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SPECIAL REPORT

RESEARCH AND TRAINING IN MEDICINAL CHEMISTRY IN SOUTH AND CENTRAL AMERICAN COUNTRIES AND SUB-SAHARAN AFRICA*

Improving the therapeutic and sanitary conditions of different countries is one of the objectives which, at present, receives much attention from diverse organizations and governments throughout the world. However, it is well-known that the therapeutic needs are different from country to country. In some countries, the principal problems are linked to cardiovascular diseases, degenerative diseases and cancer, for example, while in others, infectious diseases are the principal causes of morbidity and mortality. In any of these cases, medicine, as a sanitary tool, is part of the universal heritage, with important implications for sanitary and economic interests. Medicinal chemists are the health professionals charged with the responsibility of synthesizing new compounds for testing as part of the discovery process for new medicines.

Medicinal Chemistry is a chemistry-based discipline, also involving aspects of biological, medical, and pharmaceutical sciences. It is concerned with the invention, discovery, design, identification, and preparation of biologically active new chemical entities (IUPAC Medicinal Chemistry Section 1996).

The Medicinal Chemistry Section within IUPAC decided to gather statistical and anecdotal information about the collaboration and the barriers to progress among countries. We were particularly interested in those countries that are at present unable to contribute a significant part of their resources to research and education in the discovery of new medicinal agents. Our initial actions are intended to determine the current situation; subsequently we will seek channels to facilitate the above type of collaboration. Here we publish the results of our first study with the aim of stimulating international contact and collaboration.

In this first review, both South and Central America, as well as Africa, have been considered. A subsequent study will include other geographic areas of interest, such as Asia.

Work rationale.

A medicinal agent is part of the universal heritage, in spite of the fact that a difference has been

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established between countries that carry out research on new medicinal agents and those countries which are only consumers. For the purposes of our discussion, it must be pointed out that there are countries which promote Medicinal Chemistry in their universities, research centers and companies, while in some others, it is common knowledge that this practice is nonexistent. In others still, it is unknown whether this practice is carried out.

This is a constantly changing world, and great civilizations have disappeared while new ones have emerged. In this context, is the present situation in which there are countries that carry out research versus countries which only use the results, likely to continue in the future?

The discovery of medicinal agents contains both old and new elements. The techniques are new while imagination is old. Instrumentation is new but the careful and well-documented observation is old. The methods of reporting are new and yet communication, as the most characteristic concept for defining man, is old.

The discovery of medicinal agents is usually carried out by large research groups, but small ones can also be successful when they know their profession well and their members are researchers of great talents. The discovery and invention of new medicinal agents calls for well-endowed libraries but access to these installations no longer requires the immediate physical presence of the researcher; such access can be remote. The discovery and invention of new medicinal agents requires information, but this tool is not found in traditional libraries. Can old civilizations that have conserved a traditional medicine which has proved itself effective, in spite of its ups and downs, be simply ignored?

The events relating to this question date back to different examples, one of them being the discovery of America in 1492. This example can be applied to today's present situation. A continent which was well-developed in the arts, philosophy and sciences, met up with another continent whose development, in general, was very different. These circumstances changed the history of all humanity. But it is in the field of medicine and the area of therapeutic remedies where the great revolution in therapeutics would take place. What has happened since then? The developed countries have considered the traditional medicines of the New World to be of great interest. But the research has been carried out outside the discovered territories. This generalization is applicable to Africa, Central America and South America and has resulted in the development of both research and the derived clinical experience in countries other than those where the plants had been found. Thus, many compounds within the scope of modern therapeutics have their origin in the plants used in the traditional cultures for therapeutic purposes. The current studies with *Taxus* and *Uncaria* are examples of this.

As a result, the panorama is divided as in the sixteenth century. However, the situation is not the same. The countries of South and Central America as well as those of Africa are finding their way in the social, political and even in scientific fields. The twenty first century will be important for many reasons. We would like to point out that in the near future, true collaboration among countries can be an important alternative, among others, for the global development of medicinal chemistry. Possibly, it is in this context, that medicinal chemistry of the next century should be developed.

Cooperation already exists between equals, well-developed companies and well-developed research centers. The time has come to cooperate with the lesser developed institutions. Contemplating our planet Earth from up on the Moon clarifies many things with regard to the differences of races and countries, of cultures and of industrial development.

With the proposal to search for universal cooperation in the field of medicinal chemistry, the IUPAC group has elaborated a line of work divided into two phases:

a. An awareness of the true situation of medicinal chemistry in the different geographic areas

of the world.

b. A proposed set of actions as to achieve more effective cooperation.

This report presents and discusses the results of a questionnaire carried out in Central and South America as well as in sub-Saharan Africa. The method used was a written questionnaire and interviews.

General considerations. The survey was designed to cover four distinct areas: (i) the medicinal chemistry teaching field; (ii) research in medicinal chemistry; (iii) opportunities for the development of research, teaching and training in the field of medicinal chemistry; and (iv) ways in which cooperation in the practical training, academic teaching or research in medicinal chemistry could be carried out.

Addressees of the survey. Surveys were received by mail by March 1, 1996 from South and Central American countries and sub-Saharan Africa. The senders were from Chile (B.K. Cassels, S. Sepulveda-Boza); Peru (E. Montoya); Nigeria (M.O. Fatope, S.A. Adesanya); Cameroon (N. Barthelemy, B.L. Sondengam); Zimbabwe (L.F.S. Chagonda); Ethiopia (D. Abate); Madagascar (P. Rasoanaivo).

Surveys carried out by interviews. The respondents were from 15 countries: South and Central America: Argentina (G.D. Ferraro); Bolivia (A.G. Turba); Brasil (A. Brag a de Oliveira, A.J. Lapa, E. Barreiro); Colombia (R. Pinzon); Costa Rica (G.A. Mora); Cuba (R. Pellón); Chile (B. Cassels, E. Gonzalez, P. Huenchunir); Ecuador (X. Chiriboga); Guatemala (A. Caceres); Panama (M. P. Gupta); Paraguay (E.A. Ferro); Peru (E. Montoya; O. Lock); Republica Dominicana (M. Vasquez); Uruguay (E. Manta, G. Seoane); Venezuela (J.N. Dominguez).

RESULTS FROM ANALYSIS OF THE ANSWERS RECEIVED

Medicinal chemistry Teaching Field. In this section of the questionnaire, a request was made for information concerning the type of institution where medicinal chemistry is taught, the strong points and the deficiencies observed in the system and the perceived needs and the actual situation concerning collaboration with other countries.

The fundamental situation is that the teaching of medicinal chemistry, as currently defined, is not present in the developing countries. However, complementary disciplines such as organic chemistry, pharmacognosy and pharmacology are considered. In some cases, the studies in medicinal chemistry are related to the identification and preparation of biologically active chemical entities, not new chemical entities.

The surveys indicated interest in considering medicinal chemistry as a new discipline to be included in the curriculum. The result is that the studies related to medicinal chemistry are dispersed throughout different institutions. Interesting initiatives have been found in the promotion of medicinal chemistry education. One noteworthy example is that of the group of professors from Brazil (56 Schools of Pharmacy) who are working on new study programs, both academic and training, incorporating the internationally recognized tools. This type of initiative is not alone in South America, and the Peruvian group can be cited as one more example. Argentina is yet another interesting case which adapts the studies of medicinal chemistry to the current parameters used by those countries with a long tradition in this specialty .

From a teaching standpoint, the needs are, in general, substantial and important. Three different areas should be considered: (1) professors, (2) reference literature, and (3) reagents and equipment. With regard to the teaching staff, in general, it is well trained and quite interested in the subject. Very often many of these professors have had long stays in universities and research centers of great prestige as part of their training. Making adjustments within the field of education so as to allow professors from related disciplines to contribute to the task of teaching Medicinal chemistry, does not appear to present special difficulties. From a reference literature standpoint, important needs have been found; they derive from two facets: on the one hand, from the lack of a research tradition, so vital for consolidating the libraries and on the other, economic problems derived from the cost of this essential tool. In general, it can be said that there are important deficiencies in the bibliographic area. The lack of reagents is equally important. Once again, the economic aspects conflict with the teaching practice.

Aid is needed in the three areas previously mentioned. With regard to teaching, a need exists in respect of the collaboration of experts who give courses in these institutions. They need to be able to collaborate in drafting the programs and be capable of receiving professors for training in their universities. Material aid for the acquisition of reference literature and of supplies for practical training in the laboratories is a foremost necessity. In addition, the maintenance of laboratory equipment by the supplier companies is a frequent problem .

Research in medicinal chemistry. In this section, a question was formulated with regard to one centers and personnel dedicated to the study of medicinal chemistry concerning the fields of research as well as the research offers and needs. Research in medicinal chemistry in the countries which have been considered, is almost exclusively centered on the field of natural products. For the countries being considered, this appears to be the focus for initiatives related to medicinal chemistry research.

The situation is simply a result of their history. This approach emerges from the knowledge of plants with medicinal activity in cultures whose origins are very remote, and from the circumstance that very little effort has been put forth in the fields of technology and scientific investigation in the search for and improvement of active compounds by molecular manipulation. All those who answered the questionnaire showed great interest in not being mere suppliers of plants.

For an initial approximation to medicinal chemistry and taking the natural products as a starting point, it is necessary to consider the following:

A. Strengths: correct identification of the plants (in general, good botanists exist in these countries); the gathering of plant material and the preparation of extracts.

B. Weaknesses: difficulties in the determination of biological activities, in the validation of extracts; in the determination of the structures responsible for a specific biological activity; in industrialization and commercialization.

Independently of the degree of development, there is considerable interest in entering the field of medicinal chemistry research. The scientific authorities of these countries are interested in collaborating in research relative to natural products with biological activity.

This is an important point to be considered: the authorities of the countries studied consider the plants to be part of their heritage and a possible source of wealth. They are aware of the fact that they are obliged to attempt, by all means, to retain the greater part of the resulting capital gains. In some cases, the bureaucratic requirements necessary for obtaining plants or extracts

from their place of origin, are overwhelming. In some cases, failure to satisfy these requirements can result in judicial actions.

Opportunities for the development of research, teaching and training in the field of medicinal chemistry. The proposals in medicinal chemistry as presently defined, are not considered in general terms. In this way, the collaboration is centered almost exclusively within the framework of natural products. On the other hand, the collaboration which is being offered presents a wide variety of possibilities. This is also an important aspect to be considered, the possibilities of collaboration with countries that are leading the way to research education in medicinal chemistry are so diverse that they could cover practically any area of interest in the therapeutic field.

In a true sense of collaboration, it is important to work on questions which are characteristic of these countries. A representative example is Chagas' disease or Malaria. It is a question of considering the fact that there are diseases, such as AIDS, which were once restricted to certain countries but are now a universal problem. An illness such as diarrhea, no longer considered to be a problem in developed countries, is of great concern to the countries which we are now considering; the approach to this issue can also be considered, at least partially, from a medicinal chemistry standpoint. Ophthalmologic diseases are another example of interest for these societies, in which there is a different focus from those in the developed countries.

All of the aforementioned are examples of approaches of interest for the countries that are developing within the field of medicinal chemistry. The question here is that working on these issues is not only resulting in a great contribution to the development of and interaction with other societies, but it is also leading to the discovery of new opportunities for those societies that have found their way into the field of medicinal chemistry.

Ways in which cooperation in the practical training, academic teaching or research in medicinal chemistry could be carried out. The matter of cooperation is a need which appears in all of the questionnaires. The impression created in this regard is that there are countries which circulate on a railway on board a train while others run alongside asking for help to get on. It is necessary that the former extend a hand in such a way so as to respond to the request made from the latter.

The requests are very diverse. There are countries, such as Cameroon, that are considering this aid, including in its very initial stages, such as the commercialization of the plants in which active compounds appear. But, in general, the cooperation being requested stems from the correctly prepared extracts. In other cases, the request was related to the identification of active molecules and in still others, to the determination of biological activities.

Once again the general request that has appeared is that of being able to participate in the processes of research and development so as not to remain mere suppliers of plants.

The cooperation can be set-up along three fundamental lines of action:

(a) Via courses, seminars, etc. which permit relationships between institutions and persons within the teaching field; (b) via joint scientific investigation, emphasizing activities which allow development of the centers. Requests for joint research projects; and (c) via greater presence of pharmaceutical companies in the scientific collaboration with those countries that sell their products.

COMMENTS

The responses received have not been numerous enough to allow us to propose a statistical study of much significance. However, in spite of this fact, certain tendencies constantly appear,

allowing us to come to conclusions which can be presumably generalized.

First of all, it appears necessary to point out that similar problems exist in the three areas studied. The activity in medicinal chemistry is greatly linked to the degree of development and economic possibilities of the countries. On more than one occasion, medicinal chemistry has been considered a luxury of developed countries.

In the three areas being considered, the medicament is studied by using plants and traditional medicine as the starting point. Perhaps it is this starting point that served historically for other areas, currently more developed. From a pragmatic point of view on the subject, it would be interesting to take into account the reality of these countries when setting up the corresponding academic programs and when putting forth proposals of collaboration in scientific research.

In this respect the opinions of scientific authorities are not indifferent, at least not in the Latin American countries.

With regard to the collaboration within the aspects of teaching, no special difficulties seem to appear; most likely, this collaboration should establish itself based on mutual knowledge and aid from the institutions and foundations. The actions to be taken in this area are not especially difficult; they appeal fundamentally to the generosity of professors and researchers in the dedication of their time. One aspect to take into consideration would be the at times difficult access to travel fares for academic professors.

In this area, special importance is given to the circulation of reference literature and bibliographic material. Any type of collaboration on this point should take into consideration each and every aspect relative to intellectual property, with regard to the editors and the authors. Finding the formulas which allow access to these resources on the part of those countries of limited resources, is a true challenge to the imagination.

With regard to materials and reagents, the cost derived for their acquisition, can only be solved by economic collaboration.

An interesting consideration which is deduced from the survey has to do with equipment maintenance. It is observed that some centers have had access to valuable equipment as a result of government support, aid from private foundations, etc. However, in the majority of these cases, the upkeep of this equipment, which is usually quite costly, in monetary terms, is not taken into consideration. This point is especially important in those countries which cannot readily maintain instruments in working order because maintenance service is not justified on the part of the companies that produce the equipment.

With regard to the possibilities of collaboration in scientific research, it is necessary to start off from a position that contemplates the true situation of the institutions: their strengths as well as their weaknesses.

At present it is possible to obtain quality extracts from plants which have proven active in traditional medicine. This is important for those countries which have the plants and know their scientific possibilities.

However, in the present state of development of medicinal chemistry, the possibility of obtaining extracts from plants which have never been studied should not be underestimated. Structural novelty now appears on the scene and with it, an enormous interest when considering the possibilities of patents.

The determination of biological activities, their validation, and the elucidation of the structures responsible for these activities should all be present in the collaboration; in this case, as an offer from the most advanced countries.

The discovery of new medicinal agents cannot be realized without the active presence of the pharmaceutical companies.

In our opinion, it is an important juncture for both parties. Just ponder for one moment, the

ssibility of new ideas which can result from the previously cited collaborations, contemplating servations never before considered.

From the medicinal chemistry perspective, there are some interesting considerations ncerning the relationship between these two groups. The first consideration would be to estion if a true cooperation is being developed between the groups or if, on the other hand, the ferences are increasing. The second consideration would be to question if we are capable of ognizing the possibilities of collaboration, for mutual benefit, between the areas in which the rld of research is truely divided at this time.

From the surveys, a request for collaboration in which the natural products should be sidered as a starting point, has been made on the part of the developing countries; this could y well be of interest to both societies.