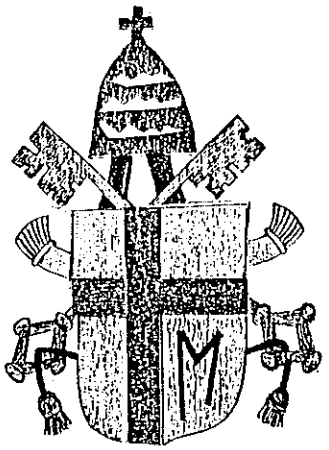

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Proceedings of the First International Conference

organized by the Pontifical Commission for the Apostolate of Health Care Workers on

Pharmaceuticals at the Service of Human Life

October 23, 24, 25, 1986
Synod Hall - Vatican City

Sessions chaired by

Prof. Konrad E. Bloch
Nobel Prize Winner in Medicine

Prof. K. Sune Bergström
Nobel Prize Winner in Physiology
Pontifical Academician

Prof. Max. Ferdinand Perutz
Nobel Prize Winner in Chemistry
Pontifical Academician

Contents

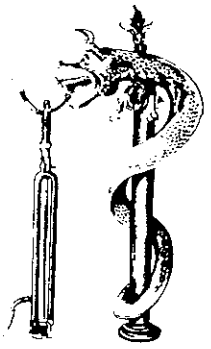
The illustrations for this issue have been taken from For a History of Pharmacy and Pharmacists in Italy: Venice and the Venetian Region, *edited by Angelo Schwarz, vol. II (Skema Publishers, 1981) and* Pharmacies and Pharmacists in Piedmont and Valle d'Aosta, *edited by Angelo Schwarz (Skema Publishers)*

First Session

The Ethics of Pharmaceutical Programing

Second Session

The Ethics of Pharmaceutical Research



Third Session

The Ethics of the Use of Pharmaceuticals

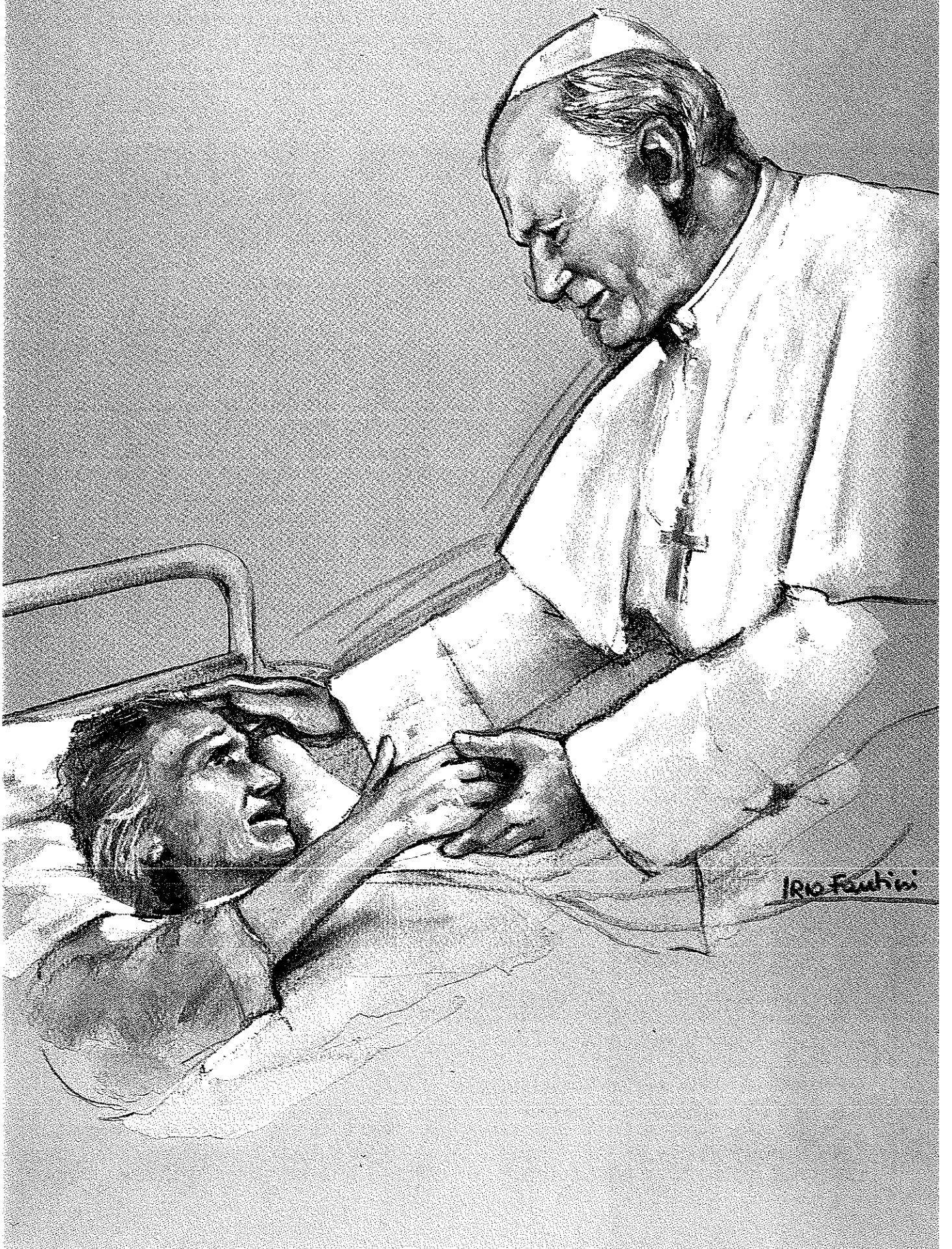
A Very Strict Moral Code Is Needed for the Use of and Experimentation with Drugs

Pope's Address to Conference

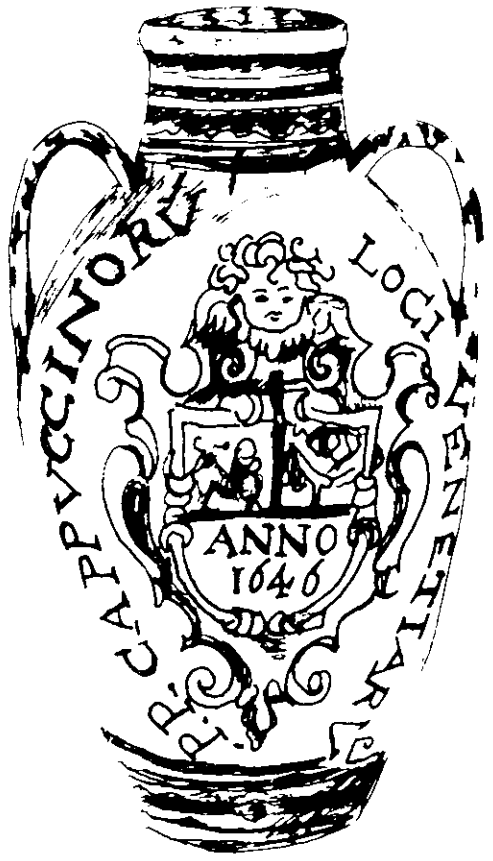
1. It is with joy that I greet you, participants in this International Conference, which witnesses once again to the importance the Church accords to the service of the sick, the suffering, and to those who labor in the vast domain — delicate and complex — of health and hygiene. This field of apostolate is an integral part of the mission of the Church.

This conference is well representative of the activity of the Pontifical Commission for the Apostolate of Health Care Workers, and I am happy to take this opportunity to congratulate and thank its President, Cardinal Eduardo Pironio, its Pro-President, Archbishop Fiorenzo Angelini, and their collaborators. In a world where the very understanding of social and health services is evolving considerably, and where it is becoming apparent that they have ever more complex implications, it has become indispensable to coordinate and to promote the Church's presence. This conference is proof of this presence, as are also the other initiatives which have been undertaken or which are in the process of implementation. Among these I would like to mention the vast revision of all the Church's health establishments; we are thus becoming more aware of the extension and of the capillary ramifications of her presence and service on behalf of the human person, now subject to the particular trial of psycho-physical illness.

2. The choice of the main theme of this conference also seems very appropriate to me. Medicines are in fact the means by which the doctor is not only able to cure diseases, but also to prevent them. A great number of those which, in the past, decimated populations have largely disappeared today; others can be treated far more effectively. Children are more rarely afflicted by the terrible defor-


IRO Fanfani

A large pitcher (Caltagirone, seventeenth century).



mation of polio and rickets. Surgery, thanks to an ever more satisfactory contribution of pharmacology, has been able to make extraordinary advances. The average life span has notably increased. All of this we owe above all to serums, vaccines, and so many other forms of medication at our disposal today. This applies at least to the developed countries.

BENEFITS AND PROBLEMS

3. Nevertheless, if it is true that medicines have brought immense benefits to humanity, they have also raised serious and partially unresolved problems with regard to their development, diffusion, and their use and accessibility to all sick persons, regardless of their class or nationality. The preparation and manufacture of medicines is increasingly complex and costly, and this has obvious economic and social consequences. Medicines can stimulate or impair the function of various organs or tissues, or even mental activity. These characteristics make them useful for increasing resistance to certain diseases or for checking the development of others. It is true that one may occasionally question the opportuneness, for the balance of the human organism, of an excessive consumption of these artificial products, in certain countries and according to the tendency of certain practitioners. But, above all, medicines can also be employed for purposes which are no longer therapeutic, but rather alter the laws of nature to the detriment of the dignity of the human person. It is clear, then, that the development, distribution, and use of medicines should be subject to a particularly strict moral code. Respect for this code is the only way to prevent the demands connected with the production and cost of medicines, in themselves legitimate and important for their distribution, from deflecting them from their meaning and their end.

4. During this congress you also considered the problem of experimentation with medicines. In the present state of scientific knowledge, it is not possible to predict with sufficient accuracy the properties and the characteristics of new medical preparations. Before being used in treatment, they must be tested on laboratory animals. In my address to the participants in the Study Week on biological experimentation which took place in 1982 at the Pontifical Academy of Sciences, I have already pointed out the delicate character of this type of experimentation, stressing that it should be conducted with respect for the animal, not subjecting it to unnecessary suffering. In a second stage, before being made available for general use, medicines should be tested on the human being, on the sick and sometimes even on a person in good health. Clinical experimentation is subject to strict laws and norms which regulate it and aim at offering all possible guarantees. We may at least hope that the day will come when, thanks to the progress of scientific knowledge, the risk and the unknowns in the area of experimentation with medicines will be notably reduced. However, in any event, great prudence is necessary to prevent man from ever becoming a mere object of experimentation, and at all costs avoiding danger to his life, sanity, equilibrium, and health, or worsening his condition.

5. At the same time it is urgent to promote real international collaboration, not only on the normative level, but also to reduce and eliminate the differences among countries.

Among the problems that still remain unsolved, I would like to mention those which concern the situation of certain developing countries. Although access to health care is recognized as a fundamental right of man, large sections of humanity are still deprived of even the most elementary medical care. The problem is one of such dimensions that individual efforts, valuable and irreplaceable as they may be, are insufficient. At the present time, it is absolutely necessary for us to try to work together, and to coordinate, at the international level, policies of aid and thus of concrete initiatives. We know how the World Health Organization is engaged in this, as well as other associations and initiatives which show solidarity without frontiers.

Developed countries have the duty to place their experience, their technology and a part of their economic wealth at the disposal of those that are less so. However, this can be done only with respect for the human dignity of others, without ever wishing to obtrude. The protection of health is closely bound up with the different aspects of life: whether they be social or economic, or related to environment or culture. For this reason it requires a prudent and responsible approach, with open and mutual collaboration. It frequently happens that local traditions offer invaluable points of support which should be taken into account and improved. Christians understand that there is excellent ground for fraternal assistance and for humble and respectful service.

THE CHURCH'S CONTRIBUTION

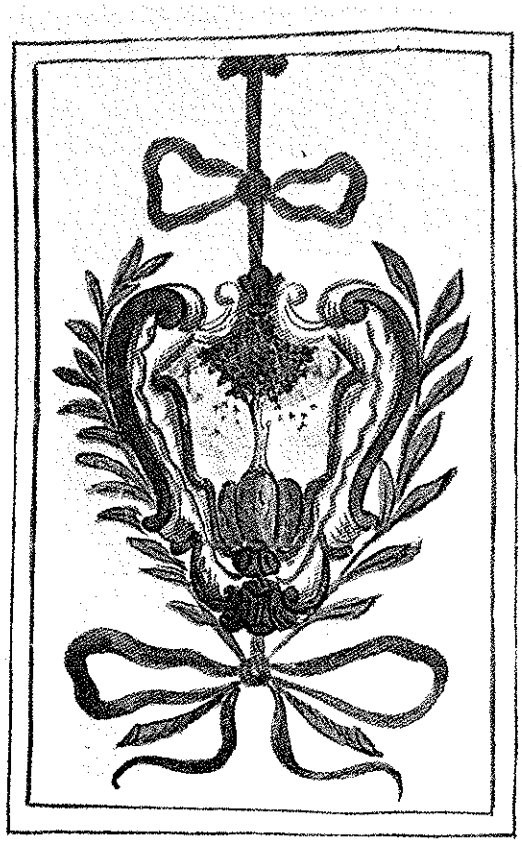
6. In this context, we cannot forget that there are still medicines which, for almost exclusively commercial reasons, have not been given serious attention and are not benefiting from research and scientific progress. These are often necessary not only for the treatment of certain rare diseases, but also for those which strike millions of people in the poorer tropical zones. In this respect, it is necessary in the first place to discern the objectives and their order of priority, then to see how the economic and political barriers which impede the research, development, and production of such medicines might be overcome.

7. To all those who work in health care and who must confront these difficult and complex problems I would like to reiterate here the encouragement of the Church. Christian doctrine — of this we are convinced — makes a very important contribution to these areas. It offers sure principles to point the way towards solutions which guarantee the dignity of the person, sustain his moral and social progress, and develop solidarity. In this sense, it brings light and hope to those who experience doubts, questions which cause anxiety or discouragement at the sight of the painful condition of the sick and infirm.

On the one hand, the Church shares with the sick their desire for healing and relief and their hope for a fullness of life. She also respects the mystery of their suffering and invites them, above all if they have faith, to situate their trial in the plan of God, in the plan of the Redemption, in union with Christ the Savior, who offers them an opportunity for spiritual elevation and offering in love, for the salvation of the world. This is a mystery that can also benefit those who take care of them. I have often had occasion to speak of this to the sick.

On the other hand, this immense world of sickness is at the same time a challenge offered to your capacities as doctors, pharmacists and scientists, to see if you can find a scientific and humane solution to the problem of health, in all its different aspects. Recently, while visiting the sick and those who care for them in the cathedral of Saint-Jean, in Lyons (5 October 1986), I encouraged scientific research in this sense and I congratulated all those who, like the Good Samaritan of the Gospel, are cooperators with God in the defense of the lives of their brothers and sisters. Yes, not only has the Church constantly urged forward, in the spirit of the teaching of Jesus, the creation of works of mercy for the sick, but she is also anxious to support technological progress, the spread of knowledge, and their wise use in the service of man. Far from closing itself to the legitimate desires of the contemporary world, Christianity strengthens them, and helps to fulfill them.

May this assurance accompany you always and strengthen your commitment, whatever the area of your activity within the health services! It is God who has given us the intelligence and the heart to better discover and implement whatever supports and develops the life of the human being, the expression of the person: may he affirm you in your research, in your professional service, and may he fill you with his blessings — yourselves, your families and those who are dear to you!



Illustrations of certificates to practice as a pharmacist, the Privilegium in Arte Aromataria *(Padua, eighteenth century)*

Greeting

by Cardinal Ugo Poletti, Vicar General of His Holiness for the Diocese of Rome

Honored Sirs,

In opening this First International Conference, promoted by the Pro-President of th Pontifical Commission for the Apostolate of Health Care Workers, Monsignor Fiorenzo Angelini, it is my honor to offer you the respectful greetings of Rome, the Church and the City, in whose history and perennial mission there has always been the duty of showing cordial, intelligent, open-hearted, and sincere hospitality.

You will have the pleasure of meeting with the Bishop of this unique and quite singular Church of Rome, the Holy Father John Paul II, and of receiving his word of encouragement and enlightenment for your mission, which can itself, correctly understood and lived, be compared with the dignity of the priesthood: that is to say, a mediation between the life of man and the eternal and infinite life of God.

It is, however, the duty of his Cardinal Vicar to offer you the first address of greeting.

Welcome, then, and thank you for the contribution which you will make in the ceaseless search for the good and development of human life, the image and mirror of the life of God.

The theme of the Conference, "Pharmaceuticals at the Service of the Human Person," may, at first sight, seem to slight what is a most noble discipline and profession, Pharmacology. In reality, however, the simple words "at the service of the human person," do express its scope and nobility in the interdisciplinary integration of Medicine: that is, the nurturing of human life, to which the whole of creation, macrocosm and microcosm, is directed in the loving design of the Creator, the first Friend of man and the guarantor of the inviolability of the dignity of his person, so fragile and vulnerable, but yet projected towards eternity.

The progress of medical science through the most sophisticated techniques the mind of man has elaborated continually evidences the interdependence of Medicine and Pharmacology. To exemplify this, one word alone is enough — immunology — in order to understand how the most arduous conquests in the sphere of the defense of human life, including organ transplants, can so easily be compromised without the support of the research and development of adequate drugs.

Nevertheless, this one example, although it makes many of you hold your breath, is but a small one, if we consider attentively the growing importance of medicines and drugs, the many sophisticated products which are connected with all the complex problems of life, sometimes to defend it and sometimes damaging it. Grave moral problems derive from this, both in the theoretical

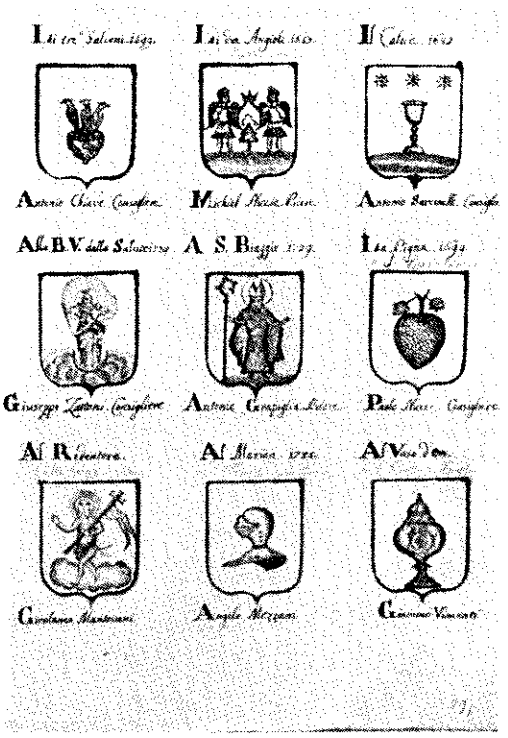
planning of drugs and in their development and use. This could be a most interesting and difficult topic among the official papers, deliberations, and addresses at this Conference.

The possibilities for good or evil that we have mentioned give rise to the necessity of submitting medications to a rigorous ethical code, particularly as regards their use and wide-scale distribution in the differing social classes in both the first and the third world, especially if, in their production, there are built-in interests stemming from a diversity of motivations, from the financial to the ideological.

Here too, a reference is in order: some developing nations are asking that many as yet unsolved moral and social problems be dealt with in a rational way, in a spirit of fraternal cooperation among peoples, with an open mind but also with rigorous faithfulness to the commitment of Medicine to the safeguarding, defense, and development of human life.

Christian teaching, always respectful of true scientific research and attentive to all the good or bad consequences this may have, is always a valid source of enlightenment for men of good will, uprightness of character, and quickness of mind that do not allow themselves to become the prisoners of mere curiosity or the allurements of advanced techniques, but rather are able to question and evaluate them in all their implications. Christian teaching stands alongside men of science in order to enlighten their path, to help them find an answer to the gravest anxieties of humanity in the realm of health and life; an answer that will not suffocate the expectations of the world of today, but will respect and value them.

With these brief reflections, which are really questions, not proposals for resolving the serious problems you have before you, I would like once again to offer you my best wishes for your work and our welcome and respect for your persons and your mission of such great responsibility.



Signs from the Venetian spice shops (eighteenth century).

Pharmaceuticals at the Service of Human Life

by Archbishop Fiorenzo Angelini

I am especially pleased to be able to present this First International Conference organized by the Pontifical Commission for the Apostolate of Health Care Workers.

The interesting nature of the theme, the prestige of the place, the authoritative competence of the speakers, the representativeness of the participants all illustrate the importance of this initiative and the commitment it evidences of those who, in the Church, work in the world of health and medicine.

The three areas the Conference touches upon (ethics of pharmaceutical planning, ethics and pharmaceutical research, ethics and the use of pharmaceutical products), all point to an underlying truth which links them together. The plea for life and health that arises from mankind, today as yesterday, is linked to pharmaceutical products. There is no progress in Medicine without development in Pharmacology and Pharmaceutics. At the same time, all the problems connected with medical science find an immediate point of contact in the planning, research, and development of medicines. Clear confirmation of this is the range of topics which this Conference is going to discuss.

I have always been of the opinion that the relationship between Medicine and medicines is a relationship of cause and effect, and that this has been so from the dawn of humanity. In fact, Medicine made its appearance, at the same time as Man, as a search for medicines, in that the first attempt at the defense and recovery of health was a search for the right medicine, the antidote to disease. Without wanting to force an interesting analogy, it seems to me that we can detect in that instinctive, but conscious sense of shame after the first sin, as narrated by the Bible, almost the precursor of the quest for medication, a medicine. It is significant that the Fathers of the Church and Christian literature in general speak of grace as a "medicine" and the virtues and spiritual values as "medicines."

The present vast cry for health that rises up from mankind is a vivid appeal, sometimes a desperate one, for Pharmacology and Pharmaceutics; and if the *research and use of medicines* involve grave and precise moral problems, no less do the planning and projection of medicines. In fact, the cry for health evidences some undeniable priorities, expressed, for example, in the area of so-called orphan drugs. It was for this reason too that we wanted to open what we hope will be a series of conferences on health and medical problems with a conference on medicines. The problems that they raise go beyond medical science and involve a philosophical, political and economic vision of society. Problems connected with the planning, research and application of pharmaceutical products call into question political power, economic forces, the use of resources, the destination of investments, and, for those who view

these things from a Christian viewpoint in the service of man, the very credibility of ethics and social morality.

There are problems where it is necessary to go back to ethical and moral principles so as to be able to evaluate them correctly and resolve them properly. There are others which need deeper study and the attainment of the targets of research. For both, an ethical and Christian vision does not represent a brake but an incentive to look with growing awareness at the primary and priority finalities of medicines. Such a sensitivity cannot either arrest or delay the progress of Pharmacology in all its branches, but rather stimulates and hastens it.

The scientists, researchers, and experts in ethics and morality who will be addressing this conference intend to move along these lines. May I be allowed to express our warmest thanks for their contributions and for the widespread interest shown in this conference. Such a promising start cannot but have promising prospects for the future.

A World on Its Way Towards Greater Solidarity

by Cardinal Paul Zoungrana, Archbishop of Ougadougou

Allow me to express my gratitude, as a representative of the Third World, to the organizers who invited me to this Conference; I thank especially Monsignor Angelini who, out of friendship, wanted me to come to this International Conference on the ethical aspects of pharmaceutical treatment.

The being of man is a unity; for this reason, a pastor cannot but be interested in the progress of Pharmacology, above all in its human and moral aspects. Indispensable human solidarity, which our modern world makes ever more evident, unites the destiny of men and nations. The disorders caused by the misuse of certain discoveries and inventions strike individuals and entire peoples who up to now did not even know they existed. It is therefore normal that mankind should share the benefits of good inventions and learn to use them for the good of all the components of the human family.

We Christians know that all men are united by a common vocation to filiation with Christ, who has freed us from the evil of sin; with Him we must learn to be brothers. With the intelligence and will bestowed on him by the Creator, man is capable of controlling both nature and his own happiness. Health is an important constitutive element of this happiness, to which all men and all peoples are called, with respect for their own individual dignity and originality. If, following Christ, man learns

truly to love his brothers, with all the demands that this implies, he will carry out to the full the rôle that has been assigned to him in creation, and he will make this earth more habitable for all.

In this context, we who come from the Sahel countries are very interested in these kinds of discussions, where scientists, pharmacists, and doctors share their points of view and work together in order to ensure a better future for mankind. In particular, experimentation and application of pharmacological products with a correct respect for the individual human being and society, which must be the aim of all service, is of great interest to us.

We therefore place confidence in such a highly qualified assembly; you represent for us a guarantee and a hope. A hope that, in all the types of conflicts of interest that can arise from pharmacological advances, man himself will not be forgotten, that entire peoples will not be overlooked by those who have in their grasp enormous possibilities of assistance. You are for us the guarantee that all this research will be placed at the service of Life, the dignity of man, and the glory of God, who is God of the living.

It is precisely in this sense that we greeted the establishment, on the part of Pope John Paul II, of the Commission for all those engaged in the field of health care. You must be the conscience of a world striving for greater justice, brotherhood, and solidarity.

With this Christian hope, I offer you the fraternal greetings of the Church which is in Burkina Faso.

cultivating: those living there must be the prime movers in this. But your conference has once again opened our eyes to solidarity in research and the betterment of health care for all peoples. The various discussions of these days struck me for their insistence on the need for cooperation and efforts your countries are making, together with the World Health Organization, to assist our nations in research for the betterment of health conditions through ever more effective products. A pastor of souls cannot but join with his brothers in the Third World to thank you for this cooperation and human solidarity.

Further, I was struck by the spontaneous and concrete gesture of the organizers of this conference, especially Monsignor Angelini, who, uniting words with actions, offered the Holy Father modern medical supplies of the highest quality for Third World countries and Poland.

On behalf of all our countries, those who represent them, allow me to express my own, and their, deepest gratitude. Your gift symbolizes your determination to further scientific reflection with true love towards those who have such need of your fraternal assistance.

May this Conference represent an important step forward towards a clearer valuation of man and his dignity, both in the sphere of pharmaceutical treatment and in all scientific research worthy of God and of mankind.

I thank you.

Words of thanks
from Cardinal Zoungrana

I am very happy and honored to have taken part in this Conference as a representative of the Third World. Although I am an outsider, the various topics that have been discussed interested me a great deal, and I was struck by the high quality of the discussions. I am confidently hopeful that it will give rise to a great good for mankind, especially for mankind in the Third World and the Sahel.

Our vast regions, still frequently scourged by infectious diseases, need clearing and

Tribute to His Holiness John Paul II

by Prof. G.B. Marini-Bettolo

Your Holiness, on behalf of the participants from many different parts of the world at this International Conference, I have the honor of presenting our warmest greetings and of expressing our gratitude for the fact that, notwithstanding your many and important engagements at this time, you are here with us today.

We accepted with enthusiasm the invitation to take part in this important meeting, attracted by the zeal and capability of Monsignor Fiorenzo Angelini, the tireless leader, with his collaborators, of this new organism, the Pontifical Commission for the Apostolate of Health Care Workers, the precious gift that You, Holy Father, guided by wise inspiration, have bestowed not only on the Catholic Church but on the entire world.

We have been called together to discuss a delicate theme which is one of the statutory tasks of the Commission and which concerns all nations: *Pharmaceuticals at the service of human life*.

In the course of these last decades of the century, Science has made extraordinary progress, and makes its influence felt, through technological advances, in an ever increasing way on modern society and on man himself.

For every scientist at work in any field of scientific research, the moral problem of the evil misuse of scientific discoveries is becoming ever more acute. If we are to ensure a future for the human race, then it is necessary that in the heart of every scientist and researcher, science — the desire to know — does not infringe moral principles. Pharmaceutical products are not exempt from this rule either.

At every stage of the development of a drug, from its planning to its administration to the patient, different ethical problems emerge with increasing urgency for the experts.

It is our desire that this Conference, the first of its kind, may develop new lines of action and behavior that combine the scientific and technological aspects of the development of new drugs with the moral and ethical aspects implicit in every stage of the elaboration of the product.

Holy Father, on the eve of a great event, promoted by your extraordinary love for mankind, the Meeting at Assisi to pray for the Peace of the World, we ask you to remember too the results of our Conference. They are the fruit of our collaboration as scientists and researchers, true seekers of peace. True science, medicine especially, in its interdisciplinary aspect and its mission to mankind, represents peace and fraternity among men.

Holy Father, all the participants from all the specific disciplines that work together to produce new and better medicines for man, the authorities that distribute them on a world-wide level, such as the World Health Organization, and on the national level, the researchers in state and industrial institutes, the doctors and pharmacists, the biologists and chemists, and all others here present who are involved in the sphere of health and medicine express their deepest gratitude to you for your presence among us and their most respectful recognition of your dedication to ensuring the advancement of mankind.

With filial devotion, we await, Holy Father, your word and your teaching.

First Session

The Ethics of Pharmaceutical Programing

RALPH F. HIRSCHMANN

Innovative Drug Invention: Criteria, Purposes, and Economic Aspects

Synopsis

The mission of those involved in drug discovery will be discussed. Its goal is to contribute to the physical and mental well-being of men and women, to reduce morbidity and mortality, to reduce pain and suffering, and to increase the ability of men and women to lead useful and productive lives. Such research must be purposeful and innovative. It must have as its goal to meet significant medical needs and to serve the individual patient.

The separate but interactive roles of academia, government and of the pharmaceutical industry in the drug discovery and approval processes will be mentioned. Some issues relating to the safety of medicines will be discussed. Emphasis will be placed on the contribution of vaccines and of drugs to mankind, such as their impact on both life expectancy and on the quality of life. These issues will be analyzed in relation to both the developed and the developing countries.

The promising role of ivermectin in the control of river blindness in the developing world will be discussed in scientific terms and in relation to the steps that are being take to ensure that ivermectin will reach those who need the drug.

The benefits to society from vaccines and medicines will be examined also in economic terms. The risks and costs involved in the drug discovery process will be analyzed. It will be pointed out that only one of perhaps 10,000 compounds synthesized and tested by the pharmaceutical industry will ultimately be approved by regulatory agencies. The time interval from initial discovery to approval is about 10 years and involves the expenditure of approximately $100 million.

It will be pointed out that the overwhelming number of our modern medicines are the fruits of an environment which promises a fair and reasonable reward for those who are prepared to take the risks and who have the skills, dedication and persistence to succeed in the art and science of drug discovery and development.

Issues relating to orphan drugs, use of animals in drug discovery will be mentioned. The opportunities for the future will be briefly examined. It will be suggested that the fruitful interaction of chemistry, immunology, biochemistry, molecular biology, neurobiology, and biophysics will allow the biomedical community to take great strides in the conquest of diseases such as dementia, atherosclerosis, inflammatory disorders, cancer and others. Finding the ways and means to make these medicines available to all men and women who can benefit from them will take at least as much creativity and imagination as their discovery.

Introduction

Professor Bloch, Ladies and Gentlemen,

First of all, I should like to express my deepest appreciation to His Excellency, Monsignor Fiorenzo Angelini for having given me the great opportunity to come to Rome to attend this very important conference and to meet such an extraordinary audience in this world-famous synod hall. As the biomedical sciences become more complex, it can only be of benefit to mankind that a body such as this distinguished conference is searching for a larger understanding of problems relating to drug discovery in the pharmaceutical industry.

It is the mission of all of us involved in drug discovery to contribute to the physical and mental well-being of mankind, to reduce morbidity and mortality, to reduce pain and suffering, and to increase the ability of men and women to lead useful and productive lives It is our purpose to provide agents which, whenever possible, prevent or cure disease or, at least, mask the disabling symptoms of disease. Such research must be purposeful and innovative. It must have as its goal to meet significant medical needs and to serve the individual patient.

We must seek to accomplish these ends with great concern that the drugs and biologicals which we make available to the physician are safe, and that a careful assessment of the benefit-to-risk ratios has been made. We must also have appropriate concern for the

animals which we use to discover and develop our drugs and biologicals. We must show due regard for the environment in which we live. Collectively, we must be sensitive to our humanitarian instincts and, yes — moral obligation — to make the miracles of modern medicines, preventive and therapeutic, available not only to those who can afford such entities, but also the poor, in the developed countries and in the Third World. In searching for solutions to these Herculean tasks, we must be careful to avoid simplistic proposals which fail to appreciate, or choose to ignore, the facts of drug discovery. Almost without exception, the drugs in the armamentarium of the physician are discoveries of the pharmaceutical industries of the developed countries. Few people outside that industry truly understand how difficult and expensive it is to discover and develop a new drug. The risks involved are very great. The overwhelming number of our modern medicines are thus the fruits of an environment which provides a fair and reasonable reward for those who are willing to take these risks and who have the skills, dedication and persistance to succeed in the art and science of drug discovery and development.

Let me now discuss some of these and other issues in greater detail.

The drug discovery process: its basis, achievements, and obligations

The roles of government, universities and research institutes, and industry

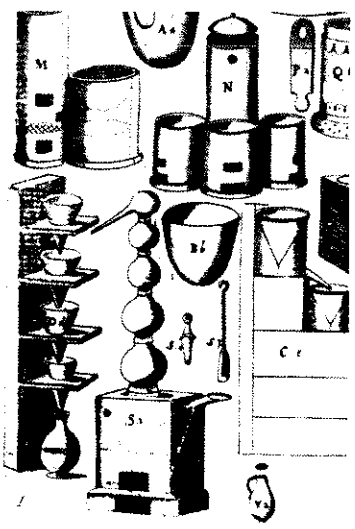
Many professionals play an essential role in the drug discovery process. These include scientists in universities and research institutes throughout the world, working in diverse disciplines in the physical and biological sciences. It is the university professor and the scientist and researcher who are in the best position to tackle long-term basic research programs. Very often these scientists do not envision any practical application or they perceive it only in rather non-specific terms. Those of us who work in the pharmaceutical industry are greatly dependent on this long-term basic academic research which is partly funded by industry, by foundations, and by philanthropic individuals, but which depends, for the largest part, on government support. It is the task of the pharmaceutical industy to *apply* basic knowldge in biology and chemistry, from whatever source, to the discovery of new medicines. This type of research is also difficult, because it has as its goal the synthesis of new chemical substances with *predetermined* physical and biological properties. This goal-oriented research is the raison d'etre for the pharmaceutical industry. I am convinced that we are in a far better position to undertake this part of the discovery process than our colleagues in universities and government, partly because interdisciplinary research, both basic and developmental, is our strength and because we are goal oriented in our endevors. Thus, I see universities, research institutes, government and industry as a team where each component plays its own essential role along a long and arduous path which culminates in the clinical use of safe therapeutic agents which represent a significant clinical advance. It is part of the responsability of those of us working in industry to design, implement and interpret appropriate experiments which test the *safety* of the products we wish to make available to the public. It is also our obligation to inform regulatory agencies and the physicians of the result of these studies as promptly as possible, especially when adverse reactions have come to light. Thus, the government plays a vital role, not only because of its funding responsibility referred to above, but also because the governmental regulatory agencies incur a profound moral and ethical responsibility in the approval process. On the one hand, the regulatory agency must insure that the drugs are safe and effective before they are approved, but, on the other hand, such agencies owe also a second obligation to the public: to insure that important new medicines and biologicals are made available to the physician as rapidly and expeditiously as is consistent with an appropriate concern for safety. Denying the public

access to new medicines which are safe and fill a need is a disservice.

It may be worth noting that intervention in life processes through pharmacological agents and at pharmcological doses is almost certain to be accompanied by some unwanted side effects in at least some of the patients treated. For the most part our "magic bullets" are not sufficiently selective, not sufficiently "magic," to avoid side effects altogether. We have a scientific understanding of some of these side effects Let me use the well-known lock and key analogy and let us call a given drug the key. If the lock associated with the *desired* therapeutic effect is indistinguishable from one or more locks associated with side effects, then the key will fit all of these locks and, as a result, it will, in most cases, not be possible to separate the desired from the unwanted effects. Thus, it is one of the most important responsibilities of the pharmaceutical industry, of the regulatory agencies, and of the physician to determine whether or not, in the case of a given patient, the benefit-risk ratio — that is to say, the potential for benefit versus the potential for adverse effects — justifies the prescription and administration of a given drug. Clearly, many different considerations will influence such a decision. For example, in the case of a cancer patient, therapeutic intervention with relatively toxic drugs may well be appropriate and useful, whereas use of such a drug would be unacceptable in a situation which is not life threatening. It will also make a difference whether a drug is to be given for a short period of time, or whether it is to be administered chronically. An antibiotic is often given for only a few days in a hospital setting, whereas an antihypertensive agent may well become lifetime therapy, taken by the patient in his home day after day. One must obviously have a greater concern for long-term safety in the latter case.

Increases in life expectancy

The medicines which have been developed by the major pharmaceutical companies throughout the world represent achievements of which we are proud, because they represent a remarkable record of service to mankind.



Benefits resulting from the discovery and development of innovative drugs may be measured in a number of ways. Reduction in the incidence of disease and an increased life expectancy are key measures of such progress. Since 1940, the use of drugs and vaccines has dramatically reduced the incidence of certain diseases. Great gains have been made in the improvement of health and the reduction of death rates in both the less developed and the more developed countries. Data from developed countries, especially the U S., provides the most complete assessment of the benefits of drug therapy. To the extent that relevant information is available to me from less developed countries, I shall include it in this presentation. Since World War II, the changes in life expectancy have been more rapid in the less developed region due to the expansion of previously limited or even nonexistent health care programs.

Life expectancy was measured in the less developed countries between 1950 and 1955 and again between 1975 and 1980. During this 25 year time interval, life expectancy in the Third World increased by about 13 years, from 42 to 55 years. This gain was at least as great as the gain between 1900 to 1950, a most encouraging result. In the more developed regions, life expectancy in the 1950's was about 65 years compared to 42 years for the Third World. Twenty-five years later, the gap had narrowed from 23 years to 17 years [1]

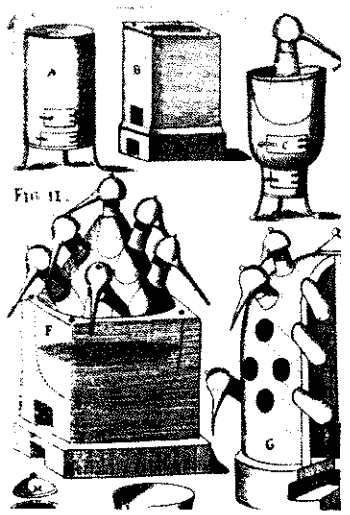
The eradication of smallpox, a major tiumph

One of the greatest advances in health care in the 20th century is the eradication from the face of the earth of that dreaded disease, smallpox. Vaccination against smallpox was introduced by Jenner in 1796, surely one of the milestones in the history of medicine. 131,697 cases of smallpox were reported in 1967, at the inception of the World Health Organization's intensified eradication program. This figure is undoubtedly low. It has been estimated by the World Health Organization that in that year there actually were 10 to 15 million cases of smallpox, 2 million of which resulted in deaths. Hopefully, the last case of naturally occurring smallpox was diagnosed in Merca, Somalia in 1977.[2]

The benefits from other vaccines

The U.S. Center for Disease Control recently conducted a benefit, risk, and cost study concerning immunization for measles, mumps and rubella. Based on prior trend information, it was estimated that without an immunization program there would have been 3,325,000 cases of measles in the U.S. in 1983. Because of the vaccination program, all but 0.09% of these cases were prevented Similarly, all but 0.2% of an estimated 1.5 million cases of rubella, and all but 1.6% of an estimated 2.1 million cases of mumps were prevented.[3]

Vaccines have also virtually eliminated diptheria and polio. There were almost 58,000 cases of polio in the U.S. three years before the Salk vaccine was introduced. In 1984, there were only 4 reported cases.[4] Equally impressive gains were recorded for the prevention of whooping cough. Data from the less developed countries is more limited. However, broad generalizations can be made. Reductions of the incidence of infectious and parasitic diseases, including cholera, measles, diptheria, and whooping cough have accounted for an estimated one quarter of the decrease in mortality in the less developed countries during this century. Preventive measures have thus resulted in a significant decline in deaths throughout the world.[5]



Ivermectin and river blindness, a breakthrough

Allow me to say a word about a novel, exciting approach to the control of onchocerciasis, one of the leading causes of blindness in the developing world. This desease, also known as river blindness, afflicts an estimated 40 million people. It is caused by a parasite, *Onchocerca volvulus* and is transmitted between humans by a genus of blackflies. These flies transmit larvae that mature into adult worms. These adult worms are usually innocuous, but their progeny, the microfilariae, migrate throuth the body tissues and cause severe lesions. The most serious of these lesions occur in the eye. Perhaps one fourth of the 40 million people afflicted by onchocerciasis suffer from ocular tissue damage. In some villages in the endemic areas of Africa over 15% of the population may be blind because of this disease.

Unfortunately, there has been no suitable method to treat or prevent this devastating disease. Chemotherapy has been limited to two drugs, diethylcarbamazine (DEC) and suramin. DEC, the drug of choice, is plagued with a variety of severe adverse effects and complications, and it must be administered daily for seven to ten days under medical supervision. Suramin, either as alternative or as added therapy, must be given intravenously once every week for at least six weeks and it can also cause very serious toxic

effects. Therefore, neither drug is suitable for safe or practical mass chemotherapy.

I am proud to say that the Merck, Sharp & Dohme Research Laboratories have discovered a drug called ivermectin which has recently given exciting promise to the chemotherapeutic approach to the control of the disease. Ivermectin is a derivative of avermectin B^1, one of a family of macrocyclic lactones produced by the actinomycete *Streptomyces avermitilis*, which are anaerobic bacteria. Ivermectin is active in single low doses against a wide variety of animal parasites, including nematodes (roundworms) and arthropods (insects, ticks, and mites). In 1982 Aziz et al. reported the first experience with ivermectin for the treatment of onchocerciasis in humans.[6] A single oral dose 30-50 ug/kg was found to drastically reduce, with minimal toxicity, the density of the dermal microfilariae. The microfilariae can migrate in and out of the eye. We believe that the safey of ivermectin is due in part to the fact that this drug does not get into the eye and that it therefore kills the parasites elsewhere in the body without causing any serious problems. Follow-up studies seven to eight months after therapy showed a sustained reduction of microfilarial density in most patients.

A further study investigating a range of doses was conducted in Tamale, Ghana; single oral doses were used in patients with heavy loads of dermal microfilariae, some of whom had ocular involvement. Invermectin was confirmed to be an effective microfilaricide; moreover, the dermal microfilarial density decreased slowly, without causing the ocular damage reported with DEC. The dermal microfilarial density remained near zero for at least 12 months after doses of 100 to 200 ug/kg. Microfilariae decreased in number in the absence of any adverse ocular reaction and disappeared by three months after treatment.

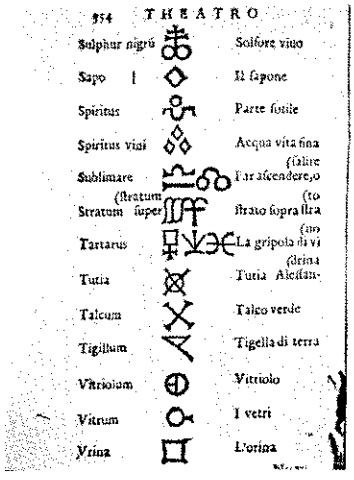
Double-blind studies comparing the efficacy and safety of ivermectin, DEC, and placebo in patients with a high dermal microfilarial density and (in most cases) ocular involvement have been completed recently in Senegal, Ghana, Mali, and Liberia. Data from all four studies confirmed earlier findings. Thus, the administration of a single oral dose of 200 ug of ivermectin/kg every few months is expected to be relatively safe for both men and women.

The evidence discussed suggests that onchocerciasis may perhaps be controlled by the administration of ivermectin as a single oral dose twice yearly in uncontrolled hyperendemic areas and possibly once yearly in vector-controlled areas and in savanna areas, where transmission occurs only during the rainy season.

If ongoing studies confirm the findings that have been described regarding efficacy and safety, ivermectin may prove to be a major breakthrough in the treatment and control of this devastating disease.

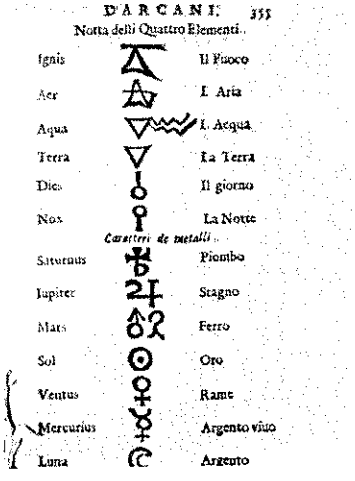
Will ivermectin reach those who need it?

While this scientific breakthrough is most gratifying, it is clear it will not fulfill its promise to the developing countries if this compound cannot be made available to those who need the medicine. Happily, it is clear that this problem is being addressed, although details remain to be worked out.



Merck & Co and the WHO have collaborated extensively on the development of ivermection for onchocerciasis. Merck intends to continue to cooperate with the WHO, the Onchocerciasis Control Program, and endemic country governments in their efforts to develop and implement programs so that the drug, when approved for use, can be distributed efficiently

The special circumstances of this disease and the interest of several organizations and governments have caused Merck, from the outset, to consider ways of accommodating a variety of objectives. First and foremost is ensuring that the drug will be put to optimum use for the benefit of onchocerciasis patients and others who may run the risk of developing this disease. The Company concluded that the best way to achieve the full potential of ivermectin was to find ways to ensure that the economic circumstances of patients and governments in onchocerciasis-endemic areas would not prevent or restrict widespread use of the product once it is approved. Consequently, Merck, in collaboration with other interested parties, is undertaking to make appropriate arrangements to make needed quantities of the drug available to these governments and patients, at no cost to them, for the treatment of onchocerciasis.



Alchemistic-pharmaceutical symbols from Ludovico Locatelli's Theater of the Arcane *(Venice, 1667).*

Quality of life

Fortunately, the discovery and use of new biologicals and of medicines have not only increased life expectancy both in the developed and in the developing countries, but they have also improved the physical and mental quality of life. Many diverse examples can be cited Because of time constraints, permit me to give only a few illustrations. The treatment of patients suffering from rheumatoid arthritis with anti-inflammatory drugs often pemits these patients, who might otherwise be bedridden or confined to a wheelchair, to go to work and to lead productive lives. Modern medicines also improve the quality of life for individuals suffering from congestive heart failure. As a result, these individuals and their families can enjoy life more fully. As you know, asthma is another disease which severely limits the ability of patients to lead normal, productive lives. Here again, treatment with modern medicines has provided a significant measure of relief to asthmatics. The treatment of patients suffering from Parkinson's disease with appropriate medicines has contributed much to permit them to lead more normal lives.

I should state clearly that often available medicines and biologicals are by no means optimal. The pharmaceutical industry therefore has the responsibility to devote part of its resources to the discovery of drugs or vaccines which maximize the therapeutic or preventive benefits in relation to the unwanted effects.

Societal economic benefits resulting from drug discovery

So far, I have talked about the benefits provided by drugs primarily in terms of reduction in morbidity and mortality, and in improving the physical and mental quality of life. I should now like to say something about the economic benefits to society and to governments. The fact is that medicines are the least expensive forms of medical therapy and that they substantially reduce overall health care costs. For

example, it has been estimated in studies by Arthur D. Little, Inc. that in the United States alone beta adrenergic blocking agents might save as much as $3 billion a year in health care costs when used to prevent second heart attacks,[7] and that the annual benefit of their use in treating glaucoma may be in the order of $700 million because they can make eye surgery unnecessary.[8]

The advent of a new class of antiulcer drugs, typified by cimetidine, has had a marked impact on the direct and indirect costs of this illness. The introduction of cimetidine in the United States by Smith Kline Beckman in August of 1977 coincided with a dramatic decrease in the rate of hospitalization for peptic ulcer disease in young adults, in a decrease in the need for surgery, and a marked decrease in the number of days lost from work. One study indicates that the number of surgeries in the U.S. was 21,000 to 31,000 fewer than would have been predicted from the trend before 1977.[9]

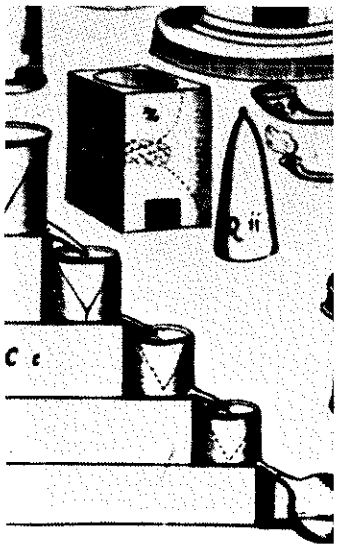
In the United States the rising costs of hosital confinements have become a matter of profound concern. They contribute by far the major expense of medical care. By contrast, medicines make up only 5% of what the United States spends on health care.[10] For this reason, drugs such as antibiotics, which shorten hospital confinement and which often eliminate the need for surgery, are of enormous economic benefit to society.

Allow me to cite a few additional examples. It has been estimated that the use of polio vaccines has saved more than $1 billion per year between 1955, the year before the Salk vaccine was introduced, and 1961, when the Sabin vaccine was introduced in the United States.[11] Similarly, the measles, mumps, and rubella immunization programs mentined earlier may have saved $1.4 billion in 1983 alone. Based on the actual incidence of the disease, the costs of treatment, plus the costs of the vaccination programs, the resulting benefit-cost ratio was about 14 to 1.[12]

Unfortunately, there are few cost-benefit studies of immunization programs in developing countries. Those that do exist strongly support the health and economic value of such programs. Actually, the costs of vaccines themselves represent only a small part of the overall expenses. The delivery systems are the most significant impediment to expanding the scope and efficiency of these programs. This is clearly a challenge for the governments of the developed and developing nations and to the World Health Organization.

The cost of drug discovery

The cost of discovering, developing and producing new chemical entities is high for a number of reasons. First, we must consider the risk involved. On average, more than 100,000 compounds have to be tested to generate approximately 100 Investigational Drug Applications. These are applications which have to be filed with the U.S. Regulatory Agency and approved before clinical studies may be undertaken. Of those 100 compounds which enter the clinic, only 10 are eventually approved. In other

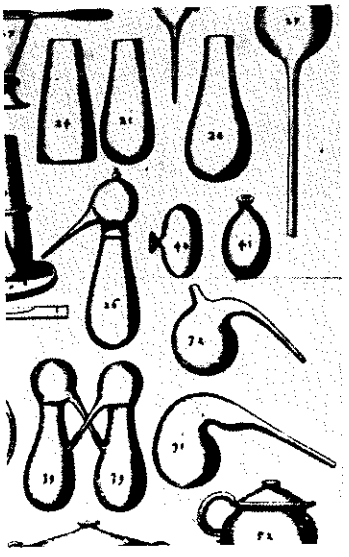


words, only one out of 10,000 compounds synthesized and evaluated eventually becomes an approved drug. The discovery program, the safety assessment studies, and the clinical trials of one new drug cost about $100 million, and more than 10 years are required for these studies. These are long lead times and staggering odds. Thus, when a new medicine is approved and launched, $100 million will have been spent, exclusive of capital expenditures, 10 years will have elapsed, whether the product subsequently produces annual sales of $20 million, or — in rare cases — $100 million per year.

I want to stress that the income from that one compound — after 10 years time and $100 million of Research & Development costs — must not only pay for its own arduous journey toward approval by regulatory agencies, but it must pay also for the synthesis or isolation and for the testing of the remaining 10,000 compounds which fell by the wayside somewhere along that difficult obstacle course that is our business.

A turning point in the economics of drug discovery came in 1962 with the amendments made to the Food, Drug and Cosmetic Act in the United States. The lead time from a basic research discovery to approval of a new product has doubled since 1962. This longer lead time and the related increased testing requirements have more than doubled the total cost of developing a new drug since the pre-1962 era. Effective product life has been shortening as well. For example, remaining U.S. patent life when a new medicine has been approved by the U.S. Food and Drug Administration has fallen from 17 years pre-1962 to seven years as of 1981. The U.S. patent restoration act will ameliorate this problem, but this legislation will not really have an impact until the late 1990s. Finally, the inroads made by generic competition have drastically lowered the level of sales which may be counted on by innovative, research oriented pharmaceutical companies after patent protection ends.

It is, I believe, a fact that effective drug discovery has been restricted to only a few countries and that in these countries the important new contributions to therapy have emerged primarily from the pharmaceutical companies, which must operate at a profit. Countries that lack such companies have not contributed significantly to new drug discovery, even when there is government supported biomedical research. The Office of Health Economics studied the seven nations that account for more than three-quarters of world pharmaceuticals — the U.S., the U.K., West Germany, Switzerland, Japan, France, and Italy. One conclusion of the study is that "The past success of the pharmaceutical industry, in these countries, has been due largely to a good balance between the need to encourage a profitable research-based industry and the need to keep pharmaceutical expenditures down to reasonable limits."[13] Ways and means must therefore be found to make these medicines available to all mankind without denying a fair return to the pharmaceutical industry, which discovers and develops these medicines and biologicals.



Orphan drugs

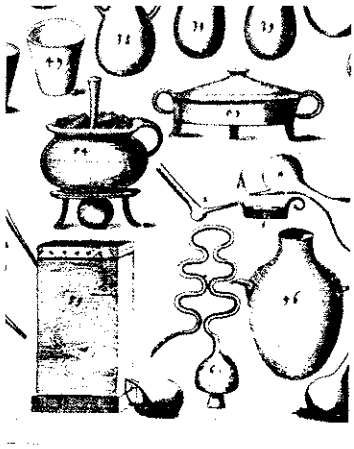
The pharmaceutical industry has long provided drugs to treat rare diseases for which companies expect there will be only a very small market. The production and marketing of such drugs are usually undertaken because of a company's specialized expertise in either development or manufacturing. These products are called "public service drugs" or "orphan drugs," because the estimated patient population for such a drug may be as low as 100 patients.

Merck & Co., Inc. has played its part by creating such public service drugs. Over the years, when opportunities have arisen, we have developed products that may be needed only by a relatively few patients.

In 1978, our application for approval to market the enzyme ELSPAR, our brand of L-asparaginase, a new drug for leukemia, was approved by the FDA. The history of this drug is illustrative of the kind of service offered by innovative companies. In 1967 we undertook to develop the enzyme because it appeared to be useful in the treatment of certain leukemias. It took more than 10 years of effort working with the National Cancer Institute to obtain an approved New Drug Application for ELSPAR. During this period, through the expenditure of millions of dollars, we were successful in developing a production process which makes it possible to provide the enzyme in the quantities needed and at a much lower cost.

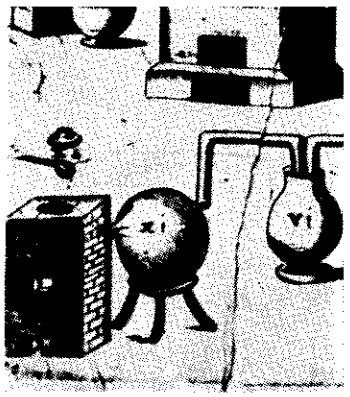
ELSPAR has only a limited market, and we will probably never recover all the expense of this effort. However, we consider the effort to have been fully justified as a contribution to society.

Among our other public service drugs are: COSMEGEN, for treatment of Wilms' Tumor; DEMSER, to control the elevated blood pressure associated with pheochromocytoma, a rare adrenal gland tumor; INDOCIN I.V., used to correct a heart defect in certain premature infants; and, finally, Merck's most recent public service drug CUPRID, for the treatment of Wilson's disease, a rare genetic disorder of copper metabolism. I should stress that between 1983 and 1986 the Food and Drug Administration has also approved an additional eleven orphan drugs from other pharmaceutical companies.[14]



The use of animals in drug discovery

There are individuals who oppose the use of animals in biomedical research, partly because this practice is thought to violate the "rights" of animals and also because it inflicts on conscious beings avoidable pain and suffering. It is beyond the scope of this talk to explore the moral, ethical, and religious basis for the opinion that the use of animals in biomedical research is justified because of the benefits such research has brought and continues to bring to mankind, and yes, also to livestock and to pets. It seems clear to me that the use of animals continues to be an absolute requirement if biomedical research is to continue. Having said this, I hasten to add that we must surely be mindful of our obligations to animals. We must, of course, comply with the laws governing the care and housing of laboratory animals. We must seek to minimize the number of animals used wherever possible. For example, we should seek to substitute *in vitro* for *in vivo* testing when the former method can provide the required information. But it is clear that *in vivo* testing will never be replacable by *in vitro* testing across the board. We must provide clean and appropriately sized caging for animals and we should use primates only when other species cannot provide the required information.



we do not presently have any therapy that truly arrests the progress of the diseases. Examples are dementia, atherosclerosis, rheumatoid arthritis, osteoporosis, and others. Finding the ways and means to make these medicines available to all men and women who can benefit from them will take at least as much creativity and imagination as their discovery.

RALPH F. HIRSCHMANN
Merck Sharp & Dohme Research Laboratories
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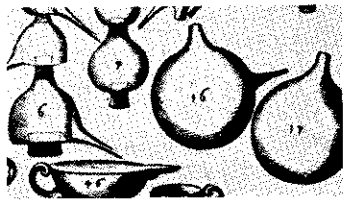
Outlook

Finally, let me take just a moment to look to the future. During the past ten years or so, we have witnessed a dramatic change in the drug discovery process. There is today less random screening but instead a greater emphasis on a rational approach to drug *design*. There is a greater tendency to think of intervention in life processes in molecular terms. In my opinion, the impact of molecular biology and of genetic engineering will vastly alter the drug discovery process. The fruitful interaction of chemistry, immunology, biochemistry, molecular biology, neurobiology and of biophysics will allow the biomedical community to take great strides in two respects: first in finding new medicines where existing therapy leaves something to be desired; and secondly, for illnesses where



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Engraving with the portraits of famous druggists from Antonio Sgobbis' Pharmaceutical Theater *(Venice, 1662).*

BERNARD SCHNIEDERS

The Medical Value of Innovative and Non-Innovative Drugs

I. Introduction and definitions

Before we begin to consider the medical value of innovative and non-innovative drugs, we must define what a drug is and what it can do.

In human medicine, *drugs* are substances which, when used on or in the human body, heal, relieve, prevent or diagnose disease, suffering, injury, or discomfort.

The *effects* of drugs are understood to include all reactions caused in man or animal, in vivo or in vitro, which are measurable, feelable or otherwise observable.

The *effectivity* of drugs, on the other hand, implies medical judgement of the degree to which the actually observed effects achieve the desired or expected therapeutic benefits. It is the sum of all wanted effects in a specific therapeutic situation.

Safety means that the predictable risk of unwanted effects is medically justified by the expected effectiveness.

II. Value-determining factors

The *value* of any treatment is based on its ability to prolong life expectancy or improve the quality of life, that is, the freedom from physical and mental suffering and disability.

The individual user of a drug usually expects quick and complete alleviation of his complaint. His asks the physician to restore his health. If he is given a drug therapy, then he will evaluate the value of this therapy according to the degree to which his expectations have been met.

In daily practice, the physician is faced with a person as a whole and in a specific environment. The physician evaluates the success of the therapy and therefore the medical value of the drug on the basis of the effects on this entire personality.

The *medical value* of any drug is not only dependent on the characteristics of the drug itself, but also on the appropriateness of the situation in which it is used and its proper application. This is true for any drug, innovative or non-innovative. Therefore, let me first try to identify the factors which determine the medical value of a drug before describing the advantages and disadvantages of innovative and non-innovative drugs and, lastly, the value of drugs in general.

A) Product dependent

Drugs must be effective for the indications claimed, their unwanted effects should be medically justified by their wanted effects, and they should have good pharmaceutical quality.

The benefits of drugs are limited by the possibility of the occurrence of harmful and unintended reactions which can be caused by the active or the auxiliary substances, even when the drug is used properly.

Since characteristics of the physical or psychological make-up vary greatly among individuals, certain unpredictable risks are unavoidable. The importance of the unwanted effects varies widely according to the organ or system affected, its severity, the frequency with which it occurs and whether the effect is reversible or not.

Unwanted effects can occur with every drug and cannot always be predicted for individual patients. Allergic reactions can occur in individual patients at any dose. Such dose-independent reactions — skin changes, minor or serious changes in the immune system with changes in the make-up of the blood and anaphylactic shock with risk of death — must be anticipated. The patient can only be protected from contact with the substance after the first reaction has already taken place. Dose-dependent side effects are easier to predict.

Usually the difference between the dose which is therapeutically effective and the dose which produces damage, the therapeutic range of a drug, is relatively large so that, even considering individual differences, side effects caused by an unintended overdose are rather improbable.

There are some drugs with a narrow therapeutic range — digoxin, for example — which can cause serious unwanted effects when an overdose is taken — especially when excretion is disturbed by reduced kidney function. In addition, some drugs have unwanted effects even in the therapeutic range. For example, cytosta-

tics used to fight cancer affect the cell division mechanism of the quickly dividing cells such as those found in the hair and the mucous membranes just as harmfully as they affect the cell division of the tumors. The use of drugs with narrow therapeutic ranges of toxic mechanisms of action is only justified by life-threatening diseases.

When a drug is intentionally used improperly — for suicide or because of addiction, for example — the user does not want to utilize the healing properties of the drug, but rather the toxic effects which are expected at high doses. An intentional "underdose" or a too short period of intake can also cause damage when a disease which requires therapy is left insufficiently treated; such is the case for diabetes or bacterial infections.

In these cases the non-effectiveness or unjustifiable unwanted effects are not caused by the drug itself, but rather by erroneous human behavior and thus do not affect the value of the drug itself.

Modern drug laws require that a pharmaceutical manufacturer present adequate pharmaceutical, pharmacological/toxicological, and clinical evidence of the efficacy, safety, and quality of his product before it is placed on the market. Thus the physician and the user can assume that an approved product is safe; that is, that according to the state of knowledge at the time of approval the probability and the medical importance of the beneficial effects of the product justify the possibility and the severeness of the unwanted effects.

But even drugs which are considered to be effective and have been correctly applied do not work with the same quickness or intensity and do not continue working for the same period of time when used by different individuals. A physician must always carefully observe the individual reactions of the patient during treatment.

B) Appropriateness

However, as I have said, the medical value of a drug does not depend on the characteristics of the product alone, it also depends on the appropriateness of the situation in which it is used and its proper application.

First, the right drug must be used for the right condition. This requires precise diagnosis and the choice of the most appropriate therapeutic strategy.

Obviously, a drug which is effective in the treatment of a certain disease can only be used appropriately when the related diagnosis has been made properly. The use of the methods of differential diagnosis increases the probability that the most appropriate drug therapy will be chosen. Unsharp diagnoses such as "vegetative dystony" and "organ dysfunction" decrease the probability that the therapy chosen will be optimal.

The choice of the best possible drug therapy requires a consideration of the individual risks and benefits of all possible therapeutic alternatives. Of course, the inherent risk of the disease itself must be included in this consideration.

A drug should, therefore, be used only when there is a high probability that the benefit for the patient in his specific present situation will outweigh the eventually expected risks of the product, and the probability of harm through non-treatment or alternative therapies is higher.

The correct choice of a drug therapy requires a broad knowledge of the advantages and disadvantages of possible drug — and alternative — therapies. We can, therefore, assume a direct dependence on the amount of knowledge available about the causes and mechanisms of the disease, the effects of the possible therapies, both positive and negative, and the education and continuing education of health professionals.

Physicians, pharmacists, and users must be kept constantly up-to-date about those effects of therapies which affect the benefit-risk evaluation for the therapy.

Since about 50% of the knowledge of a physician is out-of-date within 10 years, a constant information process is absolutely necessary.

Modern drug laws require that officially controlled professional and user-information sheets be provided for each product. The consumer information should be oriented to the needs of the user and be written in language he can understand.

Only use which is appropriate to the indication/diagnosis and the observance of

the special characteristics of the patients can produce the expected therapeutic effects and prevent drug-induced harm to the patient.

Drug therapy should be reduced to the minimum necessary for the individual patient considering the individual benefit/risk relationship and the possibilities of alternative strategies. Drug use is only justified when the specific situation of the individual patient allows the conclusion that the probable development of the disease without intervention would, in the long run, be more intolerable to the patient than the supposed development when drug therapy is used.

Not everything that can be done should be done; the inviolability of the dignity of man and the right to self-determination must guide the physician's actions.

Special consideration should be given to borderline situations of the human condition such as the terminal stages of incurable diseases. The value of the prolongation of the death process is questionable. In this situation, the patient should have the opportunity to die with dignity. The patients should have the right to choose between a shorter life of higher quality or a longer life with lower quality.

Furthermore, since treatment infringes on the physical integrity of an individual and therefore affects his right to self-determination, the person affected must be informed about the therapy in a way which is appropriate to his needs and level of knowledge and must give his consent.

The provision for basic human rights, including freedom of choice, also requires that the type of therapy be chosen by the individual, whether this therapy is scientifically or traditionally based.

C) Proper use

Even after the best possible therapy has been chosen, it must be applied properly. The patient must follow the directions on the package insert or the doctor's order.

The compliance by the patient, that is, the strict observance of the doctor's orders, requires that the mechanism of the disease be known and that the physician inform the patient about the disease — its probable development, treated and untreated — as well as the probable effects of the drug used.

The observance of doctor's orders is, in turn, also determined to a large extent by the trust of the patient in the skill and judgement of his physician; that is, the physician-patient relationship. Patients have become more questioning and critical. The fear of drug risks has lowered the willingness to use drugs as directed. We must remember that drugs can produce harm to health — harm from intended or inintended improper use or from misuse — but also harm from non-use, especially with conditions without disagreeable symptoms over a long time period, as may occur with high blood pressure and some thyroid diseases.

In order to assure proper use of the drugs — especially OTC-drugs — consumers must also be kept informed.

The use of drugs for self-medication for minor aches and pains requires both information about the drug and general health knowledge. The better general health knowledge and the stronger the motivation for healthy habits and lifestyles, the more appropriately the drug will be used and, therefore, the greater value the drug will have. Distribution of health information which contributes to thoughtful and health-conscious use of drugs is thus necessary.

Self-medication is the most economical therapy for minor and transient illnesses such as colds, headaches, travel sickness, and constipation. These drugs are usually mild and generally have few side effects. They usually provide relief after only short periods of use at low doses.

The public must be kept aware of the dangers of these minor diseases and the necessity to contact a physician when the symptoms continue or become worse.

We have considered factors which influence the value of drugs. Let us now consider the different values of innovative and non-innovative drugs. First, what do we mean by innovative and non-innovative drugs?

III. Innovative vs non-innovative

A) Definitions

Non-innovative drugs are drugs whose active substances are known to medical science; that is, substances which are now used in medical practice. We also mean new drug products whose active substances are almost identical to known substances when these new drugs do not have therapeutic advantages over presently used drugs.

The non-innovative drug products also include generics. These are copied products whose medical value can be considered to be the same as that of the original product when the amount of active substance and labelling are identical and the pharmaceutical quality and bioequivalence are guaranteed. A generic which copies an innovative drug must therefore also be considered innovative when considering its use in practice.

Traditional medicinal products such as herbal remedies are also, by definition, non-innovative drugs.

Innovative drugs are drugs which, at the time of their introduction to the market, represent new therapeutic principles or an improvement over old ones.

The advantages of these drugs are based on provision for

— treatment of previously non-treatable diseases

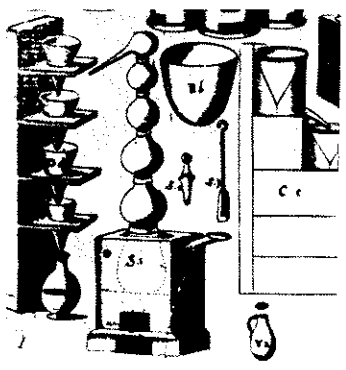
— treatment of causes rather than symptoms

— treatment which is more effective

— treatment with a reduced rate of occurrence of unwanted effects through dose-reduction or more exact dosing

— use of new application forms such as slow-releasing or transdermal systems whose use can improve safety.

As we have seen, the value of a drug depends on its proper use for the proper conditions and, therefore, to a large extent on the knowledge of its effects. The nature of this knowledge is different for innovative and non-innovative drugs



B) Knowledge

In general, for *non-innovative drugs* we have much practical experience with wanted and unwanted effects, but very often little theoretical knowledge of — for example — the mechanism of action.

The individual physician is, normally, dependent on published or personally communicated experience of other physicians when he does not have enough comparable cases to make his own benefit/risk assessment of a drug. This is especially true for the assessment of the drugs for long-term treatment or for treatment of patients with special risk factors such as kidney or liver misfunction.

The amount of knowledge about non-innovative substances is usually greater when the drug has been reevaluated according to modern drug laws. This review includes the collection and evaluation of all documentations of investigations of efficacy and safety, and reports of practical experience, and an assessment of the benefits and risks of treatments with this drug.

In spite of all this, the safety of these drugs can, and should, be improved by risk-reducing measures such as monitoring for rare unwanted effects. The use of non-innovative substances is however, generally considered to be relatively safe.

All *innovative products* require approval. Since for the approval of a new substance the results of pharmaceutical, pharmacological/toxicological,

and clinical investigations must prove that the substance is of good pharmaceutical quality, safe and therapeutically effective, the theoretical knowledge of the wanted and unwanted effects of the substance is generally good. In the approval process, the benefits of the product for the therapy of a specific condition are weighed against the risks of the drug and of the condition itself.

However, the decision on the efficacy for a specific indication is based on data which have been derived from a relatively small and select group of patients. The relevance of these data for use in practice when patients are subject to many influences and can have many concurrent diseases is not automatic.

The safety of a product is not necessarily guaranteed for each individual since very rare unwanted effects cannot be excluded by clinical trials with the usual number of patients. For the discovery of an effect which occurs in one of one hundred thousand patients, on the average, about three hundred thousand test persons are needed. Thus a new drug may seem to be more safe and effective at the time of approval than it turns out to be in practice.

Because of this, prescriptions are automatically required for new drugs so that they will receive special attention from physicians as to their safety and effectiveness in practice.

Until now the frequency of reports of unwanted effects has reached its peak about three years after placement of a new drug on the market.

Thus for innovative drugs we often have great theoretical knowledge, but little practical experience. A greater probability of benefit from innovative drugs must be weighed against a possible unknown risk, which can never be excluded.

An evaluation of the appropriate position of innovative drugs among alternative strategies can be made only after they have been tested in practice; the medical value of the drug can be determined only later.

IV. Value of drugs for society

In spite of the fact that drugs can affect individuals negatively, I don't think we can doubt the benefits that drugs have brought society.

A) Benefits

The benefits of drugs for society can be assessed exclusively by the average degree of alleviation of complaints, the number of people suffering from the complaint treated, and the seriousness of the complaint.

Drugs can be measured by the benefits from the therapy in many patients suffering from the same kind of disease. Progress in drug therapy has been made in the past through earlier innovations; here are a few examples:

— the prevention of disease by innoculation for measles, influenza, polio, etc;

— greatly improved chances of recovery from infections, acute childhood leukemia, Hodgkin's Desease, and ulcers;

— effective longterm therapy for diabetes, growth disturbances, and hemophelia through substitution of substances missing in the body;

— supression of the symptoms of high blood pressure and rheumatic disease;

— reduction of the risk of surgery in spite of increasing complexity through progress in anesthesia and post-operative care methods;

— surgical treatments for many heart and brain diseases and organ transplantations which are made possible by new drugs.

Furthermore, the development of new therapeutic principles, such as for example, the principle of calcium antagonist therapy for high blood pressure and heart disease have greatly contributed to progress in the treatment of these diseases.

Developments must not, however, take place in large steps. Improvements in the range of effectivity through variation of molecules, better tolerance, increased bioavailability, extended shelf-life, more exact dosability or more comfortable and safer application of older drugs can represent great advantages to the consumer.

New indications for drugs with already known risk profiles — for example, the use of acetylsalicylic acid for the prevention of thrombosis — or the development of new ap-

plication forms or therapeutic systems which make it possible to employ a specific amount of a drug continously for a long period of time also represent improvements.

As a whole, the value of drugs for health care is largely unquestioned and hardly replaceable by alternatives. It has been estimated that drugs contribute to about 80% of all healing, either as a determining or contributing factor. The use of drugs has allowed a prolongation of life expectancy and an improvement of the quality of life.

A complete renunciation of drugs would result in an absolute prevention of unwanted drug-effects.

However, this could only be obtained at the cost of the benefits received from drugs. If we consider the dangers of many diseases which, left untreated, inevitably lead to death or years of suffering and disability and the fact that absolutely safe alternatives do not exist, we must come to the conclusion that drugs are necessary.

A reduction in the use of drugs would, however, be possible if unhealthy life styles — inappropriate nutrition, overuse of alcohol and cigarettes, etc. — are avoided and the threshold of tolerance of suffering from minor disorders (pain, sleep disturbances, annoyances, worries, stress, etc.) is raised. This can only be achieved when it is generally recognized that, although drugs can heal, they cannot heal everything.

B) Future innovation

There is, however, a general public desire for improvements in restitution of health and reduction of discomforts which requires improvements in the drugs available as a part of medical services.

Strategies for innovation are, therefore, desirable

—for the treatment of diseases which cannot yet be causally treated, such as tumors, tropical diseases, defective immunological processes, and degenerative processes;

— for the prevention of mass diseases caused by unhealthy lifestyles and epidemics;

— for the early detection of diseases;

— for the treatment of serious diseases which affect only a few people in each area — orphan drugs — but are worldwide.

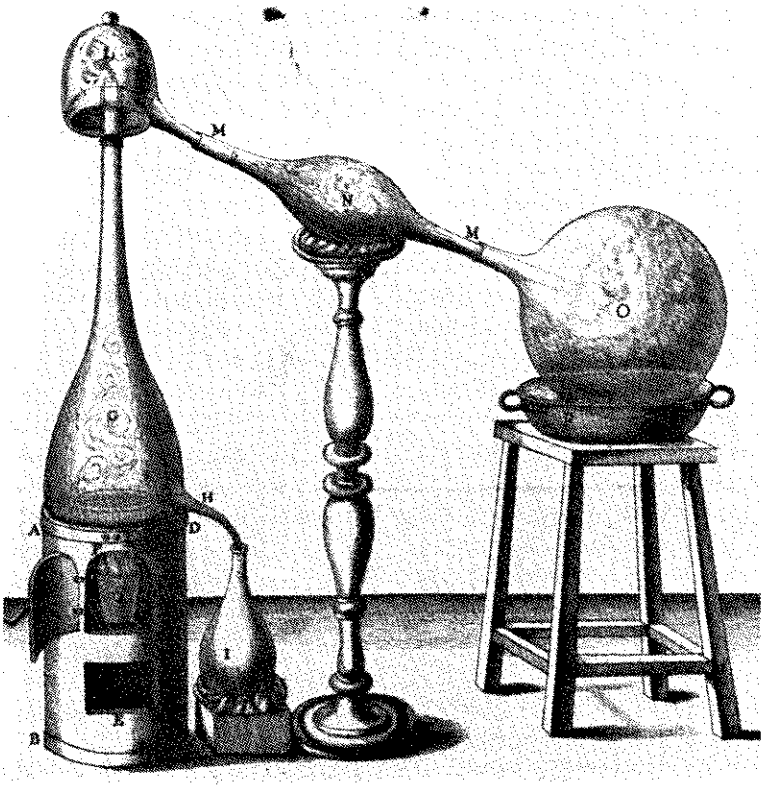
Although the goals of pharmaceutical research are broad, the number of innovations is decreasing. The inductive-empirical discovery process has reached a critical boundary and must be replaced by a deductive-analytical process which requires intensive basic research on etiology and pathological processes.

V. Conclusion

In conclusion, let me remind you that even optimal health behavior and conditions cannot prevent illness and suffering. The use of drugs has allowed a prolongation of life expectancy and an improvement of the quality of life.

The value of drug therapy to any society is thus dependent upon the importance placed on the length and quality of life in that society and is thus embedded in the entire value system of the society. These values are reflected in health policies, whose conception and execution are influenced by cultural, religious, philosophical, ideological, social, and, increasingly, economic factors.

The medical value of drug-therapy is dependent on the actual living conditions of a society as seen in the general environment, the medical service system, the availability of resources, the infrastructure, etc. Varying conditions must lead to varying assessments of the medical value of drugs in general and of specific drugs in each country.



If the highest possible life expectancy and best possible life quality are desired, then preventive medicine — diagnosis and therapy — is needed, and individuals will need therapy.

The physician acts on the principle that each individual patient should get the best possible treatment. Therefore, after making a precise diagnosis, the physician should consider all alternative therapies and choose that therapy with the greatest promise of healing and the smallest risks. The desires and the personal suffering of the patient must be carefully considered: false hopes should not be raised and unnecessary fears should be avoided

If no non-innovative therapy is adequate or if the therapies available have unjustified risks or if a greater benefit is expected (for example, with life threatening or acute serious diseases) so that a larger risk can be justified, then innovative drugs should be used. If, however, known drugs are available which produce adequate results with justifiable risks, the non-innovative durgs should be used.

Physicians must usually consider two aspects: the need for therapy and the costs of therapy — so that in the choice among therapies of the same value the cost/benefit relationship must be considered. This is true not only for choices among drug products — innovative versus non-innovative drugs, scientific versus traditional drugs, original versus generic drugs

The considerations should adequately reflect the principle of the best possible therapy and do not influence the specific medical value of the use of innovative or non-innovative drugs.

Innovative drugs which offer large advantages over previous drugs will quickly gain acceptance. Those which offer only minimal advantages will first be used only in the special cases in which this small advantage is so decisive that the increased risks are justified. In both cases, it is only a matter of time until a new drug becomes known in medical science and take its proper place among alternatives; that is, until an innovative drug becomes a non-innovative drug.

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Innovation: A Great Revolution at the Service of Man

1. Introduction

Modern medicine has achieved a series of impressive successes which have greatly changed our lives (1, 2). Some diseases which only a few decades ago killed or debilitated millions of persons have been conquered by vaccines, antibiotics or other drugs. For many other diseases treatment is available which, although it cannot cure the disease, attenuates the suffering of the patient and improves the quality and expectancy of life. Surgery and diagnostics have made extraordinary progress. Scientific research has so advanced that no conquest appears beyond its reach. Yet under many aspects medicine is in crisis. Important drugs are used empirically, in some instances without knowing the nature of the diseases which they cure. The glorious days are gone of the great scientists who required only modest means and who could therefore devote themselves to purely humanitarian ideals; today progress needs sophisticated and expensive equipment and is subject to economical and political conditioning. While saving millions of lives, modern drugs have in some countries aggravated the problem of assuring every human being his basic rights, thus revealing the limitations of scientific progress which does not involve the human condition as a whole. After having boldly entered the scene, with its ability to accumulate new basic knowledge and stimulate medical progress, molecular biology has revealed a terrifying capacity to manipulate life itself. Bioengineering, together with contraceptives, some psychotropic drugs and the legalization of abortion have dramatically reposed the old problem of the limitations and ethics of medical intervention.

In this complex, varied, and contradictory picture the signs left by three great processes are evident: scientific innovation, technological innovation, and the innovation of molecular biology. These processes may not only help us to understand the present crisis and the future prospects of medicine, but may also teach us a more general lesson.

2. Scientific innovation

Modern medicine was born between the 18th and 20th centuries when the understanding of diseases and their physiological basis became the primary interest of scientists, and therapy its corollary, a logical consequence. The protagonists of this major scientific innovation were Magendie, his pupil Bernard, Virchow, Pasteur, and other great physiologists and pathologists too numerous to mention. They laid the foundations for many subsequent discoveries transforming medicine from an empirical art into science.

Physiopathological knowledge made it possible to develop the so-called "physiological drugs," i.e., therapeutic means which are directly inspired by human natural mechanisms *: vitamins, vaccines, hormones, and others. Since they reproduce or mimic mechanisms already widely tested by nature, their possible risks or disadvantages can be easily predicted. For example, when Jenner decided to give the smallpox vaccine to his son he had already obtained the necessary information by studying the corresponding naturally occuring phenomenon. The safety of physiological drugs primarily depends on two requisites: a solid physiopathological knowledge and a guarantee that the drugs correspond exactly, in composition and dosage, to the mechanisms they mimic.

A good physiopathological knowledge of diseases also permits their rational treatment with "artificial drugs," such as antibiotics; similarly, a good mechanic knows how to repair a car even without original spare parts. Artificial drugs, nonetheless, substantially differ from physiological drugs from the point of view of development and practical application. They are a novel creation of man for which there is no prior experience. They must thus undergo the most careful testing before being used on man. Following the tragic consequences of some artificial drugs, the health authorities have imposed rigorous chemical, biological, and toxicological

* Keeping this definition in mind, it is understood that the terms "physiological" and "natural" do not necessarily coincide. For example, many antibiotics, morphine and high doses of cortisone are natural in origin but are not physiological for man. Physiological drugs are, instead, always natural substances which can be obtained or reproduced by synthesis

testing. As a result, artificial drugs have been rendered safe, but their development has slowed down and is more expensive.

If we take a careful look at the features of scientific innovation, it is apparent that it was not exclusively based on the concept that physiopathological knowledge is the prerequisite for therapy; it was also based on the concept that medicine should not transform man, but restore the normal condition that existed before the disease. When possible, this goal should be attained with physiological drugs that have the great advantage of exploiting mechanisms already widely experienced in nature. Artificial drugs can be used as well, but require more detailed and accurate testing

At the beginning of scientific innovation, research could often be carried out with modest means and this enabled scientists to work independently without being conditioned by external factors. Moreover, the writings of the great protagonists in scientific innovation re-echo the awareness that health is one of the fundamental assets of man. Medical progress was thus stimulated not only by pure scientific interest, but also by humanitarian ideals

3. Technological innovation

Starting from the second half of the last century, in the wake of the technical and industrial development which was transforming the economical and social structure of Europe, a technological innovation was taking hold and exercising a profound impact on medicine. Laboratories were enriched with new equipment, the fields of study for scientists broadened and some of them began working with the chemical industry, exploiting its capacity to produce a vast number of compounds of medical interest. This combination of science and technology generated the pharmaceutical industry, which soon became a major protagonist of medical progress.

Technological innovation permitted a better and more rapid practical utilization of basic scientific knowledge. In this respect, antibiotics serve as a good example. The production of antibiotic substances by some microorganisms was first described in the past century (3), without this important finding having any practical consequences. When it was confirmed by Fleming in 1929, the situation had changed, and a few years later Chain, Florey, and Abraham successfully isolated penicillin in a relatively short time, making it possible to produce the substance on a large scale (4).

At the turn of the century, some important drugs were discovered: acetylsalicylic acid, morphine, quinine, various chemotherapeutics, and so on. Technological innovation later had a growing impact on medicine, leading up to the great discoveries of the last decades that have transformed our lives.

At first the advances in medicine appeared to depend on an equilibrium between science and technology. This delicate equilibrium was, nonetheless, slowly upset, as the pace of technology was much faster than that of basic physiopathological research. Consequently, the physiopathological knowledge accumulated by entire generations of scientists was drained by an increasingly efficient technology without the possibility of being restored. After the important results obtained in diseases like infections, hypovitaminosis and endocrine disorders, physiopathological research seemed to mark time. Various diseases such as epilepsy, tumors, schizophrenia, and other mental conditions remained obscure (Table 1). In this deadlock a few scientists realized that many diseases could be reproduced and studied in the laboratory even without knowing their nature. For example, Merrit and Putman (5) took advantage of the fact that animals submitted to electroshock exhibited reactions similar to these of epileptic seizure and used this empirical model to examine many compounds. Diphenylhydantoin, the prototype of modern antiepileptics, was the consequence of this approach. Other investigators successfully transplanted cancer cells into healthy animals, thus obtaining results similar to the corresponding tumor pathology. This empirical model was also used to study a variety of compounds, some of which proved to be active and were success-

fully used for the treatment of different tumors.

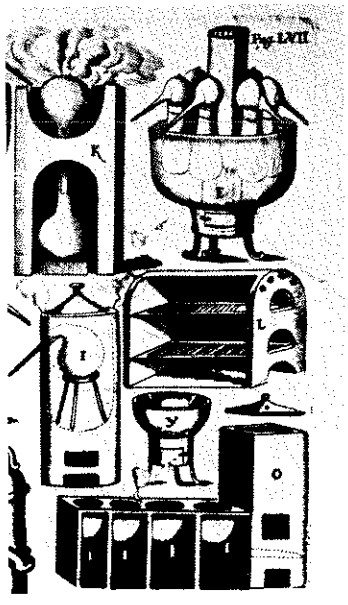
In some instances these empirical models of disease were inspired by the properties of already available drugs such as chlorpromazine, imipramine and acetylsalicylic acid. Although the mechanism of action of these substances is unknown, they exert characteristic effects in the laboratory animal. * These pharmaceutical models proved particularly advantageous in developing drugs similar to existing ones, but more potent and safer. This strategy proved quite successful. Consequently, a new class of drugs appeared, no longer generated by physiopathological research and knowledge, but by the use of empirical models of diseases (Table 2). These drugs understandably required more complex and sophisticated testing and had very important practical consequences.

To better understand this point, it should be recalled that the critical phase in the development of physiological drugs is basic research. It involves painstaking and lengthy efforts. Its immeasurable costs weigh on the entire community, extending beyond geographical and political boundaries, as it is mainly carried out in academic centers which make the results freely available. The subsequent phase of developing and testing these drugs can be relatively fast and safe. On the contrary the most important phase for artificial and empirical drugs is the testing that they are subjected to before being introduced into therapy. The latter entails consistent organizational and economic efforts, together with different specializations which are easily found in large industrial organizations, but not in the academic and state-controlled research centers.

These brief remarks are valuable in understanding the reasons why drug development was progressively transferred from the academic centers to industry as scientific innovation slowly gave way to technology.

The pharmaceutical industry has been, for better or worse, the great protagonist of technological innovation. With its organizational capacity and sophisticated technology, it has facilitated the transformation of theoretical knowledge into practice. It has also led to the development of new drugs when the slow pace of basic research made it seem improbable. It has assumed the financial burden of applied research and testing of drugs, an effort costing hundreds of millions of dollars. The pharmaceutical industry has not done this in the disguise of a benefactor, but in its business role of industry which must make profits in order to survive and develop. It has thus demanded patent rights for its drugs and adequate prices. It oriented research towards profit-making pathological fields. It has sought and often obtained political support. There have also been abuses and speculations, but this is unavoidable, as in any sphere of human activity. All this is not easily compatible with the humanitarian tradition of medicine, which considered health a valuable priority over and above all else. Nevertheless,

* Based on the assumption that the study of drugs could provide insight into the nature of diseases, some drugs have been used in basic research. For example, anti-psychotic drugs inhibit dopaminergic transmission and this led to hypothesize that schizophrenia depends on an excess, or more generally speaking, a disturbance of dopaminergic transmission. Acetylsalicylic acid has been important in clarifying the role of prostaglandins in some physiologic and pathologic processes. However, with some drugs like antidepressants, this approach was unsuccessful or even misleading.



those who denigrate the pharmaceutical industry should remember that these drawbacks must be weighed against the fact that for the first time medicine has had access to safe and effective drugs made available in unlimited amounts and at relatively low costs. Moreover, the pharmaceutical industry has too often been held responsible for problems which instead require the joint efforts of industry and government. A typical example is the so-called orphan drug (6).

A more important problem is the pace of technological innovation, which has proved far too rapid for a society which is often incapable of managing it. Millions of people have been saved by antibiotics, but society has been unable to provide decent living conditions for all of them. Mental patients have been helped by psychotropic drugs, but they very often lack adequate social assistance. This teaches us that medicine must grow within the entire social framework.

4. Innovation in molecular biology

We have seen that the magic moment of medicine occurred when there was a balance between science and technology. In time technological developments surpassed scientific ones. This phenomenon did not hault the development of new drugs, but laid different foundations for medicine.

In this context, the third great innovation, that of molecular biology, came into the scene. It put new vigor into basic research, providing it with new and highly potent means. This point is worth commenting. It has already been mentioned that modern medicine arose as the result of the systematic exploration of physiological and pathological processes and the application of this knowledge in the treatment of diseases. The basis of this exploration is reason, the essence of all the sciences, with its two fundamental methods: induction, which elaborates available information into general theories; deduction, which uses intuition to formulate theories and then searches for experimental confirmation. Reason needs information. At the beginning of modern medicine information was obtained by directly observing natural and physiological processes by means of the naked senses and elementary instruments like the balance. In this way anatomy, physiology, pathology, and other basic sciences were born, together with the first drugs. More sophisticated instruments and techniques were later developed and used to obtain new information which was in turn employed to develop other drugs. We have also seen that some diseases, like schizophrenia and tumors, were beyond the reach of research. Molecular biology is important because it provides scientists with new research instruments, thereby opening the world of molecular events previously beyond their reach. It is reasonable to assume that this will reveal the nature of many conditions. New drugs will be discovered and many of them will be physiologic. Once again, there will be a balance between science and technology. At the same time the testing of drugs will become quicker and less expensive. In turn, these changes will influence the entire pharmaceutical sector (7).

Molecular biology has made suitable instruments available for the study and control not only of diseases, but also of natural physiological events. In particular, with genetic engineering it intervenes in the basic mechanisms which regulate life, with unpredictable consequences. These are the moments when medicine stops and reflects on the limitations and meaning of innovation and scientific progress itself.

5. Medicine at the service of man

From his origin man has been faced with the problem of the limitations and significance of progress. He discovers metal and uses it for cultivating the soil and lancing infected wounds, but all too soon it becomes a deadly weapon. "Quis fuit horrendos primus qui protulit enses?" sings Tibullus (*Elegy*, I, 10, 1-14). He discovers nuclear energy and uses it for exploring and curing disease, but the outcome is also the atomic bomb. The solution does certainly not lie in repudiating scientific progress. It is inborn in man and consequently in the Nature which it seems to alter. Progress must be go-

verned instead by principles oriented towards the good of mankind and not its destruction. In this context, the problems of medicine are basically the same as in any other science. Nevertheless, the special feature of medicine is its involvement with one of the most essential needs of man, his health. This accentuates the problem of scientific progress and also focuses on its fundamental aspects. We can therefore see that the significance of the teachings of medicine extends far beyond its boundaries.

Firstly, scientific progress should be in harmony with Nature. The practical applications of science should be based on a solid knowledge of Nature. Science has to approach Nature in the awareness that natural mechanisms are more reliable and safer than those created by man, as they have undergone incomparably longer development and testing.

Secondly, science cannot hide in an ivory tower; it must come down and face mankind in all its manifestations. Even the greatest breakthroughs in modern science could not be considered true progress when society was unprepared for them.

Thirdly, scientific progress, like other human activities, must have its ethical code.

This is a particularly delicate aspect as modern science has grown in the shadow of the Enlightenment, which established the primacy of reason and its capacity to solve all the problems of mankind. Rousseau, advocate of a return to the natural state, and later on many other philosophers perceived the limitations of this concept, but their message was not understood. In many cases it was interpreted as a regression, a return to obscurantism and superstition. In the modern world, however, there is a widespread perception of the limitations of scientific progress and of the need to subject it to principles or ethical rules of universal value. This does not mean suffocating the legitimate expectations of the modern world, but, on the contary, exploiting them, giving them a more concrete basis, and opening new horizons.

This appears to me to be the general significance of the message "medicine at the service of man."

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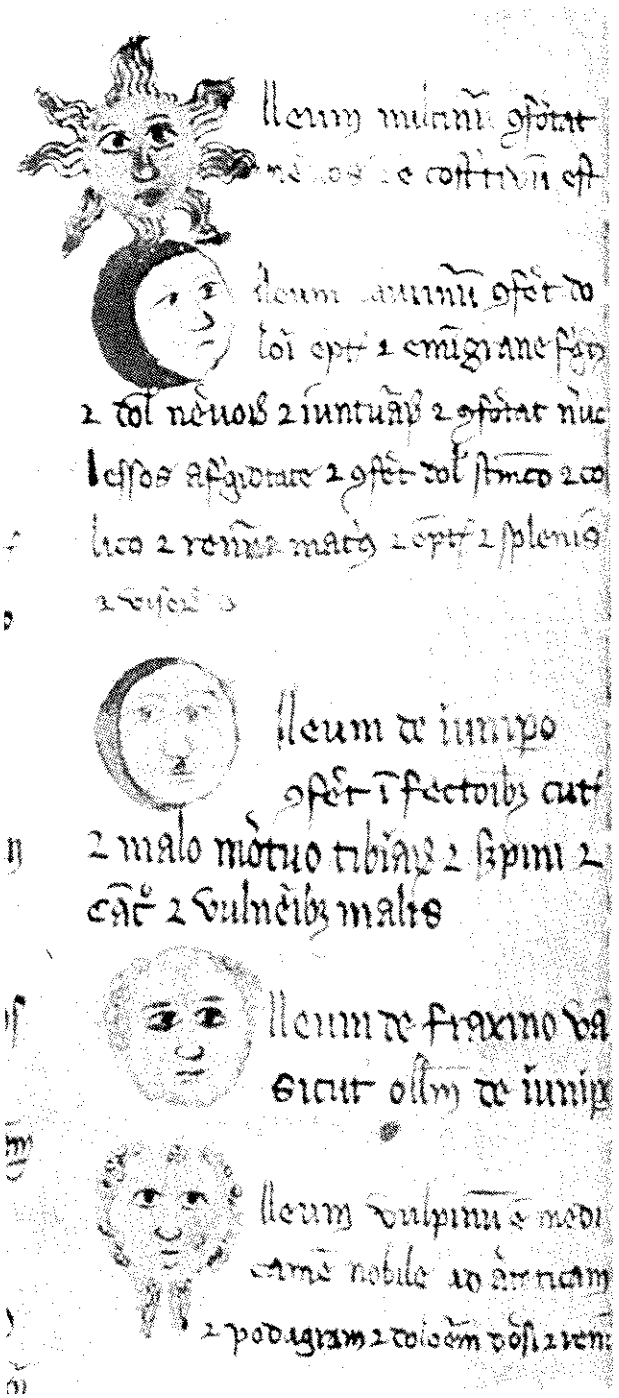
Examples of diseases the nature of which is known (A) or substantially unknown (B).

A :	B :
— hypovitaminosis	— schizophrenia, depression and other mental diseases
— infections	— tumors
— diabetes and other endocrine and metabolic diseases	— hypertension
— Parkinson's disease and other neurological diseases	— gastroduodenal ulcers
— diseases of the blood	— rheumatoid arthritis
— diseases requiring surgery	— many metabolic and degenerative diseases

Pages from the Prescription Book *at the Royal Library in Torino (thirteenth century).*



Examples of three different classes of drugs

"Physiological" drugs	"Artificial" rational drugs	"Empirical" drugs
vitamins	antibiotics	anti-epileptics
vaccines	oral anti-diabetic agents	anti-psychotics
hormones	hormone analogues	anti-depressants

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ERMINIO COSTA

Respect for Nature as a Strategy for the Development of New Drugs for the Nervous System

Introduction

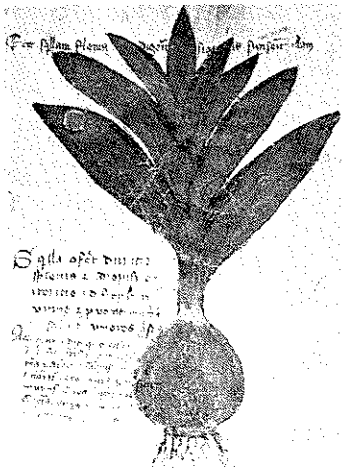
The ethical principles which guide the development of new drugs are sanctioned by the ancient saying *Primum non nocere*, which has always guided the practical application of pharmacological discoveries. An important question arises, however, regarding the real limits set by this statement, especially when confronted by the necessity to carry out high risk therapy. An example can be found in the treatment of neoplastic diseases with a terminal prognosis where a compromise must be found, and where adverse drug effects are accepted in the attempt to prolong the life of a patient in danger.

For those drugs that act on the central nervous system and, in particular, those used in the treatment of chronic psychiatric and neurological conditions, it must be decided if and when the necessary conditions exist before embarking on high risk therapy. In fact, in such a pathology, one is rarely faced with borderline cases where the prolonging of the human life forces us to exceed those limits within which risk may be warranted.

With antipsychotic and antidepressant drugs, an important ethical element is represented by the guidelines to select drugs to be tested clinically, considering our present ignorance in the etiology of many psychiatric illnesses. It is now clear that in the majority of cases, the drugs at our disposal to treat schizophrenia and affective disorders act indirectly via mechanisms which are still unknown. Some of these could participate in triggering untoward reactions brought about by the chronic usage of these drugs. Tardive dyskinesia caused by antipsychotic drugs that block dopamine receptors is a very clear example. Thus, an important ethical question requiring close scrutiny concerns the research strategy to be followed in developing new generations of drugs that are required for the treatment of many neurological and psychiatric illnesses.

Traditionally, drugs acting on the central nervous system have been developed with the intent of obtaining molecules that interact with receptors of important neurotransmitters, such as dopamine, serotonin, and noradrenalin. This strategy was both logical and ethical when it was believed that the symptomatology of psychoses could be attributed to a dysfunction of either the receptors or the synthesis, storage, and release of one of these transmitters. But now that this simplistic view can no longer be entertained, we must reconsider our strategies. The line of research which has dominated the field for the past thirty years, developed according to the strategy and philosophy proposed by Ehrlich at the beginning of this century when the basic concepts of the chemotherapy of infectious diseases were being established. The object then was to obtain chemical substances which, like "magic bullets," would save the host and selectively attack the bacteria responsible for the infection to be cured. Without any good reason, this philosophy still guides reserarch into the development of psychoactive drugs. The general research philosophy is to selectively block the receptors of a transmitter believed to be responsible for the symptoms of a particular psychiatric disorder.

When drugs developed with this strategy produced tangible results on psychiatric symptoms, it was deduced that the defect responsible for that illness was in effect either a specific activation of the neurons afferent to the receptors or a supersensitivity of the receptors, selectively occupied and blocked by the drug causing symptomatological relief



of psychiatric diseases. On the basis of the application of an ex-adjuvantibus criterion, partial success in therapy became the basis for the assertion that the etiology and pathogenesis of the disorder to be treated lay in an anomaly of the signal transduction which was known to operate in the synapses (dopamine?) blocked by the antipsychotics. For example, the view that a malfunction in the dopaminergic system is operative in schizophrenia was entertained on the basis of the beneficial effects exerted by chloropramazine, the progenitor of the neuroloptic drugs endowed with antidopaminergic action. A large number of pharmacological congeners to this drug were synthesized and tested without substantially improving our successes in the treatment of schizophrenia or reducing the side effects of chlorpromazine. Despite this standstill lasting for longer than 20 years, chlorpromazine-like drugs are still continually synthesized and tested. Another example is the theory (also developed following partially successful drug trials) according to which a deficit of catecholamine signal transduction is responsible for the pathogenesis of affective disorders. Also, here the blockade of norepinephrine uptake caused by imipramine, which, in a number of cases, relieves some symptoms of endogenous depression, has created the view that NE transmission is altered in affective disorders. In this case also, a large number of molecules blocking NE uptake were tested clinically without substantial benefits to the patients over those benefits obtained with imipramine, which still remains among the best of the antidepressant drugs available. Again, faced with a no progress situation, NE uptake blockers are still being tested and synthesized.

While in the case of antibiotic treatment a perseverance in Ehrlich's strategy brought about enormous benefits to patients, in the therapy for psychiatric diseases, the absence of progress must dictate that other strategies appear to be needed. Hence, one might ask, can persistence in developing antidopaminergic drugs be justified in the absence of substantial benefits regarding the treatment of schizophrenia? And, what about affective disorders? It would seem ethical to me to review these research strategies especially in the light of two basic considerations:

1. While it is by no means clear that a given transmitter can regulate a specific function of the central nervous system, it is true nonetheless that there are clear signs showing that one type of brain receptor cannot be blocked for any length of time without triggering the appearance of collateral disorders that can be traced to the long-term blockade of this receptor.

2. The theory according to which synaptic communication between neurons lies in the action of one single chemical signal operating in that synapse is undergoing a revision. With the evidence that a multiplicity of chemical signals take part in the synaptic communication between neurons, we must consider that there are probably some chemical signals that should be selected as a target for our therapeutic efforts. For instance, these could be the modulatory chemical signals which increase or decrease the probability for a primary transmitter to act. Probably drugs that act on these modulatory mechanisms are less prone to cause side effects because they act on the mechanism used by nature to adapt synaptic function to the changes continually imposed on brain function by internal and external stimuli.

While the first consideration suggests that the time may be ideal, in the interest of the patient, to modify the research strategy in search of new drugs to treat schizophrenia and affective disorders, the second consideration suggests that there might be a new road to be followed. In the light of the present understanding of the natural mechanisms of synaptic modulation, may it not be the case that we follow nature and attempt to produce drugs that act on synaptic modulatory mechanisms for allosteric modulation instead of continuing to produce "magic bullets" which by blocking receptors for primary transmitters impede communication between nerve cells? Certainly, we are aware that this communication is so essential for brain function that when it is blocked by drugs the brain reacts in an attempt to overcome the consequences of such abnormal status. In this balancing attempt there pro-

bably resides the origin of the untoward side effects caused by long-term treatment with dopamine receptor blockers with antipsychotic activity

The synaptic receptor is not an enemy that is to be destroyed as was the pathogenic organism in infectious diseases. Perhaps we ought to respect the synaptic receptors for the primary transmitters because we know that they are indispensable. Furthermore, why block the dopaminergic receptor when the evidence does not support the theories suggesting that schizophrenia is due to an excessive synthesis or utilization of dopamine?

As the antipsychotic effect of the neuroleptic drugs becomes evident after a latency of weeks, one can advance the theory that the beneficial effects of the antidopaminergics on the symptoms of schizophrenia arise from indirect actions set off by this blockade. In fact, in experiments with animals, it has been shown that a large number of indirect changes are set in motion as a result of the pharmacological block of dopamine receptors. During the prolonged treatment with such drugs, some of these indirect reactions vanish into tolerance while others become more severe with protracted treatment and persist after drug withdrawal. Probably we should study these indirect drug actions and try to learn from them what the critical aspect is that may lead to a better understanding of the actions that are operative in mediating the therapeutic efficacy. To discuss in detail the ethical problems involved in the new lines of research which could be followed in the future, it may be useful to touch on our present knowledge, which should form the basis for this attempt to elucidate the indirect actions of presently used drugs that we propose to use as probes to detect the crucial aspects of their therapeutic action.

2. Synaptic Receptors and Neural Plasticity

According to the classical definitions which have guided present research, the receptor for the transmitter operating in a synapse is a membrane protein which can recognize with a high degree of selectivity its own transmitter. This high affinity binding between receptor and transmitter gives rise to a structural variation in other membrane proteins, and the vector of functional modifications in the neuron is where this protein is located. These considerations have led to the use of radioactive tracers to study the characteristics of this binding. The displacing of these tracers from the binding sites proved to be an important element in identifying the specific nature of the molecular structure required in order to make a drug work on a particular synaptic function. We now know that the receptor is not a simple molecular unit, but that it is in fact made up of several molecules which are associated with each other through a complex system of relationships which are essential for the receptorial function to be expressed. This can be measured by the modifications in the electric characteristics of the neuron which are due to the passage of specific ions via channels operating across the neuronal membrane whose openings are regulated by the transmitter or by the formation of second messengers effected by the transmitter mediated activation of specific enzymes. In turn, the entry of certain ions (Ca^{2+}, for example) or the activation of certain enzymes set off by second messengers causes structural modification of the membrane proteins of the target neurons. This modification (an example is phosphorylation) generates changes in either the same receptor for the transmitter or another membrane protein associated with the receptorial domain acting as a receptor for another transmitter or neuromodulator.

Thus a cascade of events is set in motion which can modify the average life span of the second messenger, inhibiting its destruction or prolonging its biological life and causing it to migrate into the nucleus, modifying the way in which the genetic code of these neurons is expressed. Via these complex modifications, which are of a different duration, the neuron not only responds to the message which is coded in the chemical signal (transmitter) freed by the neighboring cell, but also in responding to this signal modifies itself with regard to its capacity to act as a receiving station for further messages sent out by the same

neuron or by other adjacent neurons.

Simplifying the matter, it could be said that essentially in a synaptic event the cell receives information which has an immediate effect (the generation of the second messenger or of the specific ion flow) and a protective effect on the duration of the primary receptorial response (opening of the channel or synthesis of the second messenger) and the duration and degree of involvement of other collateral structures (other membrane receptors, cytoplasmic enzymes, nuclear activity) in the response. A synaptic event therefore determines not only the type of immediate change in the metabolic activity of the target neuron, but also gives instructions regarding the spatial extension of the response and its duration. It is now evident that this mass of information is given out via more than one chemical signal freed simultaneously by the transmitter neuron. Amongst these chemical signals there are some (primary transmitters) which characterize the quality of the response evoked in the target neuron (opening of a channel or increased synthesis rate of a second messenger) and other chemical signals (modulators) which do not generate changes but condition the response and determine the quality of that response. The latter chemical signals, which do not trigger a stimulus in the receiving cell but require the presence of a primary transmitter in order to act, are used by nature to orchestrate long-term changes in cell responsiveness. Modulators in general act allosterically and increase or decrease the response to the primary transmitter. They can therefore modulate the information given out by the neuron which broadcasts these signals, increasing its duration and extension, but do not give rise themselves to a signal, nor do they determine its elimination. We are learning that the coupling between emission of the primary transmitter signal and that of the modulatory signal represents an element of variability in neuronal communication which seems to depend on the frequency of the synaptic activity itself. To make the concept a little clearer, not only the number but also the quality of the signals given out by a neuron varies according to the frequency with which they are emitted.

This continuous variability of the intensity of the response to a single synaptic event appears to be essential to the way in which our brains perform. If one considers that there are many billions of neurons and that each neuron receives signals from around ten thousand synaptic contacts and that in each of these there is a wide variability in the control of the response, one can get an idea of the functional plasticity built into communication between the nerve cells. It is in this variability that neuronal plasticity plays its role. The term "neuronal plasticity" is used to describe the use to which this infinite variability is put. This is essential in repairing anatomical damage as well as in fostering integrated neuronal responses to environmental changes, in storing or in retrieving stored information. Perhaps in our ability to use this possibility of regulating communication between cells lie also the great differences in function between individual brains.

3. Persistence of Cellular Modifications Brought About by Synaptic Events.

From the summary of our present understanding of the mechanisms which operate in our brains we can see how important the generation of second messengers is in communication between cells and perhaps also the importance of the duration of the modifications brought about in the target neurons by synaptic activity. In a certain sense, this duration represents what we could tentatively call the memory of a neuron. A large part of the information transmitted lasts a short time. In order to store a particular piece of information for a longer period (weeks?), it is necessary for the second messenger to modify the expression of the genetic code either by interfering with mRNA translation (in the ribosomes) or in DNA transcription (in the nucleus). However, if this is the case, how can one explain that such a memory may last longer than the biological life of the various neuronal constituents. However, almost through necessity, one has to admit that the second messengers can somehow modify the

transcription of the genetic message in a stable way, perhaps by shortening the introns, whose functional value is not yet clearly understood, or by transposing the sequences of the axons and via these mechanisms causing the stable modification of a DNA specific transcription. This still remains one of nature's mysteries, in which we do not yet clearly understand the molecular essence, even though we are sure that memory is longer than the average life span of each protein in the brain.

It could be that the lasting modifications associated with persistence over decades of a stored piece of information are due to diversification in the generation of the second messenger. This is somewhat difficult to understand in the case of cyclic AMP or cyclic GMP, as they are made up of simple, constant substrates such as ATP and GTP. There are, however, second messengers which are generated by phospholipids of the brain via the activation of phospholipases. This is, in fact, one of the newest issues of the day. Phospholipids, which were at one time considered to be simple elements making up the cell membrane and almost placed accidently to separate the various cells, are proving to be substantial factors in cell to cell communication because they provide the precursors of important second messengers such as diacylglycerol, archidonic acid and triphosphate or tetraphosphate inositol. The permanent modifications associated with lasting memory may be caused by the modification of enzyme structures (isozymes?) or by biochemical changes acting on phospholipases which are indirectly associated with the storing of lifelong information. In fact, memory and recollection of memory may be only a repetition of patterns of interneuronal communication that are established by the event (stimulus) that we store in our memory. According to this view, recollection might be the capability of repeating such a pattern.

4. The Pharmacology of Synaptic Modulation

Confronted by the complexity which lies at the heart of the variability in synaptic regulation, it is fascinating to consider the possibility that future research into new drugs may choose to direct its efforts towards the mechanisms of synaptic modulation. This new generation of drugs would be made up of molecules which do not act as substitutes for the primary transmitter occupying specific recognition sites for the transmitter, as has so far been done with the neuroleptic drugs and also to a certain extent with antidepressants. In fact, past experience has shown quite clearly that it is damaging to inhibit communication between neurons for long periods by occupying primary transmitter receptors.

As opposed to this, there is almost thirty years experience in the use of benzodiazepines, given to hundreds of millions of people with a practically negligible number of side effects if used under careful medical supervision. This group of drugs acts on the natural modulation of a group of receptors for the primary GABA transmitter, which opens the channels for Cl. The benzodiazepines intensify the effects of GABA by increasing the probability that GABA will open the Cl channels but do not in the absence of GABA open these channels. Thus, communication between neurons which is mediated by GABA is neither eliminated nor permanently activated by the benzodiazepines. In the presence of benzodiazepines, the frequency of emission of GABA signals or the reception of these segnals maintains a physiological rhythm: only the extension of the consequences of the signal reception is increased. This mode of action can be contrasted with that of DOPA, used in the treatment of Parkinson's disease, which replaces the physiological signal, activating the dopaminergic receptors continuously. Probably for this reason DOPA causes a number of problems after prolonged treatment. Benzodiazepines do not modify the rhythm of the communication but simply amplify the effects of the signal emitted and, therefore, because of their minor intrusion into physiological mechanisms, exercise a corrective influence on the synaptic activity which is practically devoid of important side effects.

This natural modulation of synaptic activity can be effected in different ways. One

line which could be followed appears to be the in-depth study of the receptors' modulation for primary transmitters (glutamate, serotonin, GABA, catecholamines, acetylcholine), learning the lessons nature teaches us and opening up new roads for the development of the pharmacology of modulation. Among other things, one could act by increasing the substrate for the formation of the second messengers. This therapy also does not modify the physiological rhythm but amplifies it when the store of precursors for the second messenger is not sufficient. This would be the case when using phospholipids or other precursors of the second messengers that are synthesized from phospholipids which are membrane components

Conclusions

Let us go back to the ethics of the development of drugs which act on the central nervous system. It should be emphasized that our present knowledge of the modulation of synaptic communication between neurons must be taken into account and made part of the research programs. This knowledge has for the most part been acquired via the financing done over the years by various nations and belongs to the public domain. This definitely means that in order to pursue these new lines, the industry must make new investments and indeed perhaps heavier ones than are required if one chooses to persevere along old lines of research. We cannot continue to produce chlorpromazine type drugs for the treatment of schizophrenia when over twenty years of laborious research has shown that there is no definite proof supporting the belief that the symptoms of schizophrenia are due to an excessive stimulation of dopaminergic receptors.

New routes must be taken. However, if we continue to consider the dopaminergic synapse as a precise point of attack, this attack should be conducted by attempting to evaluate how the synapse is modulated. We know that the dopaminergic neurons also contain other neuromodulators apart from dopamine and perhaps the pharmacology of these signals should not be ignored. Furthermore, in the dopaminergic receptor, the G protein mediated coupling of the transmitter recognition site with the cyclase that produces the second messenger seems to play an important part. We ought perhaps to begin studying this G protein system to see if we can obtain a modulation of the system in question by drugs acting on protein kinase activation medited by transmitters.

Similar considerations can be applied to affective disorder where the GABAergic system seems an important factor and thus of potential therapeutic interest. Another neuronal system which has so for not been greatly considered is the glutamatergic system. Now that we know that phencyclidine is a drug which allosterically inhibits a class of glutamatergic receptors and gives rise to cognitive disorders, the glutamate receptor modulation is a potentially new field of study regarding treatment of dementia. We have touched on how phospholipids act as precursors of important second messengers. I may add that gangliosides may act on synaptic signal transduction by impeding receptor mediated protein kinase C translocation, a phenomenon important in transmitter mediated modification of neuronal function.

In conclusion, ethical considerations impose changes in the philosophy and strategy of drug development. The pharmaceutical industy must be brought up to date through disregarding old schemes and adapting research programs to the new understanding of communication mechanisms among neurons. Success will by no means be immediate or easy, but new drugs will be developed through new models taking into account the new findings that basic research is continually contributing.

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BONIFACIO HONINGS

A Moral-Deontological Examination of Pharmacology

On the occasion of the Congress on the History of Pharmacy convened in Rome to commemorate the 525th anniversary of Martin V's donation to the city's pharmacists, Pius XII, in the audience of September 11, 1954, stated that the Popes had always greatly esteemed the art of healing through the use of medicines. Just as priests, in fulfillment of Jesus' command, are responsible for the care of souls with the Sacraments, so pharmacists are charged by Him with the care of bodies by means of pharmaceutical products. Pacelli went on to specify that it was true that the activity of pharmacists seemed to be of a commercial nature because in most cases medicines were supplied by large companies.[1] Nevertheless, the pharmacological art always requires considerable technical and moral responsibility, as Pius XII also pointed out when addressing the 400 Catholic Pharmacists meeting in Rome on September 2, 1950 for their first International Congress. Among the health care professions as a whole, pharmacists occupy a place of great importance, as a result of both their untiring efforts and weighty responsibilities. Pacelli continued,

Il suffit de songer un instant aux conséquences de la plus petite erreur, non seulement sur la substance, mais sur la qualité, le dosage, la durée de validité, pour entrevoir la responsabilité qui vous incombe. Qui donc oserait la prendre sur ses épaules, sans s'y être préparé par l'étude et par la pratique des sciences physiques, chimiques, botaniques, biologiques, dont peu de gens supposent l'ampleur et la difficulté?[2]

Alongside this enormous scientific-technical responsibility there exists an even more binding commitment — that of ethics and deontology, which is more pressing than ever today on account of current deviations in conscience. There are, in fact, customers who ask for products which, either by their very nature or by virtue of the user's intention, are to be employed for illicit purposes since they threaten life or the person's corporal or mental integrity. In such cases, Pius XII recommends, "Vous aurez ... fort à coeur d'unir vos efferts en vue de rallier l'opinion à la doctrine et à la moral catholique, qui ne font que promulger avec l'autorité de la religion, la doctrine même de la raison et la moral de la simple honnêteté."[3]

From this closeness of professional competence to moral honesty it is clear that the pharmacist and the pharmaceutical not only touch upon the moral order, but enter into it inseparably as subject and object. It is the duty of deontological ethics to apply the criteria of good and evil to substances capable of provoking functional modifications in an organism through chemical or physical action and to those preparing and selling such substances. I do not, however, intend to examine at present from a moral standpoint either the pharmacological product as such or the person practicing this art. Rather, the topic of my paper concerns pharmacology itself as a science studying pharmaceuticals and their characteristics of physiological action and both therapeutic and nontherapeutic applications in order to see to what degree this science is autonomous in its experimental methodology as regards man. I shall therefore divide my remarks into two moments: the first presents pharmacology as belonging to one of two varieties of scientific research; the second evaluates the impassable limits of scientific experimentation on man, with respect to both its personal and social benefits. I shall close with a brief conclusion in which I propose some of the prime ethical-deontological demands for the pharmacological industry in terms of the principle of solidarity.

1. Pharmacology: An Experimental Science

I understand science to be a kind of knowledge differing from both the commonplace and philosophical types. On account of its relevance to our problem, I would stress its doble psychological root, proper to man's rational nature, including the speculative aspect and the practical or applied dimension. The first root consists of the innate or connatural desire in man to gain ever more and better knowledge of all that surrounds him, of all that is inside him, and of who he himself is. He harbors a longing, an ardent

aspiration to acquire increasingly deeper knowledge of his world and himself. Alongside this speculative yearning and connected with it there is a second root of scientific research consisting of the insatiable — and equally natural — desire to dominate the whole *cosmos* and subdue it so that it may better serve human development. Scientific knowledge takes its origin from a speculative and practical root present in the nature of man as an existing being, *Daseiender*, in a world to be subjected to his service.

When conceived of in this way, then, scientific knowledge connotes a set of characteristics specifying it and thus distinguishing it more sharply, especially today, in relation to philosophy and faith. Above all, insofar as possible science seeks to be objective in the sense that it excludes all emotional and subjective elements from its field. Obviously, complete exclusion is simply impossible, for anyone working in science cannot prescind from either his own subjectivity or his own emotiveness. But the characteristic of the maximum possible objectivity aims at guaranteeing the most extensive or universal validity. Science, then, seeks full agreement with facts and therefore requires experimental checks as a *conditio sine qua non* for its authenticity.

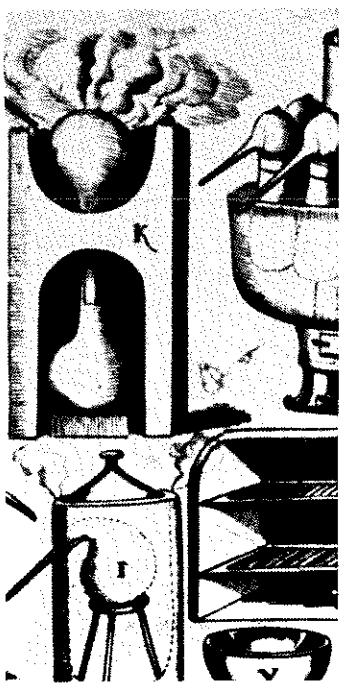
Along with this characteristic of positivity, which should not be confused with nineteenth-century philosophical positivism and does not utterly exclude the legitimacy of certain theoretical assumptions, there appears that of rationality. In effect, the need to have recourse to experience and be in agreement with concrete situations can never dispense with the fact that the subject working out science as the protagonist of research is and always remains a man: a being endowed with intelligence and freedom.

"Science can, therefore, be defined as an effort to rationalize the real; starting from empirical data, by way of increasingly broad syntheses the scientist strives to embrace the entire domain of the facts known to him in a rational system in which from a few simple, universal principles the more specific experimental laws of fields which at first appear heterogeneous are logically deduced."[4]

This rationality cannot, however, avoid the fact that experimental scientific knowledge involves the note of revisibility. As a result of the scientific obligation to check continually against the reality of the facts, in a certain sense science presents all its truths as provisional — i.e., capable of being revised, further perfected, and occasionally even subjected to thorough questioning once again. "All scientific cognitions are approximate, because of both the imperfection of the observations on which they are grounded and the necessary abstraction and schematization with which they are treated. For scientific knowledge, the concept of approximation and limited validity should thus be substituted for that of complete, perfect adjustment."[5] Yet scientific knowledge, as a final characteristic, always conserves its autonomy in the face of both philosophy and faith. It has its own field of research and study as well as its own method and source from which to obtain information. The source is nature itself, both external and internal. "The scientist need not open the works of philosophers or consult the sources of Revelation to obtain scientific knowledge, but directly interrogates nature, posing his questions and awaiting solutions from it."[6] I am not hereby denying that there are relations between science and philosophy and between science and faith — quite the contrary; philosophy in fact reflects upon the nature of science and its methods and principles, and the scientist benefits from this effort. Similarly, faith — especially for the believing scientist — furnishes prudential norms for behavior which guide him in his research so that it may preserve its human — and, therefore, moral — character. But I shall expressly deal with this in the second point of this paper; it is now of interest to stress that experimental scientific research as such — i.e., on a formal basis — does not depend upon any philosophical system and is not indebted to any dogma of faith. And the same also holds true for pharmacology as an experimental science.

Pharmacological research has a need for experimentation on living beings by way of manipulations in order to gain better knowledge of function-

al modifications in the organisms to which drugs are administered. I note that the living being here is, in the end, man, for whom the empirical science of pharmacology links the natural branch with the human one. Let it suffice to recall pharmacodynamics. Bompiani rightly asks "whether there are fundamental *links* between the manipulations of empirical-natural sciences and those of the human and social sciences: whether there are exact, distinguishable limits between the two great branches of empirical science."[7] It is true that the aforementioned author speaks of the two sciences, natural and human, in general, but, with even greater reason, I believe I can apply their linkage to the field of the science of pharmaceuticals and their characteristics of physiological action and therapeutic application.



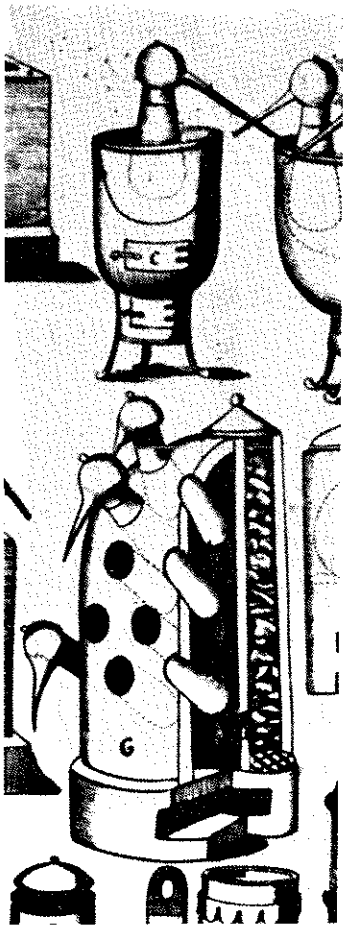
In any event, we are concerned here with clarifying what we mean by manipulation, or, rather, experimentation on living beings, particularly when the living being is man. De Vincentis and Zangan write, "A given medical activity cannot be deemed 'experimental' when it is prompted by the aim of obtaining results in man which are broadly and reasonably foreseeable, concretely on the basis of prior positive experiences, even if harmful effects may derive from it; indeed, it is from such assumptions that all the activity of the art draws life. On the other hand, those methods or treatments would be included in the domain of experimentation which are *new* — i.e., not yet employed in man — or no longer new and original, but *unknown* or, in any case, *not thoroughly known* in their multiple consequences (direct and indirect; immediate, non-immediate, and long-range; favorable and unfavorable; basic and secondary; local and general; and so forth)."[8]

Experimentation, in the field of health or medicine, thus has at least two meanings: one concerns the acquisition of technical capacity in "know-how"; the other involves continually obtaining more new experience and new knowledge. In the first meaning, experimentation amounts to a "personal participation in circumstances which for some time have been known to be spontaneously repeating themselves with sufficient regularity"; to experiment, then, means "to become increasingly capable of resolving the specific problems presenting themselves in such circumstances."[9] In the second meaning, experimentation takes on the value of a methodological instrument to enable scientific research to attain ever more and better results.

When we speak of a moral examination of pharmacology, we aim precisely to evaluate this methodological experimentation, from the standpoint of both therapeutic and predominantly innovative progress. Obviously, experimentation as a technique to acquire theoretical or practical knowledge is not hereby excluded, but it entails virtually no ethical-deontological difficulty because the risk factor is extremely reduced if not entirely absent.

2. The Ethical-Deontological Limits of Experimentation on Man

In confronting pharmacology conceived in this way, the first moral evaluation is eminently positive as regards both its scientific nature and its experimental method. The favorable judgment of the Second Vatican Council concerning radical modification of the level of both intellectual speculation and practice in fact applies, *mutatis mutandis*, to the science of pharmaceuticals as well. Moral theology fully shares the theoretical and practical scien-



tific mentality which today shapes both culture and thought in such diverse ways. From the moral standpoint, it is heartening that technology, when considered in itself, continually progresses and improves "so as to transform the face of the earth and now pursue the conquest of outer space."[10] Moreover, all of this is according to the will of the Creator, Who wants man to seek to develop his life integrally through work and talent. Today more than ever, with the aid of science and technology, man can continuously expand "his dominion over nearly the whole of nature."[11]

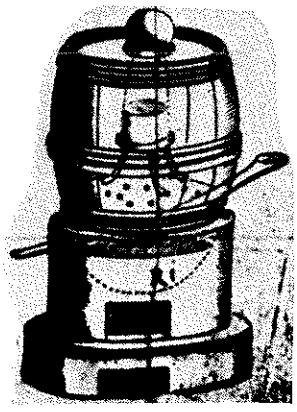
In addition, God has wanted man, in his laborious, ingenious efforts to progress through science and technology, to be independent of ideologies, systems of thought, and also dogmas of faith. "Created things and societies themselves have their own laws and values which man must gradually discover, use, and order"; the autonomy of scientific research thus becomes a legitimate exigency "which not only is postulated by the men of our time, but also conforms to the Creator's will."[12] At this point it is important to note how philosophical reflection, on a radically ontological level, furnishes science with the reason for its autonomy. It is from their created being that things in the end have their own consistency, truth, goodness, and laws giving them an intrinsic structure. This is why, in the methodical research of every discipline, man is bound to respect — i.e., recognize — "the methodological demands proper to each particular science or art"[13] Science or art cultivated in this manner not only will never be at odds with faith ("for profane realities and those of faith originate in the same God"), but leads whoever is elaborating his science or art to give things the meaning willed by God and even, finally, to respectful acknowledgement of the Creator and confidence and trust in Him. The Vatican Council Fathers are, therefore, completely right in asserting, "At this point, may we be allowed to deplore certain mental attitudes, which are sometimes not lacking among Christians as well, deriving from not having sufficiently perceived the legitimate autonomy of science, and which, stirring up disputes and controversies, led many spirits into the error of deeming science and faith to be mutually opposed."[14]

The opinion of those who think that earthly realities and, therefore, their applied sciences may be used without reference to the Creator is, however, equally false. Indeed, without the Creator things would not only fall into nothingness, but would be deprived of their final or ultimate meaning. Consequently, if man wishes to be the master and intelligent custodian of nature so as to place it at his service in a humanized manner, he cannot and must not forget that earthly realities connote an autonomy which is only relative. John Paul II, in his first encyclical, draws the follow-

ing conclusion from this "religious" relationship involving things and thus science and and technology: "The development of technology and the development of civilization in our time, which is marked by the dominion of technology itself, demand a proportional development of moral life and ethics." [15] He then goes on to observe that "the latter unfortunately seems always to remain behind For this reason, such progress, which is, moreover, marvelous, ... cannot fail to generate multiple concerns." [16] At root it is a matter of knowing whether scientific and technological progress really makes man's life on earth integrally human Does man as such really become better, that is, "more mature spiritually, more aware of the dignity of his humanity, more responsible, more open to others, particulary towards the neediest and weakest, more available to give and bear aid to all .... Are all the conquests achieved up to now and those projected for the future by technology in agreement with man's moral and spiritual progress?" [17] There are as many other basic questions posed by morals for pharmacology so that it will realize the ethical-deontological limits within which its empirical scientific autonomy must situate itself to prove to be an authentic humanizing service of man to man.

To make this clearer, let me point out that the manufacture and distribution of pharmaceutical products is undoubtedly linked to the same economic laws to which any other industrial-commercial activity must conform. Drugs as well must compete for the market and, in order to gain an ever larger share, must make a place for themselves according to specific competitive demands. The first among them certainly involves offering better and more effective products capable of provoking highly therapeutic functional modifications in man's organism. This first demand entails, in turn, both a quantitative increase in instruments and, above all, a qualitative intensification of experimental scientific research itself. From an industrial standpoint, this is all well and good, and if it is carried out in accordance with the norms of justice and equity, there is nothing to object to on moral grounds. But there is more: like all sciences, whether empirical or not, pharmacology also has meaning and value only in the measure in which it manages to serve the quality of human life. To tell the truth, the study of pharmaceuticals occupies a preeminent place among the diverse industries precisely because its aim is more the psychophysical and spiritual health of countless men than material wealth. In addition, pharmacology is important to such a degree that the progress of medical science and technology would, in a certain sense, prove useless and frustrating if there were not at the same time a quantitative and qualitative offer of corresponding pharmaceuticals.

At this point morality has something concrete to say Pharmacology, to be able to satisfy these demands of medicine, must necessarily have recourse to its methodological research instrument, experimentation, not only because it is, by nature, an empirical science, but also because many illnesses today are completely new. Our science is thus obliged to set the process of its different phases of research in motion if it wishes to meet man's demand for service in recovering his health or improving his psychophysical and spiritual conditions The task of morality in this process is to see to it that "the pharmacological industry" remains "a health



art" at the service of human life. Pius XII observed,

"..... Il appartient à la phrmacie de préparer les remédes capables d'enrayer les maladies et d'en vaincre les causes, sans toutefois provoquer d'autres dommages dans l'organisme. Problème ardu, que la marche rapide de la science oblige à reposer constamment en termes différents, à mesure que se révèle davantage la complexité inouie des organes et des fonctions, la nature des agents chimiques, qui y sont à l'oeuvre, et la possibilité d'intervenir sur eux pour en bloquer ou en favoriser l'action."[18]

The words of Pacelli retain their full weight of highly professional commitment and extremely demanding moral responsibility. In addition to the difficulties of a pharmacodynamic and pharmacobotanic nature, Pius XII also stresses the complexity of pharmacochemistry:

"La chimie par ailleurs s'ingénie à analyser la structure des molécules, à la modifier, à la reconstruire même, et chaque année quantité de corps nouveaux, souvent éphémères, voient aussi le jour dans les laboratoires. Choisir parmi eux ceux qui offrent des garanties de succès, les expérimenter longuement, vérifier avec soin leur toxicité pour l'organisme humain et, finalement, mettre au point les méthodes les plus rapides, les plus sûres et les plus économiques pour réaliser la production en masse; voilà les problèmes qui se posent couramment à l'industrie chimique pharmaceutique." [19]

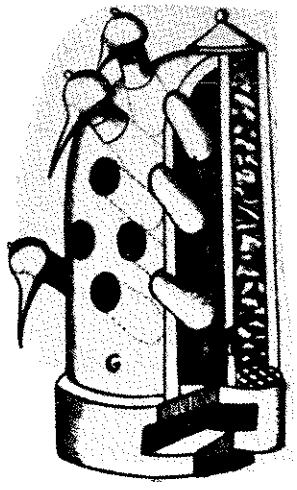
Research to solve such an unquestionably arduous problem is continually stimulated and upheld by the beneficiary, the sick man. "Qui recueillera enfin le profit le plus tangible de tout ce travail sinon le malade auquel les rémèdes ainsi préparés apportent soulagement et guérison?" [20]

Now, in order for pharmacology truly to remain a service to the ill or to scientific progress, it is necessary for research to effectively meet the demands of human dignity. Morality, to guarantee the patient's personal dignity, has always proposed the principle of integrity, which in fact seeks to inculcate the Hippocratic ethic not only of not causing the patient harm or injustice, but of promoting his health as far as possible.[21] I must, however, immediately point out that the principle in question does not have absolute value, as has already proven evident from its application to the field of surgery. No one has ever questioned the licitness of sacrificing a part when the good of the "whole" so requires; rather, with today's technological progress, such a sacrifice most often becomes simply obligatory.

In any event, in the field of pharmacology, the principle would act as a *norm* for experimentation on man.

Since experimentation, in and of itself, constitutes a methodological factor intrinsic to pharmacology as an empirical science, the moral problem shifts entirely to the question of the finality and modality of the use of such a method. As regards the finality, pharmacological experimentation may be called clinical-therapeutic or biological-nontherapeutic, i.e., purely scientific; that is, the experimentation may not be directed towards caring for the health of the subject undergoing it, but towards the progress of pharmacology itself as a science. In this case of scientific experimentation another principle comes into play: that of solidarity, in the sense that the subject offers himself because he is motivated by the bond with his fellow man.

There remains no question, however, that the principal and essential finality of subjecting oneself to experimenta-



tion is the improvement of one's own state of health. The principle of integrity thus continues to be the ethical-deontological limit for any kind of experimentation to which man intends to submit himself.

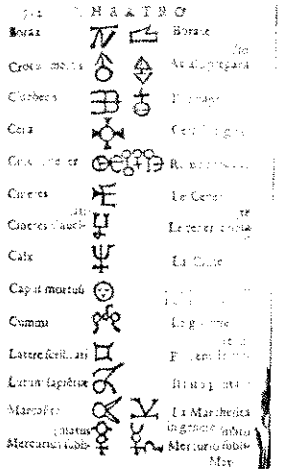
From this there follows a highly significant moral demand, that of informed consent, which connotes a kind of contract between the experimenter and the experimental subject. This consent is ethically grounded in the patient's freedom, insofar as he and he alone is entitled to give or withhold consent. In order for him to be able to exercise control over his own body and himself responsibly, he has the right/duty to know what will happen during the experiment on him. Moreover, it is clear that man is and remains the measure for evaluating all sciences, including the one we are dealing with, precisely because he surpasses them axiologically. Man always possesses the value of an end and can never be reduced to the value of a means or an instrument. John Paul II expresses himself as follows:

"Science is not the highest value to which all others must be subordinated. Higher on the scale of values is precisely the personal right of the individual to physical and spiritual life, to his psychic and functional integrity. The person is, in fact, the measure and criterion of goodness or guilt in every human manifestation."[22]

In the area of pharmacology, the foregoing means that by informed consent we do not understand a generic attitude of trust on the part of the patient in dealing with the doctor, but "a moment of conscious evaluation of the risk-benefit relation when faced with treatments still encumbered by margins of unforeseeableness, an evaluation not left to the experimenter's discretion."[23]

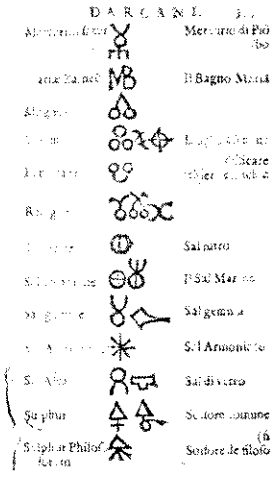
The ethical norm, formulated by the principles of integrity and solidarity, must, then, enlighten and discipline not only the phases of research, but also the application of the results obtained. Respect for the person, for his dignity, unquestionably holds priority in all scientific research and all use of its products in the service of man. Consequently, if a new method of investigation, for instance, harms or threatens to harm the right to live in a way worthy of the human being, it cannot be regarded as licit, even if it increases the patrimony of knowledge. In short, research in the field of pharmacology and the therapeutic application of its products must be highly attentive to ethical norms, at the forefront in protecting the dignity of the human person.

Evidently, consent, though informed, on the part of the subject undergoing experimentation also has its ethical limits. "Experimentation is, in fact, justified *in primis* by the interest of the individual, not by that of the collectivity. This does not exclude the possibility that the patient, while safeguarding his substantial integrity, may legitimately take on a share of the risk to contribute with his initiative to the progress of medicine and, in this way, to the good of the community. Giving of oneself, within the limits marked by the moral norm, can constitute an extremely meritorious witness to charity and an occasion for such significant spiritual growth that it compensates for the risk of possible nonsubstantial physical diminution."[24] In terms of teleology or finality, pharmacological experimentation, both out of personal interest and to benefit the com-



munity, is licit provided it remains within the ethical-deontological demands of substantial integrity required by the dignity of the human person

This precise moral limit now leads us to the question of evaluating the modalities to be respected in pharmaceutical research and application. John Paul II categorically asserts, "Clinical pharmacological experimentation cannot be initiated without having taken all the precautions to guarantee the innocuousness of the intervention. The preclinical research phase must, therefore, furnish the broadest pharmaco-toxicological documentation."[25] This is basically due to the fact that even the most accurate and professionally most conscientious research does not exclude all potential risk. In the face of man's undisputed right to preserve his substantial integrity, pharmacology, especially the innovative type, must acknowledge its intrinsic riskiness on account of its scientific-experimental nature.



Morality thus requires that pharmaceutical research and particular applications go through certain stages offering as many other phases in guaranteeing man's personal dignity. I shall follow the different stages proposed by Polli because they entirely conform to those required by the principle of substantial integrity. Initially, the action of substances on the human organism of the young, the elderly, the healthy, and the sick is studied apart, and the ways in which the human organism conditions pharmacological activity (by absorbing it, metabolizing it, and so on) are determined After this pharmacodynamic phase we pass on to researching the morbid form in which the substance used in the initial experiment may be administered with utility. The most effective dose is carefully specified at the same time as close attention is paid to reducing harmful side effects to a minimum. Once good results have been obtained, the third phase involves planning the pharmaceutical's therapeutic use through comparison between a group of persons treated with it and another group treated with a drug already proven by experience. This method enables us to assign the pharmaceutical the place it deserves among therapeutic instruments for specific diseases. When these preceding phases offer sufficient guarantees that the pharmaceutical is truly beneficial, the phase of generalized experimentation commences: the drug is introduced into public use by way of medical prescription. From that moment on the phase of studying positive and negative effects at a distance also begins, precisely to verify the degree of maximum innocuousness of the pharmaceutical. When this final phase is truly positive, the drug warrants scientific recognition as reliable. From a moral standpoint, not only are there no reservations any longer regarding the pharmaceutical, but pharmacology itself as a science deserves praise for having responded to God's purpose — it has really served man. In this manner, moral examination presents itself not as a check upon pharmacological progress, but, instead, as a stimulus to this progress, for it forces the research and application of its results to be and become increasingly "humane and humanizing."

* * *

From this humanitarian priority I would now like to draw some conclusions of a moral nature. Today "awareness of

the eminent dignity corresponding to the human person, superior to all things," is constantly on the increase, "and his rights and duties are universal and inviolable. We must, therefore, make all the things necessary to lead a truly human life available to man "[26] In a negative sense, this means that pharmacology should never lend itself to producing substances which degrade man and damage his life, not to mention those which prevent his life from beginning and seeing the light of day I am more concerned, however, about the positive meaning of the human dignity of every man and of all men. In the face of the health problems of the Third World, the pharmacological industry cannot remain indifferent—it is naturally responsible for finding ways to deal with the legitimate demands of so many peoples. National and international organizations will certainly manage either individually or in collaboration to encounter the paths leading to the solution of the enormous problems of entire populations. I shall merely recall here that today's morality obliges everyone to overcome an individualistic ethic on both a national and a continental level. This overcoming is a duty of justice and of love, which increasingly require a contribution to "the common good according to one's own capacities and the needs of others" and the promotion of and assistance to "the public and private institutions as well which serve to improve men's life conditions "[27] Socialization, as a sign of the times, has, moreover, made us grasp that, in order to attain our own perfection more expeditiously and integrally, it is necessary for "every group to take into account the needs and legitimate aspirations of the other groups, indeed of the common good of the whole human family "[28] This human and humanitarian solidarity opens a vast field of human promotion to the pharmacological industry, and in so acting its "artificers" will one day hear the beatifying words "I was sick, and you offered Me the best pharmaceutical."

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NOTES

[1] Cf. Pius XII, "Insegnamenti della storia della farmacia," *Discorsi e Radiomessaggi,* vol. XVI, 1954-1955, p. 141. Montini expresses his esteem in these terms: "Nous avons volontiers accepté, Mesdames et Messieurs, cette occasion de vous rencontrer au moment où vous achevez à la fois les travaux de la vingt-cinquième Assemblée générale de la Fédération internationale pharmaceutique et du trente-quatrième Congrès international des Sciences pharmaceutiques . . Cette rencontre . . Nous est agréable: elle Nous donne l'occasion de vous exprimer notre respect" (Paul VI, *Insegnamenti,* vol. XII, 1974, pp. 798-799).

[2] Pius, XII, "Grandezza e responsabilità della professione del farmacista," *Discorsi e Radiomessaggi,* vol 12, 1950-1951, p 178.

[3] *Ibid.* Montini states, "Les exigences que Nous venons de rappeler demandent aujourd'hui beaucoup de conviction et de courage, dans la situation de compromis où baignent nos contemporains Mais ces difficultés ne doivent pas vous faire reculer car les orientation prises par la societé dependront en partie de la vigueur de votre sens moral" (Paul VI, *Insegnamenti,* vol. XII, 1974, p 798).

[4] *Enciclopedia Filosofica,* "Centro di studi filosofici di Gallarate," vol. 5, under the heading *scienza*, p 1159.

[5] *Ibid.*

[6] *Ibid.*, p. 1160

[7] A. Bompiani, "La sperimentazione clinica dei farmaci: stato attuale del problema normativo e proposte di riforma," *Medicina e Morale,* 1982/1, p. 98.

[8] De Vincentis and Zangan, "Sulla liceità e sui limiti della sperimentazione sull'uomo," *Giustizia Penale,* Part I, pp. 322, 334 as quoted in Bompiani, *op cit*, p. 101.

[9] Bompiani, *op. cit*, p. 101.

[10] The Pastoral Constitution on the Church in the Contemporary World, *Gaudium et Spes,* no. 5 (Hereafter cited as *GS*)

[11] *GS,* 33

[12] *GS,* 36.

[13] *Ibid*

[14] *Ibid*

[15] John Paul II, The Encyclical Letter *Redemptor Hominis,* no 15 (Hereafter cited as *RH*)

[16] *RH,* 15

[17] *Ibid*

[18] Pius XII, "La speciale importanza dell'origine e diffusione dei prodotti farmaceutici," *Discorsi e Radiomessaggi,* vol. XVIII, 1956-1957, p 594

[19] *Ibid*

[20] *Ibid.*

[21] Cf. L. Edelstein, "The Hippocratic Oath Text, Translation, and Interpretion," in *The Bulletin of the History of Medicine, Supplement 1 (Baltimore, 1984)*

[22] *John Paul II,* "La persona, non la scienza, è misura e criterio di ogni manifestazione umana," *Insegnamenti,* vol. III, 2, 1980, p. 1005

[23] Bompiani, *op. cit.*, p. 110

[24] John Paul II, "La persona . ," p 1009.

[25] John Paul II, "La persona . . ," p.1008.

[26] *GS,* 26

[27] *GS,* 30

[28] *GS,* 26

Second Session

The Ethics of Pharmaceutical Research

A pharmacy servant from The Venetians' Dress *by Giovanni Grevenbroch (1731-1807)*

LUIGI LASAGNA

The Role and Responsibility of Industry in Research

Society maintains a paradoxical attitude toward pharmaceutical products and the industry which develops and delivers those products. Drug discoveries during the last half century have been numerous and impressive, yet the drug industry is often criticized for being too profit-oriented and not sufficiently socially-minded. Medical progress is not possible without the deployment of resources, and when progress is made, whether it be in the form of new drugs, new surgical procedures, or new diagnostic and therapeutic devices, additional health care expenditures — at least in the short-term — are required if patients are to benefit from such advances. In the abstract, everyone desires the best health care, not only for themselves but for others, but in reality, compromises are made every day in the name of fiscal prudence and the allocation of scarce resources.

In considering the role of industry, I would propose that the problems in this area fall into different categories. One set of problems relates to the production and distribution of the remedies already on the market which are not accessible to certain patients who need them, i.e. the problem of under-utilization. A second set of problems has to do with the overuse or misuse of remedies which are either unneeded or suboptimal in regard to efficacy, safety, or both. A third set of problems relates to the need to develop new and better remedies. I cannot think of a single therapeutic area where the sick could not profit from better drugs, and for some diseases, our modern pharmacopeia contains nothing of significant value.

Most new drugs come out of the activities of capitalistically based entrepreneurial pharmaceutical companies, located in developed countries, and utilizing basic building blocks of information derived either from their own laboratories or from academic laboratories or clinical research supported by industrial grants or contracts, federal monies, or grants from private foundations. Even the development of folk remedies, as is now being so vigorously pursued, for example, in the People's Republic of China, or the development of the products of genetic engineering and biotechnology, which has had a strong academic base, ultimately requires the skill and resources of industry if new drugs are to be effectively manufactured, distributed, and used.

Hence, pharmaceutical progress depends on the availability of economic resources — the capital of individual investors, of corporations, and of the taxpayers who make possible governmental participation in the process. This process is not made any easier by the long lag between investment and return on investment; in this regard the drug industry is like the natural gas and petroleum industry — one digs many holes before hitting gas or oil, and even when one finds an energy source reservoir, the financial return on such a discovery is not fully realized for many years. The same scenario applies to new drug research, and both industries have to spend a lot of money in order to thrive.

To poor countries unable to make available to their citizens the remedies already on the market, it may seem as if research on new remedies is an extravagant luxury, but for the currently untreatable victims of cancer, of such neurologic diseases as multiple sclerosis or Alzheimer's dementia, of degenerative muscular disorders, etc., not to search for new remedies is to consign these patients to a philosophy of despair.

Fortunately, the development of new medicines is not a zero sum game where someone wins only if someone else loses; with pharmaceutical progress, it is possible for everybody to gain. Since private industry needs to earn money in order to exist, and since there is little evidence that governmental drug development would be either more effective or less expensive than private development, I submit that to ignore the need for profits and patent protection or other guarantees of exclusivity is to imitate the ostrich. One can debate, to be sure, how *much* profits industry should make — "too much" would mean taking undue advantage of the sick, "too little" may destroy the incentive to find needed remedies. (I recognize the difficulty in agreeing on the definition of such terms.)

What, then, are the specific research responsibilities of in-

dustry? They are, I would propose:

1. Identification of appropriate research goals.
2. Optimization of collaboration with non-industrial scientists.
3. Quantification of the benefits of drug use as well as its costs and risks.
4. Maintaining high ethical standards in animal and human research.

Let me begin with research goals. Industry must, it seems to me, maintain a balance between developing modifications of known drugs and developing completely innovative chemicals. Marketing the identical twin of an already available drug is of benefit in engendering price competition in a free market, but is otherwise not socially advantageous. On the other hand, "molecular modification" can lead at times to important advances. The earliest sulphonamide drugs, for example, have been followed not only by pharmaceutical relatives that are better anti-bacterials, but as well by some that are diuretics, uricosurics, anti-glaucoma drugs, or anti-diabetic agents. The original penicillins have been folowed by other penicillins superior in many ways to the earliest versions, e.g., by being orally active, by being effective against penicillinase-producing organisms, and by having a much broader spectrum of antibacterial activity. Indeed, if one looks at the WHO List of Essential Drugs, it is interesting how many of the drugs on that list are *not* the first drugs marketed in their respective classes; with time, the original breakthrough drugs have yielded to pharmaceutical descendants with improved efficacy, greater safety, or both. It is also worth noting that improvements which at first glance may seem trivial can in fact at times represent major advances; making an injectable drug into a version effective by mouth, for instance, or vice versa, or devising a palatable suspension which dramatically improves pediatric compliance with the prescribing intent of the physician and the need of the patient.

But industry must also search for completely different chemicals, lest we never become able to treat the diseases for which we currently lack truly effective drugs. It is my impression that innovative firms are in fact devoting a greater percentage of their research budgets to this purpose now than in the past, motivated in part by social needs, and in part by the realization that cost containment efforts by governments will increasingly force the allocation of health care dollars to unique and important remedies that will deserve reimbursement approval.

A special challenge resides in the unmet needs of the Third World and of patients with rare diseases. There is an "orphan drug" problem as well as an "orphan disease" problem. Orphan drugs are those whose utility is reasonably clear or even unquestioned but which will not repay the investment on their development and manufacture. Society clearly needs to address the problem of how to deal fairly and honestly with this challenge. "Orphan diseases" are those for which no treatment exists. Such diseases afflict patients in developed countries as well as those in developing countries, but diseases which primarily or exclusively affect the citizens of economically depressed countries pose a special problem because of the possibility that effective treatments for even common diseases in these countries, if discovered, will not repay the investment on their development. This problem deserves to be adressed on a global basis. It should not be assumed that one can solve these problems by assigning the fiscal and ethical responsibility for such drug development solely to drug companies, which could go bankrupt, even if successful in discovering such drugs, if they focus to a predominant degree on the search for remedies of this type. Nevertheless, research on such remedies does go on as part of the research and development effort of individual firms.

Another set of research goals has to do with post-registration research. Some of the most important uses of drugs may not come to light until after a drug is marketed, and sometimes not until many years later. Lidocaine, a life-saving anti-arrhythmic, was used for years as a local anesthetic before its other use was appreciated. Diazepam was long used as a tranquillizer before its value as a treatment for status epilepticus was

discovered. Amantadine was developed and marketed as a preventive against influenza; its utility in Parkinsonism was discovered serendipitously. Drugs introduced as anticancer agents have turned out to be useful for diseases as different as psoriasis and arthritis. There is a long list of such examples. We must find a way to reward manufacturers for pursuing such research on drugs for which market exclusivity no longer exists.

Additionally, research needs to be done on the individualization of therapy. At the time of initial marketing, we almost never know which patients are best treated with a new analgesic or antibiotic or antihypertensive, and which will do better on older drugs. There is as much progress to be made, I suspect, from the better use of old drugs as from the development of new drugs, but it will take research and education to achieve this goal.

The question of academic-industrial rapport in the search for new drugs is also important. The situation varies greatly from country to country, and from company to company, but even in the most research-intensive countries, such collaboration has lagged in the past. I am happy to note that this is changing for the better and the situation should improve still further in the future. There is much social good to be derived from a greater involvement of academic expertise and imagination in applied research, although there are some risks as well, such as the distraction of universities from their traditional academic educational and training functions.

The quantification of benefits as well as of costs and risks has also lagged, but will become increasingly important as economic pressures on industry, physicians, and patients increase. Since for many drugs such quantification is not easy, methodologic research in this area must be encouraged and supported. Because information on the benefits and risks of a drug does not remain static, repeated assessment may be in order.

Ethical issues abound in pharmaceutical research, from the animal laboratory to the clinic, and also exist in the quality and purpose of pharmaceutical promotion. Animal research cannot be eliminated without scientific loss, which is a pity, since humans are the only species that can freely volunteer to be research subjects. But we must avoid animal research that is unnecessary, we can often study fewer animals than has been traditional in the past, and we can try to develop in vitro substitutes for animal research wherever possible. Needless to say, the animal subjects of research, no less than human subjects, must be treated with respect, and not involved in cruel experiments. At the level of human research, we must keep improving our skill at obtaining informed consent. Although securing such consent can never be a perfect process, it is nevertheless ethically imperative that we be honest with potential subjects in describing to the best of our ability the purpose and risks of experiments and in communicating the fact that we cannot describe in advance either all the possible risks or all the possible benefits from a proposed experiment. We must exercise special care when planning research on such vulnerable populations as children, psychotics, the demented elderly, and the retarded of all ages. Not to search for remedies for such groups is to render them therapeutic orphans, but they are not in general able to truly volunteer.

How ethical is it to repeat adequately performed and convincing clinical experiments? Replication is, to be sure, the essence of science, and no one wishes to market a drug on the basis of data that are not convincing. But there is a difference between thoughtful and convincing substantiation of what has been seen in early studies and chauvinistic or bureaucratic demands that trials be repeated in each country. Genetic, nutritional, and other factors that impact on drug response do vary across countries, but a rational concern for such factors should be differentiated from irrational nationalistic pride or regulatory arrogance in making demands for data to achieve registration.

What about generic versions of innovative products? Generic competition is believed to help keep health care costs down, but it is important to demand adequate documentation of the interchangeability of such versions with the innovator product. In

vitro tests are seductive because they are quick and cheap, but clearly fail all too often to predict in vivo results. And in vivo testing for bioavailability is usually limited to small numbers of young healthy male volunteers studied under completely artificial circumstances with the results of the study not even replicated once. Is it ethical to allow the marketing of multiple versions of a drug without being reasonably confident that patients will not be harmed by substitution of multi-source drugs?

As the drugs in our therapeutic cupboard increase in number and quality, as our remedies become safer and more effective, morality will demand ever more scrupulous justification for initiating clinical research. And if human research on a new drug candidate will be difficult to defend, what of placebo controls in clinical trials? I would propose that the ethical propriety of placebo controls is inversely related to the availability of effective drugs and to the seriousness of the condition under study.

In advertising and promoting pharmaceuticals, it is important that exaggerated claims be discouraged and truth encouraged, and that ignorant and vulnerable populations not be taken advantage of, whether we are talking about developed countries or developing countries.

Finally, I believe that industrial scientists in developed countries should, along with the scientists from non-industrial sectors of society in these lands, help developing countries to address their health care needs. Scientists should shoulder this burden not specifically as members of industry or academia, but as caring human beings. What we need is a "Caritas Populi" movement, which will mobilize the natural tendency of most people to help their fellow humans. In times of disaster, such as war, earthquake, flood, or famine, such admirable (and at times heroic) propensities are readily mobilized. We need to mobilize this love for one's fellow humans in our efforts to cope with more chronic and less dramatic problems.

Third World countries face formidable barriers to the achievement of optimal health care: poverty; hunger; lack of clothing, shelter, and pest control; educational deficiencies; political instability; lack of scientific and clinical intrastructure; and inadequate health care delivery systems. Such deficiencies are by no means unique to the Third World — the richest country has some hungry and ignorant citizens, and what country has never been embarrassed by some politicians who failed to discharge their responsibilities? These problems are greater, nevertheless, in some countries than in others. Yet there are ways to ameliorate the situation. National pride may hinder foreign assistance of certain kinds, but with the proper spirit, such obstacles can be overcome sufficiently to justify the effort.

Pharmaceuticals and biologicals such as vaccines are, when properly employed, the most cost-effective form of health care. Each developing country will have its own set of health care problems and its own set of priorities as to what to accomplish with scarce resources. Foreigners have no right to tell the citizens of another country what their priorities should be, but outside expertise may be helpful in devising an approach to the attainment of health goals that is as efficient as possible. I suggest that those of us who are more advantaged should consider it a duty to help those who are less advantaged in regard to health care, in other countries no less than in their own. One can call this "caritas," "noblesse (or richese oblige," or what you will. It is the principle that counts, not the verbal packaging we choose. And it is the *implementaion* of the principle which counts even more, not the acceptance of abstract theory. The challenge is there. Can we meet it?

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Ethics of Drug Experimentation

Ethical Importance and Paradoxes of Pharmacological Research

I think that it can be stated that the relationship between ethics and medicine is equal to that between soul and body; in my opinion, this analogy is true not only because the vital principle of medicine is, after all, an ethical principle — to serve man and take care of his health — but also because in the same way as the soul is present in its wholeness and acts in every part of the body, ethics is present with all its values in every great commitment of medicine.

Thus, at the moment of the experimentation with drugs, an essential moment for therapy, the whole of ethics is involved.

For nobody, in fact, can it pass unnoticed that we are confronted with the greatest ethical themes, even if we deal with a defined and rather limited moment of the scientific commitment: the question is to establish the right balance and the correct relationship between the progress of science and support for the life of man, on whom experimentation is performed; the problem is to determine the relationship between the welfare of the individual, the person who submits to the experimentation, and the common welfare, that of all those persons to whom the possible success of the experimentation may bring a benefit.

And since in experimentation it is man who is responsible for the life of his fellow-being and, on the other hand, the person on whom the experimentation is done is, also, a man, there is a relationship between freedom and responsibility.

At stake, therefore, are the greatest human values, the personal as well as the social ones: the value of the search for truth, the values of life, freedom, responsibility, solidarity.

Another observation occurs to me while I am facing this problem. The more deeply we go into the ethical problem of pharmacological experimentation on man — not just in a restrictive sense, that is, enunciating principles, but also verifying their practical application — the more we realize the complexity of the historical situation through which we are now living: a situation in which contradictions and paradoxes come out which must at once be underlined and taken into consideration in this foreword.

Let us start from the years of the Nuremberg trial and the issuing of the Nuremberg Code (1946), followed by the 1948 Geneva Declaration issued by the World Medical Association, and the Helsinki Declaration (1964) by the same World Medical Association, with the title "Recommendations As a Guideline for Physicians in Clinical Research," reviewed and completed during the 29th Assembly of the same Association held in Tokyo in 1975 and revised during the 35th Assembly in Trieste (1983) with the title: "Recommendations as a Guideline for Physicians in Biomedical Research." Along this route there has been an almost complete development of deontological doctrine offering defined and detailed guidelines for ethical behavior aimed at defending those on whom experimentation is performed, as well as the professional physician, or researcher. The points left out by the body of the deontological rules are very few.[1]

However, in contrast with this positive event are contradictory and adverse situations, inasmuch as these deontological rules were not converted into precise legal provisions: in many nations suitable, up-to-date rules on pharmacological experimentation are lacking, and what is above all lacking are international agreements harmonizing the legislation of the individual States and regulating the registration of the drugs approved in one State and their marketing in another. In Europe, EEC directives (1965/65 and 1975/318) have not yet been accepted and applied in the individual countries, with the result of serious gaps in implementation and lack of security in control.[2]

Furthermore, after the rather rigorous, stern mentality immediately following upon the Nuremberg Trials, with their denunciation of the crimes perpetrated in the field of experimentation on man, today we are witnessing the renewal of wild, unrestrained experimentation in delicate fields, such as human embryos and foetuses, with which we shall subsequently deal, in the

unter absence of law. There is, therefore, an initial paradox, from the stardpoint of social ethics: we have deontological rules, but we lack civil laws guaranteeing their application, and there are human beings still exposed to illicit experimental proceedings.

This fact shows at once that the ethics of experimentation cannot be considered only under its technical aspect, in the moment of its application, but is conditioned by social organization and presupposes the ethics regarding the duties of the State.

Another paradoxical situation is worth recording, which is partially connected with the one mentioned above: regrettable cuts in research funds are to be observed in many countries; the lack of public financing must be denounced. At the same time, however, we witness a marketing of useless drugs, which means funds expended in an equally useless way. The data which are being cited in reports and meetings are increasingly alarming, and we are thus made aware of the existence of a twofold experimentation, one fostered by the logic of profit while the other one lacks suitable funds and resources; the interests of the patients do not coincide with those of the market.[3]

These general subjects will be dealt with by other speakers, and therefore, after this necessary outline, I wish to restrict the sphere of my reflections to the title of the report I was asked to present.

The whole moral question of experimentation of drugs on man may be brought back to what we could define as "the ethics of the method."

We know that human action draws its ethical qualifications from its purpose, means, and circumstances. Method is the totality of the means and circumstances. As regards the matter we are dealing with, the purpose is the one defined by the planning of the drug and is, in general, a valid purpose: the health of man. I say "in general" because it is often coupled with some other purpose, as, for instance, industry's profit, which may be consistent with or go beyond the intrinsic purpose of this type of research. In any event, if we take for granted that the question of the morality of the purpose has already been ascertained and made clear, the question of experimentation, I repeat, mainly regards the method, that is, the totality of means and circumstances considered in their actuality. The peculiarity of this type of method lies in the fact that, in the domain of means and circumstances, we find man — ill or healthy — on whom the experimentation is performed; and man is not a means like any other, or a circumstance, but a subject. We should therefore speak of experimentation *with man* more than experimentation *on man*.

This act of experimentation is hence enriched by a particular ethical density and complexity: man is the one who plans and carries out the experiment, and man, or the health of man, is the purpose of the experiment; man is the means, that is, the subject on whom the experiment is done; as every man is a subject and not only an object, the peculiarity of this ethical moment cannot be ignored by anybody.

I have no intention, within the horizon of reflection of this report of mine, to repeat the comprehensive treatment of general aspects now included in the deontological sphere, for these are a "doctrine" common to and summarized in texts and manuals for the physician's formation.

I shall refer to it only in passing. I think that it is instead more interesting to deal with some recent and new features of this matter. Therefore, the central part of my paper will be focused on some recently discussed aspects regarding the ethics of patient randomization, the ethics of placebo use in experimental research on drugs, new experimentation frontiers, and, finally, the control system for experimentation programs, that is, the ethical committee.

I cannot dispense, however, for the sake of overall clarity, with recalling the key points of Catholic morality and, first of all, the teaching of the recent Pontiffs.

The general principles of experimentation on man in Papal Teaching

The sources and official references concerning general moral trends in the matter of experimentation on man are of two orders: the addresses of the Sovereign Pontiffs, above all Pius XII and John Paul II,

Detail of the fresco depicting a fifteenth-century spice shop. (Castle of Issogne - Valle d'Aosta)

who had occasion to touch on these subjects (and this is the main and specific reference source of Catholic morals). Another source is the above-mentioned deontological codes issued by the World Medical Association, which do not refer to ethics but to deontology, and we know that the two viewpoints do not necessarily coincide. In many respects, however, these deontological codes on the matter contain elements having not only a technical-scientific character, but also an ethical importance; inspired by rational ethics, they merge — and often coincide — with the indications of Catholic morals.[4]

Many qualified moralists, specializing in the field of medical ethics, have in manuals, specific works, and papers read in congresses amplified and coordinated these reflections and it is only for the sake of brevity that we quote them in a bibliographic note.[5]

We have mentioned the indications coming from the Sovereign Pontiffs' addresses and messages and we cannot avoid recalling at least those interventions having a more explicit and direct reference to the subject and from which any moralist could draw sure points of doctrinal orientation.

The first meaningful and important statement is that of Pius XII, *Address to the Participants in the 1st International Congress of Histopathology of the Nervous System, on the "Moral Limits of Medical Methods of Investigation and Treatment,"* on September 14, 1952.[6]

At the Congress, held in Rome, the representatives of 40 nations took part. It is the famous address in which the Holy Father ("making himself the interpreter of the moral conscience of the researcher and the scientist, the learned and the professional man, the non-Christian as well as the Christian, who, moreover, walk on the same road") throughly examined the three ethical motivations proposed "in the moral sphere to justify the new attempts and methods in research and medical treatment": the interest of medical science, the interest of the patient under treatment, and the interest of the community.

In this talk, the statement was accepted and clarified that science as well as research and the attainment of results must be inserted into the order of values, though in the interest of science a true value most be acknowledged, and, furthermore, the relationship of trust between physician and patient, the patient's right to physical and spiritual life in its psychical and moral integrity — these are, among others, the values superior to scientific interest. The principle is here discussed of the necessity of consent, of the limits of the body's manipulation by the patient and the physician.

Though recognizing, on the grounds of the principle of "totality," the patient's limited power to control the parts of his own body for the good of the whole, he states that the individual "has no right to volunteer his physical and psychical integrity in experiments and medical research when destruction, mutilation, wounds, and serious dangers will, sooner or later, derive from these interventions." And, finally, it is in this same address that the principle is recalled that "man in his personal being is not after all ordered to be useful to society, but on the contrary, it is the community that is made for man,"[7] and this was in reference to the third reason justifying experiments on man. In this statement he set very precise limits for experimentation, be it performed on the healthy or the sick, when it exposes them to risk, even with their own consent.

The Address by Pius XII also considers the case of an experimental and risky therapy — lawfully used — in a last effort to save the life of the dying patient.

In another famous address held at the *16th Session of the International Office of Documentation of Military Medicine,*[8] October 19, 1953, Pius XII applied these principles to the military physician, taking a position against experimentation on war prisoners, defining the status of the physician as that of a worker of peace and recovery, including aid to wounded enemy soldiers, and definitely stating that international medical law and international control of such law were a must.

Limits to the freedom of volunteering one's own sick or healthy body when the experimental intervention may

cause significant damage to physical and psychical integrity and consequent limits to the physician's nontherapeutic experimentation on man, are confirmed by the Holy Father in the *Allocution to the 8th World Medical Association Congress* delivered on September 30, 1954.[9] On this occasion, the Pontiff once more clearly states the limits to experimental intervention with a therapeutic purpose for the dying patient. And in this same Allocution it is specified that the limits which are valid for the patient and the healthy volunteer must also be taken into consideration in the case of experiments performed by the physician on his own body.

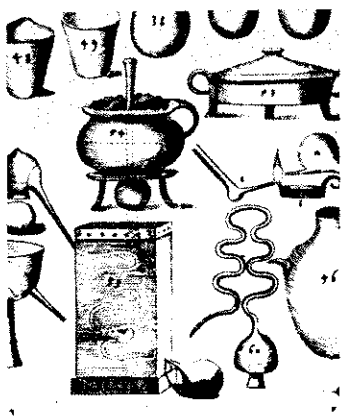
We may say that in the Teaching of Pius XII, the fundamental points of Catholic ethics on experimentation were already present.

We should also recall here Paul VI's renewed encouragement of the scholars and experts working in the field of medical science and research aimed at cancer treatment as regards the integration of science with ethics and Christian faith, on December 31, 1969, on the occasion of the *Eleventh National Congress of Pathology*.[10] The Church, Paul VI reminded, "cannot remain indifferent to your activity. The Church is not afraid of scientific progress but, on the contrary, it encourages and honors it and fosters its best utilization for the welfare of mankind." And this is the animating principle of the moralist's attitude as regards experimental research: "the best utilization for the welfare of mankind," mankind wholly present in every single man.

His Holiness John Paul II had occasion to continue this teaching and to offer new and consistent observations in connection with the frontiers opened in the biomedical field by the scientific discoveries on the possibilities of experimentation on man.

There are four talks which we consider significant for the subject we are dealing with.

The first one, in order of appearance, was addressed to the participants in two Congresses held at the same time: the *81st Congress of the Italian Society of Internal Medicine*, and the *82nd Congress of the Italian Society of General Surgery*, held on October 27, 1980.[11] In these discourses the Holy Father reminds us in the first place of the general ethical trend according to which "scientific knowledge has its own laws to follow. It must, however, acknowledge, especially in medicine, an impassable limit in respect for the person and the safeguarding of his right to live in a way worthy of a human being. *Science, in fact, is not the highest value* to which all other values must be subordinated. Still higher in the range of values stands precisely the personal right of the individual to physical and spiritual life, to his psychical and functional integrity. *The person, in fact, is a measure and criterion of goodness or guilt in every human manifestation*. Scientific progress, therefore, cannot claim a place in a sort of neutral land."[12] But in this same address the Holy Father goes into the specific theme of experimentation and, in particular, that of pharmacological experimentation, recalling, among other things, the duty to request consent after providing information, the need for a preclinical phase in experimentation, for "experimentation is justified *in primis* by the interest of the single person, not that of the collectivity," and underlining that "this does not exclude the possibility that the patient, while preserving his own substantial integrity, might lawfully take it upon himself to share the risk."[13]



Even if not directly referring to our theme, John Paul II's Address at the *16th Congress of Catholic Physicians*, held on October 3, 1982, represents a clear defense of the value of human life and a

restatement of the physician's task to defend it. We have here a comprehensive and thorough exposition of the service and witness which the physician by profession — especially if he is a believer — is asked to offer to man in all the wide diversity of support for health in its multifarious moments of fragility.[14]

Directly aimed at the theme of experimentation in biology is the address of the Holy Father to the participants in the *Meeting of the Papal Academy of Science* held on October 23, 1982. While laying stress on the hopes which are growing in the field of therapy of genetic and chromosomatic diseases thanks to biology and genetics progress, as well as the benefits brought to human nourishment of needy populations by the application of genetic engineering techniques, this Address contains the famous passage which represents an insuperable ethical barrier against the introduction of the quite recent techniques of biological manipulation of the human embryo: "I have no reason for concern about the *experiments in biology* carried out by scientists who have — as you have — a deep respect for the human person, because I am sure that they contribute to the *full good of man*. On the other hand, I most explicitly and formally condemn experimental menipulations of the human embryo because the human being, from his conception till death, can never be made an instrument for any purpose whatsoever. In fact, as was taught by the Second Vatican Council, *man is the only creature that God wanted as such*."[15]

Another clear contribution to our theme and the new experimentation frontiers is that offered by the Holy Father in his *Address to the Participants in the Meeting of the "Movement for Life"* held on December 3, 1983, the subject of which was "Prenatal Diagnosis and Surgical Treatment of Foetal Malformations."[16]

Though dealing with the theme of surgical experimentation, the Holy Father enunciates principles which can be referred to our subject. "It is therefore clear that endouterine research aiming at precociously detecting taints in embryos and foetuses (be they hereditary or not) so as to be able to readily eliminate them through abortion must be considered faulty from its origin and, as such, morally not admissible. Equally unacceptable is any form of experimentation on the foetus which might damage its integrity or worsen its conditions, unless it is an ultimate attempt to save it from certain death, as in this case a general principle holds true, the one which forbids making a human being an instrument for the advantage of science and other people's welfare."[17]

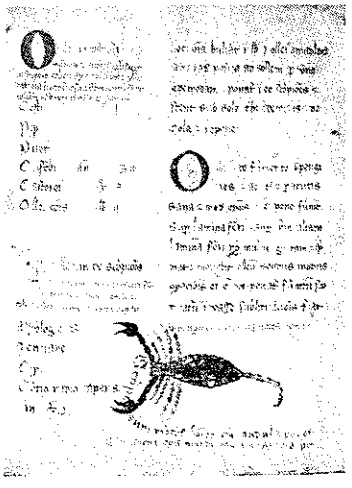
Papal Teaching, has therefore, touched on all the key points of the most controversial experimentation problems of the moment, not only their general principles, but also some outstanding application aspects.

Doctrinal Synthesis

The principles and fundamental values of the Papal Teaching we have recalled may thus be summarized as reference points:

— *The human person is the main and fundamental value*, having, as such, priority as regards society as well; therefore, he cannot be considered as a part in comparison with the whole, but as the center of social life itself; this value has the force of a law and is absolute, for the subject himself as well, who therefore lacks full control over his life.

— *The principle of totality*, according to which we may therapeutically intervene in human corporeity, and this has to be understood in the sense that the body is a whole resulting from parts organical-



Title page of the "New and Universal Pharmaceutical Theater" (Venice, 1617)

ly and vitally united. It is hence allowed to intervene on a part of the body only for the benefit of the whole and with the consent, explicit or assumed of the subject himself or of one who acts in his stead. This principle is also called the *therapeutic principle*.

— *The principle of social value*, which has to be understood in the sense that an individual may lawfully expose himself to a risk for the common good, provided he does it freely, within limits and under conditions which will not impair his essential physical and psychical integrity

— *The principle of subsidiarity*; it is a principle regarding the obligations of the State, which must help individuals when they cannot — alone or associated with other people — satisfy their vital needs or fundamental rights: this is the role of biomedical research in fighting diseases and stimulating the progress of medical science.

— To appeal to the so-called "teleological principle" to justify harmful or fatal experimentation on human beings for the sake of scientific progress or social welfare would be to re-introduce, under a different color, the false justifications which led to the crimes perpetrated in the concentration camps of the last war, and to overturn the person-society relationship: it would be an infringement of the first principle of this relationship.

We may, therefore, formulate the rules which become essential in the application phase and in the specific field of pharmacological experimentation.

We notice that there is — in great part or at least along general lines — a remarkable convergence between the teaching of Catholic morals and the important documents of medical deontology codified by international bodies.

I shall not repeat here the technical aspects of pharmacological experimentation in its various preparation and execution stages because we are speaking before an audience which in this matter is fully expert, and, besides, this is beyond the sphere of the subject I have to deal with. I shall only recall that the authors generally identify four phases: the "pre-clinical stage" of laboratory tests on animals; the "toxicity verification" stage, usually on healthy subjects; the "planned or restricted clinical experimentation" stage, which often avails itself of a group of patients to whom the drug is not administered and is replaced by a placebo. There is subsequently the "generalized clinical experimentation" stage aimed at verifying, through the use of the drug on a great number of subjects, its so-called long-range effects. It is after these stages that normally, when legislation on the matter is in force, the drug is granted the registration which allows its use on a wide scale. [18]

The most remarkable difference, as far as ethical judgement is concerned, is that between so-called *therapeutic* and *non-therapeutic experimentation*: the former has a diagnostic-therapeutic importance which concerns the patient himself who is the subject of experimentation; the latter aims at directly verifying scientific hypotheses without a correlation of benefits with the needs and conditions of the patient or of the healthy person on whom it is carried out; the ultimate purpose of both types is always the same: to make available to society, through scientific progress, new therapeutic means. In the first type, a direct purpose — treating the individual — prevails; in the second, what prevails is the social purpose. [19]

We could list moral indications in this matter and specify them in the following points:

a) clinical experimentation with drugs, as a necessary means to fight disease, if it is correctly performed under morally acceptable conditions, is not only lawful, but represents a service to man and shares in the goodness and value of science, which the Teaching of the Chruch has always encouraged and recognized; [20]

b) it is a precise duty of the State and the community to encourage, finance, and regulate scientific research for the relief of suffering mankind and the prevention of abuses and profits to the detriment of individuals and the community. Cuts in funds for scientific research are as much to be condemned as leaving children without food and patients without medicines; to neglect

the regulation of this sector would mean to favor the enslavement of science to profit and betray the patients in their expectations; [21]

c) the stage of pre-clinical experimentation requires the greatest care so as to acquire the maximum valid knowledge and minimize risk in the stage of application on man. From this standpoint, tests on animals, though with due respect for protective rules, should not be so conditioned by law as to represent an increase in risk for the stage of application on man; [22]

d) experimentation should be performed by a competent person and controlled by an equally competent and conscientious clinician; [23]

e) the clinical stage of experimentation, both therapeutic and nontherapeutic, should present a risk quotient proportionate to the purpose and such as to guarantee the integrity of the subject on whom the experimentation is performed. Experimentation itself should be discontinued as soon as this proportion and this guarantee no longer exist. The risk quotient should also be evaluated in the case of voluntary subjects and of tests carried out by the physician on himself; [24]

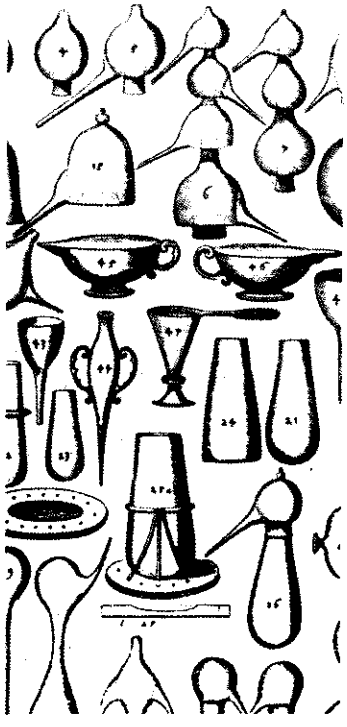
f) informed consent is absolutely necessary when the experimentation is not therapeutic and its benefit and aim have no immediate connection with the subject on whom it is carried out; therefore, from this type of experimentation all the subjects unable to give completely free and fully conscious consent must be excluded. As for informed consent in medicine, and particularly as regards experimentation, we must repeat that the consent, when requested, be truly informed, i.e. based on full, understandable, and fully understood information, so that it be really free, involving persons who have no form of moral dependence or physical constraint (children, convicts, subordinates, prisoners, or death-sentenced persons). This informed consent is normally also requested for therapeutic experimentation; it may be assumed or omitted when there are very serious reasons in safeguarding the patient's life. The case may occur when an experimental drug is employed with urgency in an extreme attempt to save the life of a patient when all the other therapeutic means fail. It may also occur when the request for informed consent would oblige us to give the patient information on the state of his disease which could induce him to harm himself (patients with cancer). We shall examine separately the case of consent for experimentation on minors. [25]

After having set forth these concepts — based on the person's pre-eminence over scientific values and social needs — some particular aspects over which there is heated discussion today remain to be clarified.

Randomization, placebo, and double blind

We know that experimentation to verify the effects of a given drug, requires quite often the method of control involving two groups of patients to whom two kinds of drugs are administered or, more often, with a group to which the drug is administered and another to which the drug is not given; since the selection of the subjects of both groups is made at random, this technique is called "randomization."

In order to keep the subjects from discovering if they belong to the first or the second group — to prevent the incidence of a subjective factor of a psychological nature — to the group of "witnesses" (or controls) a *placebo* is administered, a neutral substance



known to have no effects on the organism. Sometimes not only the subjects on whom the experimentation is done, but also the experimenters are unaware of this distribution and selection so that the person who controls the performance of the trial alone knows the actual drug and placebo distribution; in this case the experiment is labelled "double blind."

In the use of these methods of randomization, placebo administration, and double blind techniques with patients submitted to experimentation, ethical problems may arise alongside the technical problems.

These specific ethical problems are essentially the following: the patients to whom the placebo is administered are normally deprived of their usual therapy so that the experiment may prove valid, and thus during the experimentation period these patients remain without therapy; in the same way, it happens that the group of patients who receive the drug being tested, deprived of their normal therapy, have only the support of the new drug; both groups may risk suffering harm from this discontinuance of treatment. Therefore, to the known and expected risk involved in any type of experimentation, a further risk is added due to the interruption of normal therapies.

The ethical significance of the problem lies not so much in the number (more or less statistically important) of the patients submitted to the experiment — especially during the second stage (toxicity tests), where generally negative results may seem insignificant or irrelevant — as, rather, in the fact that it is chance and not the physician that decides which patients must be treated with a placebo and which with the drug and, above all, as we have seen, in the fact that the discontinuance of the usual therapies may cause harm to the patient.[26]

The experimental tests which involve interruption of normal therapies performed on subjects selected for the experiment, and, especially for those drawn by lot for placebo intake, would be criminal attempts should they be carried out in the Third World Countries on subjects suffering from infections and mortal diseases (typhus, yellow fever, etc.), without the knowledge of the subjects themselves.[27]

In order to offer behavior guidelines on this matter we should take into consideration that informed consent is not always easy to obtain, particularly in the case of diseases of a psychic or psychosomatic type, because of the inability of some subjects to understand this kind of information and also because in these cases information regarding even the simple fact that specific experimental psychoactive drugs will be administered may alter the result of the experiment; in such cases, if we wish to use, for instance, the double blind method, we may find ourselves in a dilemma: either do without the consent or risk the possibility of altering the results.

It is in fact known that in double blind experimentation, to find out the degree of the actual effect of the drug, global response and response to the placebo must be compared, but it is assumed that response to the placebo is not influenced by subjective or suggestive factors.[28]

To summarize the ethical clairification of this problem, I could set forth the following observations:

a) when we start the experimentation of a new drug for nontherapeutic research on patients under therapy, it is ethically necessary to ascertain that the discontinuance of the usual therapy does not expose the health or the life of the patient to harm or risk. Besides, should the method of the double blind be applied, the consent of the subject is equally to be requested, even if it limits the experiment and the methods employed. Should this not be feasible — as in the case of psychodrugs — the "double blind" method cannot be ethically admitted. The deceit in this case, not even prompted by requirements of the patient's health, has no ethical justification whatsoever and in the end would only harm the medical class and hospital credibility;[28]

b) when the experimentation is carried out with a therapeutic aim, we should make sure that discontinuance of usual therapies will not represent a risk or cause harm to patients and that it be assumed, inductively speaking, that the effectiveness of the drug administered for the experiment is not lower than

that of the already known one [30]

Pharmacological experimentation on embryos and foetuses

Recent scientific and technological progress in artificial procreation *in vitro* (FIV)* offers the possibility of having available surplus embryos or even of producing them for the explicit purpose of experimentation. The refining of diagnostic technologies offers new possibilities of foetal observation and intervention in the uterus (echography, foetoscopy, placentocentesis). The legal and illicit spreading of the voluntary interruption of pregnancy (IVG)** made it possible to carry out pharmacological experimentation on foeta just extracted, still alive. This is a page in which abuses, for their disregard of ethical rules, are getting near to those that were usual in the Nazi concentration camps.

The information given on this matter deals not only with experimental studies on embryos *in vitro*, but also experimental activities with foetuses in the uterus and extracted alive and viable on the occasion of voluntary interruption of pregnancy. It is on these subjects and crimes that the Teaching of John Paul II took a position in recent years with the Addresses which we have recalled above.

The anthropological presupposition which must underlie every type of intervention is given by the acknowledgement of the human status of the embryo and the foetus. The human embryo and foetus must be considered human subjects and persons in the stage of development.

This is not the right place to repeat the discussion on the biological and anthropological status of the embryo and the foetus, which in recent times has become a rather controversial matter occupying the debates of moralists, jurists, and international political bodies. We shall simply state that we cannot accept either on the scientific plane or on anthropological grounds the toned down and reductive definitions of "potential personality," or even "pre-embryo" for the first development stages of the human being, definitions which are purely instrumental.

We think it also needless to list the evidences of the existence of abusive and unlawful practices in experimentation on living and viable or living and not viable foetuses, as well as a tolerance or even a sort of legalization of experimentation on embryos obtained by "*in vitro* insemination."

As to experimentation on live foetuses obtained from Caesarian operations, with or without the consent of the mother, we have the position expressed in the European Parliament Resolution dated October 18, 1983 and the denunciation so often repeated by well documented works.[31] As regards tolerance of the rules — apart from the *de facto* tolerance due to the lack of rules — let it suffice to recall the well-known Warnock Report, according to which experimentation on the human embryo can be done up to the 14th day of life,[32] and also a kind of explicit admission in W.H.O. documents.

As regards the moral evaluation of what we have just said while speaking of not strictly therapeutical experimentation, it will suffice to recall, in the light of our anthropological principle, the serious moral prohibition of any kind of experimentation on living embryos and foeti (even if alive and not viable). We quote here the words of the Holy Father John Paul II in the above-mentioned Address of October 23, 1982: "I most explicitly and formally con-

demn experimental manipulations of the human embryo because the human being from his conception till his death can never be made an instrument for any purpose whatsoever." [33] Apart from the risk intrinsic to these experiments and the brutality of a possible and pre-established elimination of the subject, we have to bear in mind that the embryo or foetus cannot give needed consent to non-therapeutic experimentation.

The case is different when treatments not yet experienced as valid and, therefore, experimental would be employed for the purpose of saving the life of the unborn, or just-born, child as an extreme measure when there are no validated therapies available. In this instance, we can quote the words of the Holy Father himself, expressed in connection with the possibility of experimental surgical therapy in his Address of December 3, 1982: "Every form of experimentation on the foetus which might damage its integrity or worsen its conditions is not to be accepted, unless it be an extreme attempt to save it from certain death, given that in this case the general principle holds true which forbids us to make a human being an instrument for the benefit of science or the welfare of other people." [34] In this case, the reason for the exception is that therapeutical experimentation is used not so much for direct experimental purposes, but rather with the chief aim of making an attempt to save a life.

Experimentation on Children and Minors

Through our enunciation of the general principles, we have made it clear that these subjects are included in the number of those who are not capable of giving valid consent, and, therefore, experimentation on these subjects is legal only if it is carried out for a therapeutic purpose, for the benefit of the individuals themselves, and with the consent of their parents or legal representatives.

Recently, however, the medical press set forth more differentiated answers. First of all, a distinction is introduced between real mental capacity and legal capacity for informed consent: as regards consent, the case of a 5-year child is different from that of a 15-year boy, who is also allowed to enter into a valid marriage.

Besides, we recall that there are experiments whose risk is almost nil, as, for instance, the drawing of a few cc. of blood for haemogas-analysis which has to be conducted on healthy persons so as to observe the difference in haematologic patients. Therefore, according to some authors, not only the age factor should be considered, but also the risk; the case of experimentation of a drug in dermatology which may cause the irreversible falling of hair is different from the above-mentioned drawing of blood, which also has an experimental purpose.

A rather utilitaristic or "teleological" consideration was introduced as well on the grounds of the great advantages brought by some experiments, unlawful in themselves, for the treatment of diseases immune to known drugs, as was the case of the Salk vaccine, which allowed us to wipe out poliomyelitis.

Finally, stress is laid on the possibility of the integration ("identification") of the parent's or legal representatives' consent with the explicit consent of the minor having the use of reason: the latter, being capable of acts of generosity, may also accept, if he is instructed, an altruistic act involving some risk. [35]

The Helsinki Declaration updated by the World Medical Association uses a wording for this matter which is not quite clear, but conveys a possibilistic sense, even if subject to some conditions: "In case of legal incapacity, and especially in the case of minors, consent should be requested of the legal representative, taking into account national legislation. Should a physical or mental incapacity make it impossible to obtain informed consent, the authorization of responsible close relatives replaces that of the subject to some extent. When the minor is capable of giving his consent, this should also be obtained, in addition to that of the legal representatives." [36]

Here, as can be seen, for those who are really incapacitated for consent, the hypothesis is offered of the "substitute" consent of close relatives.

In wishing to express an ethical opinion, apart from

legal rules which may also change, I would summarize it as follows, with the support of the opinion of moralists of great authority and, above all, the Teaching texts of the Church.

a) First of all, I believe that in the case of subjects who are really incapable of consent, just as with those who do not yet have or will never have the use of reason, no therapeutic experiments are morally to be admitted. In this event, we can consider the experimental use of a drug only as a last attempt at saving the life of a minor which could not be saved by already known drugs: in this case, it would more properly be therapeutic experimentation, even if it could yield, in case of a positive result in an unexpectedly lucky turn, precious data for science and society.[37]

b) When there is legal incapacity, but real capacity for informed consent, this consent, strengthened by that of the legal representatives, could be considered valid for nontherapeutic experimentation, on condition that there are no significant risks for the life or physical integrity of the subject.[38] The existence of these conditions should be strictly controlled by an ethics committee.

c) The fact that the minor subject really or juridically incapable of consent and condemned by his disease is headed towards certain death does not change the nature or the extent of his moral protection.

I shall leave out discussion of subjects sentenced to death in those States where the death penalty is still in force both because I am morally opposed to the persistence of this law and because nontherapeutic experimentation even on such a subject appears unjustifiable in terms of either pseudo-consent or the substitution of the kind of penalty. In the same situation as minors really incapable of consent, we should consider those who are incapacitated through mental disease or other impediments to freedom (prisoners, persons depending in a moral sense on the experimenter).

Ethical Committees

The existence of a legal void in some States, the possibility of eluding the law, and, in any event, the complexity of the problem are the factors which have now made the creation of ethics committees necessary for control of experimentation in hospitals and in all the Institutes of biomedical and clinical research.

There is much current discussion on ethics committees,[39] and many doubts are put forth as regards their legal status, the regulatory value of their indications, and their operational effectiveness. There are, however, different models for ethics committees for the humanization of hospital assistance, the defense of patients' rights, and advice in connection with individual medical interventions. The committee we are speaking of should have a precise activity of its own as regards the survey of the conditions and the required qualities of morality and deontology in pharmacological experimentation.

The most delicate problem of the said committees lies not so much in the uncertainty of their juridical standing, which will be easily overcome when the law itself recognizes their role, but rather in the fact that it is not likely that all their members will share common ethical viewpoints and have the same philosophy on man and medicine.

I have no intention to deal here with the whole specific problem relating to composition, operation, and the range of control functions (previous approval of the experimentation, control of its perfor-

mance, acceptance of petitions, appeals, etc.).

I wish only to emphasize two firm beliefs and two exigencies which are also ethical:

a) Ethics committees for the verification and control of pharmacological experimentation are not only useful but necessary. They must verify the existence of and respect for the moral and deontological rules of the protocols for experimentation on man, availing themselves of qualified persons including representatives of patients who are not responsible for the performance and utilization of research. This utility-necessity arises from the need to contrast technological-scientific exigencies with ethical and deontological-legal ones. Every research protocol involves this need for contrast among various branches of knowledge.

b) Ethics committees, in order to be effective and valid in their function, must adopt a set of parameters leading to a well-defined anthropology: what secular or pluralistic circles should safeguard as "the rights of man" underlying the international and deontological codes of the World Medical Association.[40]

Conclusions

Owing to the commitment of Catholics, one of the greatest and most delicate tasks that history has ever assigned to the Church is now commencing: the defense and promotion of life and of the human person through the active confrontation of ethics against technological-sicentific progress. Ethics and experimental science — these are the new terms of relation, a relation which, for its importance, is not less than all those which the successive generations have had to face throughout the history of the Church: classical knowledge and Christian wisdom; political power and freedom of the Church; humanist philosophy and supernatural anthropology; enlightened reason and Christian revelation.

It is a challenge that we feel everywhere as a the need for a saving encounter: ethics becomes incarnated and vital if it succeeds in illuminating scientific-technological progress; scientific and technological progress can remain at the service of man only if it is connected with ethics.

In this phase of human experimentation as well, we have been able, I hope, to ascertain the urgency and magnitude of the task, a task for which we believers are responsible in the face of truth, the Lord of history, and future generations.

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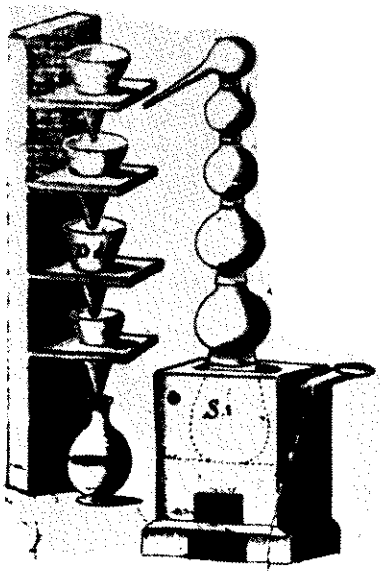


* Italian initials for "fecondazione in vitro" = in vitro insemination
** Italian initials for "interruzione volontaria della gravidanza" = voluntary interruption of pregnancy (n.d.t.)

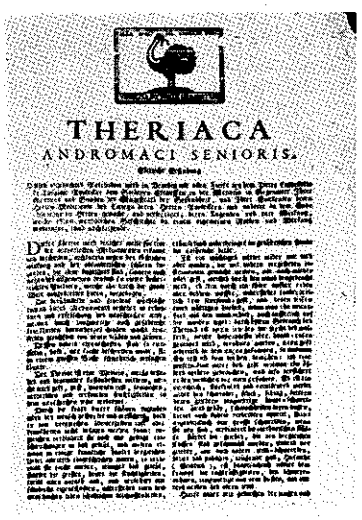
NOTES

[1] For information on deontological codes dealing with the defense of human rights in the context of experimentation on man, the following works may be consulted: M. TORRELLI, *Le médecine et les droits de l'homme* (Paris: Berger-Levrault, 1983), p. 466. *Le médecine et les droits de l'homme* (in press), edited by the Council of Europe's Department of Advanced Studies and Research, Strasbourg. S. SPINSANTI, *Documenti di deontologia e etica medica* (Torino: Paoline, 1985), p. 225.

[2] E. SGRECCIA, *Bioetica. Manuale per medici e biologi* (Vita e Pensiero Publishers, 1986), pp. 310-318

[3] W. T. REICH, "Human Experimentation," in the *Encyclopedia of Bioethics,* II (New York: The Free Press-MacMillan, 1978), pp. 683-710. I. ILLICH, *Nemesi medica. L'espropriazione della salute* (Milan: Mondadori, 1977), p. 84. See also "Regolamentazione della sperimentazione clinica in Italia e nei Paesi del MEC," in the *Proceedings* of the Symposium held in Milan and published in *Rassegna clinico-scientifica,* 49 (1983), pp 201-257

[4] FOR THE ASPECTS MOST CLOSELY RELATED TO DEONTOLOGY, SEE L. VILLA, *Etica e deontologia della sperimentazione* (Torino, 1986). C. GENTILI, G. ALVARO, *et al.*, "Considerazioni etico-giuridiche sulla sperimentazione di farmaci nuovi nell'uomo," in *Rassegna clinico-scientifica,* 48 (1972), pp. 376-385. G. DE VINCENTIIS and P. ZANGANI, "Sulla liceità e sui limiti sull'uomo," in *Giustizia penale,* 1 (1968), p. 321 and following. A. BOMPIANI, "La sperimentazione clinica dei farmaci: stato attuale del problema normativo e proposte di riforma," in *Medicina e Morale,* XXXII (Università Cattolica, 1982), pp. 95-134. A. MARMONT, "La problematica etica della sperimentazione clinica," in *Medicina e Morale,* XXX (Università Cattolica, 1980), pp. 39-52. A. FASOLI, "Considerazioni sul consenso informato nella medicina pratica e nella sperimentazione clinica," in *Medicina e Morale,* XXXV (Università Cattolica, 1985), pp. 523-530. P. STEFANINI, "Aspetti etici della sperimentazione clinica," in *Medicina e Morale,* vol. 3 (Rome: Orizzonte Medico, 1970), pp. 19-25.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ANDROMACI SENIORIS.

[5] For works by specialists in medical ethics, see G. PERICO, "Sperimentazione clinica," in *Dizionario Enciclopedico di Teologia Morale,* (Rome: Paoline, 1981), pp. 1025-1034; and *Problemi di etica sanitaria* (Milan: Ancora, 1985), pp. 83-96. A. VALSECCHI, "Principi etici generali sulla sperimentazione clinica," in *Medicina e Morale* (Rome: Orizzonte Medico, 1970), pp. 27-38. B. HÄRING, *Etica medica* (Rome: Paoline, 1972), pp. 340-355. D. MONGILLO, "La sperimentazione sull'uomo. Riflessioni etiche," in *Medicina e Morale,* XXIII (Università Cattolica, 1973), pp. 29-39. E. CHINACCI, *Morale della vita fisica* (Bologna: Dehoniane, 1979), pp. 22-28. S. SPINSANTI, "Vita fisica: la sperimentazione sull'uomo," in *Diaxonia (Etica della Persona II)* (Brescia: Queriniana, 1983), pp. 228-232. THOMAS A. SHANNON (ed.), *Bioethics* (New York: Paulist Press, 1981), pp. 235-245; H. Jonas' article, "Philosophical Reflection on Experimenting with Human Subjects" (pp. 235-261), is especially useful. R. PLANT, "Human Experiments. Philosophical Problems," in *Dictionary of Medical Ethics,* edited by A. S. Duncan, G. R. Dunstan, and R. B. Welbourne (London, 1981), pp. 234-236. A. R. JONSEN, "Experimentation with Human Subjects," in *A New Dictionary of Christian Ethics,* edited by J. Macquarrie and J. Childress (London, 1986), pp. 219-221. C. H. PESCHKE, *Christian Ethics* (Dublin: C. Goodliffe Neale, 1981), pp. 340-341. ANDREW C. VARGA, *The Main Issues in Bioethics* (New York: Paulist Press, 1984), pp. 149-164; and Sgreccia, *op cit.,* pp. 305-325.

[6] PIUS XII, *Discorsi e Radiomessaggi,* vol. XIV (Vatican Polyglot Press, 1953), pp. 317-330.

[7] A number of key passages such as this one have been included in F. Angelini (ed.), *Pio XII: Discorsi ai medici* (Rome: Orizzonte Medico, 1959).

[8] PIUS XII, *Discorsi e Radiomessaggi,* vol. XV, pp. 415-428.

[9] PIUS XII, *Discorsi e Radiomessaggi,* vol. XVI, pp. 167-179.

[10] PAUL VI, "Discorso ai partecipanti all'XI Congresso Nazionale della Società Italiana di Patologia su 'La genesi dei tumori'," in *Insegnamenti di Paolo VI,* vol. VII (Vatican Polyglot Press, 1969), pp. 717-720.

[11] JOHN PAUL II, "Ai partecipanti a due congressi di medicina e chirurgia," in *Insegnamenti di Giovanni Paolo II,* vol. II/2 (Libreria Ed. Vaticana, 1980), pp. 1005-1010.

[12] *Ibid.*, p. 1008

[13] *Ibid.*, p. 1009

[14] JOHN PAUL II, *Insegnamenti,* vol. V/3 (1982), pp. 663-677.

[15] JOHN PAUL II, *ibid.*, pp. 895-898

[16] *Ibid.*, pp. 1609-1613.

[17] *Ibid.*, p. 1511.

[18] A. BOMPIANI, *op. cit.*; F. B. NICOLAS, "Le fasi della ricerca terapeutica," in *Rassegna clinico-scientifica,* 49 (1973), p. 248.

[19] SEE "CODICE DI HELSINKI: INTRODUZIONE," included in S. SPINSANTI, *op. cit.*, pp. 39-40

[20] *Ibid.* PIUS XII, "Allocuione al I° Congresso di Istopatologia del Sistema Nervoso," in *Discorsi e Radiomessaggi;* PIUS XII, "Allocuzione all'VIII Assemblea della Associazione Medica Mondiale del 30-IX-54," included in F. ANGELINI (ed.), *Pio XII. Discorsi ai medici,* p. 358; PAUL VI, "Discorso ai partecipanti all'XI Congresso della Società Italiana di Patologia" (October 31, 1969), in *Insegnamenti di Paolo VI,* vol. VII, p. 717.

[21] PAUL VI, "Messaggio per il XX anniversario della fondazione dell'OMS" (April 28, 1968), in *Insegnamenti di Paolo VI,* vol. VI (1968), p. 182. JOHN PAUL II, "Discorso ai partecipanti al XV Congresso della Federazione Internazionale delle Associazioni dei Medici Cattolici e al XVI Congresso Nazionale dell'Associazione dei Medici Cattolici Italiani" (October 3, 1982), in *Insegnamenti di Giovanni Paolo II,* vol. V/3 (1982), p. 675.

[22] PIUS XII, "Discorso al I° Congresso Internazionale di Istopatologia del Sistema Nervoso," found in F. ANGELINI (ed.), *op. cit.*, p. 208; "Codice di Helsinki" (I, 1), in S. SPINSANTI, *op cit.*, 40.

[23] PIUS XII, "Discorso al I Congresso Internazionale di Istopatologia del Sistema Nervoso," in ANGELINI, *op cit.*, p. 309; PIUS XII, "Discorso alla XVI Sessione dell'Ufficio Internazionale di Documentazione di Medicina Militare," in ANGELINI, *op. cit.*, p. 303; "Codice di Helsinki" (I/3), in S. SPINSANTI, *op. cit.*, p. 40.

[24] PIUS XII, "Allocuzione ai partecipanti al I° Congresso di Istopatologia del Sistema Nervoso," in ANGELINI, *op. cit.*, pp. 192-193; "Codice di Helsinki" (I/5, 6, 7), in SPINSANTI, *op cit*, p. 41

[25] PIUS XII, "Allocuzione ai partecipanti al I° Congresso di Istopatologia del Sistema Nervoso," in ANGELINI, *op. cit.*, pp. 200-201; "Codice di Helsinki," I/9, 10, 11, in SPINSANTI, *op cit.*, pp. 41-42; SGRECCIA, *op. cit.*, pp. 317-318; A. FASOLI, "Considerazioni sul consenso informato nella medicina pratica e nella sperimentazione clinica," in *Medicina e Morale,* XXXV (Università Cattolica, 1983, pp. 523-530; C. GENTILI, G. AIVARO, *et al.*, "Considerazioni etico-giuridiche sulla sperimentazione dei farmaci nuovi nell'uomo," in *Rassegna clinico-scientifica,* 48 (1972), pp. 376-385.

[26] P. ARPAILLANGE and S. DION, "Considerations sur l'éthique de la Randomisation," in *Biomedicine and Pharmacotherapy,* 38 (1984), pp. 426-429.

[27] PAPPWORTH, *Human Guinea Pigs. Here and Now Experimentation on Man* (London: Routledge and Kegan Paul Ltd., 1967).

[28] P. E. LUCCHELLI, "Placebo e guarigione: pregiudizio e fede nella risposta terapeutica," in *Federazione Medica,* vol. XXXVI, no. 9 (1983), pp. 804-808.

[29] BOX SISSELA, "L'etica della somministrazione del placebo," in *Le Scienze,* Italian edition of *Scientific American,* vol. XIV (8th year), no. 78 (1975), pp. 11-17

[30] P. ARPAILLANGE and S. DION, *op. cit.*, p. 427.

[31] C. JACQUINOT and J. DELEY, *Les traficants de bebé à naître* (Lausanne: Favre, 1984), which includes the text of the resolution. Information on this gloomy subject may also be found in the journal *Profils medico-sociaux* (January 17, 1984), cited in *Vox Vitae,* vol. XI, no. 114 (1984). See also D. TETTAMANZI, *Bambini fabbricati. Fertilizzazione in vitro, embryo-transfer* (Casale Monferrato: Piemme, 1985).

[32] Cf. the complete text of *The Warnock Report*

[33] *Insegnamenti di Giovanni Paolo II,* vol. V/3 (1982), p. 891.

[34] *Insegnamenti di Giovanni Paolo II,* vol. V/3, p. 1511.

[35] B. R. REDMON, "How Children Can Be Respected As 'Ends' Yet Still Be Used As Subjects in Non-Therapeutic Research," in *Journal of Medical Ethics,* 12 (1986), pp. 77-82; R. MCCORMICK, "Proxy Consent in the Experimental Situation," in *Perspectives in Biology and Medicine,* vol XVIII, no 1 (1974), pp. 2-20

[36] The Helsinki Code updated by the World Medical Association (I, 11) See SPINSANTI, op cit., pp. 41-42

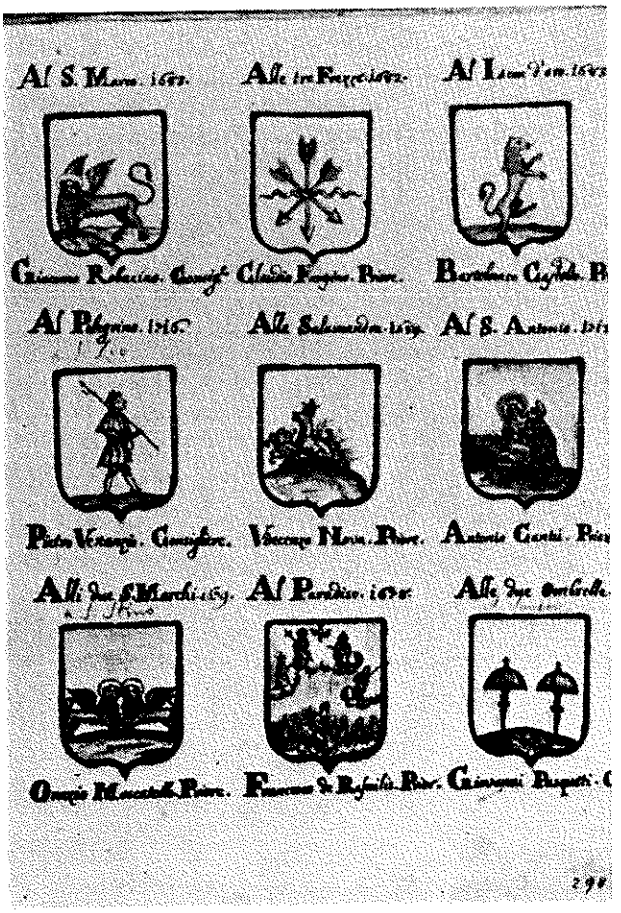
[37] PIUS XII, "Allocuzione ai partecipanti alla VIII Assemblea dell'Associazione Medica Mondiale," in *Angelini, op. cit.,* p. 357.

[38] B. R. REDMON, *op. cit.,* p 80.

[39] A. SPAGNOLO, "I comitati etici negli ospedali," in *Medicina e Morale* (Università Cattolica, in press) provides information on a recent meeting devoted to the subject and on the current state of the question; F. ROSNER, "Hospital Medical Ethics Committees: A Review of Their Development," in *Jama,* vol. 253, no. 18 (May, 1985), pp. 2693-2697; J. M. FACCINI, P. N. BENNETI, and J. L. REID, *"European Ethical Comittee. The Experience* of an *International Ethics Committee Reviewing Protocols, Drugs, Trials," in British Medical Journal,* vol. 289 (October 20, 1984), pp. 1052-1054.

[40] SPADEA M. SCALABRINO, "Comitati etici e diritti dell'uomo," in *Medicina e Morale* (Università Cattolica, in press).

The seal of Venetian pharmacies



DUILIO POGGIOLINI

Drug Control As a Safety Measure in Society

Drugs are subjected to various interventions by regulatory authorities which take place in the course of their whole lifetime; I am referring to their planning, the scientific research they involve, their use by physicians.

Among these interventions, the one in which the ethical aspect takes on particular relevance is that of control by States.

These interventions aim at a goal of a highly ethical nature: the defense of the consumer.

In this address I shall try to analyze the various levels at which the lofty and weighty responsibility of ensuring this defense is shared.

At the first level of responsibility we find the producer: he must perform all the studies needed for the demonstration of the efficacy and security of the new drug, mentioning all the relevant results obtained, be they favorable or unfavorable, and all the original values supplied, so as to allow a critical examination of the results independently of the interpretation given to them by the inventor.

From the pharmaceutical producer ethical behaviour of great relevance is hence required; he has a high responsibility because the correct performance of testing and the careful criticism of the data obtained allow a previous judgment of the actual therapeutic characteristics of the new drug and eliminate from the marketing proposal any purely commercial and economic motivations.

The producer, viewed in this light, becomes, therefore, a partner of the pharmaceutical regulatory authority.

Authority, however, has also a relevant role in the various pharmaceutical regulation functions with a peculiar ethical and moral importance inasmuch as they are carried out in defense of man and in favor of his health.

The responsibilities lying with the pharmaceutical regulatory authority are manifold and complex. They underlie a series of interventions on the drug and are all aimed at guaranteeing to the consumer a fair degree of quality, security and efficacy.

This condition is ascertained and established in different phases.

The first phase of control must be established right from the start of the experimental course of the drug through the scientific laboratories where toxicological and pharmacological tests are performed. It is in fact absolutely necessary to ascertain that these trials are carried out in technical-experimental conditions that can be considered acceptable and that suitable measures are adopted as regards the keeping and care of animals. This is provided for by the GLP.

Ascertainments and controls performed when the new drug — preclinical tests on animals being concluded — undergoes clinical testing on man are particularly relevant.

Some nations, including the United States, the United Kingdom, and Italy, carry out a careful check during the various phases of the clinical test in order to ensure that it is performed in suitable security conditions for the patients.

As regards Italy in particular, it is interesting to underline that the controls to be carried out prior to the authorization to perform clinical tests take place in two different phases: before the preliminary or "pilot" clinical test and, subsequently, before the enlarged clinical tests. Various experimental data of a chemical, toxicological, and pharmacological nature are carefully examined prior to the granting of these different authorizations. It is also interesting to observe that these controls are intended not only to ascertain the test's safety, but also its actual usefulness on the basis of the foreseeable degree of therapeutical advantage thus obtainable.

In this way the best possible degree of defense is ensured to the clinical test subjects (be they healthy volunteers or patients) inasmuch as they are not subjected to clinical tests not strictly needed.

The same purpose is behind the EEC rules established by Directive 65/65, which considers the possibility of the manufacturer's preparing, for known products, only the bibliographical documentation so as to avoid the performance of useless clinical tests.

The final assessments regarding the establishment of the risk/benefit balance of a drug are made at the moment of the granting of its marketing authorization by the regulatory authorities.

The responsibilities underlying this fundamental moment are of really great significance.

Regulatory authorities must in fact establish with the utmost objectivity that all the studies provided for by the rules in effect have been actually carried out with satisfactory technical modalities and that, on the basis of the scientific knowledge available at the moment, the usefulness of the drug resulting from them is greater than the unavoidable risks connected with its use. This evaluation is of the utmost importance as it regards the final goal to be reached, i.e. to ensure the patients' defense, and the authorities' behavior in this instance is determined not only by the common responsibilities of an administrative and criminal character, but also by a fundamental exigency of an ethical nature to which the above mentioned responsibilities must in the end be referred.

If the fundamental principle of *primum non nocere* is at the basis of the control, the exigency of guaranteeing the safe sure efficacy and appraisable advantage of any new therapeutical realization is no less compelling in thus avoiding to the greatest possible degree that these realizations be turned into simple commercial operations which make no contribution whatsoever to the real needs of patients.

And it is precisely for these reasons that in Italy the Ministry of Health, inspired by such criteria, has recently required the clear identification of the therapeutical placing and role of each product as compared with drugs of the same group, and that any and all possible differences in therapeutical behavior as well as possible peculiarities in pharmaceutical technique be pointed out.

In fact, the new EEC rules state that: " The main purpose of the clinical documentation is to demonstrate the therapeutical effect of the medicinal specialty in question, comparing it, if needed, with already existing therapies."

The coming into force of these rules has already yielded substantial results, as is shown by the data supplied in the preceding tables.

In particular, during the January 1, 1986/September 30, 1986 period only 40 new medicinal specialties were registered.

No matter how ample and exhaustive the preclinical and clinical trials may be prior to the marketing authorization of a new drug, no matter how well they predict the physiological and pathological conditions of its actual use in man, today it is generally acknowledged that the true demonstration of a new drug's safety as well as its efficacy is really acquired only after a first period of its use on wide strata of the population.

And it is just in these conditions of use that it is possible to observe those side effects which in fact — on the basis of statistically evident evaluations — may come to light only in population strata wider than those which were the object of the clinical tests carried out before the marketing authorizations.

For this very reason, the first marketing period of a new drug acquires particularly delicate features.

Moreover, the regulatory authorities are once again invested with a great responsibility in ensuring that this first period of a drug's use takes place in conditions of acceptable security for the patients.

This responsibility is originated by a moral obligation and it is symptomatic that the more developed countries have recently implemented suitable pharmacovigilance systems which make it possible to observe and report the significant side effects of the drug, thus allowing proper measures to be taken for the safeguarding of the citizens' health and integrity.

In these last years a new science was thus born: pharmacovigilance, which avails itself of complex survey and evaluation methods in order to establish the real causality link between the use of the drug and its untoward effects.

In such a system, the professional responsibilities involved are multifarious, and among them those of physicians who, generally on a voluntary basis, have to promptly supply a complete report on the observed unfavorable effect are particularly important; their moral obligation is therefore very necessary, but that of the authorities is undoubtedly of equal importance; they in fact must, through their experts, make wise decisions in order to protect the patients from unexpected or serious or particularly frequent unfavorable effects, avoiding, at the same time, overly emotional decisions which in the long run

could prove not profitable for the patients, who would thus be deprived of delicate drugs which could still be useful for them.

At this point another assessment of the risk/benefit balance is required, and this new evaluation should be considered more delicate than the one performed in the marketing of the drug; it is, in fact, carried out on the basis of the data coming from the widespread use of the drug on man and therefore every examination, evaluation, and decision must be "parametered" on the fundamental exigency of giving the utmost guarantee to the welfare of man in his physical, psychical, and spiritual wholeness.

But the regulatory authorities are again required to perform the essential ethical-moral task of seeing to it that the use of drugs is always beneficial for man when they must — also long after the drug's approval — verify its efficacy on the basis of new scientific knowledge. A broad review operation on the old specialties which in the light of modern scientific knowledge prove obsolete and no longer useful is increasingly frequent in an increasing number of countries. Their withdrawal from the market is therefore a moral commitment of paramount importance because in this way useless or deceptive treatments prejudicing the patient are avoided.

In this connection, I should like to recall that the review of obsolete drugs has been one of the strong points of the Italian pharmaceutical policy.

Besides, we must not disregard other interventions by the regulatory authorities, suggested by an ethical approach aimed at the defense of human rights. I wish to refer to the control carried out by some States (including Italy) on the content of information and advertising addressed by the pharmaceutical industry to physicians in the case of "ethical" products, and to the public at large in the case of "counter products."

In addition, this control has to be inspired by a great sense of responsibility because only through accurate information and advertising are patients and consumers in general protected from mystifications, excesses, and deviations which, in the long run, may prove harmful to their health.

Various other drug control activities aimed at protecting man, ensuring that drugs are used for his benefit, could also be cited.

I shall recall only an extremely delicate intervention carried out by the control authorities in close cooperation, that regarding narcotics and psychoactive drugs.

Everybody is aware of the decisive importance of this control for the psychophysical defense of man and the safeguarding of society.

At this point it may be interesting to give some examples of the results which can be obtained from a serious commitment to pharmaceutical regulation based on the ethical criterion of the benefit to man.

Allow me to show you some data regarding our country.

Conclusions

Drawing toward the conclusion of my address, I would like to recall once more the fundamental concept of responsibility inspiring the most important choices in the drug field.

These responsibilities are originated by strict moral principles which must guarantee one of the supreme blessings of man: health.

These responsibilities involve research workers and pharmaceutical producers, on the one hand, as well as regulatory agencies, on the other.

And it is by these very fundamental principles that the European Economic Community was inspired when it re-

ITALY
MANUFACTURERS OF DRUGS FOR HUMAN USE

YEAR	NO. OF MANUFACTURERS	INDEX (1962 = 100)
1962	770	100
1964	735	95
1966	747	97
1968	643	83
1970	595	77
1972	531	69
1974	494	64
1976	464	60
1978	410	53
1979	398	52
1980	390	51
1981	365	47
1982	348	45
1983	345	45
1984	340	44
1985	335	43.5

CONTROL ON PROMOTIONAL ACTIVITIES

Year	Published Texts Examined	Regulatory Remarks	
1982	1550	1044	66
1983	2700	1938	71
1984	2053	790	39
1985	2500	448	20
1986 (Aug. 31st)	490	54	11
Total	9293	4274	46

cently issued instructions for the preparation by pharmaceutical producers of "expert reports" to be filed together with the applications for new drug authorization.

The experts must make a critical evaluation of the product. This critical justification becomes a particularly important part of the clinical documentation, which is, after all, the only factor resolving all the authorization problems, because it is precisely on the basis of the clinical protocol that in the end the final decision must be made along with the evaluation of the risk/benefit balance done.

By accepting this job, the expert undoubtedly takes upon himself a responsibility of his own.

In fact, he must evaluate all the aspects of the product, both favorable and unfavorable, and make its risk/benefit balance; and in this way he is responsible. Because the first risk/benefit balance derives from the expert's report.

In any event, the expert gets introduced into a responsibility scale which also involves the authority that has to express a considered judgement through the evaluation report.

As regards pharmaceutical regulatory authorities, I think that they are increasingly aware of the great moral responsibility which lies with them.

This feeling, ever more widespread and profound, will yield undeniable benefits in guaranteeing the health of man, while at the same time this same responsibility drives

SPECIALIIES AND PACKAGINGS ON THE ITALIAN MARKET

Year	Medicinal Specialties Number	Medicinal Specialties Index (Italy = 100)	Packagings Number	Packagings Index (Italy = 100)
1960	12,550	100.0	27,952	100.0
1962	12,972	103.3	26,677	95.4
1964	12,209	97.3	24,858	88.9
1966	11,976	95.4	23,424	83.8
1968	11,204	89.3	21,716	77.7
1970	10,900	86.8	21,130	75.6
1972	10,136	80.8	19,776	70.7
1974	8,932	71.2	16,814	60.1
1976	8,932	71.2	16,814	60.1
1978	7.564	60.3	13,979	50.0
1980	6,502	51.8	13,214	47.3
1982	6,091	48.5	12,900	46.1
1983	5,995	47.8	12,650	45.3
1984	5,926	47.2	12,128	43.4
1985	5,779	46.0	11,974	42.8

PHARMACOVIGILANCE ACTIVIIIES (1980 - MAY 1986)

No. of Reports	No. of Patients	No. of Resulting ADRs
22,696	**5,086**	**7,543**

regulatory authorities to cooperate more and more closely and intensely with one another.

Instances of this cooperation are clearly perceptible at the level of international bodies, such as WHO, EEC, EFTA, as well as at the level of relationships and bilateral agreements among the more developed countries.

Since the health of man is a universal blessing, and the increasingly powerful and sophisticated therapeutical means placed by modern science at the disposal of mankind are equally universal, it clearly appears that the various regulatory authorities must progressively shape their behavior on a single pattern of ethical and moral coherence which also has a universal dimension.

In the light of these considerations, we may hypothesize that it is precisely by bearing in mind and following these principles of ethics, rather than the slow and sometimes contradictory process of international and Community events, that pharmaceutical regulatory authorities may more quickly reach that uniqueness of orientation and decision which is the goal we all hope to attain for the defense of citizens all over the world as well as for the advantage of every enlightened pharmaceutical industry, which can no longer operate within national boundaries, but must project itself in a worldwide dimension.

PROF DUILIO POGGIOLINI
Director General
Pharmaceutical Department
Italian Ministry of Health

ITALY
MEDICINAL SPECIALTIES REGISTERED (1975-1986)

YEAR	MEDICINAL SPECIALTY
1975	101
1976	224
1977	31
1978	207
1979	173
1980	173
1981	181
1982	234
1983	235
1984	306
1985	253
1986 (30/8)	41

TEUDIS CARDOZO SOTO

Drug Experimentation in the Developing Countries

Since the early times of Christianity, Christians have realized that a significant part of our life has to be addressed to the care of the sick and invalid, looking after them with a self-sacrificing spirit to relieve their sufferings and, insofar as possible, cure their diseases. When the Holy Church of Rome was founded, provisions were taken to promote the health of the world known at the time, to look after and cure suffering man, to eradicate diseases, to accompany the infirm Christian up to his last stage of life, sharing in his sorrows and pains, helping him to live and to die.

I shall start this address by quoting St. Matthew's Gospel (8:1-13): "After he had come down from the mountain large crowds followed him. Suddenly a man with a virulent skin disease came up and bowed low in front of him, saying, 'Lord, if you are willing, you can cleanse me.' Jesus stretched out his hand and touched him, saying, 'I am willing. Be cleansed.' And his skin disease was cleansed at once. Jesus then said to him, 'Mind you tell no one, but go and show yourself to the priest and make the offering prescribed by Moses, as evidence to them.' When he went into Capernaum, a centurion came up and pleaded with him. 'Sir,' he said, 'my servant is lying at home paralyzed and in great pain.' Jesus said to him, 'I will come myself and cure him.' The centurion replied, 'Sir, I am not worthy to have you under my roof; just give the word and my servant will be cured. For I am under authority myself and have soldiers under me; and I say to one man, "Go," and he goes; to another, "Come here," and he comes; to my servant, "Do this," and he does it.' When Jesus heard this, he was astonished and said to those following him, 'In truth I tell you that many will come from east and west and sit down with Abraham and Isaac and Jacob at the feast in the kingdom of Heaven; but the children of the kingdom will be thrown out into the darkness outside, where there will be weeping and grinding of teeth.' And to the centurion Jesus said, 'Go back, then; let this be done for you, as your faith demands.' And the servant was cured at that moment."

The Nicea Council (325 A.D.) issued criteria for assistance to the sick, to be provided in special places; St. Basil founded the first hospital in the East, at Caesarea (370 A.D.), and on the inspiration of this Christian principle another hospital was founded in Rome (400 A.D.), mentioned by St. Jerome in his letters.

It is estimated that about 40% of the earth's surface corresponds to regions with a hot climate and these regions, found especially in developing countries, are inhabited by human communities.

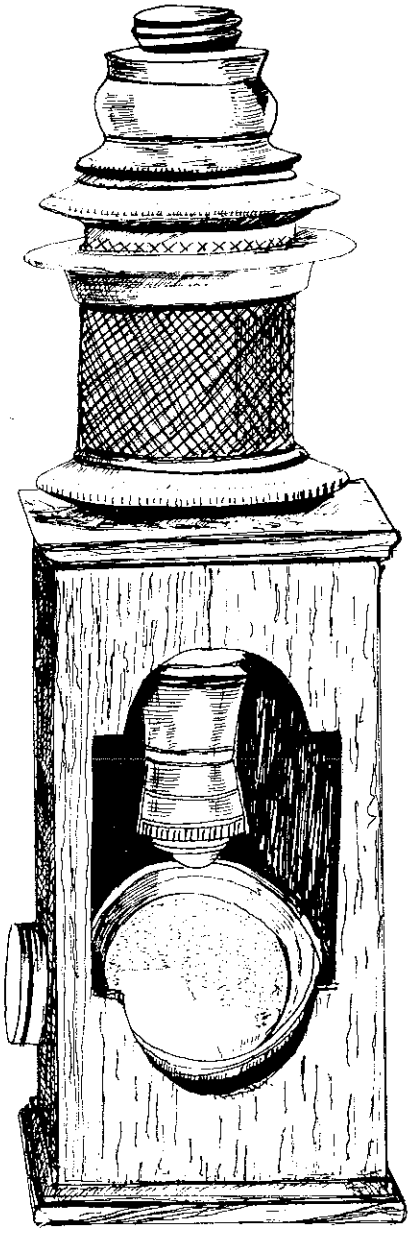
We find there large, primitive rural areas where these human groups settle in concentrated agglomerates or live scattered around. Life in these countries is ruled by characteristic socioeconomic and cultural factors as well as by biological conditions which are the cause of serious, epidemic diseases strictly linked to etiological or causal agents and their transmission processes, the inner mechanisms of which are inherent to ecologic and climatic particularities of the tropical regions. These diseases are, on the whole, the most frequent and characteristic pathologies of the populations living in the intertropical geographical area.

The populations corresponding to the emerging countries have a limited development in their productive activity due to the incidence of these diseases.

It is easily understood that the wide geographic distribution of these pathologies not only curbs the socioeconomic development of these emerging countries, but also extraordinarily increases their general death rate. It is therefore urgent to improve knowledge of these aspects of geographic medicine. Tropical areas on the geographic maps coincide with regions with different degrees of development; from the geographic point of view, they include all the earth's area from parallels 23 and 30 North latitude, to 23 and 28 South latitude, respectively, between the Tropics of Cancer and Capricorn.

From the climatological point of view, the concept may be applied to the earth's regions ranging from 0 to 800 mt. above sea level with an average yearly temperature ranging from 24° to 28°C, an atmospheric humidity of about 50%, and a rainfall rate above 500 mm. per year. These climatological and geographic conditions heavily weigh on the physiology and biology of the populations living in these specific geographical areas. There microclimates are produced, as well as biotic

A microscope of wood and millboard (seventeenth century)



areas and ecologic niches or centers of infection which condition the endemicity of these diseases, fostering the proliferation of anthropodes, vectors, and intermediate hosts of the pathogenous agents responsible for them.

The man who works in the fields in these latitudes of the earth, particularly in Tropical Latin America, makes only a small effort to protect himself from the inclement weather by building a primitive house with mud walls and a thatched roof. These conditions represent the ideal habitat for the ecology of endemic diseases, as in the geopathology of worm infestation (geohelminthiasis), biohelmintiasis, anthropozoonosis, a pathology of worms due to protozoars (Chagas disease), paludism (malaria), and other pathological entities of particular medical-sanitary importance. And these diseases represent great problems as regards the production of specific drugs due to the high cost of research aimed at obtaining new drugs with low toxicity and integral therapeutic action.

To obtain these new drugs with the above-mentioned characteristics (recently called "orphan drugs") close cooperation is needed among universities, Research Institutes and the pharmaceutical industry so as to establish co-ordinated priority research programs in the fields of etiology, pathogenous action mechanisms, and mechanisms governing the transmission dynamics of causal agents, with the aim of obtaining and producing new drugs for the developing countries, where tropical endemic diseases are themselves an important negative factor hindering the development of these populations.

Before initiating the particular considerations on each of the diseases, we should deal with some of the nutrition problems of the populations of the rural and marginal areas of the countries in question because they are important factors in the persistence of infections and parasitic diseases.

Nourishment poor in proteins, vitamins, iron, and other minerals causes severe pathological conditions and favors the development of diseases such as ancylostomiasis, and the corresponding anaemia.

These scarcities, associated with infections and toxic factors, create the conditions for the pathological structural basis of severe liver diseases such as cirrhosis and fat infiltration. The lack of good quantity proteins and vitamins, especially the vitaminic B-complex, in the nourishment of these populations appears to favor the progress of Chagas disease.

In the rural populations of Africa, Asia, Oceania, and Latin America we frequently observe infantile multideficiency syndromes associated with sideropenic anaemia aggravated by infestations found in ancylostomiasis and nectoriasis.

The prevalence of this syndrome goes from the first months of life till the age of 5, and we may think that it is the result of serious nutritional deficiencies associated with intestinal helminthiasis. It is not rare to find in these regions children that have lost more than 40% of the weight cor-

responding to their age, with significantly delayed growth and development, gastro-intestinal troubles, clinical manifestations of neurological and mental disorders associated with signs of anaemia, pellagra, disorders of skin pigmentation, children who look at us with a deeply sad and disheartened face.

The death rate is high and post-mortem examination calls our attention to fat infiltration in the liver, as well as cellular necrosis and liver fibrosis.

In facing this pathological situation, accompanied by negative social-economic conditions, it is mandatory to establish medical treatment suited to the population's exigencies, based on a diet rich in proteins, multivitamins administered parenterally, riboflavine, ascorbic acid, B12 vitamins, A and D vitamins; anaemia must not, of course, be neglected and should be treated with oral iron, folic acid, and B12 vitamins.

Intercurrent respiratory tract infections are the most frequent and should be treated also with antibiotics. It is besides recommended to observe the general conditions of the children of these areas, without neglecting treatment of the associated multiple worm infections of the intestine.

We recommend the development of studies for the production on a wide scale of the drugs called "orphans." The programs for control of these diseases will be more effective in the measure in which these developing countries have at their disposal drugs with specific action. Owing to the great social significance of these drugs, we must stress that to promote their production is an international responsibility: they are a great help to fight against endemic diseases in the emerging countries, even if the commercial benefit from their production is not attractive, in view of the large investment. It is, however, urgent to pass over the economic as well as other types of barriers which hinder or slow down the evolution of these sectors of pharmacology and the development of the production of these drugs.

Only joint international action will succeed in attaining these goals and stimulating the production of new drugs which are on the point of being obtained. These drugs would be of great usefulness for the treatment of the more common diseases of the torrid zones, mainly among the population of the rural and marginal areas.

I shall begin these particular considerations with schistosomiasis (bilharziosis), a parasitic disease which attacks about 200 million human beings, distributed in 74 countries. The more sweet water distribution in these countries is increased, the more the endemic areas become extended.

In Egypt alone about 9 million cases of infection, involving particularly the child population, call our attention to the fact that the increase in this disease is parallel to the increase in efforts to raise living standards of the populations. This phenomenon in fact is associated with programs to improve the quality of life in the rural areas of the country, which are directly connected with the distribution of the waters of the river Nile. This river crosses Egypt from South to North with a course of more than 1000 Km. prior to flowing into the Mediterranean sea.

"Schistomiasis" is the parasitic infestation due to the presence of digenetic trimatodes which colonize the blood vessels of man in the hot areas of the earth. We observe that it is the most serious and important of human helminthiasis because of its widespread geographical distribution, the pathological alterations of the tissues, the wide and irreversible lesions it produces on the human body. Its consequence is, therefore, a limitation of the development of the affected communities.

This disease was already known in ancient Egypt; in fact, we find it recorded in the medical papyri. It has been known in America since 1902, and its first centers of infection were observed in the Caribbean Islands.

Schistosomiasis, due to Mansoni Schistosoma, is the most widespread and is the only one which may be found in Tropical America; it is known as bilharziosis of the intestines, liver, and spleen.

Mansoni Schistosomiasis lives in man's portal vein system, especially in the lower mesenteric vein where it lays a high number of eggs, many of which remain in the infested tissues stimulating the production of inflammatory granulomas which start a generalized fibrosis process, especially in the liver and the large intestine.

Mansoni Schistosomiasis is endemic mostly in the African countries, in South-East Asia,

and the Northern part of South America: Venezuela, Brazil (one of the greatest endemic centers of infection, with 10 million persons infested), Suriman, Puerto Rico, the Dominican Republic, Martinique, Guadalupe, Antigua, Santa Lucia, San Kitts; we must also add Saudi Arabia and other countries of the Persian Gulf.

In the evolution stage of this disease we find that the first manifestation of medical interest is dermatitis due to cercariae which develops as a response to the larval forms of penetration and migration into the skin.

The skin lesions of this clinical form are connected, in their pathogenic form, to the sensibilization processes which take place in the persons living in endemic areas, where the infection has been present since ancient times.

In successive stages, coinciding with the migration of the parasites, we observe fever, diarrhoea, myalgia, abdomen pains, adenopathitis, and a significant wasting away of the body. This clinical picture is associated with the production of specific antibodies which, in the presence of an excess of antigens, form immunity complexes in the vessel endothelia of the various organs, activate the complement and trigger an inflammatory response, i e of vasculitis obliterans, which explains the systemic manifestations in this toxemic stage.

The presence of eggs of Mansoni S. in the lumen of vessels produces inflammatory parasitic granulomas that form in their whole the systemic disease mostly seen in the tissues of the portalmesenteric venous system and which ultimately results in widespread fibrosis and portal hypertension.

In the chronic stages of the disease, bleeding in the gastrointestinal tract is the main symptom, often complicated by shock due to hypovolemia mostly associated with fever, melena, oedema of legs, ascitis. Physical examination reveals hepatomegalia with enlarged liver having a hard border end, knotted surface, associated with more or less enlarged spleen. Different seats of the bilharzia granulomas may produce severe forms of illness, according to the involved organs.

When the parasitic origin of the disease has been fully recognized as well as the specific immunological changes, we must proceed with a specific treatment, but only in patients showing parasite activity. At present new drugs are available that are very effective at the very beginning of the illness as well as in early forms of hepato-intestinal and hepatosplenic involvement.

Czamniquine (6 hydroxymethyl-2 isopropylaminomethyl-7 nitro- 1 2 3 4 tetrahydroquinine) is a compound derived from tetrahydroquinoline. It must be given orally and has schistosomicide activity.

It is well tolerated; only dizziness and drowsiness were reported and, less frequently, hallucinations, excitement, behavior disorders. All the effects are temporary; no fatal cases to be ascribed to the drug have been reported. This drug is greatly effective in the chronic as well as in the acute stage of the disease, and its recovery percentage ranges from 80% to 100%.

Praziquantel (2 cyclohexylcaronyl 1, 3, 4, 6, 7, 11 Bhezachlor 2H pyrazine [2, Ia] 4 isoquinoline, derived from pyrazine isoquinoline), to be given orally, every four hours.

It is well tolerated; the side effects reported in a group of patients are only dizziness, abdominal troubles, asthenia, headache. It is effective in the acute and chronic stages of the disease and its recovery percentage goes from 80% to 90%.

Experimental Pharmacological Institutes should start research leading to the discovery of drugs, as well as useful and effective biological products for the therapy of the advanced forms of schistosomiasis. Even if these drugs are of limited commercial interest, it is imperative to foster suitable investments with the aim of attaining this socially significant goal.

We recommend linking the efforts of public bodies and private institutions so as to foster the demand for these drugs with the aim of reaching a suitable bio-technological level capable of obtaining a specific therapy for the various forms of this disease, in order to reduce its incidence and open the way to a possible eradication of this calamity of the torrid areas of the earth.

To reach this goal the efforts of private bodies and national States should be joined, especially of those who are directly devoting themselves to the promotion, support, and financing of scientific activities leading to the obtainment of low cost specific drugs (orphan

drugs). These drugs could hence be easily purchased by the more needy patients, who represent the most important part of the people of the developing countries.

Latin America, Venezuela, and Brazil may be cited as examples for their active participation in the programs and plans aimed at improving the quality of life of their more needy neighbours.

The Venezuelan Ministry of Foreign Affairs is at present promoting and fostering a broad aid program for the socio-economic development of the Ceribo countries; The special office for Ceribo Affairs, directed by Ambassador Dr. François Moanack, coordinates a well structured plan of integral medical assistance for the Ceribo countries, with a pilot center on the isle of Grenada, a program of vaccinations, medical assistance, treatments, therapeutic evaluations, and production of new drugs. This Venezuelan program, perfectly coordinated and directed by Ambassador François Moanack, will offer excellent results in the near future, and its impact on the Ceribo populations' health will be evident and appreciated at all levels.

One of the diseases which every day take on greater importance because of the increase of its prevalence in the endemic areas and the sever eye lesions it causes is the human onchocercosis characterized by the production of nodular subcutaneous lesions and eye lesions resulting in the total loss of sight. It is a parasitic infestation affecting more than 30 million persons all over the world, particularly in West Africa, Asia and the Persian Gulf countries, and Tropical America (Mexico, Guatemala, Columbia, Brazil, Ecuador, and, mainly, Venezuela).

It is interesting that in the small region of Burkina Faso (high basin of the river Volta) alone, there are 70,000 blind people as a consequence of onchocercosis.

The clinical characteristic of the disease is determined by the infestation pathogenesis, the vectorial capacity of the local species of similarium, and the genetic characteristics of the human population, every region having its own characteristics. In Africa this disease is characterized by abundant subcutaneous nodules (onchocercomas) always accompanied by sclerotizing keratitis and total blindness.

In the Persian Gulf countries (Yemen) onchocercosis localizes in the lower limbs. This disease has its origin in the endemic regions of South America. The skin lesions it causes may involve head, trunk, and limbs, and they are always severe, as is choroidoretinitis and optic atrophy caused by the degeneration of the optic nerve, erysippelas, keratitis, fever, palpebral and face oedema. These are all the symptoms characteristic of onchocercosis.

When the parasites are scarce and there are not yet severe lesions, prognosis is favorable, while in cases with opposite conditions (a high number of parasites) treatment involves risks or may cause the aggravation of pre-existing lesions that may become irreversible. Moreover, hypersensitization to the remains of microfilaria or to adult worms may also be triggered, as well as renal impairment due to the drugs.

Up to now, two drugs have been available. Diethylcarbamazine (hetrazan), is given at a daily progressive dosage for two weeks. This drug has a microfilaricide effect, but it also has the drawback of often causing severe hypersensitivity reactions.

The other drug is Sodium Suramine (Moranil), which should be given following the DEC therapy, in increasing doses. It has microfilaricide effects acting on adult filariae; its use may cause severe renal impairments, and it has proved to be toxic. Compounds of the benzimidazole (albendazoli, fulmendazoli) as well as ivermictina appear to have a better microfilaricide effect. However, I think that its teratogenic effect has not yet been sufficiently studied, and its toxicity has not been thoroughly tested. These drugs may cause severe pain and inflammation in the site of the intramuscular injection.

The cost of this drug is high, and this induced the drug producing firms to work in collaboration with W.H.O. for the research of new drugs, capable of obviating these harmful actions. The ideal would be to obtain a drug to be taken orally and having a minimum toxic action.

Another therapeutic possibility is invermetine, the microfilaricide action of which was ascertained in experimental onchocercosis (O. Gibsoni). Recently (1982) this action could be verified in cases of human on-

chocercosis with slow microfilaricide effectiveness. Even if I think that it is still too soon to express an opinion on the toxicity of this drug, serious investigations should be carried out in this direction.

In addition to a comparative study on the microfilaricide effects of DEC, we recommend that the microfilaricide action be durable and extensive and also that the onchocerca larvae structural modifications be determined so as to ascertain if some of them remain alive after the treatment and reach the state of larvae infecting the mosquito, vector, and intermediate host.

In these investigations, the actual harmful effect on the posterior segment of the eye should be considered, as well as the possibility of allergic reactions (Mazzotti reaction). Should these negative effects be avoided, we could recommend these drugs for the individual treatment of the populations attacked by onchocercosis.

Pharmacological and toxicological research in the framework of a joint program developed by the firm CIBA-GEIGY and W.H.O. is now near to its conclusion. These studies regard three new chemical compounds codified with the abbreviations C.G.P. 6140 (Diphenylamine methylpiperazine), C.G.P. 20376 (a benzothiazilic compound), and C.G.P. 24914 (a benzoxazolic compound); they all have experimental microfilaricide action against O. Gibsoni strains, but they have not yet been sufficiently experimented in the pathological, teratological, and parasitological (embryastatic) fields.

Doctors E.A. Friedheim and Y. Coles are investigating the filaricide action of arsenium compounds, such as melaminothioarsenite, which have shown important microfilaricide action against O. Gibsoni. Research by Melarsonye with potassium as a therapeutic agent in human onchocercosis have been discontinued owing to the ascertained risks of arsenium encephalitis (Duke 1970), and irreversible damage to the liver.

On the basis of the above, it proves necessary to find a new group of filaricide durgs, by investigating biochemical synthesis, metabolism, and biochemistry of the filariae pathogen for man.

W.H.O., with its special program for research on tropical diseases, and FAO-UNDP are putting into action, with these aims, a program on the populations of the Burkina Faso catchment-basin (river Volta). This program is financed by the World Bank of the Wellcome Foundation Research Laboratories, Beckenham, Kent, United Kingdom.

Great hopes are raised by these projects through the devotion and intelligence of the researchers and their great patience. We must, therefore, trust that soon we shall have available a good drug able to cure human onchocercosis.

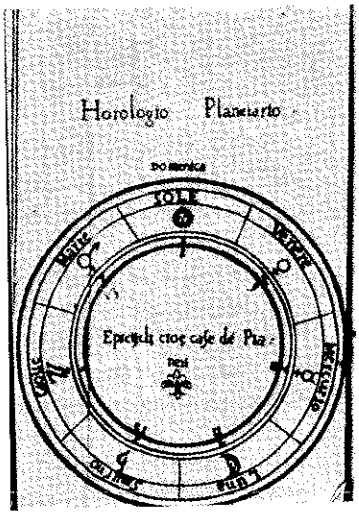
Malaria continues to debilitate humanity and limits the development of the Third World countries where it predominates and reaches endemic proportions.

Its existence was known in Egypt in 3000 B.C., where it was one of the most frequent causes of death. The populations of Babylon, Syria, India, and Southern China were decimated by it.

In ancient Greece the intermittent fevers associated with splenomegalia were described by Hippocrates in the 5th century B.C., and they were related to stagnant waters.

Alexander the Great probably died of malaria in 323 B.C.

It is believed that malaria had an influence on the Greek and Latin civilizations' decline. In



From the Mirothecium *treatise on pharmaceutical chemistry (Venice, 1683)*

the early Middle Ages malaria spread throughout Southern Europe, Asia, and Africa. St. Thomas Aquinas died in 1277 of malignant malaria.

Though malaria may have existed on the American continent in the pre-Columbian epoch, it is believed that the Spanish conquerors and African slaves introduced into neotropical America ganetocytes in the blood and vector mosquitos (anophelines).

Malaria — or paludism — is only a human disease. The four species of malarial parasites (plasmodia) pathogenic for man do not attack animals.

This disease, because of its high incidence and the high death rate it causes, higher than that of any other transmissible disease, represents a serious problem for public health.

In 1980 about 8 million cases in 55 countries were recorded. The number of cases estimated now in the endemic areas of the earth is from 9 to 10 million, with about 1 million deaths per year. To this high mortality rate we must add fevers, anaemia and asthenia, which curb the work activity of the patients, who are mainly farmers. This reduces the production of essential food and causes the abandonment of agriculture by communities damaged in their health, thus limiting their development as well.

The prevalence of malaria parasites is not homogeneous throughout the world. *P vivax* and *P. falciparium* prevail in the endemic areas, while *plasmodia malariae* and *ovale* have a more restricted distribution area.

P. falciparum, which causes malignant malaria with thrombotic intravascular lesions in the deep internal organs (viscera) (brain, spleen, etc.) has a wide geographic distribution: Neotropical America, Africa, Asia, and Oceania. It has developed an obvious resistance to the antimalaric drug chloroquine (4-aminoquiline).

P. vivax is abundantly found in India, Pakistan, Bangladesh, Sri Lanka, and South America. Its association with *P. falciparum* produces mixed infections, very frequent and severe in their chemical-pathological aspects. *P. malariae* is cosmopolitan but not frequent (0 6%), while *P. ovale* is almost only African.

I shall not go into real parasitological considerations. The time I have available does not allow me to dwell upon clinical and pathological considerations, nor linger over diagnostic methods. I shall only bring out the present situation of research programs for identification, production, and experimentation of new antimalaria compounds which might replace the effectiveness of known drugs or improve it.

Available antimalaria drugs (quinine alcaloids, acridine compounds such as atebrine, or 4-aminoquinoline such as chloroquine or 8-aminoquiline, such as plasnoquine, biguadine, and diammoprimidine) in their specific schizonticide action, interrupt malaria attacks, reduce parasite generations, and impede the formation of gametocytes inasmuch as they destroy the schizonti within the blood cells. Their action involves prophylaxis, treatment, and suppression: in their gametocide action they destroy the sexual forms of the parasite or produce alterations which interfere with normal multiplication. This action is therefore called "transmission prophylaxis."

The ideal drug to be produced should be a medicine capable of acting in all the stages or evolution forms of the parasite, blocking its development and totally destroying the mature forms which cause the fever attacks. It should also act on the plasmodia which remain hidden in the liver cells, preventing their transformation into the forms which develop in the blood cells, which are a parasite storehouse, responsible for the frequent relapses characteristic of malaria due to *plasmodia vivax*.

This ideal drug, acting in forms outside the blood cells, would be a radical therapy for the disease. It is to be hoped that this drug might also act on the gametocytes which infect the transmitting insects.

The Walter Reed Institute of Medical Research of the U.S. Army (Washington, D.C.) is making a decisive contribution to the attainment of this aim by studying native medicinal plants empirically used and traditional in various Asian countries.

Work is actively carried out in the field of schizonticides in tissue cells (8 aminoquinoline) to reach a reduction of their toxicity and, at the same time, in the field of isomers of primaquine. Investigations are being done in Brazil on the clinical aspects of blood schizonticides (mefloquine), triacine and aminoacridine, always with the purpose of reducing toxicity.

Similarly, studies are in progress in Brazil for the obtainment of a drug with selective action on gametocytes and sporozoites, initiated with primaquine. Investigations are now carried out on the preparation of this compound, consisting of a combination of primethanine and a sulfanomide or a sulfone (biodegradable polymers). This compound, administered parenterally, could obtain prolonged therapeutic action. It has, however, to be borne in mind that the toxicity of antimalaria drugs has a great importance because it can produce irreversible organic alterations and, precisely for this reason, investigations are being mode with parmoate of pyrimethanine, chymazoleine, and a combination of schizonticides.

Another aspect of the present problem of antimalaria drugs is the resistance of malaria parasites to these specific drugs. This resistance phenomenon was observed in the *plasmodia falciparum,* resistent to chloroquine (1953). A worldwide program has been started to analyze this resistance in South-East Asia and the Western Pacific Ocean. It is therefore necessary to professionally train the personnel in charge of the vigilance and control of the manifestation of this resistance and to establish a system for the drawing up of maps based on *in vitro* tests fo carriers, useful indicators at a peripheral level for the early discovery of resistance to drugs.

We do not yet have antimalaria vaccines; however, we are actively working on the antigenic material starting from the cultivation of plasmodia. We have been able since 1972 to successfully immunize human beings against *P. falciparum* and *P. vivax* by irradiated sporozoites in carefully supervised experiments. It seems that the active immunity caused by this method for every parasite strain is specific.

Any type of vaccine would be a complementary instrument in the anti-malaria fight. Before concluding, however, I think it is important to call our attention to the problem represented by the vectors' resistance (mosquito "anopheles") to D.D.T. pesticides. This physiological resistance to D.D.T. is the primary cause of the failure of many countries to eradicate malaria.

It is necessary to obtain new pesticides to replace D.D.T. and other organo-phosphorated pesticides, as the anophele population has developed a great resistance to the existing ones.

The 7th Asiatic Conference on Malaria and Health for All by the Year 2000 acknowledges that for the year 2000 the discovery, treatment and fight against malaria are important parts of the attention devoted to health, stating once again that the interantional community's participation in official programs is necessary to obtain the eradication of this disease.

On the basis of these considerations, we recommend:

A) the strengthening of international technical cooperation to help the developing countries;

B) the strengthening of close links between Universities and qualified Institutes of the industrialized, as well as the developing, countries;

C) the continuation of bilateral and multilateral cooperation, when necessary.

Chagas disease in one of the most important tropical diseases and represents a serious problem for public health, particularly in the endemic areas where it mostly attacks the rural population.

It is a parasitic metasenic disease, which has an endemic form in tropical and sub-tropical Latin America. It is caused by the trypanosoma Cruzi (Chagas, 1909), a protozoan transmitted to man by haematophagus hemipters. In its early stage it manifests itself as an acute generalized disease with acute miocarditis, which subsequently turns into chronic miocarditis.

Trypanosoma Cruzi is an intracellular protozoan; the amastigotes actively multiply by bipartition within the cell cytoplasm of the reticuloendothelial system during the acute stage and in the miocardic fibers during the chronic stage, producing the pathological structural basis of the disease.

American trypanosomiasis is characterized by acute inflammation within tissues, infiltrative cell reaction, with vasodilation, inflammatory exudates, associated with degenerative and necrotizing processes, manifesting themselves, clinically and pathologically, by symptoms of miocarditis, periocarditis, pleuritis, pneumonia, encephalitis, and ascitis. Death supervenes due to miocardic insufficiency, pulmonary oedema and central cardiorespiration.

The cells chronic inflam-

matory infiltration causes the onset of a progressive chronic cardiopathy associated with a perivascular inflammation and the production of newly formed fibrous tissues aiming at healing. This histopathologic process leads to the loss of heart contractility with alteration of the conduction of the heart impulses. All these phenomena cause the clinical evidence of altered excitability, conductivity, contractility (extra-systoles, blocks and miocardial failure, and generalized oedema).

Chagas disease in its untreated acute stage is fatal in 10% of the cases.

It is believed that the most frequent cause of sudden death is ventricular fibrillation and alterations such as the total A.V. block of chagasic origin. The generalized acute form is mostly observed in children living in the endemic areas and is accompanied by clinical primary manifestations of penetration signs, such as ophtalmoganglional complex and the chagoma due to inoculation, local inflammation of furuncoloid type, with skin infiltration not causing necrosis and lasting 4-8 weeks.

A great problem not yet solved is represented by the treatment of Chagas disease with chemotherapeutic agents. We have been searching for many years for drugs with therapeutic action against this disease. We now have available two active drugs against trypanosoma Cruzi. It seems that their specific and therapeutic action is partial, as we have not yet obtained a complete recovery in the treated cases. These two drugs are:

— nifurtimox, of the nitrofurani group, commercially known with the name of Lampit, and

— benzonidazol, of the nitroimidazoli group.

Nifurtimox is indicated in the acute stage of the disease, with a significant percentage of parasitologic recovery in experiments carried out in Argentina and Chile, serologically checked. With this drug the block of the acute stage can be obtained, thus avoiding the production of fatal processes and evolution towards the chronic stage.

In the chronic cases, with this drug we obtain the suppression of more than 90% of parasites, and no serological negativity is reported.

Benzonidazil, known under the name of Rochagan, is now under clinical observation in Brazil. We believe that the results obtained in the acute stage look promising. The use of this drug in chronic patients may produce some beneficial effects as regards the decrease of the parasitic infestation. I think, however, that we do not yet possess a drug to treat Chagas disease which we could consider near to the ideal one. The drugs we have mentioned, in fact, produce undesirable side effects, mainly in adults, while they are better tolerated by children and teen-agers. Besides, treatment has a long duration, about three months in the acute form, up to four months in adult patients.

The main toxic effects of these drugs are: anorexia, loss of weight, neuropsychical disorders, reversible above all in neurotic elderly and old patients, convulsions, allergic skin manifestations, gastro-intestinal troubles, loss of sleep, and blood alterations.

It is recommended to thoroughly investigate embryotoxic effects and it is therefore advisable not to use these drugs during pregnancy.

Investigations must be continued to obtain a drug with very low toxicity and high therapeutic action, without side effects and which could be used during the whole pathologic process, controlling the post-treatment period with xenodiagnoses divided into series and immunological tests. The former are useful when blood parasitic infestation is present, inasmuch we may observe the disappearance of the parasite in the blood.

Immunological reactions allow us to evaluate the reduction of the specific antibodies after 90 days of treatment. In cases of cardiopathy, complete rest is needed, a hyposodic diet, and corticosteroids acting on the inflammatory process of this disease.

The group of the most important endemic diseases of tropical and intertropical geographic regions is completed by those diseases caused by the Leishmania group, protozoan intercellular parasites, pathogens for man, with dermotropic and viscerotropic biological affinities, which colonize the reticulo-endothelial cells of teguments and internal organs, such as liver, vessels, bone marrow. They actively reproduce in these cells, consequently causing a histopathologic process within the cell and starting the disease pathology.

Leishmaniases are parasitic

metasenic diseases in which phlebotomies and lutzomias are the transmitting vectors and intermediate hosts of the parasites.

Leishmaniasis of teguments, skin and mucosae in tropical America is produced by an etiological leishmanic complex (Leishmania Brasiliensa), clinically characterized by ulcerous lesions of the buconasopharingeal mucous membrane, which is invaded by parasites with pathological activity, producing the destruction of this membrane with the mutilation of all the soft tissues of this wide region.

The clinical picture of this disease changes its form in relation to medical geography. In the cases analyzed in Guatemala, Venezuela, Brazil, and Peru, clinical changes with pleomorphism of the skin lesions are observed.

For the same type of transmitting phlebotome there are different responsible strains, strictly connected with the geographical particularities of the endemic areas supporting their eco-existence and their ecologic balance.

The leishmaniases produced by Leishmania Tropica, with much more benignant clinical forms which do not affect the oral mucosa membrane and with different transmission dynamics, are known as leishmaniases of the ancient world.

Visceral leishmaniasis (Kala-azar), produced by Donovani Leishmania, is caused by the invasion and colonization of the cells of the reticuloendothelial system by parasites in amastigote form. In the liver, vessels, and mainly in the bone marrow, in tissues rich in cells of the reticuloendothelial system of these infected organs, a pathological inflammatory and infiltrative process is produced causing a tissue reaction which clinically appears with fever of long duration, hepatosplenomegalia, anaemia, leucopenia, lymphomonocytosis, anorexy, progressive loss of weight, generalized lymphodenopathies, oedemas of the lower limbs and, in severe cases, cachexy was found.

Kala-azar is under strict observation in the Savannah regions of Venezuela, where the child population is more attacked. The endemic regions of Latin America are well delimited. This parasitic infestation is the object of careful and coordinated observation by groups of researchers in various scientific institutes of the continent. I deem it appropriate to recall that this parasitic reticularhistiocytosis is also characteristic of islands and regions of the Mediterranean coast.

Pentavalent antimonium compounds are the drugs now used for the therapy of visceral leishmaniasis: glucantine (antimonium N-mathyl glucamine), with deep intermuscular or slow endovenous administration for 12 days, is generally well tolerated if administered in the correct way, in a dosage not higher than 6 grs. per day for adult people. Antimonium is slowly eliminated through urine. This drug, however, has cumulative toxicity with side effects, such as anorexy, nausea, general body discomfort, intense myalgiae, headache, rash, bradycardia; electrographic variations are also present, such as T-wave inversion, P-wave increases, a prolonged QT interval, and extrasystoles; kidney disorders are frequent. These toxic effects of the drug are for us a stimulus to continue investigation in the parasite infestation sector of pharmacology with the aim of obtaining a much less toxic drug, easily eliminated. It is thought that liposomes could be useful as carriers of the active principle. This would enable us to reduce the dosage, with a decrease of the toxic effects. Liposomes are hypothetically ingested in the same way as the parasite by the cells of the mononuclear phagocytic system, which appears to be stimulated by antimonium action which, through this indirect

mechanism, destroys the amastigote strain of the parasite.

Amphotericine B is the other drug useful in treating leishmaniasis through slow intravenous administration; however, it is not free from toxic side effects, among which thromboplebitis is to be feared. In these regions reesearch on other drugs continues, including Allopurinol, which appeared to be less toxic in laboratory tests on animals. Aminoquinoline (MR 6026) possesses characteristics similar to those of Allopurinol; both are at the stage of preclinical testing, and the *in vitro* effects are still being studied, along with those of pharmaceuticals like Miconasol (anti-mycotic), Sinefungina, and Formicin.

This work must now be increased experimentally.

In Venezuela, Convit *et al.* (1983) report positive results in patients with diffuse anergic leishmaniasis obtained through intradermal administration.

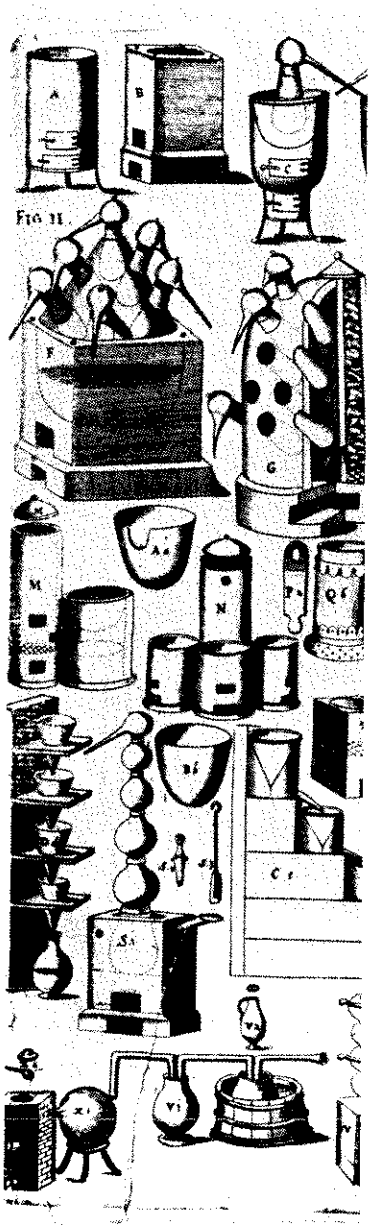
With a compound prepared from BCG and extracts of the amastigote and promastigote species of L. Brasiliensis treated through the autoclave (leishmania), regression or stabilization of lesions and a favorable response to chemotherapy have been observed, with reduction in the number of parasites and in lymphocyte infiltration of the lesions.

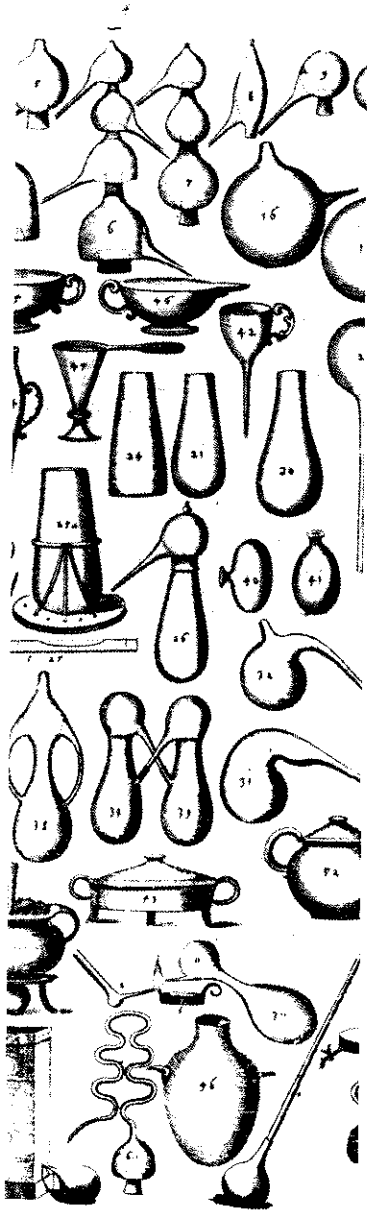
This work in immunotherapy is still at an experimental stage, and the results obtained provide grounds for abundant hope; all necessary aid and assistance should be given this group of researchers so that their efforts will be crowned with success. This is not the occasion for me to dwell upon parasitological, biological, and epidemiological considerations regarding the leishmaniases afflicting men in so many parts of the word, nor can I pause to deal with the significant impact of other tropical diseases such as intestinal and extra-intestinal ambiases, intestinal helminthiasis the migratory visceral larva syndrome, South American histoplasmosis, sporotrichosis, chromomycosis, leprosy, foot fungus, viral encephalitis transmitted by mosquitos (Venezuelan equine encephalitis), yellow fever, toxoplasmosis, and other nosological entities of the tropical medicine sector, and, therefore, of the countries of the Third World.

I am glad that this meeting of specialists offers me the opportunity of formally recommending the creation of an Institute of Tropical Medicine, coordinated and directed by the Holy See, for the study of a complex of diseases prevailing in wide areas of the world. In these areas, bioecologically characterized by their hot climates, well-defined pathogen complexes which have a specific dynamic of transmission, are a cause of pathologies, common among the native and the rural populations.

This Institute of Tropical Medicine should give specialized medical assistance to all the patients who apply for its services, to those with parasitic and infectious diseases caused by viruses, bacteria, fungi, protozoans, helminths, malnutrition, multi-deficiency conditions associated with sideropenic anaemia caused and aggravated by necatoriasis.

This Institute of research and





medical assistance, specializing in these pathologies, could be placed in one of the Mediterranean regions or in one of the countries of the Caribbean area.

Its financing could be obtained through a common effort of the more developed countries, international bodies working for the development of emerging populations, international bank institutions, and private and public foundations.

I wish to point out that, in addition to the above mentioned diseases, to hidden hunger (multi-deficient undernourishment), a permanent companion of children living in marginal and rural areas of the developing countries, we are menaced by the action of a new exterminating calamity: contraceptives and unpenalized abortion. The former are responsible for the toxic contraception which damages the health of a significant part of the young population of our society, lamentably misinformed and disoriented by exogenous pressures of a cultural and social-economic nature, joined with an ethical formation lacking a sound basis in values which give a real sense and quality to life.

Oral contraceptives are harmful; they may cause cardiovascular disorders or worsen them when they already exist. Besides, when fertilization occurs in spite of the use of contraceptive pills, babies are born with serious defects. The use of I.U.D. also entails severe risks: skin inflammatory processes, infections, permanent sterility (cases of death have been recorded due to pathological complications caused by the use of this intrauterine device).

Unfortunately, groups of researchers are deplorably working to obtain new contraception techniques and products, such as Capronor, a biodegenerative tablet placed under the skin which may release contraceptive substances for a whole year. And another product is Norplant 2, removable 5 years after its placement. About 30 other contraceptive methods are now in different stages of experimentation, and some of them are ready for the markets of the developing world, such as the diagram impregnated with spermicide, the RU-486 pill, which interrupts pregnancy in its very first stages, and the contraceptive for men, a biodegenerative compound lasting 3 months, in the form of a tablet to be placed under the skin and which, among other side effects, may cause permanent impotence.

Luckily, in Venezuela we have an association which fights indefatigably to protect life from its beginning. I refer to the Pro-Life Association, directed and coordinated by Mrs. Cristina de Vollmer, who is endowed with a remarkable capacity for work and a deep vocation for the social welfare of the communities most in need of assistance.

Venezuela AMADE (World Friends of Children Association), the President of which is also the untiring Mrs. Cristina de Vollmer, addresses its activity to the needy children of the communities living in marginal, rural, and isolated areas of our country. At present, its commitment involves building centers

for the nourishment of children supplied for integral medical attention and school care in the areas with the above-mentioned characteristics, and there are plans for the future to extend this action to the Caribbean region.

I shall end my talk by quoting Ecclesiastes (38:1,2,7,9,12-14):

"Honor the physician as it is dutiful according to need. He too was created by the Lord. By the Most High healing is bestowed as gifts are bestowed by kings."

"God has given knowledge to men so they may glory in His wonders. With it the physician cures and relieves pain and the apothecary prepares the mixtures."

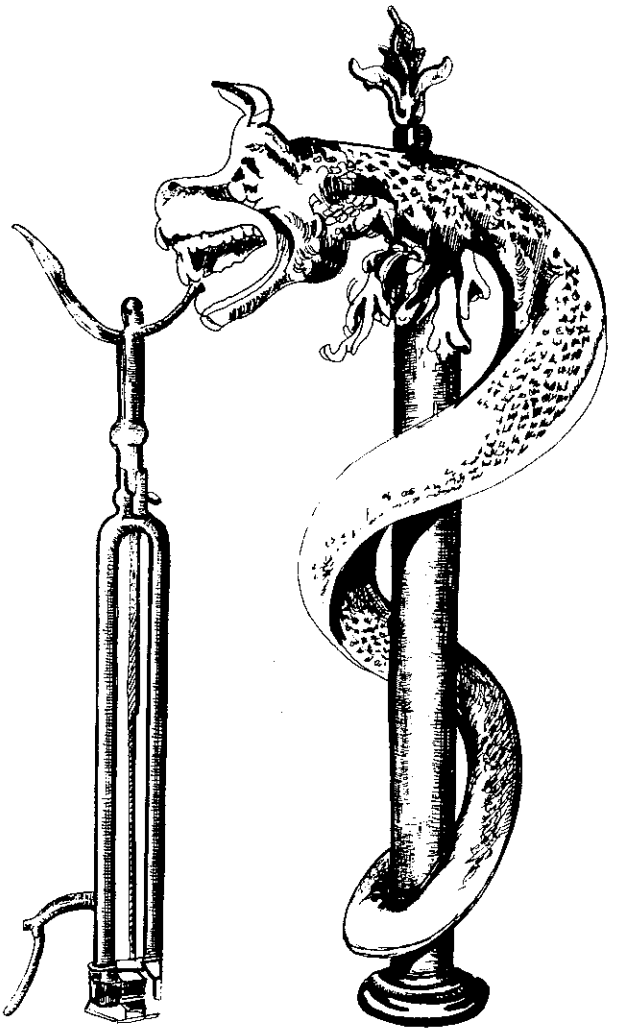
"Son, do not lose heart in illness, but pray the Lord and He will cure you."

"Immediately have recourse to the physician. Our Lord has created him too; let him stay near you because you need him."

"There are cases in which success is in the hands of physicians; they too ask the Lord to guide them successfully in the relief and cure of diseases, so that the sick may come back to life."

DR. TEUDIS CARDOZO SOTO
Chief of the Section of Tropical Medicine, Parasitology and Microbiology
Faculty of Medicine -
Central University of Venezuela

Third Session



The Ethics of the Use of Pharmaceuticals

Detail of a pharmaceutical balance (eighteenth century)

HALFDAN MALHER

Rational Drug Use in an Irrational World

Mr. Chariman, distinguished gathering:

1. WHO has a Constitution that makes it clear that health is more than the mere absence of disease or infirmity; it implies physical, social, and spiritual well-being. Now, it may seem out of place to some of you for health policy-makers to be indulging in spiritual matters. But the spirit and the body cannot be separated if health is to be *enjoyed* by people. What is more, human beings are social creatures, so living together in harmony is also essential for their well-being.

2. Are people throughout the world living together in harmony? The international political situation seems to indicate that they are not. But if there is one aspiration that transcends political, ideological and religious differences, that aspiration is health. So we have to look at the world around us and ask ourselves, Are we anywhere near that health harmony? I am afraid we are not.

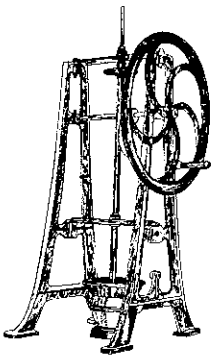
3. One thousand million people, living mainly in rural areas and urban slums, exist in a state of social and economic poverty. They are the victims of a vicious circle of unemployment and under-employment, economic poverty, scarcity of worldly goods, a low level of education, poor housing, lack of water, poor sanitation, malnutrition, affliction by disease, social apathy, and the lack of the will and the initiative to make changes for the better. It is difficult to conceive of spiritual well-being under those circumstances. And I am not referring to the kind of temporary emergency situation that attracts worldwide attention; I am referring to a permanent situation of deprivation to which the world remains oblivious.

4. In many parts of the least developed countries of this earth that we all share, out of every thousand children born this year two hundred will die before they reach the age of one. Another hundred will die before they reach the age of five. And only half will remain alive at the age of forty. The average life expectancy in these countries is less than fifty years of age. Compare this with the most developed countries, where out of a thousand new born this year 990 will still be alive at the age of one, and only one child more will die before the age of five. The average life expectancy in these countries is more than seventy years of age. Or compare the number of women who die in childbirth in rich and poor countries. In the former the rate is as low as 2 for every 100,000 births; in the latter it is as high as 1,000. Yes, 500 times higher!

5. In the developing countries people die like flies from diseases that could be prevented but are not. Diarrhoeal disease and acute respiratory infections in infants and young children continue to be major scourges. So are a number of infectious diseases that could be prevented by immunization, but far too few children are immunized. More than half the world's population live in malarious areas and although there are no accurate figures, it has been estimated that a million children die of that disease each year in Africa alone. A whole host of other parasitic diseases continue to undermine the health of people in developing countries. Tuberculosis and leprosy are as rampant as ever in these countries. Hundreds and hundreds of millions of people in these countries suffer from undernutrition. The hardest hit are children, whose resistance to disease is therefore reduced and whose ability to learn in school severely undermined.

6. And at the same time in other parts of the world obesity is on the increase due to overeating. The industrialized countries have severe health problems too, but incomparably fewer than those in the developing countries. Yet while in the developed countries people spend on health US $250 per person per year in the public sector and another US $250 in the private sector, totalling US $500, the comparative figures in the developing countries are in the range of US $ 2-7. So people in developed countries spend roughly a hundred times more on their health than their sisters and brothers in the developing countries, whereas the people in the developing countries have infinitely more serious health problems.

7. The gap between the health haves and the health havenots can be summed up in one word — inequity. And need I remind you that that word closely resembles iniquity — a sin. And it *is* a sin — a collective sin. Mere repentance



by the world at large will not help. Action is required.

8. Action was set in motion by the world's supreme health policy-making organ — WHO's World Health Assembly. In 1977 it decided that the main social target of governments and WHO for the coming decades should be the attainment by all the people of the world by the year 2000 of a level of health that will permit them to lead a socially and economically productive life. That is popularly known as health for all by the year 2000.

9. What does health for all really imply? Well, it is a declaration of faith in human development, inspired by a sense of decency, compassion, and the desire for social justice regarding health. It recognizes that the world's underprivileged must not be condemned to survive in misery, if they survive at all, but must have the opportunity of developing their physical, intellectual, and spiritual capacities in dignity. These were the moral foundations of the Health Assembly's decision. That decision was a display of empathy, not of pity, a platform for international health justice, an expression of universal moral and social values that transcend all political, geographical, ideological, and religious beliefs and practices. And it presented, and continues to present, an ethical challenge to all concerned — governments, nongovernmental organizations, religious, voluntary, and philanthropic organizations, people in all walks of life, WHO, and bilateral and multilateral organizations.

10. I have indicated what health for all implies. What does it mean in practice? No, it certainly does not mean that by the year 2000 there will be enough doctors and nurses to provide medical care for everybody in the world, for all the existing ailments. And it certainly does not mean that by the year 2000 nobody will be sick or disabled. But it does mean that by the turn of the century there will be a more equitable distribution of all the resources available to health. And it does mean that people will use better approaches than they do now for preventing disease and alleviating unavoidable illness and disability. And it does mean that health begins at home, in schools, at the work place, because it is where people live and learn and work that health is made or broken. And it does mean that essential health care will be accessible to all individuals and families in an acceptable and affordable way, and, above all, with their full democratic involvement. And it does mean that people will have the opportunity of learning how to shape their lives and the lives of their families free from the avoidable burden of disease. And it does mean that, graced with this understanding, people will adopt better ways of growing up, growing old, and dying in dignity. I should add that health for all aims at *all* people, whatever their present level of social and economic development, but social justice demands that greatest attention be paid to the underprivileged.

11. In 1978 an international conference held in Alma-Ata declared that primary health care is the key to attaining health for all. What, then, is primary health care? Well, if health is made or broken where people live and learn and work, that is where health care has to be provided first and foremost, supported by the rest of the health system. So primary health care ensures essential promotive, preventive, curative, and rehabilitative care in a way accessible to people. And it is ensured at a cost the country and people can afford, with methods that are practical, scientifically sound, and socially acceptable. To be successful it needs the active involvement of people as both subjects and objects of their own health destiny. Many social and economic sectors in addition to the health sector have an important role to play.

12. At the very least, primary health care includes eight essential elements. These start with the education of people on health matters so that they understand what is conducive and what is detrimental to their health and can therefore take an enlightened part in maintaining it. Proper nutrition and safe water and sanitation have to be ensured. All aspects of family health are important, and particularly the care of mothers and children. The prevention and control of locally endemic diseases have a prominent role, and that includes immunizing children against the major infectious diseases. On the curative side, primary

health care includes the appropriate treatment of the common diseases and injuries, and that of course brings in its wake, last but not least, the provision of essential drugs.

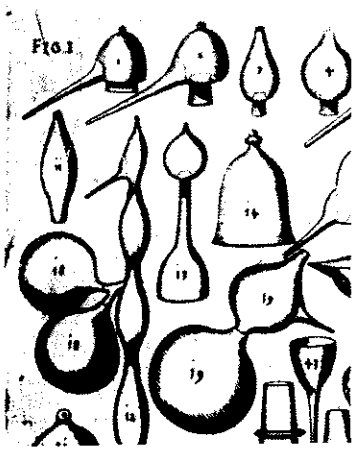
13. That last element — ensuring the availability of essential drugs — sounds innocent enough, but I can assure you that it is not; it is fraught with difficulties of all kinds — commercial, social, financial, managerial, and ethical difficulties. For the world drug situation is a reflection of the world health situation; there are drug haves and drug havenots. Some people use too many drugs; the vast majority of people whose plight I referred to before have few, if any, drugs to use. Three billion people, that is 75% of the world's population, who live out their existence in the developing countries, use only 15% of the world drug production. During the past half century some remarkably effective drugs have been placed at the disposal of humankind. When that is the case, when life-saving products are potentially available, but in practice inaccessible, when that happens I humbly submit that the situation is unethical, immoral, a flout of spiritual values.

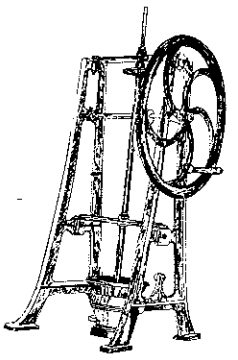
14. And to ensure the *rational* use of drugs in addition to their availability is asking a very great deal. It is asking for no less than the introduction of rationality in a very irrational world. It demands honesty in a dishonest world, generosity in a greedy world, altruism in an egoistic world. It requires transparency in a technically mystified world, intelligence combined with humility in a crass and arrogant world.

15. To restore international social justice in drug matters, WHO introduced the concept of essential drugs. What does that concept mean and how did it come into being? The challenge was and remains getting to the majority of the world's population the drugs that they most need, that are effective, of acceptable quality, safe and obtainable at a reasonable cost. To meet that challenge, in 1977 WHO convened a committee of outstanding experts from all over the world in public health, medicine, pharmacology, pharmacy, and drug management. They put forward a list of some 250 generically named drugs and vaccines that appeared to them to be most needed for the health care of the majority of people and should therefore be available at all times in adequate amounts.

16. To some people, and they are very vociferous, 250 drugs may seem very little. To most people in the developing world, the silent suffering majority, it is a huge number. Most of them are unable to obtain even those drugs that they need from as short a list as 20 to 30 drugs that are vital in primary health care. I am referring to drugs for such conditions as pain of all kinds, acute infections, anaemia of pregnancy, malaria and other parasitic diseases, worm infestations, tuberculosis, leprosy, trachoma, and scabies. WHO has stated clearly that its model list is not a dictate; it is a guide. Every country has to work out its own list in accordance with its specific needs and resources. The model list is up-dated periodically in keeping with scientific progress and in the light of experience.

17. As I said a few moments ago, this may all sound very simple. The drugs are there; all you have to do is to get them to people. Well, I am afraid that getting essential drugs to underprivileged people in developing countries is not at all simple. It has profound implications for international trade in drugs. It depends very much on having well defined national drug policies, national drug regulations, and provision of impartial information for health personnel, the public and policy-makers. Making information of that kind freely available is crucial. Much of the polemic surrounding the





use of drugs has arisen around the ethical principle of telling the truth, the whole truth, and nothing but the truth and the all-too-often unethical practice of not doing that. Ethical promotional practices are no less important, as are adequate health infrastructures with efficient supply systems, trained health personnel and managerial manpower, and sufficient money to buy drugs as well as hard currency to buy them abroad.

18. To ensure these is the very pillar of WHO's Program on Essential Drugs. This Program has raised suspicion on the part of certain governments, health personnel, and the pharmaceutical industry, sometimes even open hostility. On the other side of the coin, it has been accompanied by highly outspoken criticism by consumer groups of industrial and commercial behavior and intensive lobbying by them to bring about change. It has given rise to the demand for international regulation of pharmaceutical practices. As I stressed at a Conference of Experts on the Rational Use of Drugs held in Nairobi last November, these international dust-storms were tending to obscure the essential, and that is ensuring that the people in developing countries have access to the drugs they need most at a cost they can afford. And that aim, I repeat, was inspired by the ethical doctrine of social equity.

19. I should just like to emphasize one additional aim that is relevant for all countries, industrialized and developing ones alike, and that is to ensure that drugs are safe. We must do all in our power to prevent the thalidomide disaster from repeating itself. Early warnings of such potential disasters are the only ethical approach. I am sure you will be interested to know that WHO disseminates that kind of information to all its Member States on a continuing basis.

20. The Nairobi Conference had at least one important consequence; it brought home the need for cooperation rather than confrontation in solving the world's drug problems. Most important of all, it defined the responsibilities of all those whose cooperation will help to make drug use more rational. The list is long. It starts with governments, it includes industry, health personnel involved in prescription, dispensing, supply and the distribution of drugs, universities and other teaching institutions, professional nongovernmental organizations, the public, patients and consumer groups, and the mass media — in short a cross section of society. WHO has updated its drug strategy in the collaborative spirit of Nairobi. That strategy reinforces advocacy of sound national drug policies as part of sound national health policies, based on justice, honesty, and empathy. As part of the strategy, WHO continues to avoid any kind of supranational regulatory stance. Drug regulation is a national responsibility, and it is for the people in each country to decide what shape that regulation should take. The World Health Assembly endorsed that strategy a few months ago, and I remain optimistic about the future, guardedly optimistic, however, for devils are not easily put to rest.

17. Distinguished gathering, the ethical value system that gave rise to the concept of health for all by the year 2000 also gave rise to the concept of essential drugs. So here we have an outstanding example of a spiritual dimension leading to a highly practical dimension in health care. The successful implementation of the practical dimension will surely give cause for spiritual satisfaction. So I return to the outset of my talk — the spirit and the body are inseparable for the health of individuals and societies.

Thank you.

DR. H. MAHLER
Director-General
of the World Health Organization

FERDINANDO SALLEO

Pharmaceuticals for Developing Countries: The Need for Cooperation

When the ministers making up the Interministerial Committee for Foreign Affairs decided, in 1982, to give priority status to health care as an area of Italian cooperation, it was difficult to imagine that, in such a short period of time, our country would reach such a vast and well structured level of intervention in the Third World as it has today.

It is only right to recognize that until the late seventies the image of our country was exclusively in the hands of those extraordinary ambassadors, our Italian missionaries and volunteer workers, who were able to create the health facilities and educational centers which formed, in the developing countries, those persons that nowadays often hold significant posts of leadership.

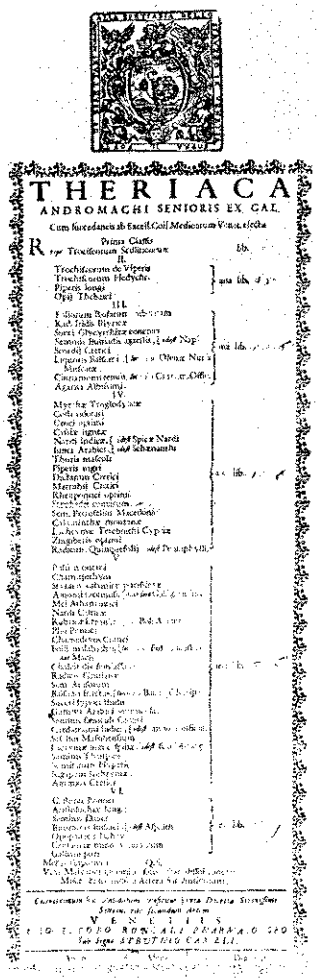
This presence could not but be followed by the awakening of awareness on the part of the public authorities, and this gave rise to the decision on the part of the ICFA.

The ICFA, at its October 1982 meeting, by declaring health care a priority area, like agriculture, education and energy, did not just fill a gap at the political level, but went much further: anticipating the ensuing debate that would become so impassioned and inflamed, it declared that Italian cooperation had to be directed, in the medical field, primarily to the poorest peoples, those stricken by famine and drought, those most neglected and most severely afflicted by disease and malnutrition.

It is easy to recognize in that description those peoples of Africa and the worst regions of Latin America, above all the two major priority areas for us. Living in rural areas, they have less access to the medical facilities of their countries and, therefore, frequently have some of the lowest levels of health and quality of life. A few years before, in 1978, the WHO and UNICEF had organized a Conference at Alma Ata that was destined to be of historic importance for health care in the Third World: the guidelines that emerged from that Conference indicated the need to involve the populations in the work of bettering their standards of health, and this had to be done chiefly by promoting basic medicine programs, the vaccination of babies, the education of mothers, etc. This was a confirmation of the political line that was gradually being formed for the whole enterprise of cooperation, founded on the idea of the centrality of man in development, the new humanism of cooperation that has rediscovered the wisdom of the past seeing man — not things — as the protagonist of his own progress.

Even before the Department made a concrete start on the first interventions in the health care sector, our country distinguished itself, at the World Health Assembly of 1977, by its promotion of a global plan for essential medicines directed to developing countries.

This ambitious and basic plan, which the Director of the WHO has described in detail,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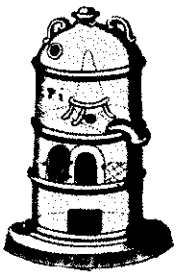
Printed posters advertising medicines (eighteenth century).



came about thanks to the pressure which Italy brought to bear at the World Health Assembly, in particular by those who represent our country in the pharmaceutical field; this was immediately taken up personally by the Minister for Foreign Affairs, as soon as the restructured health care section of the Department was in a position to operate effectively.

In perfect accord with the practices of WHO and UNICEF, which was just beginning to show interest in this field, we have always held that the policy of providing essential medicines for developing countries must not represent a compromise conditioned by scarcity of resources, but a definite choice, supported by science and technology; medicines are not viewed in terms of consumer goods, but as some of the most important components of a health strategy devoted to giving priority to what is of primary importance in the context of basic health care, a cardinal point as regards the positive effect they can have in the betterment of life for two thirds of the world's population.

Our cooperation in the pharmaceutical sphere is not just limited to providing a sufficient quantity of medicines, but rather is aimed at contributing to the creation of an organizational and educational system throughout the health care network of a country, and that is coherently expressed in the realization of:

— policies of registration and importation;

— efficient transport, storage and distribution systems;

— initiatives aimed at the supervision and analysis of the ways drugs are employed;

— programs for the medium and long term of education in the skills needed for developing the pharmaceutical sector in an active way, not just minimal administrative abilities that inevitably reveal themselves to be inadequate to meet various needs (medical, financial and organizational) which must be faced in this field.

Today, therefore, the development can be foreseen of a policy of close collaboration, though with the inevitable reciprocal dialectic of interests and priorities involving industry, international agencies, individual countries and representatives of the consumers. A priority rôle in this must obviously be assigned to education in all disciplines that meet in the same sector, with particular attention to giving developing or importing nations the capacity to analyze the relationship between pharmaceutical products and health care priorities.

It is not appropriate for a body like ours to enter into theoretical arguments such as how health care structures should be organized so as to guarantee real improvement in health in developing countries; if I may here be allowed one reminder, I would recall some of the comments made by our Minister for Foreign Affairs to the effect that while many discussions have been going on in Rome for the past two years as to what to do and how to do it, with new arguments being found every day to fuel wearisome polemical stances, the Department, with the important support of its outside consultants, members of the Health Consultative Group, transformed formal statements into practical action, with bilateral and multilateral programs, these latter being worked out in agreement with the competent international organizations such as WHO and UNICEF.

I feel it is, therefore, of help to recall that, in the course of the last year in particular, we have asked the most competent scientists and specialists to go to the places concerned to check on what has been done and to control — I am not afraid to use the term — our enterprises and thus to make it known in Italy too that we have tried to

operate with concrete gestures, not just mere words. The reports of Professors Pocchiari, Toti, Durand, Zanussi, Guzzanti and Poggiolini all urge us to continue on the path on which we have embarked, making, of course, the modifications and corrections in our route that are needed to ensure increasingly better results.

Having promoted, as I have mentioned, the creation of a plan of action as regards essential medicines for developing countries, along with WHO and UNICEF, in tandem with an even more important — in terms of financial commitment — program of infant nutrition, we have been the first to organize an aid plan for five African countries chosen among those with the least favorable indicators of infant survival. The Ministry of Foreign Affairs has allotted for this program in Guinea Bissau, Burkina Faso, Mozambique, Somalia, and Ethiopia the sum of fifteen million dollars over four years; operations got under way two years ago. Results so far obtained are only partial: our ambition was to harmonize the financial and technical resources that Italy can offer with the structures and abilities of the two organizations involved. The idea was, and remains, a fascinating one, and we are convinced that a global pharmaceutical program should — as this one does — presuppose a linkage between supply, stockpiling and peripheral distribution, quality control and information for those who are going to use the medicines. Our first evaluations of the program have revealed, however, that there is still an imbalance between supply and the other stages which we continue to consider more important and useful. Since the operational responsibility belongs exclusively to UNICEF and WHO, we have analyzed the methods employed, revealing that there is a measure of breakdown in contacts between the two bodies both at the center and on the periphery, and this has in fact set back the time scale of the original plan of action, already retarded as a consequence of natural and man-made events in the countries concerned which further weakened their already limited capacities for making the best use of international aid.

Our forthcoming inspection will be discussed at the next Health Consultative Group meeting; this should decide the terms of reference of a mission to the five countries concerned by expert officials from our Health Ministry, the Superior Health Institute, and the National Research Council.

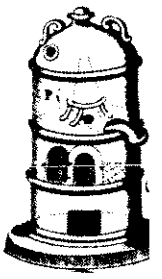
New guidelines for the second two years' work should follow from the on-the-spot inspection and be conveyed to the two executive agencies so that they can be incorporated into an unprecedented kind of operational plan.

As regards the activities that have been organized on a bilateral basis, I think it worthwhile to look first of all at our relations with the world of production in Italy.

We have carried out a rigorous critical analysis of the procedures for purchasing in Italy medicines for developing countries that were in effect up until 1982: the results of this analysis and the prospects of greater financial assistance that were opening up with regard to cooperation, urged us to ever closer contacts with the world of industry, by means of its associations, so as to involve, as far as possible, the whole of the Italian pharmaceutical sector and to become aware of the difficulties it faces, so as to build up a dialogue that would permit us to adopt a common and coherent line of action that could also be built up on the international level, overcoming the mistakes and deficiencies of the past

From this point of view, the objectives we have reached are: a) a commitment on the part of the Pharmaceutical Industry to supply products of the highest possible quality, with quality control of all products sent by us to be carried out by the legally competent organism, the Superior Health Institute, on the basis of the agreement worked out between us and the Institute; b) instructions for use on every product in the language of the target country; c) special packaging of the products to allow their immediate distribution in outlying areas, to which, in the majority of cases, they are sent.

The agreement with the pharmaceutical industry that was submitted for the scrutiny and modification of the Health Consultative Group before its recent renewal and

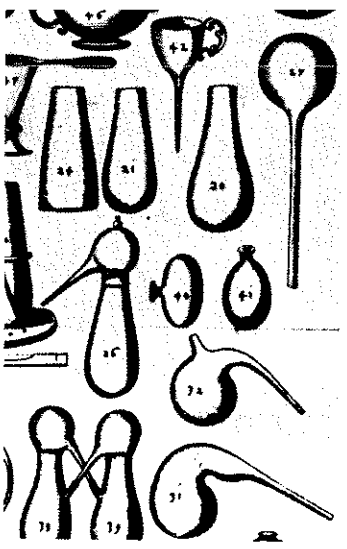


the General Directorship of Pharmaceutical Services of the Ministry of Health represent for the Department a starting point for other initiatives and joint schemes of an increasingly close kind with the whole world of industry.

While speaking of the promotion of the rôle of Italian Cooperation in the health care sector, mention must also be made of research. The Department works from two different viewpoints here: research into appropriate technologies for developing countries and scientific experimentation properly so-called. In the first case, some programs that we are promoting for the vaccination of babies have an important rôle: there will shortly be unveiled to the public a new type of refrigerator powered by a solar cell, of completely Italian manufacture, which is designed to meet the need for an effective and efficient source of continuous cooling required by vaccines so that they may be employed in even the most isolated dispensaries in any part of the world. This is but one of many examples of the various initiatives financed by us or worked out in agreement with Industry to develop new and simplified techniques that can be adopted even by developing countries with very limited financial resources available for health care.

In the field of scientific research, I shall just mention that Italy is one of the major contributors to the WHO special program for research into tropical diseases and the development of new research programs in the realm of orphan drugs, whose importance is rightly underlined by Professor Marini Bettolo.

In this regard, our industry has not yet been able, except in rare cases, to understand the message; nevertheless, our willingness to enter into serious dialogue and collaboration is there. The National Research Council cannot help being involved here, and indeed is working out a project aimed at developing this area; this holds the promise of being able to gather around it all the possibilities our country is capable of. It is serious to have to note that, in contrast with the enormous progress that has been made, for example, in the field of cancer research, there has not been the same interest shown for research into medicines and vaccines for diseases such as bilharziasis, malaria, leprosy or tuberculosis, which still afflict millions and millions of people.



In other fields, which at first sight may seem less important, the Department has made great strides forward. It has been demonstrated that a third of infant deaths in developing countries are caused by dehydration following diarrohea, while a correct use of rehydrating salts administered orally — the Director General of UNICEF, Grant, is insistent about this — can eliminate the problem. But it is not UNICEF that is the front runner in this struggle, but Italy. The WHO has confirmed that the formula to be used for Oral Rehydration has to be reworked, and the pharmaceutical industry, on the basis of the data furnished by the Department, has taken the necessary steps and notified its allies of the composition of our products; other new products are being studied so as to resolve the problem of the lack of iodine in the countries concerned, or Vitamin A, a real scourge in

Table of the pharmacist's alchemical equipment in Antonio De Sgobbis' Universal Pharmaceutical Theater *(Venice, 1662)*

very many developing countries.

Finally, let me mention another salient aspect of our activity in this sector, the local manufacture of essential medicines, which is part — the most important one from the socio-economic point of view — of the transference of technologies. The Department encourages and finances these activities and the building of pharmaceutical factories on the spot according to WHO directives and after a thorough analysis of the market and the economic capabilities of the countries, so as to avoid the disastrous mistakes already made by others who have built "cathedrals in the desert" which require for their survival continuous financial support on the part of the benefactor for unlimited periods and with exorbitant costs.

It is obvious that in such cases we look with interest on the creation of mixed associations with the participation of those of our industries that are able to ensure the education of native technicians and transfer mechanisms that give rise to continuous technological exchanges between Italy and the receiving country.

An example which illustrates this process is a recent program for Italian aid to a drug factory that will produce essential medicines in Indonesia in large enough quantities to satisfy a third of the country's entire needs: Italian aid, apart from the necessary equipment, consists of planning, the formation of the staff, and the transfer of knowhow.

In concluding, let us mention appropriate technologies, research, and formation: three activities with the same aim but with different methodologies which the Department has begun in three countries in Africa: on the spot production of endovenous fluids which requires simple technology for its production, compared with an uneconomic system of transport from Italy. In Kenya such a factory is being built by an Italian company specialized in pharmaceutical processes in developing countries. In Burkina Faso, the same sort of thing will be done by one of our (non-governmental) agencies, and in Ethiopia it will be part of the multilateral WHO/UNICEF/Italian programs.

We are certain that a thorough analysis and comparison of the results of these three initiatives will permit the formulation of a standard working plan of a kind able to optimize the cost/benefit relation and serve as a model to be duplicated in any developing country.

Thus, we have a complete picture which evidences an effort and a commitment that few countries in the West can boast of today, both for the utilization of financial resources at its disposal and for the continuous and direct involvement of the countries which benefit from it, towards the improvement of whose conditions of health our attention is completely devoted. It is an approach which has great potentialities and which aims at combining rigorous scientific attention and the maximum of respect for the peoples benefited, thereby creating in part that humanization of medicine which perhaps can be more easily attained in the developing countries than in those already industrialized. To continue along this road, with the corrections that will be necessary, means, moreover, contributing to the achievement of the aim of the United Nations, health for all by the year two thousand, for which everyone must be working, for the peace and well-being of the whole of humanity.

Cooperation in health care is for us a basic facet of development policy: health, nutrition, agricultural production, and upgranding of human resources all represent the essential needs that have to be met in order that man, the aim and mover of development, may take his destiny into his own hands, aware of it and freed from the ancestral burdens that have so often kept him at the bottom of the difficult ascent towards social and human progress and impede him from giving of his best for a more stable and peaceful world.

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JEAN DRÉANO

The Pharmacist: Intermediary Between the Physician and the Drug User

To speak of the pharmacist, to place him between the precribing physician and his patient, means, above all, to speak of the pharmaceutical, the essential object in this relationship, without which the pharmacist would have no reason to exist. This will be our preamble.

The pharmaceutical, on the one hand, like the pharmacist, on the other, exists only in connection with disease in general and the patient in particular. If disease did not exist, what would be the use of physicians, pharmaceuticals, and pharmacists?

Men and women who possess the art of medicine are there to offer attention and care, to help the patient recover from his illness, recalling the Christian statement by Ambrose Paré, physician and Renaissance humanist: "I treat him; God restores him to health."

This art of healing, the result of empirical discoveries in the first stages of knowledge enriched in the course of time by all scientific progress, has used the most varied means of treatment. The imposition of hands, often cited in the Bible, has recourse to the power of spirit and will; Chinese acupuncture, primitive surgery, the science of skilled hands, and the orthopedics of the "bone-adjusters" or modern kinesitherapy do not need drugs, but these are merely exceptions with a limited horizon or prove questionable, and the pharmaceutical quickly dominates as an auxiliary or principal means of treatment.

Could surgery have survived without anaesthetics or resuscitation techiniques, or radiology without contrast agents?

I. The Pharmaceutical: A Social Phenomenon

In the face of this explosion, this multiplication of the use of and need for pharmaceuticals, we may say that medicines have become a real social phenomenon.

The last century — only a drop in the whole history of mankind — saw the birth of modern drugs.

After the first nineteenth century applications of chemotherapy, with the separation of the active principles of vegetables (whose curative properties were already known empirically), chemical synthesis has multiplied possibilities and hopes.

After fifty years — i.e., after the first antibiotics, the first cortisones, the first psychoactive drugs — the therapeutic baggage was completely renewed, and a great many treatments regarded as classical were sent to the pharmacology museum.

Patients' hopes for life increase each year; diseases once considered incurable are now cured, and chronic patients recover a normal existence.

At present this progress seems to have reached a temporary standstill. In reality, after such an extraordinary period, research is discovering new directions which are more difficult, but also more stimulating, involving the knowledge of cellular biology and the inner mechanisms of pharmacological action.

Medicines have never been more deserving of the Greek term *pharmakon,* which means both the remedy which cures and the substance which defends — the matter is, in the end, a question of dosage.

It is a social phenomenon, for the pharmaceutical has become a need of modern man, continually increasing the social cost to be borne by government in our developed societies, a social phenomenon which is at the forefront of the wishes and hopes for the future of the developing countries. It is a social phenomenon which, in manifesting itself, also poses countless problems you are all familiar with — useless or harmful overconsumption, "introgenous" disease, pharmacomania, deviations which become toxicomania.

Lastly, it is a social phenomenon because drugs have turned into an industrial product, "the pharmaceutical product," subject to economic imperatives and the rush for results of one of the most efficient sectors at present — the biochemical industry. We must add that for some time it has also formed part of the world of the mass media, marketing studies, and the myriad forms of advertising.

II. The Pharmaceutical: A Health Object

Whoever closely observes the current conception of medicines, taking into account

both general public opinion and the ideas of experts such as manufacturers, physicians, and pharmacists, will be able to situate each drug "put on the market" within two grids. The first includes the expectations of the individual in his desire for health, a general wish manifested at three main levels: 1) the desire for recovery in the case of known diseases which may become severe or fatal and which must be considered seriously on account of their medium — or long — term consequences; 2) the desire for improvement related largely to pathological conditions influenced by mental states or physical weakness, what we have come to term psychosomatic illnesses; 3) the desire for comfort, which seeks to annul all forms of occasional or ordinary minor malaise of which we contemporary men are less and less tolerant.

A second grid classifies drugs according to their functions:

a) the strictly necessary adjuvant which, in the face of an organic deficiency, acts as a real biochemical prosthesis or "crutch" (insulin and dialysis systems are examples);

b) an agent modifying a normal organism's functioning at a precise point, such as synthesis progestatives;

c) balance-modifying agents, such as hypotensive drugs and anticoagulants, which, in a naturally troubled organism, establish a new, artificial situation which will prevent more serious trouble;

d) defending agents, which checkmate and block microbiotic, viral, and parasitic aggressions, including curative or preventive medicines, like vaccines;

e) temporary aids, such as anti-asthmatics, tranquillizers antiphlogistics, and analgesics, which act quickly on a short-term basis in crisis situations;

f) psychoactive drugs, like antidepressives;

g) "sweet" medicines, which may often be described as "placebos," but whose human and social utility is obvious.

These two grids reflecting an initial approach to drugs could be further sharpened. They refer, at the outset, to the populations of the industrialized countries; but it must be observed that, if we set aside the neediest groups on earth, who are quite content to obtain a sufficient quantity of *any* of the 200 medicines selected as "essential" by the W.H.O., as the standard of living of the more favored segments of the developing countries improves, they rapidly mirror the needs of the developed world.

In all nations, including the most advanced, there are potential clients for all sorts of healers and quack doctors, magicians, astrologers, the so-called manipulators of dark forces — they are not satisfied with classical medicine.

Moreover, we should never forget that the pharmaceutical as a health object is continually under the glare of the media floodlights, through direct and indirect advertising filling the pages of magazines and radio and TV broadcasts and the journalists' permanent search for wonder drugs, the holy grail of modern times, periodically heralded with a loud din, only to plunge once again into oblivion.

III. What is the Pharmacist's Role?

The pharmacist, with his status as a university degree-holder, is involved in every phase of drug development — from the team of researchers to those preparing specific pharmaceuticals or engaged in marketing and advertising.

My words are addressed to the retail pharmacist who distributes medicines to the public in a private establishment or hospital, whether he be the owner or employee of this enterprise.

And, first of all, let us raise the question as to whether or not this intermediary is still necessary today. In remote times, in Europe and elsewhere, there were physicians — in the role of medicine's jack-of-all-trades — who by themselves prepared ointments and draughts for their patients. Some situations of this kind have lasted down to our own day; in Japan, for instance, as well as other countries, there are still "physicians functioning as pharmacists." But, in general, these are cases of a surviving tradition which is gradually disappearing, or examples of extreme economic conditions not allowing a pharmacist to live independently.

The two professions have been separated for many centuries now. The edict of Frede-

rick II, Emperor of Germany and King of Sicily (13th century), forbidding the simultaneous practice of the two professions is always cited, along with the constitution of the apothecaries' guild and the creation of the college of *aromatori* in Rome in the same period.

All of these events reflected the express will to separate drug prescribers, who made decisions, from the suppliers, who received payment: on the one hand, not to tempt the physician to prescribe expensive remedies usful only to line his pockets and, on the other, to oblige an expert who had received specialized training and been duly examined to make the preparation "according to the art," in the words of the accepted phrase

This result proved satisfactory for everyone, and the apothecary or pharmacist, who kept poisons as well as weights and measures, honorably contributed to the security of his fellow men during often troubled times. Has this professional independence, which as a general rule prepared the pharmacist for personal responsibility and private practice, been utterly destroyed by current developments?

At the beginning of this century, we in fact witnessed the industrialization of drug preparation and its almost complete abandonment of the shop.

Without, then, overlooking the small — but medically quite useful — part of preparation still performed in the shop, we must regard this inevitable evolution as, in the long run, disturbing pharmacists' image, both among themselves and before the public at large.

A transformation of their role has taken place: pharmacists are in general satisfied with their present professional status and aware of their social usefulness; it is the public, as well as the medical profession, that sometimes remains to be convinced

The evolution of medicine in recent decades has pushed the pharmacy forward. The coming years will witness the appearance of new demands obliging pharmacists to take new initiatives in acquiring greater competence, maintaining their independence, and developing their area of freedom.

Let us examine what we agreed to call the *pharmaceutical act,* which applies to the two following essential cases:

— the doctor's prescribing medicine,

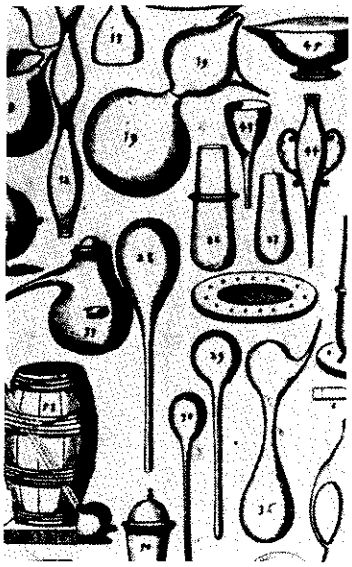
— the patient's desire for self-medication.

In both cases, what concerns the pharmacist is to move from the drug as originally discovered and produced to the medicine suited to a particular patient, a human being in a given social milieu.

a) *The case of the prescribing physician*

The physician prescribes the drug(s) which he considers necessary for the patient's recovery or maintenance of health, carefully selecting from among numerous pharmaceutical options on the basis of his diagnostic data, including his observations and the results of examinations.

It is a significant act involving a written document, the physician's signature, and his personal responsibility and is performed through the use of his own memory (with a capacity for only a few hundred drugs), a listing of medicinal



products, and, frequently, a computer as well.

The pharmacist receives the prescription from the patient or his representative, controls identities if necessary, and devotes attention to what I would term an "analytical" examination of the prescription:

— to ascertain that the prescription in fact corresponds to the patient named and that there has been no mix-up along the way,

— to see to it that the dosage prescribed by the physician conforms to the usual amount for an individual of similar characteristics, such as age and weight,

— to ensure that there has been no confusion *(lapsus calami)* involving drugs with similar names, but quite different properties,

— to uncover possible incompatibilities not anticipated by the prescribing physician in the case of multiple medication - a difficult problem, especially when medicinal interactions are not well known.

Obviously, the pharmacist, when in doubt concerning one of the aforementioned points, attempts to telephone the physician or withhold the prescription until he is able to secure the needed information or rectification. Such cases involve both the patient's security and a guarantee for the physician — possible human errors is detected in time by the pharmacist's careful vigilance in fulfilling his responsibility. But his role does not end here.

Familiarity with his client, if a usual one, along with discreet, rapid questioning, must clarify certain points: Has the patient recently been treated by another doctor, an opthalmologist, for instance, or perhaps a cardiologist? Does he take other drugs, and, if so, who prescribed them? Did he by chance come to buy aspirin the day before, or is he presenting an old prescription for sleeping pills?

Certain interaction risks which may have been overlooked by the prescribing physician are great enough to justify a short investigation aimed at avoiding later regrets.

One must ask, in addition, if the patient fully understands the prescription he has been given and what information he received from his doctor. In the event he is not altogether sure or the physician has used terms he is unfamiliar with or has forgotten or has repeated incorrectly, the pharmacist must make a guess and seek to translate into the everyday language of a woman who is an unlettered immigrant, for example, with a reduced vocabulary, or an elderly man with an enfeebled brain who no longer understands very much.

It is a routine repeated hundreds of times each day which must become a reflex action and entails being ever on the alert to notice anything abnormal or extraordinary, in the etymological sense of these terms.

At this conference I feel it is necessary to stress that the virtues of patience and caution — particularly caution in this connection — must increasingly be brought to bear by the pharmacist, who, if a Christian, will not forget the words of the Gospel: "I was sick, and you visited me." And quite often, in these everyday tasks lacking prominence and devoid of glory, I have recalled the lines of a poet:

The humble life made up of wearisome, simple work

Is a choice labor requiring great love. . . .

I shall pass over the pharmacist's administrative functions, which are more burdensome each year as a result of the different prescription-reimbursement systems being used by social security organisms; in this case as well, the prescriber's incorrect filling out of administrative forms may entail difficulties and the need for rectifications by telephone.

But even after the client has departed with his medicine and all needed explanations, the story is not yet over, for there is another service remaining to be performed after the sale, which we term *pharmaceutical follow-up*.

We once again encounter the distinction between the patient, a differentiated and individualized human person, and the disease, a scientific entity. The patient reacts individually to drugs It is not infrequent to see him return complaining in surprise of unexpected reactions: nausea, diverse allergies, tachycardia, insomnia and drowsiness, among others

The pharmacist's "analytical" function must again be exercised. While reassuring, tranquillizing, and taking care not to undermine the patient's belief in the medicine's ef-

ficacy or the physician's image, he tries to discern the drug to which such difficulties may be ascribed and whether they justify the discontinuance of treatment in the event they are not merely psychological.

And again, if necessary, he contacts the prescribing physician and suggests an analogus, but less aggressive drug with fewer side effects.

Faced by the multiplicity of medically possible aggresions, the variety of medicines being taken simultaneously, the potential effects of special diets and lifestyles incompatible with one treatment or another, some pharmacists have started to keep "clints' cards," which are, of course, facilitated by information systems preserving the patient's entire medicinal history. It is an immense task which may be carried out only by faithfully avoiding all risk for the client and receiving his overall consent.

What may our hopes be in dealing with this problem of prescriptions?

— Extreme willingness on the part of both the physician and the pharmacist to maintain telephone contact without delay, with mutual familiarity and respect: present and future pharmaceuticals are and will remain too active and too specialized to be taken lightly;

— More seriousness in the drawing up of prescriptions: more readable texts, indication of the patient's age and weight (since he does not always come personally to the pharmacy), well specified dosage;

— Less impatience on the part of clients, who must realize that preparing a prescription requires an intellectual effort involving control, verification, and often a certain hesitation which cannot be overcome in a few seconds.

b) Self-medication

The request for a pharmaceutical is not always supported by a prescription.

At pharmacies, three types of requests are usual:

1) The request for a previously prescribed drug which the client has decided on his own to start taking again, with or without the presentation of an old prescription: such drugs are quite often subject to regulations, and their continued use may be prohibited;

2) A client's request for advice: "I have such-and-such a problem" (generally of a benign nature). "Can you give me something to relieve it?"

3) The request for a specific pharmaceutical product, often belonging to the category of familiar drugs known to the public at large through direct (radio, television, newspaper) or indirect (word of mouth) advertising. To this group we must add the "sweet" or "alternative" drugs, medicinal plants, frequently distributed, like other current pharmaceuticals, in capsules or vials, which have been strongly advocated by best-selling books.

In dealing with these three kinds of requests, along with more subtle ones (the drug addict should be particularly borne in mind), the pharmacist has a most important role to play.

The request for advice no doubt proves gratifying to him, for it appeals to his knowledge and manifests the client's trust in his wisdom and discernment. The pharmacist, however, must not yield to the temptation of the "medical consultation" bordering on the illegal practice of medicine; even if, more often than not, he merely gives his client a drug which is not dangerous and proves psychologically suitable, he must, in any event, direct his client to a physician, whose intervention may be necessary or even urgent.

The giving of advice by the pharmacist requires a good knowledge of the client, frequently a fair amount of mental acumen, and smiling authority. The pharmacist must often evidence this authority when faced with requests for renewal of previous prescriptions; he is commonly obliged to refuse the sale, but must always supply an explanation or commentary. And once again the original prescribing physician's counsel shoud be sought, if needed, discreetly and without the client's awareness, for in conversation between the pharmacist and the patient, a third person is always present in the former's mind — the physician.

When dealing with certain — often vaguely formulated — requests displaying the influence of publicity or a given book making powerful promises of health benefits, the pharmacist should not always remain passive or choose the easiest solution — and possibly the most profitable one.

He must once again inquire and correct misunderstood or erroneous information, go against the stream of fashion, oppose time-serving, and resist what may be rightly termed "medical misinformation."

Some clients are always ready to abandon the serious and necessary treatment demanded by certain chronic diseases and look to any source whatsoever for salvation, be it a home remedy or the lastest "discovery" of a pseudo-science verging on quackery.

And, finally, there is the case of addicts who maintain their habits. When such drugs are readily available, the pharmacist may have to face a moral dilemma. Taking the right attitude is not an easy task, and both perspicacity and firmness are also required. In extreme instances, pharmacists' refusals have sparked violence and recently in France the death of one member of the profession.

IV. The Need for an Ethic

We have thus been outlining the daily activity of the pharmacist as a dispenser of drugs.

The drugs, we may add, as merchandise must also be purchased, stored, kept in the best possible condition, and the pharmacist, as the head of a concern, must strive to ensure that the necessary drugs are never missing or will at least be available in a few hours' time, for the finest rhetoric is of no avail if the medicines prescribed and requested are not at hand. A pharmacist's continued presence in the establishment is mandatory, along with the organization of round-the-clock service, by day and by night.

But this is another matter which I shall not discuss today and which neither the physician nor the patient need be concerned with.

We have seen that the pharmacist continually supplies information in addition to drugs. This is what the profession seeks to affirm in stating that the pharmacist "dispenses" medicine, and it is for this same reason that the pharmaceutical act is a "liberal" act, contributing an *additional value* to the industrial product supplied.

This notion of "dispensation" entails its own exigencies leading us to define what we have agreed to term the "ethics of the profession," which may be formulated as a deontological code established on the basis of resolutions by a society of pharmacists responsible for sanctioning faults. Such is the case in France, for example. But if a codified ethic is applied to the most widely observed instances of "dispersation" in conformity with prescriptions and respect for regulations governing the sale of poisonous substances, it will not be able to deal with all the moral dilemmas the pharmacist may have to face.

But we have already realized that these are manifold and crop up every day. The pharmacist, in his capacity as health adviser, is often led to warn against the use of certain drugs, for example; such warnings are not obligatory, but are demanded by his own conscience.

These *warnings against* dictated by concern for the patient's welfare might be misinterpreted by medical bodies wishing only that the pharmacist be a neutral and almost mecanical executor.

It has been stated that the physician and the pharmacist have attitudes at once contradictory and complementary as regards drugs: "The pharmacist is cautious, reserved; the physician, more daring, more innovating. This results from the fact that a pharmaceutical prompts an initial reaction of trust in the physician: a new 'cure' is offered to him. The pharmacist at first reacts to a drug with suspicion: this 'cure' is placed or may be placed under surveillance."[1]

It is here that the quality of the pharmacist's moral training is of prime importance: it is vital that, free from all conditioning — particularly by the profit motive — he be capable of judging within the limits of his responsibility what is best for the patient. We must not forget that, in a certain sense, the pharmacist should be regarded as a *healer,* even if he is not at the sick person's bedside. And what is more, in recognizing that we are faced with *moral dilemmas,* we Christian pharmacists feel spurred to devote specifically Christian reflection to these problems within our Associations of Catholic Pharmacists.

V. Towards What Future?

Is is time to conclude and attempt to provide some orientation before the uncertainty of the future.

In spite of present appearances, the pharmacist will be less and less a merchant or trader in medicines and increasingly a *consultant, information-provider,* and *mediator*

— Consultant and information source for patients, particularly the "unknown patient," in the context of prevention or therapy follow-up, often involving long-term treatment where the physician is not seen again.

— Physicians will require his information and advice even more to acquire all the data on the medicines they employ, especially as regards medicinal interactions.

— Quite recently, at the World Congress of the International Pharmaceutical Federation in Helsinki, one of the speakers defined the pharmacist as the *health mediator* in the midst of the patient, the prescribing physician, the drug prescribed and social organisms.[2]

And it is in this connection that current developments, like the reform of pharmacy studies now being carried out in France, which requires future pharmacists to spend several months at a hospital, may prove beneficial for patients, facilitating complementarity in the physician-pharmacist relationship.

The foreseeable evolution of home hospitalization and treatment for the elderly will lead the pharmacist to form an integral part of the multidisciplinary team (physicians, hospital staff, kinesitherapists) which will take care of the patient locally. In such cases, it will also be possible to survey the treatment follow-up, if need be, with the pharmacist of the hospital or center from which the patient has been discharged.

Independently of public powers, pharmaceutical manufacturers, and social security organisms, the pharmacist must broaden his field of action and free initiative.

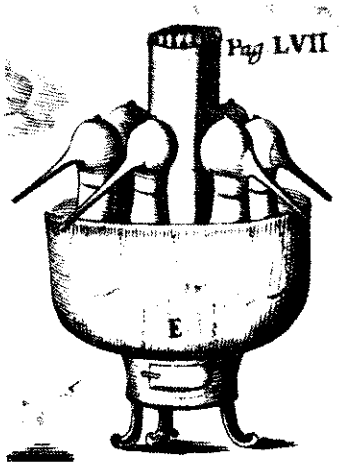
Experiments in this direction have already begun, as with the "pharmaceutical opinion" justifying a refusal to sell a product in Quebec, Canada.

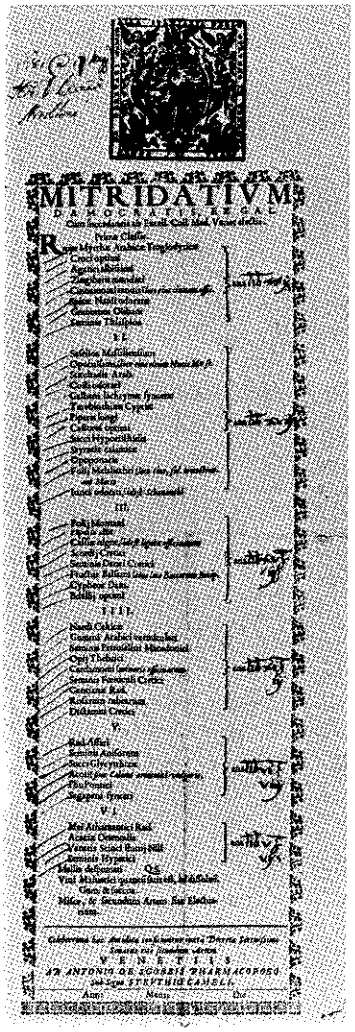
The corps of pharmacists represents too great a potential of competence and good will not to be sufficiently taken advantage of. Their skills will be constantly updated through effective continuing education (post-graduate training incorporating all the modern communications resources, such as videocassettes).

It remains for the pharmacist to closely accompany his clients and — as we have stressed — their physicians, as the one best qualified to inform on the properties, contraindications, and side effects of drugs. Along with pharmaceutical manufacturers, he may be regarded as contractually obliged to provide information, at least with respect to known risks.

New data processing techniques and access to data banks to be created in the future will make it possible to handle this particularly difficult task, wherein the pharmacist must play a key role.

Need we look further ahead? Should we imagine the pharmacist, trained as a specialized physician, assuming responsibility for treatment





within the medical team on the basis of diagnostic data. Some across the Atlantic believe so, it seems, concerned about increased effectiveness.

Many traditions will suffer change, but we are catching only the first glimmers of the dawn of the twenty-first century.

One thing appears to be certain: whatever the social context may be — and this is now true around the world, East and West — the pharmacist, as a man or woman of dialogue standing before medicine-laden shelves remaining a mystery for the layman, will continue to be a necessary, reassuring link in the chain binding the physician and his patient. Through his experience, he will participate in the commandment of charity: "He who loves God must also love his brother."

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[1] J. ARBON, "Ethique et Conseil Pharmaceutique," *Les Informations Pharmaceutiques, no. 293 (1986).*
[2] J. KAYSSETTE, *Le Pharmacien Universel* (Helsinki: F.I.P., 1986)

JEAN PIERRE SCHALLER

The Proper Use of Drugs and Medical Responsibility

A medicine can always be considered under two aspects, as an ethical good and as a consumer good. We must, therefore, specify what we mean by the former and the latter.

a) *Ethical good* Moral theology texts used to point out that ethics is a universal reality imposing itself upon everyone because man always has need of "moral reflection," which is indispensable in the practical conduct of life. It is rightly said that at every instant "life occasions [moral] situations requiring an immediate solution, in spite of their complexity and often contradictory appearances."[1]

The use of pharmaceuticals is no exception. The Christian physician and pharmacist, in the exercise of their profession, have recourse to notions of moral theology. This theology is a science which directs human acts towards an end corresponding not only to the honesty of the act performed, but also to respect for the will of God. Man thereby reaches his supernatural end.

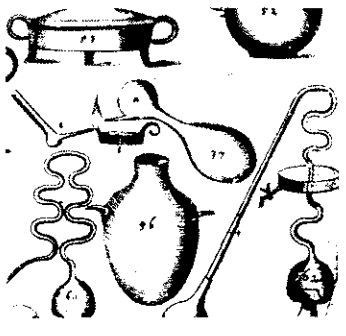
When St. Thomas Aquinas speaks of morality, he considers it in relation to beatitude, which cannot be obtained except through certain acts. It is thus necessary to analyze these acts in order to know which ones can keep us from reaching happiness. Moral theology cannot, however, remain a theoretical question, for acting is a concrete reality. It is in this way that morality becomes practice (I/II, 6, prologue). It must therefore both preserve the heritage handed down from two thousand years of Christianity and be constantly alert to the present moment.

Bearing in mind these premises, moralists emphasize that, while remaining rooted in eternal truth, we must always deal with current problems courageously. The result will be "a highly realistic dialogue with the men and the currents of thought of our age."[2] This is also the desire expressed by the last Council (*GS*, 3, I), and this Congress seeks to continue precisely in the same direction. Our perspective is that of someone using a drug, which is, in fact, a preferred means employed by the physician in therapy, but is also at the service of public health; above all, it is a reality inspiring trust in the patient. Moral theology certainly has a competent word to add on all we have mentioned.

b) *Consumer good.* Specialists teach that among economic values it is necessary to distinguish between production goods, which enable us to create additional products, and consumer goods destined to be used directly by individuals receiving immediate satisfaction from them. The pharmaceutical belongs to the second category and is catalogued as a nondurable good. In economics we must distinguish between direct and indirect goods; drugs are among the former under the aspect of immediate use.

In view of the foregoing, the physician and the pharmacist must strive in every way not to regard the patient as a mere object to which this or that remedy is applied. In a homily delivered at Banneux, Pope John Paul II placed health professionals on their guard against such a danger: "Do everything possible not to reduce the patient to an object in need of treatment, but he must be the first ally in a battle which is his battle, bearing his personhood in mind above all else; and I encourage you to find a demanding response in conformity with the respect and dignity that are due his life when you are forced to face problems presented to you, particularly at the bedside of the very seriously ill."[3] The use of consumer goods should never make the doctor or the pharmacist forget respect for the person.

This is why, in dealing with the ethical and consumer good which is the pharmaceutical, the responsibility of both the physician and the "client" is involved.



1) Responsibility and participation

In the first place, we shall take care not to confront the drug question exclusively from the standpoint of the client who can readily obtain whatever his health requires. At this point the matter really does become complicated! The last Council condemned anyone resting content with an individualistic ethic out of lack of concern or inertia. This in fact leads to not committing oneself to support the efforts of public institutions working to improve man's living conditions. Social solidarity is neglected, and all that concerns protecting health is set aside. The Second Vatican Council notes that, in reality, man should not feel obligated towards particular groups, but towards the whole universe.

And it is in this perspective that the Church must be able to rely on the assistance of communities and individuals to carry out the work of Christ, which has often been compared to that of a physician. Ignatius of Antioch, Irenaeus, Clement of Alexandria, and Origen all call Jesus the Physician of souls. At the beginning of the fifth century, Theodoretus compared God the Creator to a doctor who had sent His Son, the Savior, as a medicine for mankind. Such a spirituality favors respect in using drugs; as a matter of fact, the heart often encounters hindrances along the spiritual path precisely because of a body which is excessively depressed or enfeebled. A priest and a doctor wrote, "When a man's psychological behavior is unsteady or ailing, there is reason to believe that the balance of his supernatural life is also seriously in danger."[4]

a) *Work of justice*. In all medical and pharmaceutical circles, there is currently evidenced a need to regard everything concerning health as a reality involving not only charity, but justice as well.[5] The Church's concern for social justice is at the root of the constant efforts to make programs designed to improve health more efficient, especially in the poorest countries. The Church invites her members to coordinate their work with government health programs when these appear well thought out. Health action must hinge upon an infrastructure projecting the whole of socioeconomic development. The Church is also concerned with integral development which will raise living standards and take more effective sanitation into account.

The Church, in short, works to support services involving both preventive and elementary medicine. The latter is truly indispensable in some countries. The Alma-Ata Declaration of 1978 stated, "Elementary medical attention is truly essential. It is based upon practical methods and technology, is scientifically valid and socially acceptable, can be made available to all, both the individuals and the families in a community, with participation by everyone, and at a reasonable cost, in such a way that the community and the country may take on the aforementioned responsibilities at each stage of their development in a spirit of maturity and self-determination."[6] We can, then, speak of essential medicines as well within everyone's reach, not excessively expensive, and in keeping with the local mentality. Reference is made to a "poor people's pharmacy," adapted to the immediate needs of certain categories within the population. These considerations form part of moral theology, which tells us that the human act must be evaluated in terms of the object, the end, and the circumstances. In dealing with poor countries, we must never completely lose sight of the circumstances forming part of the development of the act. We no longer speak of humanism undertaken out of charity, but of a question of justice, which, in the case of medicines, includes financial resources.

From all of these considerations it is clear that the Church is simply continuing her history, which began with the institution of the monastery and the *hôtel-Dieu* (hospital for the poor), a history consisting precisely of the alleviation of distress, particularly in those who are socially the poorest.

b) *Uniqueness of the patient*. We must, however, take care not to reduce the sick person, with whom all health organizations are concerned, to an anonymous being, when he is an individual living out his illness in a manner different from that of his neighbor who

is also ill. A French bishop observed that the Church, when serving man in a state of diminished health, takes into consideration three painful situations of the person touched by sickness: the patient is a man who discovers his precariousness and his distress, who walks in darkness, and who is still a slave to the bonds imprisoning his body and often his spirit.[7] The physician prescribing a drug and the pharmacist distributing it must bear all this in mind. The consumer good offers ethical nuances linked to a pastoral attitude.

In her dialogues with suffering, a woman wrote, "Every patient has his own secret which can be disclosed by him alone: the theme interpreted by a flute is different from the one played on a violin."[8] We know that every patient undergoes suffering in his own way, physically and psychologically. At this point, in considering the biological underpinnings of the individuality and irreducibility which each man bears in his uniqueness, we may assert not only that the patient is linked to physical, mental, and social reality, but also that there exists a spiritual "beyond" for him which the man of science, along with the physician or therapist, cannot ignore.

The mission of the Church, which, through priests and laity, wishes to help the ill to live out their state, is, then, evident. Health has sometimes been said to consist of bearing one's sickness well. Spiritual authors, especially Pascal, continually speak of the good use of illnesses. The Church invites us to give meaning to the test, without dismissing ethics, morality, and spirituality. For this reason it is maintained that the Church, in being missionary, must be able to provide "a word of comfort which will be the sign of God's tenderness" in the world of health.

Obviously, ethics warns against those medicines whose use has no therapeutic finality and which do not respect the rights of the human person. We may cite the contraceptives which impede the nesting of the embryo as well as the so-called "day-after" or month-after pills, or clearly abortifacient products like the spiral. Some pharmacists feel that such pills, from the moment they act against life, should not be regarded as medicines. The same may be said of the "lithium cocktails," which submerge the patient in unconsciousness and accelerate the process of death. These mixtures of drugs are sometimes used even when the patient is not yet experiencing severe pain; in this way a sick person who became bothersome could easily be gotten rid of, without the slightest respect for his freedom.

c) *Psychosomatic reality.* Given the body-soul relationship existing in man, the patient must be offered the possibility of managing his own affairs, thereby enabling him to improve his condition, precisely because he "wants to recover."[9] Everyone is aware of the definition of health furnished by the W.H.O.: It is a state of complete well-being, not just physical, but mental and social as well. Consequently, health is not only the absence of disease; in this regard, Cor Unum made a very relevant observation:

> Each one of us, with his biological, psychological, and spiritual components, lives in relation to his physical and social environment, an environment which acts upon him and upon which he acts: if the result is a harmonious balance, we are "in condition"; if, however, one of our personal components is decifient or damaged and our remaining strengh is not able to restore the balance, we then suffer from some disease. To reduce illness to mere physical phenomena is to ignore man in the totality of his being; it amounts to wanting to treat only the sickness and not the patient.[10]

It follows that well-being is behavior deriving from the action of the whole society.

A little book by an Austrian physician, Dr. V.E. Frankl, has surely not been read widely enough; it speaks of the unconscious God.[11] The author states therein that too much has been said about depth psychology and too little about "height psychology." Indeed, if man were aware of everything mixed together in his subconscious, he would also be familiar with the need to seek out an ideal and an absolute. It is precisely this absolute which enables the patient to fill what is today called the existential void forming the substrate of most neuroses and nervous breakdowns. Theology gives this absolute a proper name: God! We must certainly avoid confusing psy-

chotherapy and religion. The main goal of religion is the health of the soul, whereas medicine tends to heal the physical and the psychological: the intention is not the same. But it may happen that both contribute their effects in relation to a single body-soul totality constituting psychosomatic reality.

Pope John Paul II in his addresses often dwells upon the importance of the composite of which man is formed. The Sovereign Pontiff insists on agreement between the corporal and the spiritual, for "in the compound, psychosomatic being that is man, perfection cannot consist of mutual opposition between the body and the spirit, but in a profound reciprocal harmony and the affirmation of the supremacy of the spirit." [12]

In the world of health, the synthesis of which man is made is increasingly taken into account We can understand, then, how the presence of the priest, who manifests the hierarchy of values, may play a role of prime importance.

2) The pharmaceutical and the person

The physician and the pharmacist cannot limit themselves to considering medication only in its pharmacodynamic action. Nowadays all the experts point out the psychological factor in the process of healing, for the patient is a person and, therefore, according to Boethius' famous definition, an individual substance of a rational nature. Dr. Schweitzer insisted that every patient is his own physician. Ethics thus invites us to take the individual to whom medication is destined into consideration. The patient reacts not only for a rational motive, but also in terms of motivations rooted in affectivity which often reflect an irrational preoccupation. An expert wrote, "Doctors are truly convinced when they unreservedly affirm that patients' 'morale' means a great deal to them. It is, however, difficult to convince them that this concern, to be truly useful must not be a mere sentiment, but medical and pondered, and must not be externalized just as a simple act of charity, kindness, and compassion." [13] Medicine is, then, not only a science, but an art, and medical decision-making cannot rest content with arguments grounded exclusively on the scientific while setting aside the personhood of the ill.

Professor J. Hamburger's genuinely insightful conclusions on the success achieved by the first anxiety-relieving drugs have been received with great interest. These tranquillizers responded not only to the physician's desire to mitigate the patient's moral suffering: such remedies were indeed sought out immediately by those who, though not ill, were "wearied by the din of worry, discontent, feelings of loneliness, and disappointments in everyday life. These people wish to forget and reach a truce along the pathway of their agitation." [14] With such assertions, J. Hamburger opens a set of prospects before the moralist; he in fact deems dissatisfaction to be a characteristic of man, along with the desire for food and the sexual appetite. And he adds, "Even if we eliminate hunger, privation, and illness, aggressiveness and anguish will always remain in man; they are among the biological phenomena engraved upon man's nature, and it would be a dangerous illusion to regard them as provoked completely by external phenomena." [15]

In this way, man's profound concern to provide a meaning for his existence revives. Ethology enlightens the moralist here. Robert Andrey speaks of the "triad of innate needs" assuring balanced behavior in man, who must know his *identity* to avoid *anonymity*, needs *stimulation* to oppose *boredom*, and is eager for certainty to overcome *anguish*.

a) *Identity*. Man likes to feel irreplaceable. When he is ill, he realizes that he cannot be identified with another patient because he is undergoing his illness in a different way. Basic biology speaks of individual predispositions, and therapy today defends itself against gregarious, standardized medicine which forgets the originality and unique value of every human being. Illness is not defined only under the aspect of an anatomical lesion, but also through the chemical and molecular changes provoked by it. All of this clarifies precisely why a conscientious physician changes his attitude in the face of the "identity" of each patient. The medical

"minister" thereby becomes truly fruitful.

It is in this perspective that nowadays an attempt is being made to "reconstruct" the family doctor as a participant in the personal destiny of a patient. The generalist must offer security to the sufferer, seeking to restore order in the turmoil provoked by the phenomenon of illness within the patient's lost wholeness. In confronting the sick person's despair, the pharmaceutical is not sufficient: the patient feels disoriented because he no longer recognizes himself. He led a dynamic life and now cannot control his reactions any more. All of his behavior feels these effects. Thomas Aquinas well knew that a certain equilibrium is necessary to put the good into practice: "It is clear that when the body is indisposed, man may find obstacles in every virtuous action" (*ST* I/II 4, 4). And he continues, "Bodily illness is sometimes an obstacle to spiritual health; such illness may, in fact, impede the exercise of the virtues" (*SCG*, IV, 73). Not only the shepherd of souls, but also the physician can profit from these old, but always up-to-date texts; the individual's psychology is altered as a result of some pathological dysfunctions.

b) *Stimulation*. The patient who feels his strength abandoning him and undergoes what has been termed the "body's betrayal" must always have a spur (the Latin *stimulus*) to be motivated in the effort to make his life advance in spite of everything. Even while prescribing necessary medicines, the physician should make sure that the patient does not get shipwrecked though still alive. At present the so-called "path of listening" is stressed; this situation must not lead us to forget what stimulation means. Man has a good many registers enabling him to propagate the sonata of his life. And the priest may lead a believing patient to stimulation effected by the exchange of merits in the Mystical Body. We are familiar with St. Paul's text: "I complete what is lacking in the sufferings of Christ in my own flesh for the sake of His body, which is the Church" (*Col* 1:24).

It is the task of the shepherd of souls to be truly insightful in aiding the patient to offer up his illness. A heart patient wrote that at times he was no longer capable of offering his suffering: "Someone would have had to do so for me, at my side; it would have helped me at that point to have someone praying nearby, for I couldn't any longer ..." [16] It is wonderful to help a patient to orient and live out his trial. A Christian in the world of health can carry out this mission, which goes far beyond mere prescription of medicines. Being a Good Samaritan also means accompanying the patient with a dynamic which will aid him in surmounting his illness.

c) *Security*. Good sense leads us to see that sickness is a phenomenon which "makes us insecure." It is evident that the pastoral minister can effectively support medical action by presenting to the patient the formidable reserve of biblical texts depicting God as He Who gives confidence and security. The Psalms, above all speak of God as a rock, fortress, shield, and citadel (Ps 18:2-3); as a refuge and tent (Ps 27:5); and as a shelter and fort (Ps 46:2). The psalmist even calls God "my security" (71:5). The believing patient finds a stimulus therein, precisely at the moment when the usual aids he was familiar with in good health disappear. And it is Christ Who tells us that the God who takes care even of the little sparrows shows much more concern towards us who are His children (Lk 12:6-7).

We thus come back to the notion of an absolute which alone can give stability to man's true security, whether he is sick or well, and which alone can quench his thirst for complete happiness. The desire for security is not what marks the patient's state, even if a patient is more sensitive to it. Every man lives in the expectation of unlimited joy which obviously appears impossible here on earth. Pope John Paul II admirably expressed this wound of man in his address to the university community of Louvain: "What is man? One must respond to this question, take up the challenge of materialism, of religious indifference, of corrosive skepticism. Yes, what is man, continually torn between the boundlessness of his desires and the limitation of his pleasure, between the obstinate search for truth and the crumbs of knowledge which are proposed to him?" [17] The

patient, removed from the absorbing activities of his accustomed life, better realizes this tension and division, for he has more time to experience and reflect upon it.

From what has been said it follows that the pharmaceutical is not everything for the patient after his "primary needs" have been utterly shaken. The last Council also spoke of the inner division affecting suffering man: "The disequilibria agitating the world at present are indeed linked to a deeper imbalance which is rooted in the very heart of man. In effect, it is within man that various tendencies clash. As a creature, he experiences numerous personal limits, but also feels illimited in his desires and called to a higher life. Solicited in so many ways, he is continually forced to choose and renounce" (*GS* 10, 1).

We can thus understand how the Christian physician and pharmacist must find the time to listen to the patient and not appear before him as people in a rush. Professor J. Bernard insists on the importance of hearing out the patient, conversing with him, and assisting him through complete openness. He writes, "A good doctor must not be hasty; he should devote all the time needed to listening to his patient's complaints. In this fashion, he will frequently come to discover the reasons for an imaginary illness (a flight from responsibility, the remote consequence of statements by a previously contracted physician, the fear prompted by the evolution of a relative's real illness) and will often obtain the cure." [19] Jean Bernard considers that the commonly imperfect organization of medicine today does not allow the doctor enough time to deal with every patient in a complete and thoroughgoing manner. It is too often forgotten that with attentive inquiries and a long conversation he can bring about improvement or healing of functional disorders and painful indispositions. The author asserts that one must naturally not forget to prescribe certain remedies, but these do not replace treatment which respects man in his unity and is desirous of aiding him effectively.

We can thus affirm that the remedy, including the best one, is truly not a panacea. Nowadays some physicians react against a possible abuse of psychotropic drugs; for them, indeed, these chemical substances can never totally replace dialogue with the anguished patient. An expert writes, "Everyday experience and simple good sense show us that medicines can act only as auxiliaries to broader treatment, taking the following evidence into account: it is the whole person who is ill, the person with his history, his environment, his emotional ties, and not just his brain. It would be absurd to deprive ourselves of psychotropic drugs, but to limit all therapeutic action to prescribing them is no less absurd. These pharmaceuticals cannot, in fact, claim to cure disorders, but only aspire to correct them." [19]

Today the patient's responsibility in the process of healing is stressed. There is fear of a medicine which could supplant the patient's own will or drugs serving as a kind of panacea and automatically bringing about a cure. The physician, the pharmacist, and the priest must also help the sick person to open himself and tell his story. A patient may be finding it difficult to describe his inner state. Specialists point out the difference existing between "hearing" and "listening." To perceive with one's hearing is surely not sufficient. Father L. Beirnaert, S. J. has analyzed the elements of dialogue quite well: "Experience shows that all of us have rarely encountered someone who has really listened to us in depth. How many things which were never said or which we never dared to say precisely because our interlocutor was in a hurry to get in a premature word, giving us the impression that he had no wish to listen to us further. But listening is not all; it is necessary to understand as well, that is, to identify through the words of our interlocutor what is truly of interest, what is rightfully important, what he in reality does not succeed in manifesting because it is charged with too many emotions." [20]

In 1982, at the International Congress of Catholic Physicians, John Paul II stated that to "humanize" the doctor's work it would be necessary to proclaim the dignity of the human person, taking his corporeity, his spirit, and his culture into consideration. The Holy Father added, "It is your duty to dig ever more deeply into the biological

mechanisms regulating life, in such a way as to intervene in them precisely by virtue of the power which the Lord has wished to give man over all things. But in doing so, it is also your duty to remain constantly at the service of the human person and of every demand issuing from his dignity. Concretely, each of you must not limit himself to being the physician of an organ or an apparatus, but should feel responsible for the whole person and even for the interpersonal relations which contribute to improving his health." [21]

The following year, the Pope again had recourse to this anthropological perspective to indicate what should guide the doctor in medical action: "The biological nature of each man is intangible in the sense that it is constitutive of the personal identity of the individual throughout the trajectory of his history. Each human person, absolutely unique in his personality, is constituted not only by his spirit, but at the same time by his body. Accordingly, in the body and through the body, we arrive at the person himself, in his concrete reality." [22] John Paul II was addressing the Delegates to the World Medical Association and inviting them, in accordance with the words of the last Council, to protect the identity of man, "corpore et anima unus" (*GS* 14, 1).

When the Pope insists on the dignity of the human person as represented by every patient, he is addressing not only doctors, but also the philosophers who are concerned with ethics. Claude Bruaire observes that every "individual body" is inhabited by the individual being of someone, of a person, therefore, who is constituted "beyond the elements of matter or cells of organs, by quite different realities." The destiny of this individual being "cannot be stated only through the elements constituting his organism." [23]

Consequently, the patient's fundamental questions go beyond the effectiveness of a drug or behavioral psychology. A priest wrote that, in the hospital, a place of suffering and also of death, the priest represents a paradox, for he is a witness to the Risen Christ, living today, who leads others to a new life. [24] One can only turn one's thoughts to the Lenten liturgy, which asks God, through the efficacy of the sacraments, to come to the aid of the soul and the body, "so that we may finally possess the joy of being wholly saved." [25]

The Church has always claimed its place in the environments where body and spirit suffer, and this mission of hers continues to blaze new trails today. The Pontifical Council Cor Unum some time ago stated this wish: "There is reason to hope that exchanges will enable the Church to be consulted and understood in the drafting of all legislation bearing reference to life, health, and the fundamental rights of man and the family" (*op. cit.*, p. 9).

It must, in effect, be continually repeated that the Church, in her age-old tradition, always has a word to say on everything affecting the ill.

PROFESSOR
JEAN PIERRE SCHALLER
Ecclesiastical Counselor
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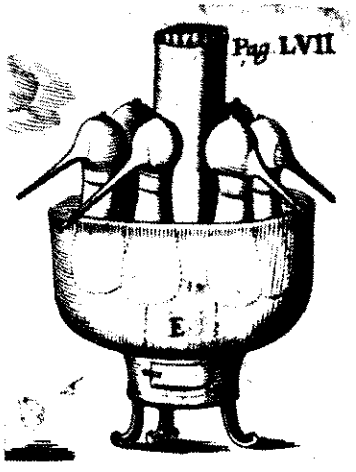

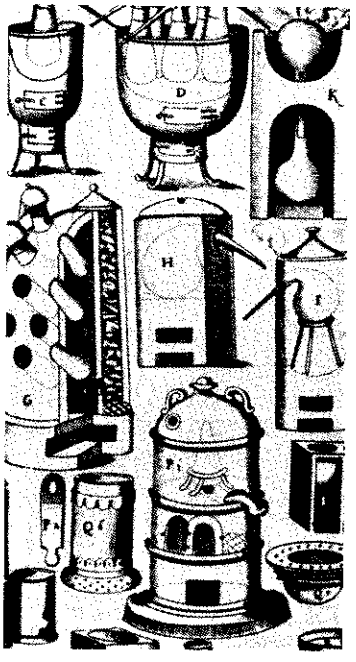

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[6] The text is found in *A New Battle for Health,* by M. P. Défossez *et Medicus Mundi* (Paris: Editions Cana, 1980), p 166.

[7] Msgr. L. Kucher presented the chaplaincy as a Church ministry in "Hospital Chaplaincy" (July, 1985), p. 25. As regards the handicapped, consult our book *Moral et affectivité* (Mulhouse, Salvator, 1962).

[8] The text is found in *Dialogues avec la souffrance* (Paris: Spes, 1941), p. 27

[9] Norman Cousins' *La volonté de guerir* (Paris: Seuil, 1980) may be consulted

[10] Cor Unum Pontifical Council, *Réflexions à propos d'une pastorale de la santé* (Health Workshop, February, 1983), pp. 2-3

[11] Dr. Viktor E. Frankl, *Le Dieu inconscient* (Paris: Centurion, 1975). The first edition, *Der unbewusste Gott,* appeared in 1948.

[12] John Paul II, Audience of December 9, 1981, in *Documentation Catholique* (February 3, 1982), pp. 41-42. Starting from what has been stated above, the Pope presents testimony to explain our future resurrected state: "This new spiritualization will thus be the fruit of grace, that is, of the fact that God communicates himself in his very divinity, not just to the soul, but to man's whole psychosomatic subjectivity." See our *Morale et psychosomatique* (Paris: Beauchesne, 1983)

[13] Dr. Norbert Bensaid, *La Consultation* (Paris: Mercure de France, 1974), p. 34.

[14] Professor Jean Hamburger, *La puissance de la fragilité* (Paris: Flammarion, 1972), p. 140.

[15] *Ibid.* See our article "L'aveu au médecin," in *Vie médicale au Canada français,* v. IX (August, 1980)

[16] This remark is found in *Aumôneriei des Hopitaux*, no. 106 (April, 1985), p 8.

[17] This text is found in *Documentation Catholique* (July 7, 1985), p. 700 The Pope was referring to the link between worship and culture.

[18] Jean Bernard, *Grandeur et tentations de la médecine* (Paris: Buchet-Chastel, 1973), p. 173. As regards the need for dialogue, see our *Direction des âmes et medecine moderne* (Mulhouse, Salvator, 1959) and *Direction spirituelle en temps modernes* (Paris: Beachesne, 1978).

[19] Dr. Norbert Bensaid, *op. cit*, p. 278. We ourselves have stressed this problem in "Psychopharmacologie et morale," in *Vie médicale au Canada française,* v 4 (January, 1975)

[20] "Aide et Dialogue," in *Etudes* (July, 1961), p. 179. See also our article "Le ministère du pharmacien," in *Cahiers Albert le Grand,* no 54 (Paris, 1983), pp. 31-39.

[21] The Pope was speaking about the physician at the service of life. Cf. *Documentation Catholique* (November 21, 1982), p. 1031.

[22] The Pope was dealing with the doctor in relation to human rights. Cf. *Documentation Catholique* (December 4, 1983), p. 1068.

[23] Claude Bruaire, *Une éthique pour la médecine* (Paris: Fayard, 1978), p. 34. The author's remarks on abortion in this work do not coincide with the teaching of the Church.

[24] See Philippe Deschamps' article in *Aumônerie des Hôpitaux* (January, 1985), p. 22.

[25] This formula is used in the Mass of the first Monday in Lent. I referred to it in "Tout entier sauvé. Psychosomatique et spiritualité," *Sources* (Fribourg, September, 1978), pp 205-215

G.B. MARINI BETTOLO

Traditional Drugs

The adoption of medicaments which, as we have seen, are the result of scientific research, creativity, technological innovation and industrial production depends on health organization in the various countries and also on modern medical culture

In many countries at present, and even more in some poorer areas, the economic factor, that is, poverty, does not allow many populations the possibility of using modern drugs.

In effect, for this purpose a medical doctor is necessary. He will make a diagnosis and then prescribe a treatment with one or more drugs.

According to the WHO survey, about half the population of the world — and these figures are optimistic because other statistics report one third — has the possibility of access to modern medicine and thus to drugs. The other half (or two thirds) is not in a position to maintain health except through traditional practices differing from region to region.

It is quite difficult to establish exactly the countries where modern medicine is adopted and where traditional medicine is still used. Generally, this happens in the tropical and subtropical areas and coincides with the level of per-capita earnings of the inhabitants. The boundaries are not clear because in poor countries modern medicine reaches the towns but very seldom villages and rural areas.

Sometimes there is an interpenetration of the two systems: traditional healers in fact borrow some medicaments from modern pharmacopoeias, and even if they use traditional drugs, when the patient does not respond, they send him to the nearest hospital.

Missionaries are well aware of these aspects of health care when operating in villages, far from major centers, sometimes isolated by poor communications and often by endemic states of guerilla warfare.

In developing countries, there is a striking difference between the inhabitants of the towns and those living in the rural areas owing to their different living standards. Even in towns the economic capacity of millions of people does not cover medical care and thus pharmaceutical assistance, but only that of cheaper traditional medicine.

Because of the dramatic situation the WHO Assembly at the Alma Ata meeting in 1978 established that primary health care should be given to everyone in the world by the year 2000.

According to careful evaluation, this goal could be reached only if the practices of traditional medicine were also used.

As you know, traditional medicine uses traditional medicaments. These, based on custom, are often neither *active* nor *safe*, and their use presents a number of dangers.

Regarding this situation, the WHO has given some guidelines and suggestions to the Governments in order to overcome these difficulties.

Before discussing this point, I think it will be of interest to summarize the present state in the world of traditional medicine, under the aspect of traditional drugs.

Traditional drugs may be of vegetable (herbs) or animal or mineral origin. The drug can be used as a single component or in concoctions, preparations, or mixtures of several products.

Drugs are generally sold in the markets (parts of plants, roots, scraped bark, leaves, etc.) or pieces of animals (horn powder, snakes, etc.), or as a mineral (powders, crystals, etc.)

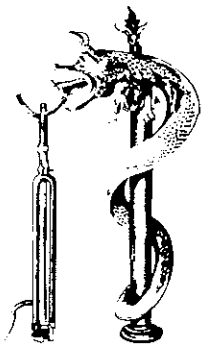
Sometimes the plant may be available in the jungle or in the vegetable garden and is collected when necessary for its direct use or for the preparation of a mixture.

In some countries there are more elaborate systems — the material is mixed with other ingredients and prepared according to century-old recipes. This system, for example, was recently introduced into China industrially.

On the basis of present information, we may classify traditional drugs into three main systems:

1. Traditional drugs described in ancient pharmacopoeias like the Ayur-Veda (2500 B.C.) and Pen'tsao (1000 B.C.), still used on the Indian subcontinent and in China.

2. Traditional drugs used for centuries through oral tradition. This happens mainly in Africa and in Latin America. Sometimes the oral tradition has been crystallized into specific reports, such as



Bernardo Sahagun's *General History of New Spain* or, more recently, by ethnographers in various parts of the world.

3. Drugs from healers' personal knowledge, as happens in Africa and South America.

Some figures may better illustrate the importance of the individual systems.

China has about one billion inhabitants, and the Indian subcontinent, about 750 million inhabitants; that means that in Asia there are roughly two billion people using traditional medicine, if we include Southeast Asia.

In China, beyond the well-known *barefoot doctors* of the rural communities, there are about one million traditional doctors officially registered in the national health service. The rules and the drugs used go back to pharmacopoeias of the first millenium before Christ. Even now books describe hundreds of plants and preparations used for different diseases. These books and recipes form the basis of the modern traditional drugs in the Chinese area, including the diaspora, which covers an area far greater than the People's Republic of China.

To make available drugs, and especially composite drugs — according to the traditional recipes — at present the Chinese drug industry cultivates huge extensions of land with medicinal plants mainly in the Szechuan province.

These plants, duly stabilized and dried, flow through official channels to the traditional pharmacies or to the village communities. Moreover, Chinese traditional medicine has accepted modern technologies; thus raw materials — plant, mineral, and animal parts — according to traditional recipes are elaborated in the form of pills, tablets, granules, drops, etc., more easily marketed and sold, even in foreign countries, to the Chinese living in the Pacific area.

They are usually marketed with instructions in Chinese and even in English. The Chinese government exercises strict control over quality on both the chemical and the pharmacological properties of its own industrial production of traditional drugs.

Even at the scientific level, there is an effort to confirm by methods of modern pharmacology the activity and the safety of the drug as either plant material or a preparation.

In Japan, one of the most industrialized and developed countries in the world, where scientific research has given us some of the most important modern antibiotics, with a leading pharmaceutical industry, two traditional systems operate up to now in many areas.

The first system is the *Kampo*, based on Chinese traditional pharmacology. The production and sale of traditional drugs in this system is currently evaluated at 100 million dollars, although relying mostly on importation. The other system, *Rampo*, derived from 16th century Dutch prescriptions, is mainly based on herbal drugs.

Even in Europe and the United States, up to the last century (before the development of basic sciences: pharmacology and chemistry — both pharmaceutical and analytical), the drugs were mainly plant material, i.e., *Simplicia*, if in pure form, and *Compositа*, if mixtures according to recipes. In recent times, the inorganic products of mineral origin changed their name from *Spagyrica* to *Chemica*.

Even now in many parts of Europe — in such countries as Germany and the U.K., traditional drugs are found by the herbalists and are extremely widespread. In the U.K. an herbal pharmacopoeia has also been published in order to establish the quality control of these traditional drugs.

The Indian subcontinent (India, Pakistan, Bangladesh, Nepal, Bhutan, Burma, and Sri-Lanka) relies on three main systems of traditional medicine.

The most important is the *Ayurvedic system*, regulated by the prescription of drugs appearing in the Ayurveda books. Ayurvedic medicine is very peculiar because of the principles on which it is based.

Drugs are described in the Ayur Veda in great detail with abundant information about their properties. Although the recipes are more then 3000 years old, they are widely prescribed even now. In India, about *750,000* Ayurvedic doctors are duly registered. There are also universities for the teaching of Ayurvedic medicine and a great number of Ayurvedic hospitals.

The same happens with the Unani system — originating

from Arabic and Greek Medicine — which used as drugs mineral salts and herbs. The Unani system is also well established, and there is now a congress in New Delhi dealing with Unani Medicine.

Arabic traditional medicine has a broad historical background as well. We recall that in the 7th and 8th centuries the basic principles of drug elaboration and even new drugs and preparations from the Middle East, due to the studies of Mesué, Avicenna, and others, were transferred to Western Europe through the Maghreb and Spain.

Even now traditional Arabic medicaments are widespread in many Arabic Islamic areas all over the world.

Apart from the above-mentioned main systems, there are also minor established traditions with historical importance, like those of Tibet, Nepal, etc.

A particular aspect is traditional medicine in Central America, mainly Mexico and Guatemala. As mentioned above, part of the oral tradition was transferred by the action of various learned friars following the Conquerors, like Bernardino de Sahagún, or indigenous such as Fray Martín de la Cruz, into important manuscripts like the *Historia General de Nueva España*, better known as the Florentine Codex and the Codex Badianus at the Vatican Library.

A more general account of the Mexican Plants was given by Francisco Hernández in the late 16th century. His report was published in the modified text of an Italian doctor, Nardo Recchi, by the Lincei in 1628 with the description of a great number of Mexican medicinal plants.

Guatemala has the Chillean Ballan, a sacred book where preparations and special beverages are described.

Even now both Mexico and Central America make use of drugs linked to their cultural tradition.

The Mexican Institute of Traditional Medicine is now elaborating a complete computer-based registration of the principles used for traditional drugs in this country.

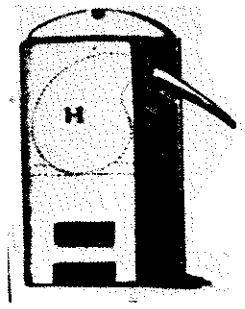
The oral tradition system characterizes Africa and South America. Plants, properties, recipes, and uses are transmitted orally by the healers to their pupils. Generally, the plants used for these purposes are known by botanists and also by pharmacologists, many as ordeal poisons — for example, *Erythrophleum* and *Strychnos*. Sometimes they were studied for their chemical composition, but generally healers keep their information quite secret and will not easily share their knowledge with other people and even less with foreigners.

Therefore, the ethnopharmacological data of many traditional drugs, largely used in Africa and South America, like the traditional drugs many claimed for birth control, are not readily available.

The choice of the plant or other materials as drugs reflects a centuries old tradition and is certainly based on the experience of generations. This does not mean the drug *is active and safe*. Among the real dangers of traditional medicaments are the plants with high toxicity. In Ethiopia, Cossus has been widely used for centuries as an antihelminthic: its toxicity is very high and if not exactly dosed causes the death of children. The Ethiopian government recently banished the use of this plant, suggesting others for the same purpose (Artemisia sp.).

On the other hand, there are plants without pharmacological activity which may be considered pure placebos but have drawbacks because they are ineffective if used for treatment of serious disease.

The third system is the single healer's own pharmacopoeia. Here secrecy is absolute. The healer personally prepares and gives the drug. The criteria for the use of a plant depend on traditional and personal experience, but



also on some properties, not necessarily connected with the pharmacological ones, like the shape of the leaves. For example, heart-shaped plants may be used to cure heart troubles, and so on!

Even in Chinese traditional medicine the ging-seng root is appreciated for its content of active principles, the panaxosides.

In some cases, the purchase of a drug from a healer may be even more expensive than an imported modern medicament. But the lack of medical doctors and other health infrastructures compels many people to use traditional practices. Moreover, many in Africa and South America know the plants used for the treatment of specific illnesses and provide themselves with them in the jungle.

One of the important aspects of traditional drugs is the psychological effect of the presence and action of the healer on the patient. The healer — sometimes also a shaman — uses not only the traditional drug but a number of practices, like dance and music, in the presence of the members of the family. It is claimed that these practices have greatly contributed to a better knowledge of group psychoterapy in the industrialized countries.

Healers, although representing tradition, live in a modern world and are well aware of modern medicaments and their effects. It is thus possible to find, as evidenced in South America, that the healer uses a few tablets of the most common and simple modern drug in addition to herbs — e.g., aspirin — mixing in drug use tradition with present scientific experience.

The traditional drugs

We may now ask what the traditional drugs are. Generally they are part of plants or animals and even inorganic products (minerals, ashes, etc.) and their mixtures, extracts, and concoctions.

Many plants used in the past have also entered into modern pharmacopoeias. I should like to cite *Papaver* (Opium) *China Digitalis, Datura, Erithroxylon coca,* etc.

In recent years it has been demonstrated that *Rauwolfia serpentina* bark, cited in the Ayur Veda, possesses tranquilizing effects and lowers blood pressure. The use of Rauwolfia is also found in Nigerian traditional preparations.

From ging-seng roots many active principles have been isolated. Moreover, other plants have recently been studied from a pharmacological and chemical point of view, like *Harungana* sp. *Psorospermum, Hypoxis, Maytenus*, and others used in traditional practice in Africa.

Parts of animals are widely used, especially in Chinese traditional medicine, such as toad skin, snakes (*Bothrops* and *Bungarus*), *horn powder*, etc.

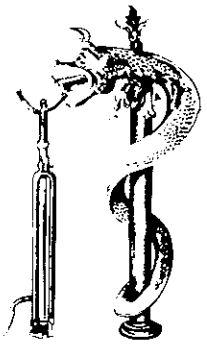
Inorganic chemicals such as clay, salts, stones, and even pearls are used.

In many cases, when ethnopharmacological data are available, chemistry has established the nature of the active principles of these medicaments. Pharmacological examination has demonstrated the activity of a limited number of these drugs. This activity is sometimes toxic. But for the majority of the traditional drugs so far examined it has been hard to demonstrate any particular property.

The work on the chemical composition of plants began in the last century, when *quinine, strychnine,* and *morphine were isolated,* and even now gives important results with the use of modern sophisticated analytical methodology. This enables us to get a picture of the main substances which constitute the traditional drugs: so far we may consider that two-thirds of the plants used as traditional drugs are known and studied. We need only study the other third in order to have the full picture of the chemicals used in traditional medicine. A number of plants, generally of minor interest, may, however, provoke some surprise. In parallel fashion, the traditional drugs are submitted to pharmacological tests to establish the properties of these substances.

This work has made available to modern medicine medicaments of great importance, like quinine, reserpine, morphine, ouabain, digoxin, ephedrin, emetin, and many others. I should like to recall that toad skin also contains alkaloids like bufotenine acting on CNS, and *Bothrops*, an anticoagulant enzyme.

The pharmacist, from Giovanni Grevenbroch's
The Venetians' Dress *(1781-1807)*



One of the most recent discoveries in traditional drugs is the *Quig-hua-shu,* an Artemisia sp. which proves to be active against the malaria plasmodium strain resistant to chloroquine.

Thus the experience of centuries has selected from thousands of plants several hundred which are used in traditional medicine in different parts of the world. Among these, some are very effective and important. But a great number of them, according to the pharmacological testing systems, do not possess any appreciable effect.

Some medical doctors, in developing countries, such as India, completely disagree with the use of traditional drugs and traditional medicine. Their point of view is scientifically correct: "Even if a traditional drug is active and safe, how can we trust its use when the diagnosis of the illness is most probably wrong?"

This is the position of modern medicine, which in India faces the vast organization of traditional medicine.

In Africa, where tradition is oral, some governments officially recognize traditional healers and traditional drugs. This happens in Zaire and Ethiopia and other countries, but not, for example, in Kenya. In West Africa and, particularly, in Nigeria, Ghana, Sierra Leone, and Liberia traditional drugs are widely used.

The countries which admit traditional medicine devote a ministry of health section to this field.

The official acceptance of traditional medicine and traditional drugs means that governments are not in a position to provide modern medicine, but also that it is very difficult to eradicate from people's minds and habits some practices constituting their roots. I remember a distinguished African medical doctor complaining that his mother, when ill, preferred to be cured according to traditional medicine.

In its effort towards health for all by the year 2000 WHO has accepted traditional medicine and traditional medicaments as well while seeking to improve the knowledge of the healers and to screen drugs used in traditional medicine. This is necessary in order to make a selection and recommend to the healers only the effective and safe ones.

This screening is taking place in every country with the help and scientific support of WHO and also through the more specialized work of the WHO Collaborating Centers for Traditional Medicine. The first Center was estabilished in Rome in April, 1979 in order to cooperate with the African countries.

Since then many other Centers have established in various countries. Their role may be 1) training of personnel in the fields of pharmacology and phytochemistry; 2) establishing a databank of traditional drugs and providing information on request; 3) training of healers in the principles of hygiene and pharmacology.

For example, the Rome center works mainly on training, and the Chicago center, mainly on documentation, whereas the centers established in Africa and India and China also deal with the problems of local training and information to healers. A great success in this field was the formation of traditional birth attendants.

The governments act in support of the WHO, improving the quality of traditional drugs considerably in recent years, although it is a very difficult task.

Ethiopia, as an example, allows the marketing of traditional drugs only in sealed bags containing material of good standard quality. In Ethiopia, healers in the villages are contacted by health service officers and collaborate in the prevention of endemic diseases through vaccination campaigns. By this channel it is sometimes possible to educate healers. Ethiopia was also able to banish the use of some dangerous drugs of plant origin through collaboration with traditional healers.

From an ethical point of view, we may consider that traditional drugs are not the best solution, but because of the magnitude of the problem — represented by the huge number of patients and their habits — it is not possible to replace them in a short time with modern drugs, even for organizational and economic reasons.

WHO suggests that the drugs should be effective, safe, naturally pure, and in a good state of conservation.

I have personally seen in

some markets in South America traditional drugs constituted by plant powders or dried plant parts, such as leaves or bark, completely damaged by insects and molds. It will require effort to educate people to consider this material not as a real drug.

The second point will be to induce healers to avoid the use of very dangerous plant material, like *Strichnos, Erythrophleum Akocanthera, Physostygma,* and many others.

I have so far focused upon the problem of traditional drugs, avoiding any judgement on the practice of traditional medicine.

We know that these drugs are not sufficient to prevent and treat many diseases, especially in the tropics. How can we ethically approve this imperfect solution, which affects half of humankind?

On the other hand, traditional medicine and drugs may be useful for a great number of psychosomatic illnesses which constitute a high percentage of the diseases, if all toxic material is definitely abolished.

I believe that further research, mainly by scientists in developing countries, may contribute to a better knowledge of traditional drugs used at the present time in the various regions of the world.

Traditional healers should be informed and later instructed on hygiene practices and become a channel for preventive medicine and primary health care, making available to village communities those few medicaments — vaccines, above all — which have changed health conditions for millions of people around the world.

Traditional drugs — even when safe and effective — always represent the past and not the future.

A moral obligation for all of us, and this is an *ethical aspect,* is to work and make every effort to improve health conditions gradually in developing countries.

I have raised the problem of traditional drugs to make clear the fact that at present half of mankind, mainly as a result of poverty, cannot benefit from modern medicine and the advantages of modern drugs. I believe that, in ethical terms, we should do everything possible to reduce this gap, which involves such an unrenounceable human good — health.

We should not permit such discrimination. I think that this is really a great ethical problem that we cannot disregard or forget.

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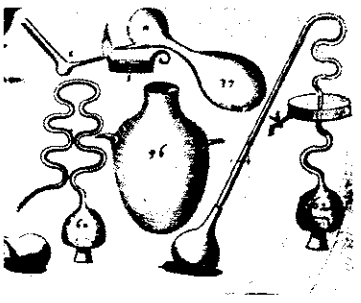


E. LAURIDSEN

Action Program on Essential Drugs of the World Health Organization

For the mother in Bangladesh, the field worker in Sudan, or the sharecropper in Mexico, the availability of pharmaceuticals poses a practical rather than a moral dilemma. When your child is acutely ill, what matters is whether the right medicine is available and whether you have the money to buy it or perhaps a relative to borrow from. For tens, perhaps hundreds of millions of people, such agonizing questions are part of daily life. The answer is all too frequently negative. The right drug is simply not available or it can be bought but costs too much.

This situation is hard to reconcile with a world in which one hundred thousand million dollars worth of drugs are sold each year; where tens of thousands of different brand name drugs exist; and where over-consumption and misuse of drugs is the problem in some countries rather than lack of access.

Dr Mahler has described the complex web of commercial, social, economic, managerial, and ethical difficulties which still prevent so many people in need from getting the 40 to 50 drugs essential for treatment of the most common diseases in developing countries.

It is, I believe, becoming crystal clear that this situation can only be reversed by cooperation at every level and every link in the chain. I think, by virtue of its charter and experience, that there is no organization better suited than the World Health Organization to argue for the moral imperative of cooperation to ensure the availability of essential drugs of good quality and at a price that people can afford. Perhaps I should mention here that by essential drugs WHO means those 250 drugs and vaccines that satisfy the health care needs of the majority of the population and are of significant therapeutic value, of acceptable safety, and of reasonable price.

Cooperation was to be the linchpin of the essential drugs concept launched in 1977, yet in its first five years WHO instead tasted the bitter fruits of confrontation:

— the pharmaceutical industry initially resisted the concept, fearing that it would result in reduced investment in research and development, thereby depriving the world of the benefits of ongoing research;

— many physicians also resisted the concept, believing that the traditional clinical freedom to prescribe the drug of their choice was threatened;

— finally, consumer activists argued forcefully that WHO should tackle the problem by the immediate adoption of stringent international codes of marketing practice.

It was thus against a background of polarized views and often heated rhetoric that WHO strove to find workable and objective solutions to the often chaotic situation of drug supplies in developing countries. It seemed for many years that no real progress was being made. I am glad to say that this is no longer the case and that a climate of change and reconciliation has developed to replace the unproductive confrontation of earlier years.

In 1981 WHO and UNICEF joined forces and, together with enlightened bilateral agencies, were instrumental in bringing down the international price levels of essential generic medicines. Even more encouragingly, the pharmaceutical industry, albeit with some reservations, finally accepted the concept of essential drugs. An increasing number of companies and industrial societies now actively support training and development projects in non-industrialized countries. There also appears to be a heightened awareness of the need for and greater adherence to strict ethical principles and conduct in the marketing of pharmaceutical products

The most important factor of all has been the political will shown by many developing countries and their determination to rationalize national pharmaceutical supply systems along the lines collectively decided in the world health assemblies over the last ten years. More than eighty countries now have lists of essential drugs for their public sector and about 30 countries, many of them large, are currently implementing policies and programs to provide their rural populations and urban poor with continuous access to the most needed medicines.

Most countries must buy their drugs with scarce foreign exchange. To assist them, UNICEF and WHO provide price information. Many countries now also avail themselves of UNICEF's procurement services and WHO and UNICEF

are trying to establish a credit facility to make procurement of drugs easier for the least developed countries.

The WHO Action Program on Essential Drugs and Vaccines, which is now fully operational, provides countries with technical, managerial, and sometimes financial support in the areas of drug policy, procurement, storage, distribution, quality control, legislation, training of health staff, monitoring, and evaluation. Well documented experience shows that with real commitment and cooperation it is possible to ensure the supply of drugs for primary health care at a cost which can be afforded by both country and community. When developing countries join hands with international and bilateral agencies, pharmaceutical industries at home and abroad, health workers, consumer and patients organizations, it is possible to achieve this vital element in the strategy of health for all by the year 2000. This frees energy and skills for long-range activities in other vital areas such as health education, promotion and prevention, improved nutrition, and hygiene.

The action program has become a tool which, if properly used, can foster the kind of collaboration needed in a sometimes irrational world where dialogue can so easily become monologue. It provides a mechanism which

— facilitates understanding and acceptance of responsibility by all concerned with the more rational use of drugs;

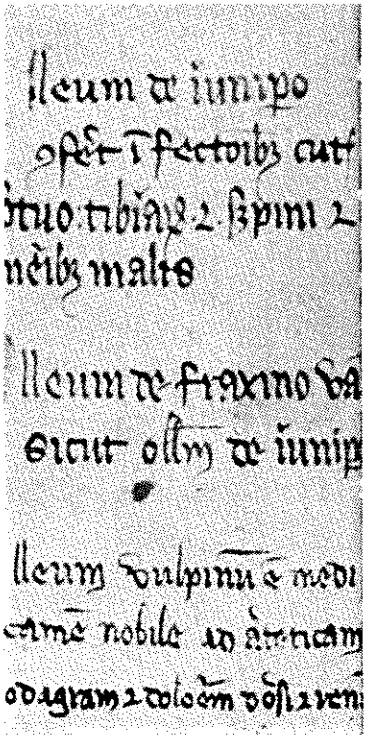
— supports governments in formulating and implementing national drug policies;

— disseminates objective information on pharmaceutical products, assisting countries to make informed decisions on their own situation.

There is no doubt that international cooperation pays off. This is amply illustrated by the global eradication of smallpox. Apart from the immeasurable savings in human life and suffering, the eradication of smallpox results in annual financial savings greater than the entire cost of WHO's program.

The tropical disease program is another outstanding example of successful international cooperation. Under the umbrella of UNDP, the World Bank, and WHO, scientists, institutions, the pharmaceutical industry, and governments come together to devise effective strategies and tools to control diseases which affect the well-being of hundreds of millions of people in developing countries.

There has been substantial cooperation in the field of essential drugs over the last few years with Canada, France, the Netherlands, Switzerland, UK, USA, and all the Scandinavian countries. The considerable support of the Italian government for a joint WHO/UNICEF program in five African countries has been particularly valuable.



The World Bank is also emerging as a strong moral and financial partner, and many non-governmental organizations have also joined forces with us. The Red Cross Societies apply the principles of essential drugs in their emergency and developmental health work.

We have also been establishing oecumenical allies. The Christian Medical Commission is a close working partner in many developing countries. The Catholic and protestant churches in Kenya, for example, recently joined with the government and WHO to plan and implement an essential drugs program for the church-administered health institutions which supplement the government-organized health services.

I can state in all honesty that, when reviewing both past and present cooperative programs, I do not recall even one instance where such cooperation has not been to the benefit of all involved.

The challenge for developing countries to ensure the availability and rational use of essential drugs is daunting but, as I have tried to demonstrate, not insurmountable. WHO is ready and willing to cooperate with all who share our common goal of a healthier world. We recognize that there will sometimes be differing views on how this can best be achieved. But it is only by constructive dialogue and by sharing our experience and knowledge that we can all learn and plan in harmony how improvement and change can be brought about. If we as human beings fail to make greater efforts for equity in health care and access for all to the vital drugs and vaccines needed to protect and preserve health, we shall, deservedly, be judged harshly by those who come after us.

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JOHN A. NORRIS

Orphan Drug Development in the United States

I am grateful for the opportunity to join Pope John Paul II, Archbishop Angelini, WHO Director General Mahler, Nobel Prize winner Bloch, and the other distinguished guests to address this conference and to describe the orphan drug approval process in the U.S., which seeks to provide drugs which might not otherwise be made available to treat or prevent serious diseases. This may be particularly valuable in making available those drugs which are most needed in developing countries.

The orphan drug program

It has long been recognized that some potentially useful drugs are not of sufficient value to warrant commercial development. This could be so, for example, if the disease to be treated by the drug were very rare so that sales could never generate sufficient revenue to pay for development, or if the drug could not be patented, so that the cost of development could not be returned to the developer, even if total sales were extensive.

Despite the lack of commercial incentive, drug companies have, over the years, developed drugs for small populations, usually with the encouragement of regulatory agencies and often with the stimulus of a particularly interested clinical investigator. This was not done in any organized way, however, and in the early 1980's, there grew recognition that drugs of potential usefulness to small populations deserved, on humane and scientific grounds, more systematic attention. Both the Congress and the Food and Drug Administration have worked to develop a systematic and ethical program and have done so with the help of the drug industry and interested academic and disease advocacy groups.

The development and approval of orphan drugs also depends on international cooperation since, when one studies a rare disease, studies throughout the world may serve as important parts of the approval process. Trientine, recently approved in the United States for the treatment of Wilson's disease, was a cooperative international project involving U.S. and U.K. scientists and patients. Recognizing that all patients with rare diseases may benefit from orphan drug research, such cooperation is essential.

Phosphocysteamine, a research drug for nephropathic cystinosis, a rare metabolic disease which destroys the kidney function of the children who develop the affliction, is showing such promise in its U.S. trials that doctors in the U.K. and elsewhere are obtaining supplies of the drug for use by their patients. Where research to develop drugs for rare diseases is undertaken, it is essential to cooperate, including international cooperation, by sharing both the work that needs to be done and the results of that work. Through such cooperation, all benefit.

Currently, research is proceeding at FDA and NIH on a vaccine to prevent AIDS, and FDA is actively seeking out drugs under development that might stop the spread of the AIDS virus or repair the damage done by the virus to the immune system.

Some treatments relevant to AIDS have been developed under the auspices of the orphan products program. Perhaps the best known of these is pentamidine, which effectively treats a severe pneumonia that frequently strikes AIDS patients. Scientists with the centers for disease control, FDA, and the manufacturer worked closely on this drug, and FDA and CDC even conducted some of the laboratory and clinical work necessary for it to be approved. More recently, some antiviral drugs have been granted orphan drug status, and clinical testing of them is under way. These activities reflect the seriousness with which we regard this disease, as well as an example of the value of cooperative activity when there is no time to spare.

Requirements for approval of orphan drugs

It is important to recognize that the Orphan Drug Act, as amended, did not in any way diminish the statutory standard for approval of new drug applications. The standards of substantial evidence derived from adequate and well-controlled studies, evaluation of safety by all reasonably applicable tests, and a showing that risks are acceptable in the

light of benefits are all applicable.

It would be naive, however, not to recognize that orphan drugs intended for few people, people who often have an intractable, serious illness without good alternative therapy, will not usually be investigated on as many people as drugs intended for wider use or use in less serious conditions. The number of controlled trials will be smaller than average, and the tests considered "reasonably applicable" under the circumstances will also represent a smaller than usual data base. Moreover, the design of the controlled trial must be carefully considered to make it practical and ethical in the light of the available patient population. This has long been true, of course. Even before orphan drugs received their current attention, they were developed reasonably frequently by manufacturers with a high sense of public service.

The Orphan Drug Act

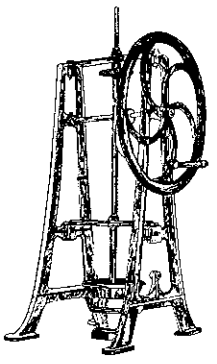
Although FDA has had an active interest in drugs of limited commercial value since the 1970s, the Orphan Drug Act of 1983 represents the principal recent agent of change in the development of orphan drugs, creating new regulatory and tax incentives and drawing attention to orphan drugs in a most dramatic way. I will, therefore, first turn to the provisions of the Orphan Drug Act.

The critical features of the Act, as amended in 1984 and 1985, are

1. An explanation of why a new law was needed and definition of an orphan drug.
2. A process for seeking FDA advice on the development of orphan drugs.
3. For drugs designated by the FDA as orphan drugs, tax credits for research and a period of marketing exclusivity.
4. For drugs designated by FDA as orphan drugs, funds for research grants and contracts to help develop orphan drugs.
5. For drugs designated by FDA as orphan drugs which show some evidence of effectiveness, encouragement to make treatment protocols available.
6. Establishment of the Orphan Products Board to monitor orphan drug activities.
7. Establishment of the National Commission on Orphan Diseases.

It should be appreciated that the law did not change the basic requirements for approval of an orphan drug under the Food, Drug, and Cosmetic Act.

Let me turn to each of these features in more detail.



Definition of an orphan drug

In defining orphan drugs, Congress at first emphasized both the unlikelihood of a drug sponsor's recovering development costs and the rareness of the disease to be treated. "Orphan drugs" under the act include biologicals, in vivo diagnostic tests, and antibiotics, as well as other drugs. In addition, a new use of a marketed drug may receive orphan drug designation. At the present time, for purposes of designating a drug as an orphan (i.e., drug for a rare disease or condition) under the act, the disease or condition to be treated or diagnosed:

1. Affects fewer than 200,000 patients in the United States; in this case designation as an orphan is automatic and does not depend on showing that the costs of development cannot be recovered.
2. Affects more than 200,000 patients; in this case it must be shown that there is no reasonable expectation that the cost of development can be recovered from sales in the United States; designation as an orphan is based on an evaluation of financial data.
3. May be a subpopulation of a more common disease when the drug may not be applicable to the larger population.

Orphan Products Board

The Orphan Drug Act set up the Orphan Products Board, a body with representatives of

FDA, NIH, CDC, and others as appropriate, to help develop drugs and devices for rare diseases and conditions. Its responsibilities are to:

1. Evaluate the effect of the new law.

2. Evaluate activities in NIH and ADAMHA.

3. Assure appropriate coordination of FDA, NIH, ADAMHA, and CDC.

4. Assure appropriate coordination of federal agencies, manufacturers, and organizations representing patients.

5. Inform physicians and the public of the availability of orphan drugs under treatment protocols or under approved marketing applications.

6. Seek sponsors for orphan drugs.

7. Recognize public and private efforts in developing orphan drugs.

8. Make a report annually to congress. The report is to:

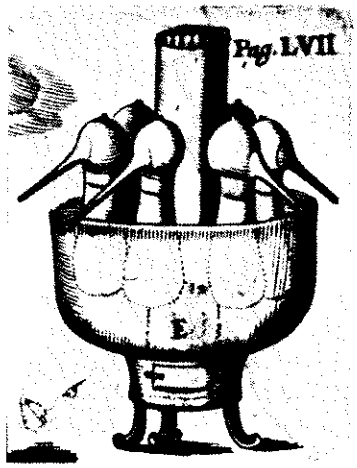
— identify designated orphans;

— describe board activities;

— describe evaluations;

— contain reports by the directors of NIH and ADAMHA on their research activities related to rare diseases and conditions, a report from the secretary of the treasury on use of tax credits, and a report from DHHS on grant activities.

One exciting and implemented recommendation of the Orphan Products Board has been the development of the National Information Center for Orphan Drugs and Rare Diseases (NICODARD), a component of the National Health Information Clearinghouse (NHIC), part of the U.S. Public Health Service and sponsored by FDA. NICODARD responds to patient, family, or physician inquiries about drugs available for rare diseases, ongoing studies of rare diseases, and general requests for information. The center has a toll-free number to facilitate inquiries. It also gathers information, interacts with rare disease organizations to prepare educational materials on specific diseases, and refers inquiries to appropriate voluntary organizations. Recently, it published a resource directly for rare diseases, a comprehensive listing of voluntary organizations and federal agencies with emphasis on the scope of their activities and the printed and audiovisual materials available.



National Commission on Orphan Diseases

The 1985 Orphan Drug Amendments established the National Commission on Orphan Diseases, a group made up principally of non-government employees to take a more global look at all activities related to rare diseases and make recommendations that will encourage effective research and treatment for orphan diseases in the future. The commission will not report until late 1987 and thus far is in the organizational phase, but its purpose and responsibilities can be described.

The purpose of the Commission is to assess the activities of NIH, ADAMHA, FDA, and other public agencies, as well as private agencies in connection with

1. Basic research on rare diseases.

2. Application of knowledge in other areas to rare diseases

3. Clinical research on the prevention, diagnosis, and treatment of rare diseases.

4. Dissemination of knowledge that can be used in prevention, treatment, and diagnosis of rare diseases.

In its assessment the Commission is to consider:

1. The appropriateness of the priorities set by the organizations evaluated.

2. The effectiveness of grant and contract programs and the adequacy of scientific activities, including the peer review programs used.

3. The effectiveness of agency coordination.

4. The effectiveness of transfer of information from

research on non-rare diseases to research on rare diseases.

The commission is made up of 15 non-government people, 10 with expertise in rare diseases and 5 representing organizations concerned with rare diseases, as well as 5 non-voting government representatives, including 4 directors of NIH or ADAMHA institutes and one FDA member.

The Commission, not later than September 30, 1987, is to report to the secretary, DHHS, and the Congress on its findings and conclusions, including recommendations for:

1. A long-range plan to use public and private resources to improve research into rare diseases and to assist in prevention, diagnosis, and treatment of rare diseases.

2. Needed legislation or administrative action.

Office of Orphan Products Development

The Orphan Drug Act, while a major event in orphan drug development, is only a part of the total effort. The FDA, in addition to carrying out responsibilities, is engaged in efforts that go beyond those responsibilities.

FDA screens requests for protocol assistance, administers the grants program, and monitors the exclusivity provisions. Further, FDA provides the protocol assistance, participates in grant review, and, of course, reviews the IND and marketing applications that are submitted.

FDA, however, engages in important additional efforts:

1. FDA's office of orphan products development (OPD) identifies orphan products other than those put forth by manufacturers and other than those eligible under the act, which considers only drugs, biologics, and in vivo diagnostic tests.

a. OPD uses a broader definition of orphan, namely: "Any promising drug, medical device, medical food, or veterinary product that requires a sponsor for completion of development and marketing or for the addition of a new use to labeling. The product may be for a common or uncommon condition." A new use, for example, may be first studied by an academic investigator who lacks resources to develop it fully. Such a use might be identified as an orphan.

b. OPD scans all active INDs periodically, in cooperation with FDA's review process to seek orphan products. At present, some 175 INDs are monitored.

c. OPD is the FDA focal point for interested outside parties (such as academics or disease-oriented organizations) who wish to identify drugs as potentially important and encourage their development.

2. OPD encourages development of orphan products in a number of ways:

a. It seeks commercial sponsors for orphan drugs, e.g., for foreign drugs not yet under development in the United States or drugs studied initially by academic investigators. This is done in several ways:

(1) By approaching directly a firm known to have particular expertise in the relevant area.

(2) By bringing the drug to the attention of the U.S. Pharmaceutical Manufacturers Association's Commission on Drugs for Rare Diseases or the Generic Pharmaceutical Industry Association's Institute for Orphan Drugs. Where possible, these organizations will seek sponsors among their member companies.

(3) By publishing a notice in the *Federal Register,* a method used when relatively wide interest is expected. When this is done, the notice will present a

review of the available literature, noting data that could be used in an application, and indicating what further data are needed for filing of the application. Seven such notices have been published to date.

So far we have been entirely successful in obtaining sponsors for drugs where the research has been substantially completed. Obviously, where more work is needed, "adoption" will be more difficult.

b. In some instances needed toxicologic studies will be carried out by FDA's national center for toxicological research (NCTR). NCTR has a limited capacity, as no new funds have become available. What resources are available must be used carefully. Such studies, however, may in some cases make development of a drug possible.

Other involved groups

The roles of the Orphan Drugs Act and FDA's Office of Orphan Products development are crucial in orphan drug development, but it is important to realize that the availability of orphan drugs depends equally on other parties.

1. Voluntary disease-oriented organizations.

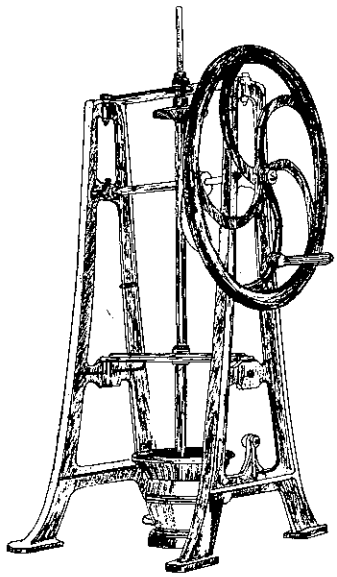
By maintaining public, congressional, and executive awareness of their interests, these organizations have helped gain attention and support in a time of stressed resources, no small feat, and they were a major stimulus to the Orphan Drug Act. They also recruit scientists to the study of orphan diseases and provide some financial support for studies. We hope that still more grant support will be provided in the future, and there are plans for this.

2 Drug companies.

Pharmaceutical companies, while profit-making enterprises, have long been willing — on humanitarian grounds — to undertake develpment of drugs unlikely to be profitable. In response to current interest, the Pharmaceutical Manufacturers Association (PMA) has formed the Commission on Drugs for Rare Diseases and the Generic Pharmaceutical Industry Association has formed an Institute for Orphan Drugs. Both organizations consider potential orphan products and, if convinced of the products' potential humanitarian value, seek a sponsor among their member companies.

3. Academic physicians.

Many of the orphan products under development or already developed represent substantially the efforts, often against rather long odds, of one or two academic physicians with an interest in a specific rare disease. They are obviously a crucial link in the path from basic observations to a viable drug product.



A manually operated mechanical mortar (1870)

International drug development under the Orphan Drug Act

The following quote from United States congressional records during approval of the Orphan Drug Act is important: "The term 'rare' in the

States is used to assure that the benefits of this bill apply to drugs for diseases or conditions which are rare here, even if prevalent in other countries. To the extent that this provision encourages the development of drugs for prevalent diseases in developing countries, the committee believes it is sound public policy." As an example of this point, the following orphan drugs are relevant to developing countries:

Drug	Disease
1) Eflornithine HCL	1) Trypanosoma brucei gambiense
2) Allopurinol riboside	2) Leishmaniasis and Chagas' disease
3) Clofazimine	3) Leprosy

I hope that this information is useful in assessing how the U.S. orphan drug activities are supportive of concerns for ethical drug research, particularly for diseases which are rarely seen in the United States but which may occur frequently in other areas of the world.

Additionally, I trust that this analysis of our search for cures for rare diseases will provide a ray of hope that some of the diseases common in developing countries may be treated successfully. Finally, I hope that new biotechnology methods may result in the prevention or cure of many of the common tropical diseases, which we are pursuing under the auspices of WHO's Tropical Disease Program. Let me conclude with just one example, the development of a malaria vaccine derived through recombinant DNA techniques which is now being clinically tested in the United States.

Thank you for giving me this opportunity to discuss these important issues.

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J.D., M.B.A.
Deputy Commissioner
U.S. Food and Drug Administration