life for those who would be permanently bedridden without it; yet all 129 member firms of the American Manufacturers Association turned down the request to manufacture it because of the small number of myoclonus patients (1000-2000) and the fact that this drug is not patentable because it is a plant extract.

Another example is carnitine [1], obtained from meat extracts and normally present in skeletal and heart muscle tissue. Europeans have consumed carnitine health tonics for years, but because of the U.S.A. patent laws, more than 30 pharmaceutical companies have refused to manufacture and distribute it.

Considering now some problems of our country, I have to remember that of the therapeutic treatment of thalassemia major (Cooley's anemia) a severe, inherited blood disorder characterized by a quantitative defect in the synthesis of the beta chain of hemoglobin [4]. The result is a marked anemia, a lifelong dependence on blood transfusion and death usually before the third decade of life.

An iron chelating agent, desferrioxamine has been and is being used in an effort to reduce the toxic iron overload in tissue of patients. It must be given by daily injection and is painful and expensive. Since 1974 more than 160 iron chelating agents were developed worldwide and screened with the hope of an effective removal of iron deposits in their vital organs [5].

The sickle cell anemia drug development program is started, and it involves design and synthesis of drugs to interfere with the binding sites of the hemoglobin-S molecule that are responsible for sickling of red blood cells. One of the responses is the synthesis of benzyl esters and small peptide derivatives to prevent sickling [4].

Another approach is based on recent advances in the understanding of the genetic control of hemoglobin F production which now appears feasible by
induction of production, using a cytidine derivative, of a high level of hemoglobin F, which may be incorporated into the red cells in place of abnormal hemoglobin.

Another problem, in which the developing countries are particularly interested, is the development of vaccines and of so-called "synthetic vaccines" [4]. Such a program is complicated by the fact that in the U.S.A., as well as in Europe, the number of manufacturers of vaccines has been declining during the past few decades. Several factors have influenced the firms' decision on whether to develop and market new vaccines.

The influential factors include a relatively small market, low profits, high capital investment requirements, extensive regulation and unpredictable vaccine liability risk. On the other hand, we are daily observing that old diseases such as malaria, that many experts had considered some time ago as declining or disappeared, are afflicting at least 300 million people a year in every part of the world and especially in undeveloped countries. Do not forget that malaria causes yearly 2 million to 4 million deaths [6]; despite nearly a hundred years of attempts at eradicating the disease, malaria still threatens 2 billion people, which is nearly one-third of the world's population.

I have presented to your attention some different examples of orphan drugs with the purpose of emphasizing not only the difficulty of a research program but also the chemical and biological variety of some therapeutic agents.

It should be pointed out, however, that in the case of many orphan drugs the basic research has already been completed by the time it comes to a company's attention.

For many others, the path to be made will be long and particularly difficult [7].

Besides private pharmaceutical companies, I think the public institutions have to be involved in a serious program. Among them, the Italian Health Institute, Universities and the Italian Research Council (CNR) laboratories must be pressed in this field.

In particular, as a member of the Chemical Committee of the Italian Research Council, I can tell you that with some finalized programs of oriented research there have already been considered some aspects of the field that we are discussing here today.

More input is coming now with the presentation of some so-called "strategic programs" regarded as a multidisciplinary effort to confront and possibly resolve some problems having to do with human life and its defense and protection.

Moreover, as a pharmaceutical chemist, I cannot forget the contribution that university research can offer and realize, especially in basic scientific knowledge.

I therefore hope that the combined action of private and public efforts will conduce, in a reasonable period of time, to some practical result that can make available useful, positive and possibly cheap therapeutic agents, both for people suffering from orphan diseases and for masses of developing countries lacking a variety of essential drugs.
REFERENCES