ISSN 2215-2016

Perspectives in Research

Journal of PRODICI (Pfizer Program for the Development of Investigation and Science)
Year II • Volume II • January - March 2011

Pfizer

PRODICI
Pfizer Program for the Development of Investigation and Science

Pfizer

Contents

PRODICI
Pfizer Program for the Development of Investigation and Science

From the Editor

Research Capacity Building in Central America and the Caribbean

Bustos-Montero D.[1]

When dealing with the reasons behind the scientific and technological backwardness of Latin American countries, it is imperative to refer to the limited space granted by our healthcare systems to research processes, a factor that has thus caused the logical difficulty to integrate these activities, so that they constitute the cornerstone of the strategies aimed at improving people's health.

Additionally, there is a lack of available funding options for the promotion of research and formal training in this field, which combines to make the task still harder and, as a result, proves detrimental to the attraction of professionals with innovative potential.

Data shown by different international organisms are alarming, and in turn trigger an alert signal to develop structures aimed at modifying the course of this situation.

In Latin America, according to the Ibero-American Network of Science and Technology (RICYT Spanish acronym) on The State of Science 2008[1] report, the ratio of researchers per thousand of economically active citizens is approximately 1-2, while for industrialized countries, such as Canada, South Korea and the United States, this ratio is 8-10. Even more worrying is the data showing that, out of the total number of researchers in the region, only 7-14% conducts their research activities in the health science field.

It should therefore not surprise us that the number of patents registered in our countries is much lower than that reported by other emergent nations: while South Korea registered an annual average of 80,000 patents during the 2008 period[2], Barbados reported 134, Costa Rica 22, and Bahamas 21. But the issue gets worse when we learn that more than 90% of the patents registered in the region, were developed by researchers not residing in our countries.[2]

From the above, we can deduct a need to promote a culture based on research, essentially supported by effective training on the part of professionals in this field, who will be able to recognize and exploit the opportunity to improve the health conditions of the population, find solutions to the problems that affect the region, and turn into active actors in a health-related history at worldwide level.

Research is development, and development necessarily implies health. However, how do we promote a research-based culture in the region? Next, a proposal –which could turn out to be interesting– to support the development of such a culture:

1. Generate economic funds to promote education and training in biomedical research, aimed as well towards the development of local or regional research protocols propounding the solution to indigenous problems.

Considering that 91% of the resources allocated for this kind of action come from the private sector, it is essential that state investment increases gradually until it reaches 1% of the Gross Domestic Product (GDP) assigned to science and technology activities. Nowadays, the Latin American country that invests the highest percentage of its GDP on this kind of activities is Brazil, with a 1,2%; the rest of the region stands below 0,6%, as shown by the data of Argentina, Costa Rica and Colombia, with 0,53%, 0,38% and 0,20% respectively.[1,2]

2. Create education and training research programs in the region, seeing that at present, the options for appropriate training for people interested in the subject are few in number.

To this end, support from the researchers in our countries is absolutely necessary, with the purpose of designing our own high-class educational model, which may guarantee academic excellence.

The above can be possible only if strategic alliances with public and private institutions are established, so that these programs respond to a country vision instead of to individual and isolated ideas of the actors involved.

3. Develop discussion and debate spaces, in search of the regulatory maturity and generation of the different strategies, proven or to be proven, which will serve as basis to those starting out in this process.

Precisely, this second volume of the Perspectives in Research journal, hopes to draw attention to the subject noted in the previous paragraph, for as part of the Central American and Caribbean Initiative for the Promotion of a Research-based Culture, the purpose is to motivate healthy debate and raise the curiosity of readers to support this culture.❖

1. Medical Manager, Cardiometabolic Franchise, Pfizer Central America & Caribbean
daniel.bustos@pfizer.com

REFERENCES

1. RICYT –Ibero American Network of Science and Technology Indicators. The State of Science. 2008.
2. World Intellectual Property Organization. World Intellectual Property Report. 2009
3. Ministry of Science and Technology of Costa Rica. Science, Innovation and Technology Indicators Report. 2008.

Quality, Drug Interchangeability and Bioequivalence: Technical Defenses or Health Needs?

Cuesta-Ramírez G.[1]

In these last few years, there has been a massive entry on the developing country markets of many drugs produced by domestic or regional companies, introduced as brand-name products, theoretically cheaper than the originals, or as low-cost generic drugs. They enjoy strong political and governmental support, backing that contrasts with the lack of collective information concerning the differences between these different types of drugs, causing common people, politicians and even physicians, to erroneously believe that all of them are "exactly alike", and therefore, "interchangeable". It is appropriate, then, to clarify some concepts that will help physicians and customers to identify to what extent these products differ from one another, and under what conditions they can be freely INTERCHANGEABLE:

Brand-Name or Innovator Drug:

"Original" pharmaceutical product, researched, developed, registered and commercialized by a pharmaceutical company internationally recognized as generator and proprietor of the research. Its active ingredient identifies with the International Non-Proprietary Name (INN), but is usually marketed under a brand name.

Generic Drug:

Product that contains the same active ingredient of the original brand-name (innovator) drug, ALWAYS commercialized through the INN. It can reach the market only when the patent period of the original has expired. For health authorities to accept the registry of a generic drug, the manufacturer must prove bioequivalence with the innovator.

Copy Drug:

Drug that supposedly has the same active ingredient of an original innovator, but manufactured by a company different from the one that researched and developed the original. Not a generic drug, since it is placed on the market under a brand name and not through the INN. Commercialized in many countries with total disregard to patent laws or international trade agreements; and almost never proves bioequivalence with the innovator.

Interchangeable Drug:

Drug that incorporates constant quality controls, both on the selection of its raw material as in the manufacturing process. When this drug is compared with the original or innovator on a scientifically controlled study, it proves to be bioequivalent to it; hence, the product reaches sufficient standards to guarantee, to physicians and final customers, clinical results very similar to those obtained with the original drug.

If this concept is so important, then what does "proven bioequivalence" mean? In order to

understand the term, we have to know that when a drug is administered to a patient, it reaches the blood and once there describes a curve, called bioavailability curve, where a series of elements stand out. (Fig 1)

An effective and safe drug must reach, in the plasma, a specific plasma concentration to reach a proper therapeutic window. This window spans between the minimum effective concentration (MEC), where the drug action is enough to treat the illness, and the minimum toxic concentration (MTC), where the product generates unacceptable toxic effects. Each drug has its own and particular bioavailability curve and its own therapeutic window.

On the other hand, some drugs have wide therapeutic windows, and the risk of their producing toxicity is scarce. With them, the care lies in maintaining good levels of effectiveness, above the minimum effective concentration. But there are also other drugs with narrow therapeutic windows, which can therefore easily fall into ineffectiveness, or even worse, into toxicity. In their case, quality during manufacture is absolutely vital. This activity of the drug, which analyzes effective and toxic doses (ED-50 and TD-50), is measured through the calculation of its therapeutic index, determined as shown figure 2.

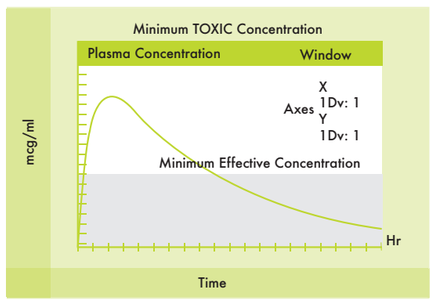

Figure 1: Elements of the Bioavailability Curve

When an innovator drug is launched on the market, the manufacturer has carefully studied and defined its therapeutic window. In order to grant the sanitary registration to an innovator brand product, state regulatory agencies demand from the manufacturer the presentation of detailed studies on bioavailability and effectiveness. Furthermore, in order to guarantee the quality of the product in the long term, research laboratories must also prove their compliance to permanent quality standards, in accordance with the international rules of Good Manufacturing Practices (GMP). It is surprising that in order to register a copy or a generic drug, the sanitary legislations of our countries DO NOT NECESSARILY DEMAND from manufacturers the presentation of GMP certificates or bioequivalence studies. Fortunately, some generic manufacturers already comply with this kind of standards, offering "brand-name generics", theoretically interchangeable, to the markets.

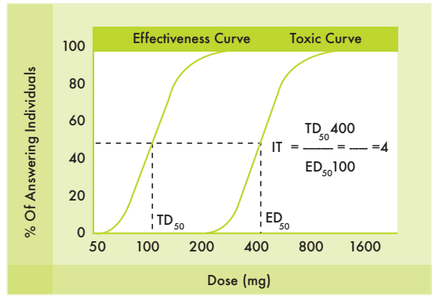

Figure 2: Drug activity.

In order to compare the effectiveness and safety profiles of two drugs containing the same active ingredient, it is necessary to bear in mind the following considerations, before declaring them equivalent and interchangeable:

Pharmaceutical Equivalents:

Drugs that contain the same active ingredient, in the same quantity and pharmaceutical form (tablets, syrup, capsules, etc.) as the original innovator drug used as standard. This is the most elemental way of establishing the equivalence between two drugs. In most of our countries, regulatory agencies only apply this criteria to grant sanitary registration to copies or generics.

Biologic Equivalents (BIOEQUIVALENT):

Drugs which, being pharmaceutical equivalents, display bioavailability curves statistically identical to those of the original innovator drug used as standard.

Therapeutic Equivalents:

Drugs which, besides being bioequivalent, produce therapeutic effects comparable to those of the original innovator drug used as standard.

Some countries with advanced health laws consider that two drugs are INTERCHANGEABLE when, and only when, besides being biologic equivalents (bioequivalent), they are equivalent therapeutically.

According to the World Health Organization (WHO), the population is warranted safe drug interchangeability only when the drugs prove their bioequivalence. This proof is carried out when, under controlled experimental conditions, the non original drug (copy or generic) has a bioavailability similar to that of the innovator drug, and there is no statistically meaningful difference of the areas under the curve (AUC) or relation of plasma concentration (Pk) versus time (t).

The figure 3 shows a typical bioavailability curve:

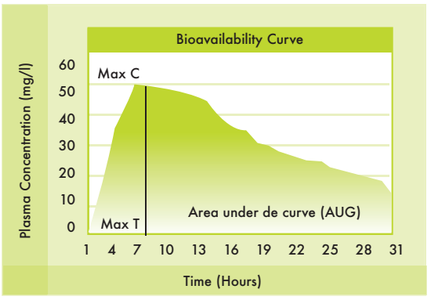

Figure 3: Typical Bioavailability Curve

In summary, if an existing product, copy, generic or brand-name generic, has not proven to be bioequivalent with its respective innovator, IT CANNOT BE freely interchangeable. Just the quality of the manufacturing processes and the compliance to technical and legal regulations grant the community trustworthy and interchangeable drugs.

Interesting reflection for some health authorities...❖

1. Medical Director,
Pfizer Central America & Caribbean
genaro.cuesta@pfizer.com

Basic Principles of Pharmacoeconomics

Heilbron-Quirce E.[1]

Health economics is a research field that studies the best use of resources for sickness care and health promotion. Health economics gives rise to pharmacoeconomics, or the economic evaluation of health interventions applied to drug use. Pharmacoeconomics deals with different aspects concerning resource distribution, use of resources and their impact on the health of the population involved. The evaluation used in pharmacoeconomics answers to: what illness are we treating? How are we treating it? And, what is the best way to treat it?[1]

The logic of any economic analysis is based on the notion of shortage, meaning that the needs exceed the resources. Resources are the staff, time, buildings, capital, good will, equipment, power, and everything needed to cover a specific need. Money is used to acquire these resources and services, and because of this, the term "resources" is often used as synonym of money.

Given that there is a shortage of resources, it is necessary to define not only the needs you want (and don't want) to cover, as well as the extent in which they will be covered. Every decision to use a resource implies a sacrifice, since when resources are used for a specific purpose; they cannot be used for another. The economic concepts of cost and benefit derive from this principle. Benefit is what is gained by covering the need chosen to be covered, and cost is the benefit that would have been gained if the same resources had been used differently. For this reason, in the economic evaluation, the costs aimed to be measured are called opportunity costs, so as to remember that the cost of the actions displayed is that of the benefits not gained for not having displayed other alternative actions. Therefore, the logic of health economic analyses is based on choices, how they are done and their consequences. It is well known that the decisions concerning health politics are rarely based just on economic criteria, and that decisions of the "all or nothing" kind are rarely taken; in general terms, what is decided is whether the services already offered are enlarged or reduced. For that reason, it is convenient to consider the cost and benefit changes as cost and benefit increases between the options involved. In this context, the margin is the increase variation of necessary resources (inputs) to produce a corresponding variation on the effects (outputs).[2]

Pharmacoeconomics

The economic pressures on the healthcare systems[3], the undeniable visibility of the amount of drug consumption[4] and, in the United States, the growing competition for the healthcare market[5], have contributed to propitiate the development of methods to evaluate healthcare costs and results. Pharmacoeconomics is the study of the costs and benefits of medical treatments and technologies. It combines economics, epidemiology, decision analysis and biostatistics. Pharmacoeconomics is becoming an integral part of drug development and commercialization, and consequently, the protocols of clinical trials that include the collection of data necessary for the pharmacoeconomic analysis are more and more frequent.

Healthcare costs are usually classified into four types: direct medical costs (sanitary staff, hospital expenses, drugs, etc.); direct non medical costs, necessary to receive medical care (for instance, transportation); indirect costs, those pertaining to morbidity-mortality due to illness, and intangible costs, which correspond to the pain and suffering caused by the illness. An economic evaluation can include some or the entirety of these costs.

Costs can be estimated from different perspectives. For example, healthcare costs may be calculated from the point of view of the patient, of the service provider, of the payer, or of society. Society costs are tantamount to the total cost of the intervention. The calculation of costs from other perspectives includes just those which are relevant to the interested party. An economic evaluation can measure costs from a single or a multiple perspective, but in any case, this perspective must be explicit. Therefore, when reading a pharmacoeconomic study, it is fitting to pay attention to the types of costs that have been excluded, depending on the perspective from which the analysis was made.

When reading a pharmacoeconomic study, it is also suitable to pay attention to the way the treatment beneficial effects or results are interpreted and presented. In pharmacoeconomics, there are four main types of analyses: cost-benefit, cost-effectiveness, cost-profit and cost identification[3,4,6]. All four measure healthcare costs, but they differ in the extent and expression of the benefits obtained with those cares. With each one of these designs, four kinds of results may be produced: an improvement of the result at a lower cost (which would show that the strategy should be adopted); a worsening of results with an increase in cost (which would imply that the new strategy should be rejected); an improvement of results at a higher cost, or else, worse results at a lower cost; these last two possibilities require more detailed considerations, concerning subgroups of patients or other circumstances which could change the direction of the results.

Cost-Benefit Analysis

In the cost-benefit analysis, the cost of a medical intervention is compared to the benefit produced. Both costs and benefits are measured with the same monetary units. It can be used basically for two purposes: to compare the total costs and benefits of a treatment to those of another, or to compare the additional costs and benefits associated to the use of one or another treatment. When the goal is to compare the costs and benefits associated to the use of a treatment that could replace another one already in use, the cost increase of this treatment and that of the benefits produced are appraised. The cost increase of a new treatment is the cost of this treatment compared to that of the conventional treatment. In like manner, the benefit increase results from comparing the benefit obtained with the new treatment with that of the conventional treatment.

One of the main limitations of the cost-benefit analysis is that results (the benefit brought on by the treatment) may be difficult to measure in monetary terms. Furthermore, it poses numerous ethical problems derived from assigning monetary values to the treatment results.

Cost-Effectiveness Analysis

The cost-effectiveness analysis compares the costs of an intervention expressed in monetary

terms with its effectiveness, measured in clinical terms (for example, number of events or avoided deaths). The results of the cost-effectiveness analysis are usually presented as a ratio between clinical costs and effects (for example, in dollars per life saved, or dollars per general average decrease of a 10% of the diastolic blood pressure). As with the cost-benefit analysis, the increments in total costs and clinical effectiveness of a new treatment can be compared with those of the conventional treatment.

Cost-Profit Analysis

In the cost-profit analysis, the costs of an intervention are analyzed and expressed in monetary units, and the results are measured as what the patients gain with the medical treatment. In this type of analysis, results are not measured with objective clinical variables, but rather with the subjective appraisals done by the patients regarding the treatment effect. Therefore, this type of analysis requires the appointment of a value, which economists call profit, to the global results of the treatment. A profit value is a measure of the patients' preferences in relation to their health status, or to the result of a specific intervention. In research, profit values are used to create a criterion or measure scale of results, adjusted by quality (for example, on a scale of 0 to 10, where 0 would be the worst health state imaginable and 10 would correspond to a perfect health). The unit of measurement in these analyses, the quality-adjusted life years (QALY), is calculated starting from the survival and preference data of patients: if a patient lived 10 years suffering from a disease associated with a health state of 0.8, the patient would have 8 QALY.

In any case, one of the main challenges of the cost-profit analysis is the development and validation, in every case, of appraisal systems performed by the patient. To this purpose, several instruments used in clinical trials have been developed, such as scales of quality life and well-being. Some of these scales assess the functional capacity in different areas, to later combine these measurements in order to produce a single profit punctuation, based on the preferences of the patients per each one of the components of the different health states included in the scale.

Cost Identification Analysis

The cost identification analysis simply enumerates the costs needed for the medical care, ignoring the results. It serves to determine the costs of providing services in alternative ways. Results are typically expressed in terms of cost per unit of provided service. Since it does not measure results, the cost identification analysis is only appropriate when it is known that the treatment results or its beneficial effect are equivalent.

Study Designs

Pharmacoeconomic evaluations can be essentially performed with the same kind of designs as other pharmacoepidemiologic evaluations.

Retrospective analyses of clinical trials that originally did not include any economic component can be performed; these studies are limited by the lack of some specific data (for example, additional pocket costs), by the impossibility of recovering information concerning life quality, or because the patient did not exactly follow the trial protocol, contingency not ever having been foreseen.

Prospective economic analyses may also be included in the design of clinical trials, especially in the 3rd and 4th stages. Although this strategy does not have many of the inconveniences of the previous one, it suffers from the obliqueness that could be introduced, in an analysis of this type, by the difference between efficacy and effectiveness.

A third large group of pharmacoeconomic studies are the ones based on information obtained from large administrative databases, of public or private systems of medical insurance. In most of the cases, these studies have great limitations, especially because they do not include any information concerning the clinical status of the patients, particularly about co-morbidity and lifestyles.

Economic evaluations require an important investment of resources. For this reason, it is especially important when dealing with the assessment of new and innovating treatments; however, its importance is less critical in the case of drugs which are therapeutic equivalents to other drugs already available.

Despite the recent development of pharmacoeconomics, it is important to consider that economic evaluations can be, in principle, subject to bias, as much or more than clinical evaluations, for if the former imply many intangible and non quantifiable costs with the same units, the latter often lack interest on the meaningful values of the patient, which not always agree with the ones measured by a clinical study.❖

1. Head of Clinical Operations,
Pfizer Central America & Caribbean
eric.heilbron@pfizer.com

REFERENCES

1. Jefferson T, Demicheli V, Mugford M. Elementary economic evaluation in health care. London: BMJ, 1996.
2. Walley T, Davey P. Pharmacoeconomics: a challenge for clinical pharmacologists. Br J Clin Pharmacol 1995;40:199-202.
3. Walley T, Haycox A. Pharmacoeconomics: basic concepts and terminology. Br J Clin Pharmacol 1997;43:343-8.
4. Siegel JE, Torrance GW, Russell LB, Luce BR, Weinstein MC. Guidelines for pharmacoeconomic studies: recommendations from the Panel on Cost Effectiveness in Health and Medicine. Pharmacoeconomics 1997;11:159-68.
5. Schulman K, Linas BP. Pharmacoeconomics: state of the art in 1997. Annu Rev Public Health 1997;18:529-48.
6. http://es.wikipedia.org/wiki/Farmacoeconom%C3%ADa Accessed on January 12, 2011

Historical reflections on antibiotic therapy, or rather, about Chemotherapy: First Fascicle.

Lovato-Gutiérrez P.[1]

When writing, a style is projected, the experience is shared, and a legacy is transmitted to the reader, to the students at their desks or on hospital morning rounds. In this case, whenever something is written about the history of antibiotics, or about antibiotic therapy, it is mandatory to first describe the evolution of the infectious disease in order to achieve, in this manner, its framing within a context that allows its understanding.

But how do you define the history of antibiotic therapy? How, the history of chemotherapy? Is there some way to describe both? To answer these questions, it is imperative to develop the subject, because along the extraordinary interest it provokes, the manner of approaching it is extremely interesting.

Hence we acknowledge it as a difficult and ambitious project, aimed at stirring up the reader's interest on a group of drugs so-called "the best friends of man" (our apologies to dog lovers), at least for the time being. A learned and documented return to the past transports us to prehistory and to the primitive communities, showing us with a direct style, the evolution of thought regarding the meaning of falling ill and curing.

How can we forget the references to the Middle Ages, represented by the great epidemics, such as the bubonic plague, the dangers of spirit alterations and sexual debauchery, behaviors still in force and which acquire special meaning in our days?

Rational empiricism and etiologic therapy, realities of our time. How hard it has been to reach this reasoning!

From Paracelsus to Pasteur, and from the antimicrobial chemotherapy to the miracle of penicillin. From Ehrlich to Fleming. With magical strokes, it is possible to contemplate the passage from magical thought to the famous magical bullet.

Without a doubt, the antibiotic era represents the true axle of medicine, just as F. Marti-Ibanez pointed out more than forty years ago. (Antibiotics Annual, 1957).

A humble perspective on the history of antibiotics

Although the identification, the knowledge and the determination of the role of microorganisms as responsible for infectious diseases are relatively recent facts in human history, the interest in knowing the causes of infection and how to combat it began, nevertheless, much earlier; such interest is as old as man, and the conscience of evil was born alongside him.

Each day, Paleopathology produces more and more data confirming the fact that infectious diseases and their treatment have always been phenomena inseparable from man's life; in this manner, the old myth of the "heavenly times", where such diseases did not exist, has crumbled down. As of the beginnings of humanity, man has fought throughout the ages against pain and sickness, so as to preserve life and health and increase his well-being. Every civilization has had to assume its evils, and has tried to combat them with the application of therapeutic remedies, in accordance with their beliefs and the knowledge acquired through experience.

In Sendrail's words: "Since man became aware of his humanity, since his mind learned to reflect himself, as his face on the virgin water of the lakes; since he raised his worshipping hands towards the first dawns, he knew as well that his body was subject to evil, and that he was extremely interested on devising, with divine help, a way to cure such evil." Historically, the fight against disease has had four means: the empirical, the magical, the religious and the scientific, the latter being the author's favorite.

A. Flexner, on his part, affirmed: "From the most distant antiquity, medicine has been a strange mixture of superstition, empiricism, and that kind of shrewd observation that is the matter itself of which science is ultimately made up. The effort throughout time, each day more and more lucid and determined, has tried to eliminate superstition, to confine the scopes of empiricism (from which we can never entirely escape) and to broaden, improve and systematize the field of observation." The first attitude of the primitive man towards illness must have been purely spontaneous.

In like manner to animals –and I confess, this is awesome– instinct was what first led man in the search of a remedy with which to relieve his ills, licking or cleaning his wounds, delousing himself, foreseeing certain infectious processes and mitigating some of its symptomatic manifestations, such as fever and pain, or simply avoiding emotional pain through the ingestion of plants.

The empiricist experience came later: on facing the repeated observation of a frequent event, such as wound contamination or the presence of parasites, usually followed by an abnormal combination of different conditions, the primitive man reacted without reflecting upon the reason why such an event occurred; he merely verified what was obvious from his experience, and acted in accordance to healing practices which had turned out to be effective in similar occasions.

Thanks to some vegetable traces found on locations of primitive human settlements, the growing of different medicinal plants and their exchange among the communities has been proven. This highlights the fact that man gradually learned to use plants as therapeutic means, although they were obviously applied with no basis and, for the most part, without understanding their effects.

At the beginning, they would have been used just as nature offered them; later on, their size would start to be reduced, so as to facilitate their administration and application, and medicinal substances would be mixed with food, such as milk, honey, fat or fruits, which would serve as vehicles.

When fire was available, man was finally able to make medicinal preparations for external or internal use, giving rise to the first pharmaceutical forms. As time went by, man passed from being nomadic to sedentary and started thinking about the past and the

future, trying to explain to himself the facts and whys of diseases (school or university teachers do not usually talk about this subject when referring to history). That was how the concept of divine punishment as cause of illnesses emerged, and religion and magic joined empiricism for their treatment. (We must admit that, although it may be controversial and underestimated by some people, religion and magic were necessary for the progress of therapeutics).

The magical religious conception was not based on the knowledge of the action of the therapeutic remedy used, but rather on the faith of the patient on magic and divine intervention, by means of the healer. Thus, medicine acts depending on who applies it (the witch doctor, the sorcerer, the shaman, the healer, etc.), magical procedure still used by many in several countries.

Although it is rooted on the rational attitude of the Greeks before sickness (what is a patient?, what is the remedy?, why do we do what we do?) and the "reasoned empiricism" of the 16th and 17th centuries, the real scientific knowledge of diseases starts on the second half of the 19th century, especially as of the establishment, on the part of L. Pasteur and R. Koch, of the microbial origin of infections and the huge display of antimicrobial pharmacology, which brought on a new manner of healing based on scientific therapeutics. The important achievements historically documented in Central America, specifically by Dr. Cloromiro Picado, and in other latitudes, by Dr. Eugenio Espejo, are part of this universal history.

The etiopathologic mentality, essentially based on Pasteur's germ theory, on Koch's postulates to establish that "such microbe" is the true cause of "such disease", and on the contribution of E. Klebs, who determined that disease is always infection, depending on the corresponding clinical manifestation of the infecting germ, provoked an essential change on the manner of conceiving disease and its treatment.

Based on etiopathology, the great German researcher P. Ehrlich was able to open a new path for the development of pharmacology, with the onset of experimental therapeutics. Pathogenesis and therapeutics were thus indissolubly united in the history of medicine. The obtaining of the famous salvarsan, strong arsenic drug against syphilis, meant the culmination of Ehrlich's works, allowing him to build the first great victory of antimicrobial therapy and laying the foundations of a new concept, which would develop later on with the introduction of prontosil and the clinical use of penicillin (products directly and strategically related to World War II); the etiologic treatment of infection, in particular, and of disease, in general.

The development of antibiotic therapy, after the discoveries of penicillin and sulphamides, has brought on an authentic transformation to the treatment of infectious diseases, which not only has changed the history of pharmacology and medicine history itself, but has been, as well, one of the facts with more repercussions on human life: as in the second half of the 20th century, infectious diseases were no longer the main global cause of mortality, though this does not mean that they are no longer a world anchor. Everything seemed to forebode that the end of infectious diseases was close. There were even solid opinions and arguments within the Senate of the Unites States; irresponsible and early words. Physicians and laymen shared the same exultation and identical illusions. Nevertheless, they were far from reality!

Throughout the last thirty years a series of facts have emerged, which allow us to continue keeping the initial optimism and euphoria of having started the "definitive battle" against bacteria: some community-acquired infections not only have increased, but have suffered a true metamorphosis that makes them more varied and much more difficult to diagnose. Certain hospital infections produced by real "supermicrobes" are increasing, and the never-ending appearance of antibiotic resistance, as a consequence of the massive and indiscriminate use of antibiotics, has already reached alarming proportions in many cases and in many health services, which despite knowing the solution or being able to contribute to its finding, prefer to look the other way.

Pharmaceutical research has made available a real therapeutic arsenal, but paradoxically, it turns out to be insufficient in some particular cases. The alarm produced by the resistance phenomenon and the emerging microbes has brought on the urgent need to have new therapeutic alternatives in the coming years. The strategies set in motion are varied and pass through the test of new molecules, through the search for more options, through the development of gene therapies, the "recycling" of antibiotics already known and scarcely used (option taken very seriously by many infectious disease specialists), and even through the tackling of new therapeutic treatments based on the physiopathology of the infectious process.

Antibiotic therapy cannot become a never-ending cycle, in a continuous generation of problems and solutions. Currently, a substantial advance in the battle against bacteria entails the rational and responsible use of the antibiotics available, forcing the promotion of sanitary education, the elimination of self-medication, and the awareness concerning the need for strict therapeutic compliance and the correct use of this health technology at different hospitals.

Similarly, it is essential to permanently control the evolution of bacterial resistance and act on its reservoirs, as well as promoting the creation and spreading of techniques of quick diagnosis, sensitive and specific, that can be easily applied not just at hospital level, but also at primary healthcare, that is, at community level. Only this way will we be able to continue believing in what Goethe used to say: "...humanity will win in the long run."

Instinct, empiricism, magic and religion: the ancient man

Paleopathology has provided proofs of the development of infectious diseases on man since the most remote times, and according to H.E, Sigerist, one of the most important medicine historians of our century, the great majority of injuries found in the bones of primitive men are the result of inflammatory processes, of a traumatic or infectious nature. How did prehistoric man face the reality of his diseases? How did he abandon the darkness of his senses and started thinking about his ills? We don't know. The lack of documents does not allow for anything else than making assumptions and deductions from our observation of what human groups are still doing, groups which life is closer to that of prehistoric societies, what some would call primitive populations.

Instinct: much more important than what we think

The first response of primitive man to sickness must have had a purely instinctive and spontaneous nature. According to M.

Foucault: "At the dawn of mankind, prior to any vain belief, every system, medicine in its entirety consisted of an immediate relationship between sickness and that which alleviated it. This relationship was one of instinct and sensibility, rather than of experience; it was established by the individual from himself to himself... It is this relationship, established without the mediation of knowledge that is observed by the healthy man; and this observation itself is not an option for future knowledge; it is not even an act of awareness; it is performed immediately and blindly."

Although with a difference of twenty centuries, A.C. Celsus expressed himself in similar terms on his famous treatise The eight books of the medicine, an incomparable summary of everything that had been said and done in medicine up to the first half of the 1st century BC: "It is not true that in its origin, medicine was the consequence of matters previously posed, for it was born from the observation of facts... Therefore, medicine was not born from reasoning, but rather reasoning came after medicine."

Indeed, in the first merely instinctive actions of man, such as licking his injuries, reproducing the conducts performed by animals, a principle of "antibiotic therapy" can be observed: amazing fact. It has been proved that licking a wound reduces the bacterial contamination and stimulates its healing, because saliva contains antimicrobial substances that include, among others, thiocyanate, nitrate and lysozyme.

By means of the "trial and error" method, prehistoric man started to find plants and mineral substances that turned out to be effective against infections, and gradually built a genuine pharmacopoeia for the treatment of infectious processes, based, if you may, on rudimentary knowledge regarding disinfection.

On the other hand, it would seem that cauterization by fire was widely used in primitive medicine, and that hydrotherapy was considered by some nations as an effective healing means, apart from being a purifying rite.

At the same time, man began to notice that some of the worse infectious diseases never afflicted the same person twice; hence he developed the necessary means to undergo them, before suffering their consequences.

Patient isolation to avoid contagion must have been widely spread in some populations, while the burying of excrement, the maintenance of clean water currents and other hygienic measures must have been common practices among the prehistoric tribes; at least, that is what anthropologic studies performed on current populations, still living under primitive life conditions, show.

Primitive medicine is mainly magical in the way it interprets disease, and empirical-magical in the way it acts before it. Magical thought of the primitive man is essentially causal: every event in his life, environmental situation or phenomenon, has a reason, a cause; nothing happens by chance. Primitive man acts before disease once he has determined the causal agent, and to that purpose, he performs the "diagnosis" through fortune-telling and foreboding, acting therapeutically through a wide range of remedies, from purely empirical treatments (herbs, hydrotherapy, etc.) or surgical treatments (mainly, trauma surgery), to entirely magical rituals that include objects (amulets, fetishes, talismans, cloverleaves, etc.), charms, enchantments, prayers, or using a mixture of all of them.

Together with oral formulas and the administration of varied substances, the transference of sickness has always occupied a prominent place in magical medicine. The transference can occur from man to man (in many of these cases, the witch doctor plays the role of "recipient" of the patient's disease), from patient to animal, or from patient to an object. Disease transference is a practice frequently used to free a population from an epidemic scourge. In some cases of man-to-man transference, and in most of the man-to-animal occasions, the "victim" is burdened with the illness and sacrificed as an offering to the divinity that has to be pleased. In the transference to objects, these are usually abandoned in some isolated place.

Magical objects, amulets, fetishes, talismans, all have a preventive effect, whether rejecting or absorbing the infectious diseases.

It would be pretentious on my part to think that with this humble opinion I can enumerate the initial and transcendental facts of antibiotic therapy; nevertheless, I believe it serves at least as a reminder, which will allow the deliver of a subsequent fascicle to the interested reader, with more information about one of the most important pillars in human medical technology, from ancient times to its current progress.❖

---

1. Medical Affairs Manager,
Pfizer Central America & Caribbean
pedro.lovato@pfizer.com

BIOGRAPHY

-Abraham EP, Chain E. An enzyme from bacteria able to destroy penicillin. Nature 1940; 146:837.
-Abraham EP, Chain E, Fletcher CM, Gardner AD, Heatley NG, Jennings MA, Florey HW. Further observations on penicillin. 1941. Lancet 2: 188-189.
-Ackerknecht EH. Medicina y Antropología Social. Madrid Ed. Akal, 1985.
-Ackerknecht EH. Therapie von der Primitiven Hiszum 20. Stuttgart. Enke. Jahrhukdert., 1970
-Belmonte A. Terapéutica antibiótica. Santiago de Compostela: Universidad de Santiago de Compostela, 1981.
-Bulloch W. The History of Bacteriology. Oxford: Oxford University Press, 1936.
-Bustinza F. La penicilina y los antibióticos antimicrobianos. Madrid: ED. Plus Ultra, 1945.
-Campillo. La enfermedad en la Prehistoria. Introducción a la Paleopatología. Barcelona: Salvat, 1983.
-Carpentier J, Lebrun F, Breve historia de Europa. Madrid: Alianza Editorial, 1994.
-Cohen ML. Epidemiology of drug resistance: implications for a post-antimicrobial era. Science 1992; 257: 1050-1054.
-Coleman K, Athalye M, Clancey A, Davison M, Payne DJ, Perry CR, Chopra I. Bacterial resistance mechanisms as therapeutic targets. J Antimicrob Chemother 1994; 33: 1091-1116.
-Courvallin P. Evasion of Antibiotics. Quebec: Ed. Butterworths, London, 1971.
-Cowen DL, Segelman A B. Antibiotics in Historical Perspective. EEUU: Merck & Co., Inc. 1981
-Chain E, Florey HW, Garnerd AD, Heatley NG, Jennings MA, Orr Ewing J, Sanders AG. Penicillin as a chemo therapeutic agent. Lancet 1940; 2: 226-228.
-C Garrison FH. History of Medicine (4.ª ed.). Philadelphia and London, 1929.
-Gracia Guillén D, Albarracín A, Arquiola E, Erill S, Montiel L, Peset JL, Somolinos J, Laín Entralgo P. Historia del Medicamento. Barcelona: Ed. Doyma, 1985.
-Grandes biografías. Barcelona: Planeta DeAgostini, 1995.
-Granjel LJS. Historia General de la Medicina Española. Salamanca: Ed. Universidad de Salamanca. 978-1982.
-Guerra F. La medicina precolombina. Madrid: Ediciones de Cultura Hispánica, 1990.

Comments on the 1966 Beecher Report[1,2]

Bustos-Montero D.[1]

After World War II, and despite the fact that the Nuremberg Code supposed the starting point to the regulation of research on human beings, the constant violation to currently admitted ethical principles was obvious, which at the time were the basis of the discussion that followed.

At such a critical time, a fundamental figure often forgotten by history emerged: Dr. Henry Beecher, an anesthesiologist from the School of Medicine of Harvard University. Beecher, possessor of a brilliant professional career, turned his eyes in the 50´s toward the ethical aspects of research on human beings, committing himself with high quality research and fearing that the performance of non ethical studies could discredit researchers in general[4,5,6].

Experimentation in Man (JAMA 1959;169(5);461-478), Beecher's first important publication on the field of research ethics, did not prompt any concern from society regarding this subject.

Dazzled by this situation, in 1965 he changed his traditional conservative model, deciding to move farther on. In an activity held at a rural area of Michigan, United States, he presented a review of 18 clinical investigations, which were, in his opinion, examples of non ethical actions, although they were being carried out in widely renowned hospitals and universities.[6]

And that was how the media came to pay attention to these facts, and Beecher started being attacked by his own colleagues for treason to the medical profession, for spreading his fears in public, and for suggesting that researches were unethical in most of the cases, not exceptional facts[6].

Loyal to his beliefs, he sent to JAMA a revised version of his 1965 presentation, which was rejected. Not wanting to give up, he presented this version for revision to the New England Journal of Medicine, which after several revisions decided to publish it in 1966, with a total of 22 cases, under the title "Ethics and Clinical Research" (NEJM 1966;274:1354-1360)[2].

This article, known as the "1966: Beecher Report", played a meaningful role on the implementation of federal regulations, ruling the conduct of researches in the United States where human beings are subjects, such as, for instance, the need to have a well-informed and clear consent from all the participants. This was contradictory to his known skepticism regarding whether it was possible to obtain a fully informed consent. In its place, he argued that the presence of an intelligent, informed, conscientious, compassionate and responsible researcher constituted the best protection any participant could hope for[3].

As history has proven, these publications did not definitely resolve all controversies; however, they forced health professionals and society in general to acknowledge the problem, raising awareness to the fact that a careful ethical revision must be part of every research in which human beings participate.❖

1. Medical Manager, Cardiometabolic Franchise, Pfizer Central America & Caribbean
daniel.bustos@pfizer.com

REFERENCES

1. Harkness J, Lederer SE, Wikler D. Laying ethical foundations for clinical research. WHO Bulletin 2001;79(4):365-366
2. Beecher HK. Ethics and clinical research. NEJM 1966;274:1354-1360
3. Moreno J. Undue risk secret state experiments on humans. New York, WH Freeman 1999;242.
4. Rothman R. Strangers at the bedside: a history of how law and bioethics transformed medical decision making. New York, Basic Books, 1991.
5. Harkness J. Henry Beecher. In Garraty JA, Carnes MC, eds. American national biography, vol w. New York, Oxford University Press, 1999:465-467.
6. BeecherHK. Ethics and the explosion of human experimentation. 1965. In the Beecher Papers, Francis A. Countway Library of Medicine, Harvard University.
7. Beecher HK. Experimentation in man. Journal of the American Medical Association, 1959;169(5):461-478.
8. Pappworth M. Human Guinea Pigs: experimentation on man. London, Routledge & Kegan Paul, 1967.
9. Pappworth MH. Human Guinea Pigs- a history. British Medical Journal 1990; 301:1456-1460.
10. Edelson P. Henry K Beecher and Maurice Pappworth:informed consent in human experimentation and the physician's response. In Doyal L, Tobias JS eds. Informed consent in medical research. London, BMJ Books, 2000.

Reading Suggestions

FUNDACIÓN
CIENCIAS DE LA SALUD

Investigación para una mejor clínica, gestión y reforma de atención primaria en España. 2010.
(only in Spanish)

Available at:
http://www.fcs.es/docs/publicaciones/investigacion_clinica_gestion_reforma_ap.pdf

UNESCO

Science Report 2010: the current status of science around the World. ISBN 978-92-3-104132-7. UNESCO Publishing 2010

Available at:
http://www.unesco.org/new/en/natural-sciences/science-technology/prospective-studies/unesco-science-report/unesco-science-report-2010/

Recommended Events

COURSE: INTRODUCTION TO
ETHICS IN RESEARCH (in Spanish)

Universidad Latina de Costa Rica
March 15, 2011 – April 14, 2011
www.ulatina.ac.cr

2011 IACUC CONFERENCE

Assuring Compliance while facilitating research: achieving the delicate balance
March 31 – April 1, 2011
Chicago, IL, USA
www.primr.org

WEBINAR

No more excuses: Building trust and capacity through the Bioethics Research Infrastructure Initiative.
Tuesday, June 14, 2011
13:00 – 14:30 ET • www.primr.org

VII LATIN AMERICAN AND
CARIBBEAN CONGRESS
ON BIOETHICS

Bioethics and Society in Latin America
Latin American and Caribbean Federation of Bioethics Institutions
June 23-25, 2011
Viña del Mar, Chile
www.cbioetica.org

Author's Guidelines

Manuscripts presented for publication on this journal must adjust to the ethical considerations and technical criteria established on the "Uniform Requirements for Manuscripts submitted to Biomedical Journals", developed by the International Committee of Medical Journal Editors.

Next, essential elements that must be included in the articles:

Title Page:

• **T**itle: Must include all the necessary information for its electronic retrieval. There should not be any abbreviations.

• Authors: Name and last names of author or authors and institutional affiliation(s). Name of department(s) or institution(s) where the work was carried out.
Release from liability (if any).

• Correspondence: Name and mailing address, telephone and fax numbers of the author to whom any correspondence should be addressed.
Sources of support: list of contributors, in the form of grants, equipment, drugs, or others.

• Short title: maximum 40 characters (including letters and spaces), on the footer of this section.

• Number of: pages, figures and tables (if any).

Conflict of Interest Page:

Consists of a declaration of all potential conflicts of interest that the authors could have. To make this declaration, the form located at the following address may be used: http://www.icmje.org/coi_disclosure.pdf.

Manuscript Body

• Abstract: This section must provide the context for the study and must include the study's purpose, basic procedure(s), findings, conclusions and sources of support. No abbreviations, references or footnotes may be used.

• Introduction: Detail the purpose of the article (that is, the nature of the problem and its importance). Points out the objective, or the hypothesis to be tested. It must never include data or conclusions.

• Methods: Clearly describe the design of the study, methods of selection of participants (if any), apparatus, laboratory analysis, procedures and statistical analysis used.

• Results: Results should be presented in a logical sequence in the text. It may contain tables and illustrations. The data represented in tables or illustrations may not be repeated in the text; tables and illustrations should be numbered consecutively with Arabic numerals, each one presented individually by means of a centered title, and any explanation note at the bottom. Figures and images must be of a professional quality. X ray films, pathologies or scans must be accompanied by their respective units or marks.

• Discussion: Emphasize the new and important aspects contributed by the study and the conclusions that follow from the available evidence. Do not repeat the same information in different sections.

• References: Follow the system suggested for biomedical journals (www.ICMJE.org). References should be numbered consecutively according to the order in which they were mentioned for the first time in the text. Avoid the use of personal communications or material not yet published (including theses and conference material); these may be recorded in parenthesis.

• Size: The size of the articles must be a maximum of 5 pages (10 pages in Word, Arial 11 font, spacing 1.5).

Manuscripts (a signed original and a copy on CD compatible with the Windows environment) must be sent to the following address:

Perspectives in Research Journal

Pfizer Program for the Development of Investigation and Science (PRODICI)
Medical Department
Pfizer S.A.
Zona Franca Ultrapark Edificio 4B
La Aurora, Heredia
P.O Box 10202-1000 San José
Costa Rica

Along with the original manuscript, the author should attach the declaration of transference of rights to the journal, available at www.pfizercac.com ❖

Printed in March 2011
Printing Technique S.A.
Costa Rica
3000 unities
Published by BRL Research Ltda.