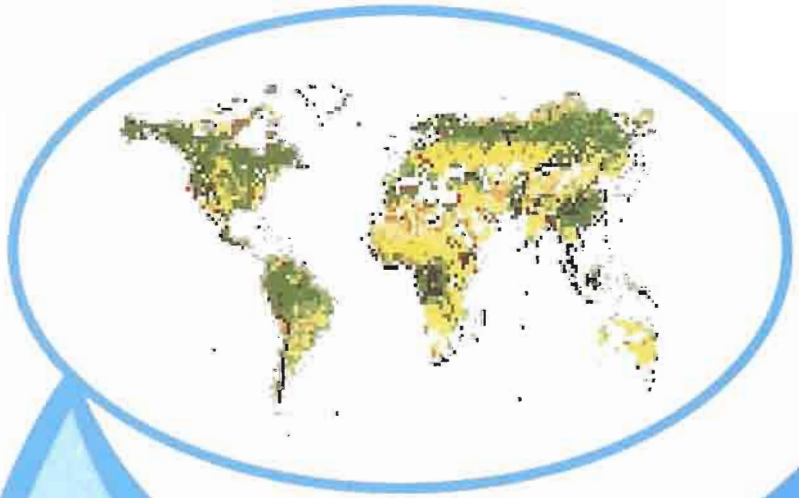
Biological Research, Education and Ethics



Biology International

The International Union of Biological Sciences (IUBS)

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Editorial

Feature Article

Opinion Paper

Science Policy Reviews

Scientific Meetings Reports

Publications Review

Calendar of Meetings

Announcement

- There has been intense competition in the structural and functional analysis of proteins relevant to drug discoveries. Research on membrane proteins and carbohydrate chains should be more focused.
- Japan has annotated 30,000 human cDNA and 80,000 mouse cDNA. It will take advantage of this lead to further research on gene expression, comprehensive protein analysis and elucidation of the mechanisms for the expression of lifestyle diseases.

(2) Biological defense mechanisms related to environmental factors

- The first BSE infection in cattle in Japan was confirmed in September 2001, leading to serious social problems, and there is strong public demand to learn more about the attack mechanism and improve the diagnosis of prion diseases.
- The number of AIDS virus carriers has been on the rise. There are also an estimated 1 to 2 million people infected with hepatitis C in Japan. The prevention of these infectious diseases is an important public health issue.

(3) Brain research for neuro-psychiatric disorders and education

- Various mental disorders have become social problems in recent times. It is important to clarify mental health mechanisms and their relevance to the body in order to overcome such illnesses.
- Basic research on Alzheimer's disease has been progressing rapidly. In an aging society, it is important to develop treatments and prophylactic strategies.
- Research on brain development is important so that discoveries can be applied in the fields of teaching and vocational training.

(4) Materials production and environmental mitigation

- Research that uses microorganisms and plants to produce useful materials and products is important. There are new synthetic methods for producing rare sugars and new biodegradable plastics, while some types of plants produce vaccines.
- It is necessary to accelerate research on proteins, carbohydrates and lipids with new functions. Glyco-biology should be developed to accelerate the mapping of proteomes.
- Environmental mitigation technologies are becoming increasingly important in the shift to a recycling-based society.

(5) Food supply and security

- Technological developments for the hygienic management of food must be strengthened on the basis of risk analysis.
- The practical application of genetically modified crops requires understanding and trust on the part of the general public.
- As the genetic decoding of plants such as rice advances, future research will center on isolating useful genes and illuminating their functions.

(6) Emerging research fields and technological developments

- The integration of biology, chemistry, physics, mathematics and computer science is creating new disciplines such as computational biology and systems biology.
- Remarkable developments are taking place in the areas of nano-biology and nano-medicine. The movement of a protein molecule has been successfully analysed on the nano scale, and the DNA strand can be directly observed using a special microscope. New markets e.g. for DNA and protein chips can be exploited by applying semi-conductor processing technologies. As Japan has some advantages in nano-technology, life science researches should make full use of them.
- Scientific measurement and medical instruments provide the foundation for actual research activities and treatments. These technological developments should be emphasized.

Editorial

Challenges and Changes for *Biology International* !

For the past ten years, *Biology International* (BI), the journal of IUBS, has faithfully served the Union and maintained a regular liaison between its members. Readers find in its pages three classes of informational products.

The first class consists of regular papers about scientific topics and ongoing research. Most of them relate to the general concerns our societies share on development, environment and the diversity of life. They express some contributions of biologists towards understanding the evolving link between humans and the living world around them. Other papers draw attention to the universality of fundamental biological processes and to their complexity that supports global diversity.

In the second place, BI welcomes data and news given by IUBS members. Scientific members present their ongoing activities: recent achievements, calls for interest, programmes and schedules of future meetings, reports on past ones. National members provide comments, reports and on occasion proposals, usually at the time of General Assemblies.

Finally, supporting the long-established policy of the Union's programmatic activities, BI is the expression vector for prospective projections and programme contents. In the Journal, readers find information about Biodiversity, Towards an Integrative Biology, Biosystematics, Biological Education, Bioethics and others.

In the course of the Twentieth Century, Biology on the whole expanded considerably. New scientific fields emerged. They are now fully organised entities and recognized disciplines with their own publications: Microbiology, Immunology, Nutrition, Physiology, Toxicology and others. ICSU federates all these Biological Unions, and their connectivity is debated by other disciplines. Simultaneously, societies developed pressing expectations towards biology. The times of mere curiosity-driven science are over. Social needs and pressures have set up a completely different environment for biologists. Clearly BI, with its regular rate of 2 to 3 issues per year and its non-growing number of readers, is no longer adapted to the rhythm of science and the ways and means of the modern information society. The future of IUBS is at stake with the present communication and publication problem. A first wave of measures were taken recently with an upgraded presentation of the journal and the launch of the IUBS website: http://www.iubs.org.

At the turn of the Twenty-First Century, IUBS is "in the middle of a ford." It heads deliberately towards a modern interactive communication policy inside the Union and with its partners, but its two tools are not appropriate: an ageing BI and a website in infancy. In May 2002 the IUBS Executive Committee considered measures to upgrade the tools and quicken the pace. If today the website is second to the journal, tomorrow the hierarchy must be reversed. This can be done if a radical change in the philosophy and in the quality provided by and through IUBS is carried through. The Committee decided to act simultaneously on the journal and on the website.

A special effort is now expected from BI, its authors, its editorial board and its referees. The present issue and a few to come should serve as a training field where IUBS members develop and test their ability to manage interactive communications and improve the quality of their exchanges.

From this issue and on, BI will present four types of contributions:

1. The 'classical' BI liaison papers
2. Scientific peer-reviewed papers. They present specific advances and/or syntheses on biological topics and on the ways they are addressed at various space and time scales and through various approaches.
3. Contributions specifically dealing with IUBS programmes. Contents and calls for interests are the starting points. The ultimate goal is to stimulate returns of comments, critiques and suggestions to foster an internal dialogue on IUBS activities and orientations.
4. Open papers from biologists about their science, their social situation and their views on the future of biology. These contributions will be classified as opinion papers, published under the responsibility of the author(s), provided they respect the shared values of the Union members. Such contributions can also originate from scientific institutions and express the foundation for their policy towards biology.

In brief, the renewed BI should open a forum for internal and external exchanges.

Today, legitimate intellectual curiosity cannot ignore complexity, interdisciplinarity and social involvements. ICSU has taken measures in this context with a reorientation of its grants programmes. It has given us a clear signal last September 2002 at the Johannesburg World Summit with an initiative on Scientists for Sustainability. And IUBS faces the challenge.

The time has come for IUBS members to develop a renewed appropriation of the journal and to use the present changes as a step towards a future where BI will be online and part of an active website open to science, scientists and society.

As the current BI editor, my wish is that readers find the premises of an evolution in this very issue. It is furthermore my hope that readers react strongly, submit ideas and many more manuscripts, and that the next issues accommodate more changes and new debates.

Jean-Claude Mounolou
Chairman, Editorial Board

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Plant Viruses and Viroids in Tunisia: development of a certification programme for plant propagation materials

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Introduction

In Tunisia, during the last decade, vegetable (pepper, potato, tomato and lettuce), grape and citrus production have been developed through increased cultivated areas of field and greenhouse crops. Heavy losses caused by viral infections are observed mainly in field crops, but also in early greenhouse winter crops, because seedlings are not raised under insect-proof conditions and are exposed to infection. The severity of losses also appears to be directly related to the lack of certified seed and to cultivation methods.

Several Tunisian growing regions were surveyed, and serological and molecular techniques were used to detect viral and viroidal infections in the crops and to characterise the biological and molecular variability of a collection of isolates, selected so as to cover the geographical diversity of these pathogens in Tunisia. These experiments demonstrated the presence of both viruses and viroids isolates in Tunisia and revealed a worrying situation for the future of vegetable, grape and citrus cultivation in this country, if appropriate control measures are not taken.

1. Vegetable, grape and citrus cultivation

Vegetables, grapes and citrus fruits are among the most important horticultural commodities in Tunisia. These crops are a vital source of human nutrition and contribute significantly to the cash income of farmers in Tunisia. The process of exchanging plant materials is laborious, expensive and time consuming. In most cases, quarantine procedures significantly delay the release of imported materials. Traditional procedures for examining plant materials are quite slow and often insufficient to detect diseases, especially virus and viroid diseases.

Currently, there is an increasing demand in Tunisia for locally produced fruits and vegetables and for their propagation materials, both for export and local markets. There are two different laboratories producing tissue culture propagation materials which are supposed to be disease-free. These laboratories contribute towards producing a small proportion of the needed vegetable material, grape seedlings and potato tubers. In addition, there is a continuous demand in Tunisia for new commercial cultivars and an expanded germplasm base for breeding programmes. Pathogen-testing programmes to ensure that only disease-free material will be distributed through local nurseries are of critical importance, but at the same time they are a hindrance to effective production. Viral and viroidal infections present an almost intractable problem to the Tunisian government, as several months or even years would be required to complete testing for these pathogens in locally produced or imported germplasm and produce virus or viroid-free plants. Thus, it is vital that pathogen testing and control procedures be improved. The development of processes to detect viruses and viroids rapidly and accurately using molecular biology and biotechnology techniques will provide regulatory agencies with the necessary tools to shorten and improve their procedures for detection and diagnosis.

Tunisia produces 190,000, 700,000 and 30,000 tons of pepper, tomato and potato, respectively. For citrus and grapes, these values are estimated at 240,000 tons and 12 Q/ha, respectively. Tunisia imports potato tubers, vegetable seeds, bulbs and seedlings of ornamental plants and fruit tree seedlings.

Most, if not all, economically important crop plants are subject to attack by several viruses and viroids which reduce both the yield and quality of the crop. Vegetatively propagated plants, such as the potato, are severely damaged when grown from infected plant materials. Viruses transmitted through true seeds, or through distributed seedlings such as those of lettuce and tomatoes, can cause even greater losses in a crop, especially when they are also transmitted by insects. The use of virus- and viroid-free plants and the elimination of virus and viroid sources by early diagnosis have already made a considerable positive impact worldwide on yield and quality of some crops. The most important virus problems affecting agricultural crops in Tunisia are: for tomatoes and peppers: tomato yellow leaf curl virus (TYLCV), pepper veinal mottle virus (PVMV), potato virus Y (PVY), tomato spotted wilt virus (TSWV), tomato mosaic virus (ToMV), cucumber mosaic virus (CMV); for potatoes: potato virus Y (PVY), potato leafroll virus (PLRV); for lettuce: lettuce mosaic virus (LMV); for grapes: australian grapevine viroid (AGVd), grapevine yellow speckle viroid (GYSVd), for citrus : citrus exocortis viroid (CEVd) and hop stunt viroid (HSVd).

The need for releasing and producing virus and viroid-free plant material either from imported or from local stocks requires the development and improvment of the certification program. Until now, the quarantine and control service of Tunisia undertakes certification of such products using biological or serological methods. Such methods are not expensive but time-consuming and subject to many problems of sensitivity. Recently, improved knowledge of pathogen genomes and optimisation of molecular biology and biotechnology techniques applied to the diagnosis of plant pathogens have stimulated studies in order to develop diagnostic methods that are sensitive, reliable and less time-consuming for detecting, and ultimately controlling, economically important pathogens affecting selected agricultural crops. The plant pathogen detection team of our laboratory is working on standardizing the developed protocols and transferring them to the quarantine service, together with the acquisition of skills in their use through training. This will enable Tunisia to streamline its indexing programmes and quarantine procedures.

2. Major viruses and viroids of the selected crops

Lettuce

Lettuce mosaic virus (LMV) is potentially the most destructive virus of lettuce (*Lactuca sativa* L.) and has a worldwide distribution. It is transmitted through seed and by aphids in a non-persistent manner (Dinant and Lot, 1992; Zerbini *et al.*, 1995; Tomlinson, 1970). Field symptoms include vein clearing, mosaic or mottling and/or leaf deformation and necrosis. Infection can severely damage the crop and considerably affect the yield. LMV can be controlled in areas where preventive measures can be applied; however, it remains a damaging virus to lettuce in regions where such programmes are lacking. LMV is a member of the genus *Potyvirus* family *Potyviridae* (Tomlinson, 1964). Its single-stranded genomic RNA is typically about 10kb and contains a single large open reading frame encoding a polyprotein. It has a viral-encoded protein (VPg) linked to its 5' end and is polyadenylated at its 3' end (Shukla *et al.*, 1994). Resistance to LMV in lettuce is linked to the recessive genes *g* and *mo*, considered to be allelic or very closely linked (Pink *et al.*, 1992) and now denoted $mo1^1$ and $mo1^2$. LMV is biologically variable and its isolates have been classified into pathotypes, according to their virulence to particular lettuce varieties (Pink *et al.*, 1992; Dinant and Lot, 1992; Bos *et al.*, 1994;

Revers *et al.*, 1997a). Of particular concern are the seed-transmissible isolates, here referred to as MOST (*mo*-breaking, seed-transmitted), that are able completely to overcome $mo1^1$ and $mo1^2$ resistance genes.

Potato

Potato leaf roll virus (PLRV), a *Luteovirus,* can reduce yields, tuber size and internal quality. The genome of PLRV consists of a single molecule of positive sense ssRNA with a 5' linked VPg and no poly (A) sequence (Mayo *et al.*, 1982). This virus is detected in Tunisia. Many studies are carried on this virus in order to characterise Tunisian isolates.

Potato virus Y (PVY), a *Potyvirus,* is a ubiquitous plant virus capable of infecting a large range of plants in several families such as the Solanaceae (potato, tobacco, tomato and pepper). PVY isolates can be classified into pathotypes such as O, N, C, NTN (Barnett, 1992). The PVY genome is a positive-sense, single-stranded RNA of approximately 9.7 kb with a genome-linked protein (VPg) at the 5'terminus and a poly (A) tail at the 3' terminus of the RNA molecule (Hari, 1995). This virus, also infecting peppers and tomatoes, has been studied. Molecular variability was performed by sequence analysis (Fakhfakh et al., 1995), and monoclonal antibodies have been produced that enable the differentiation of many isolates.

Tomatoes and Peppers

In the last few years, tomato and pepper crops in Tunisia have frequently been infected with viruses, causing heavy losses and a dramatic reduction of cropping areas. Major viruses responsible for these losses are cucumber mosaic virus (CMV), pepper veinal mottle virus (PVMV), and tomato yellow leaf curl virus (TYLCV).

Cucumber mosaic virus (CMV) is a tripartite, single-stranded (+)-sense RNA virus (Kaper and Waterworth, 1981; Palukaitis *et al.*, 1992). Its three genomic RNAs have been designated as RNA1, 2 and 3, and are 3.4, 3.0, and 2.2 kb in length, respectively (Peden and Symons, 1973). CMV has the largest host range of any virus, infecting 775 plant species in 85 families and 365 genera, including both monocotyledons and dicotyledons (Kaper and Waterworth, 1981). CMV is transmitted in a non-persistent manner by more than 60 aphid species. Tissue culture, ELISA and RT-PCR are techniques used in combative strategies. An RT-PCR assay was developed for the detection of CMV.

Pepper veinal mottle virus (PVMV), a member of the *Potyvirus* genus, is an endemic virus in pepper and other solanaceous crops mainly in West African countries. It is readily sap transmissible to a narrow range of hosts. Transmission by aphids occurs in a non-persistant manner. Its has a positive single-stranded polyadenylated RNA genome of about 10 Kb and a VPg protein covalently linked to the 5' end. PVMV shares several properties with other potyviruses such as the formation of viral inclusion bodies called "pinwheels" in the cytoplasm of infected cells. However, PVMV is serologically unrelated to several pepper infecting potyviruses such as PVY, type member of this genus, CVMV, TEV, and PeMV.

Tomato yellow leaf curl virus (TYLCV) has been extensively studied in the Middle East, where losses of nearly 100% have been commonly reported. The most serious viral disease of tomatoes in the Mediterranean region, the virus is transmitted by the whitefly (*Bemisia tabaci*). This virus is a ssDNA geminivirus spreading in Middle Eastern countries (Navot *et al.*,1991; Nakhla *et al.*, 1994). Represented by isolates different from those spreading in the Middle East, this virus is also present in Tunisia. Molecular methods for its detection by both DNA hybridization and PCR have been developed, providing evidence that this virus has been introduced into the Western Hemisphere, causing heavy losses. Using specific primers, this virus was identified in Tunisia. According to sequence analysis, Tunisian isolates are homologous to Sardinian ones. This work is conducted in collaboration with the department of plant pathology of the Wisconsin-Madison University.

Grapes

The most important diseases of grapevine in Tunisia are: fanleaf, caused by GFLV; leafroll, caused by GLRaV; stem pitting complex, particularly Kobber Stem Grooving, caused by GVA; and Corky Bark, caused by GVB (Acheche *et al.*, 1998).

Citrus and Grapes

Viroids are the smallest known pathogens and have only been found in plants. They consist of a small, circular, single-stranded infective RNA, ranging in size from 246 nucleotides in Avocado Sun Blotch Viroid (ASBVd) (Symons, 1981) to 399 in Chrysanthemum Chlorotic Mottle Viroid (ChCMVd) (Navarro and Flores, 1997). Unlike viruses, they do not have a protein coat protein and are not known to encode any proteins; hence they must rely on host enzymes for their biological function (Wan Chow Wash and Symons, 1997). Viroids cause serious diseases in economically important crops such as potato, tomato, fruit trees (mainly palms, citrus, apple, peach, grapevine) and ornamental plants. Five viroids can infect grapevine (Rezain *et al.*, 1992). These are Hop Stunt Viroid (HSVd), Citrus Exocortis Viroid (CEVd), the two grapevine yellow speckle viroids (GYSVd-1 and GYSVd-2), and Australian Grapevine Viroid (AGVd). Grapevine viroids are subdivided into three groups based on their homology within the central domain of the viroid molecule (Szychowski *et al.*, 1998). They have never been reported in North Africa. Expression of yellow speckle is ephemeral and mostly evident at the end of summer, indicating that symptoms are strongly influenced by climatic conditions. Experiments have shown that Vein-Banding disease results from a synergistic reaction between grapevine viroids and Grapevine Fan Leaf Virus (GFLV) (Szychowski *et al.*, 1998).

The various viroids detected in citrus plants are divided into five groups based on physical properties, migration rates in gel electrophoresis, nucleotide sequence similarity and biological properties. These groups are: citrus exocortis viroid group (CEVd), citrus viroid group I (CVd-I), citrus viroid group II (CVd-II), citrus viroid group III (CVd-III) and citrus viroid group IV. Citrus exocortis is a disease known to be caused by the viroid complex in which CEVd is the main component. Exocortis is distributed worldwide. Infected susceptible plants show symptoms of bark scaling on the rootstock and general stunting.

Since most measures for the control of virus and viroidal diseases are based on prevention rather than cure, it is essential to have reliable and sensitive methods for pathogen detection.

3. Survey of the present situation

LMV: The recent world-wide emergence of highly pathogenic and resistance-breaking isolates of LMV is alarming. These isolates, able to overcome the resistance genes $mo1^1$ or $mo1^2$, have a clear potential to be spread to new areas through the distribution of contaminated seed lots. This new situation has increased interest in developing tools for the study of the epidemiological properties of LMV isolates and for a better understanding of correlations among biological properties such as resistance-breaking, seed-transmissibility and molecular characteristics. We have tested a large number of samples collected in different lettuce-growing regions of Tunisia for the presence of LMV. The tissue-blotting assay proved simple, fast, reliable and very economical. As previously reported (Lin *et al.*, 1990), this simple technique offers numerous advantages when a large number of samples need to be processed rapidly. In this respect, this technique should prove very useful for epidemiological studies of LMV in the future. The sanitary status of lettuce crops in Tunisia seems satisfactory, as none of 174 random samples of symptomless lettuce was infected with LMV. Analysis of the symptomatic samples indicated that at least during our survey season, LMV was the major virus infecting lettuce in Tunisia, since it was observed in half of the symptomatic samples. Comparison of

the prevalence of symptoms in fields planted with susceptible or LMV-resistant varieties indicate that the *mo1*[1] and *mo1*[2] resistance genes still afford a significant degree of protection against LMV infection in Tunisia. Among the representative LMV isolates finally analysed, many of them induced very severe symptoms on the susceptible cv. Trocadéro and were able to overcome the *mo1*[1] resistance gene of cv. Mantilia. Using a combination of RT-PCR coupled with either RFLP analysis or direct sequencing proved equally effective for defining molecular affinities between LMV isolates. In particular, both identified all isolates as belonging to the Western Europe group, and within this group, many isolates were close to MOST ones. Whereas all other isolates were close to the common isolate and can be efficiently controlled by the deployment of varieties carrying either form of the *mo1* resistance gene. Analysis of the phylogenetic affinities of the *mo1*[1]-overcoming isolates shows that they are very closely related to known MOST isolates. The very close molecular relationships observed (sequence identity in the short region analysed) indicates that they are seed-transmitted. The presence of such isolates clearly represents a threat to the Tunisian lettuce industry. Improvement of the sanitary situation of lettuce crops in Tunisia calls for more widespread use of certified lettuce seed, if further entry of similar resistance-breaking isolates is to be averted (Fakhfakh *et al.*, 2001; Krause-Sakate *et al.*, 2002).

PVMV: Three Tunisian PVMV isolates identified in pepper and tomato fields and one isolate from Ivory Coast were subjected to biological and molecular analyses. Since these isolates induced different symptoms on tobacco, they were biologically clustered into two major groups according to their severity. As no PVMV sequence data are available, detailed sequence comparisons of coat protein gene (CP) and 3'-non translated region (3'NTR) were made. Results suggest that the 3'NTR region of the RNA genome may be directly involved in the modulation of disease symptoms (Gorsane *et al.*, 1999 ; 2001).

CMV: Biological and molecular analyses, based on symptom expression and restriction enzyme patterns of coat protein PCR product, were carried out to differentiate Tunisian CMV isolates. Amplification of the coat protein gene of Tunisian CMV isolates was successfully performed using RT-PCR on viral ssRNA. This region is 870 nucleotides in size. Analysis of restriction fragments using *HpaII* digestions supports the assignment of the Tunisian CMV isolates to two distinct groups. The CMV-Tu1 isolate (severe subgroup, S-I) and six other Tunisian CMV isolates produced only two restriction fragments after *Hpa*II digestion, but the CMV-Tu2 and CMV-Tu3 isolates (attenuate subgroup, S-II) and three other Tunisian CMV isolates produced many restriction fragments after *Hpa*II digestion. This analysis revealed a correlation between *Hpa*II restriction pattern and symptom expression. Hybridization with a specific probe showed that none of the three Tunisian CMV isolates, representing S-I and S-II subgroups, and none of twenty other isolates, was associated with a satellite RNA. Consequently, differences in symptom expression between the two Tunisian groups of isolates were not correlated with the presence of RNA satellite. This may be due to the ability of CMV Tunisian isolates neither to carry nor to support the accumulation of satellite RNA. The ultimate goal of this study is to develop a simple but reliable method for the diagnosis and control of CMV infection and classification of CMV isolates into groups. RT-PCR-RFLP could be seen as an appropriate method for detecting and typing CMV isolates. This method, when extended to many genome regions, will be helpful in detecting the emergence of new viral strains with new biological properties (Fakhfakh *et al.*, 1999).

Grapevine viruses: Detection of GLRaV3 in infected grapevine plants was performed. Viral RNA was successfully detected not only in total crude nucleic acid extracts of infected grapevine tissues but also in viruliferous mealybug vector extracts by RT-PCR. This detection was rapid, sensitive and specific without the occurrence of any background. Comparative ELISA, RT-PCR and IC-RT-PCR assays were carried out and revealed the greater sensitivity and specificity of PCR techniques (Acheche *et al.*, 1999). Furthermore, we have optimized the experimental conditions for

molecular procedures: IC-RT-PCR and RNA-capture RT-PCR. These techniques were effective to detect GFLV viruses with greater sensitivity and specificity than the direct RT-PCR and ELISA methods. A comparative study between IC-RT-PCR and RNA capture RT-PCR showed the efficiency of the nucleic acid capture procedure. Furthermore, we have identified the virus from this nematode vector using the optimized molecular techniques (Fattouch *et al.*, 2001). All these viruses were detected in mixed infection on grapevine showing rugose wood (M'hirsi *et al.*, 2001). Sequences of GLRaV3 and GFLV genome were cloned and analyzed by RFLP. These studies demonstrate the presence of molecular variants within these viruses. Expression of Coat viral protein in *E. coli* was also performed. This constitutes an excellent tool for the improvement of diagnosis methods.

Viroids: In order to develop rapid and specific detection techniques for viroids infecting citrus and grapevine cultures, we have compared biological and molecular protocols. Ideally, these procedures should allow the rapid screening of a large number of samples, and some of them should allow the detection of viroids maintained at low levels in the host plant.

Testing three protocols of nucleic acids extraction from tree leaves, our results showed that phenol protocol is the most laborious and time-consuming. The Trizol technique, reported for the first time for viroids purification, is rapid and simple but can be applied only for some plants. The cellulose procedure, which does not use organic solvents, gave a response with all the plants tested when coupled to the RT-PCR. Viroids amount as low as 50 pg RNA may be detected by R-PAGE in a routine test. The sensitivity of R-PAGE is similar to that of nucleic acid hybridization, and results are available within a day. Therefore, R-PAGE provides a suitable methodology for general screening of plant material for the presence of viroids. During double electrophoresis, viroids undergo a conformational transition by heat denaturation in which their highly base-paired, rod-like structure is transformed into an unfolded, circular, single-stranded RNA. This technique, although specific for small, circular RNAs, presents the disadvantage of its relatively low sensitivity and specificity. The polymerase chain reaction is a very powerful method. It has greatly facilitated detection of plant pathogens which would be difficult or time-consuming to detect using conventional techniques. PCR method offers a greater degree of specificity and involves fewer handling steps. The ubiquitous occurrence of viroids in *Vitis* varieties and rootstock selection both in California and Europe was noted by Szychowski *et al.*, (1991). Given the wide exchange of grapevine material throughout the world, it is not surprising to find AGVd in Tunisia, even if it has not been reported before outside California and Australia. If AGVd turns out to be latent in these species, efforts should be addressed to the eradication of this pathogen, thus avoiding the establishment of field reservoirs that could be transmitted to susceptible crops. It must be remembered that AGVd results from recombinations among sequences of PSTVd, CEVd, ASSVd and GYSVd-1, cultivated close to each other in several areas around the world. It is the first example in which such rearrangements appear to have taken place between viroids within two separate viroid subgroups (Mc Innes and Symons, 1991). These data are confirmed by hybridization signals obtained when AGVd genome was used as probe. A simple and rapid method for nucleic acids extraction in a microcentrifuge tube scale is described, enabling the processing of a large number of samples. These techniques are very suitable for control of a viroidal disease which is induced by multiplication and the use of contaminated propagating material (Elleuch *et al.*, 2002).

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The Ethics of Innovative Medicine: from the possible to the permissible ?

By Bernard-Marie Dupont
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"He often told me how much he would have liked to lie down and sleep like everyone else. I think that on the last night he deliberately tried to sleep lying down. The pillow was soft, and his head lying on it probably fell back, thus dislocating his neck. It would seem that his death resulted from a pathetic and hopeless desire which dominated his entire life, to be like everyone else."[1]

Introduction

Joseph Merrick, better known as the Elephant Man, wanted to sleep "like everyone else" at least once in his life. It proved once too often: his head, which was deformed and too heavy for his frail shoulders, was not prepared for such normalcy. Seeking a break from the sitting position, he broke his own neck. This is how Frederick Treves, his doctor, describes the death of the Elephant Man toward the end of the Nineteenth Century, an ending re-enacted by the character of Joseph Merrick in the eponymous movie.

Let us take this desire to be normal (*"to sleep like everyone else"*) as the starting point for some thoughts on the ethical problems raised by new reproductive technologies. What follows is not a technical treatise (at any rate: not technical in origin, and far from purely technical). Rather, we shall take an epistemological approach to consider the significance and consequences of the new technological aids to medical procreation, attempt to define the essence of biomedical technology, identify the ethical stakes involved and, finally, address the primary function of that singular and noble art called medicine, namely: to promote the perpetuation of the species.

At the 2002 meeting of the French Genetics Society, François Thépot asked three questions: What qualitative norms apply to medical intervention? What price are we willing to pay? Who makes the decisions, and how are they made? We have structured our thoughts on these questions around three themes: diagnosis, therapeutics, and responsibility; i.e.: the diagnosis of genetic malformations; therapies (sperm donations, surrogate mothers, etc.); and responsibility (on the part of the dispensers of treatment, of those treated, and ultimately of society as a whole) *vis-à-vis* the desire for children and even more: the desire for the perfect child.

The diagnosis of malformations

The word "diagnosis" comes from the Ancient Greek verb *diagignôskein*, which means to discern, to know, to understand. If, as Canguilhem asserts, medicine is indeed an art, a science and a technique spanning the intersection of several sciences and several arts, it is equally true that medicine was never in search of truth for its own sake. Medicine is something to be practiced; it is knowledge

[1] Sir Frederick Treves, MD, in M. Howell and P. Ford, *The True Story of the Elephant Man*, Allison & Busby, London, 1980

for the sake of treating and healing. But how can one apply treatments and perform cures without early, comprehensive and accurate diagnoses?

How can doctors treat patients if their knowledge is not founded upon and guided by ethical intentions that anticipate paraclinical and clinical investigation? Medical treatment begins with the first contact, the specific dialogue between the individual who comes to formulate his/her complaint and the professional whose task is to translate the subjectivity of the complaint into an objective, scientific truth.

Joseph Merrick had an obsession: to sleep *"like everyone else,"* i.e. in a reclining position, so as to be an integral part of the community of humankind, a desire for universality. At the same time, in the specific dialogue that takes place between patient and healer, every patient wants to be seen as a unique individual. Thus, universality and uniqueness form a double ethical bind. Contemporary medical epistemology can be seen as a tug-of-war between individual and supra-individual norms. Every doctor concerned with treating infertility must be completely conscious of this.

Over the last few decades, medicine has been undergoing a revolution so profound that even its underlying epistemological paradigms have changed. It is certainly no exaggeration to say that medicine is at a turning point in its history, with a transition from the individual to the supra-individual norm as its new basis of reference.

Georges Canguilhem once wrote that the definition of illness always proceeds from the notion of the individual human being. This insistence upon the singularity of each patient seems increasingly debatable in the field of bio-medicine today. Thus, in the newspaper *Le Monde* of 23 December, 1998, one reads, *"...ten years from now, this will be the only way to proceed, a rational development, raising the general standard to the top level: patient X will be treated as if he/she were under the care of one of the fifteen great specialists of Europe or America, since every responsible doctor will be guided by the consensus reached by these authorities through consultation among themselves."*

Such consultations among doctors are stimulated by the desire to universalise knowledge and, in the case of medicine, by an unflagging drive to improve treatment of the ill. However noble this endless quest, this absolute mission of medicine may be, the question is: is it still compatible with the ideal which we have upheld since the days of Hippocrates: to accompany each patient individually, to treat each patient's illness in an individualised way, to start anew every time and establish a unique doctor-patient relationship in each and every case?

Let us consider the current, affirmative trend towards universalisation within the context of the epistemological framework for medical knowledge. A number of questions emerge: if we are only interested in treating patients X, Y and Z, where does that leave the unique individual? What rank is to be assigned to the specific request of one couple for its own child? What fate is in store for one particular embryo as opposed to another, and by what criteria? What will be the role of the patient with respect to pathology? Will he/she still be of any use at all?

More fundamentally, does this drive towards universalisation of medical knowledge and practices (akin to the "globalisation" of the economy) not presuppose that medicine is or could become an exact science, a science of the human-object? – that there are only one or very few models that medicine (and thus doctors) should/would strive to restore or reproduce?

The diagnosis of disease can only be based upon a clear distinction between the normal and the pathological. This is a minimum epistemological imperative. Does this mean that universality necessarily corresponds to normalcy? If one goes along with Georges Canguilhem and believes that *"normality does not have the rigidity of a factual collective constraint but rather the suppleness of a norm that transforms with respect to individual conditions"*[2], then the boundary between what is

[2] Georges Canguilhem, Le Normal et le pathologique, PUF, Paris, 1998 (1966), Chapter 4, « Maladie, guérison, santé », page 119

normal and what is pathological becomes blurred. Infertility doctors should not to be too quick to confound anomaly and abnormality: pathology may not be linearly deduced from the definition for "normal."

So how else can pathology be defined? As any value deviating from the established norm by more than 100 percent? Careful! – guidelines are not always rational! If we imagine Man as a perfectly circumscribed circle, i.e. knowable and manageable, then we are forgetting that science is based on laws, and that *"these laws are theoretical abstractions."*[3] Human beings do not live entirely within and with respect to laws; rather, they live with other human beings and are continually confronted by events that upset these laws.

The illusion of knowledge and control is acceptable only as the unattainable, far horizon of the possible. Diagnoses of infertility, genetic malformations, etc. fall under this double constraint: to envisage the unity of the species, without denying or overly counteracting the uniqueness of each patient, parent, child, or indeed embryo.

Therapeutics

Nature is a partner that we can never completely control. Diagnostics and therapeutics must come to terms with this fact. What is more, nature is not always a docile partner. Sometimes, it can be violent and act in violation of itself and its own laws. Nature is full of monsters. The word 'monster' comes from the Latin *monstrum*, which in turn comes from *monere*: to make think of, to draw attention to. By definition and essence, monstrosity must attract the attention of the doctor, since it is a manifestation of life that questions the very definition of life.

As Georges Canguilhem used to say, life is experience, i.e. improvisation. This continual improvisation on the part of Nature must be met by improvisation on the part of the healer. Herein resides the grandeur of the medical profession: in the capacity for taking risks. Interventionist medicine is rendered vulnerable through its own powers of detection. While showing the patient his/her options, it is itself laid bare by its own possibilities. Patient care is never a neutral act; treatment, whether performed or received, involves knowing how to take risks.

Taking risks

Even if the worst is not certain to occur (uncertainty principle), the mere possibility of a major risk (principle of irreversibility) should make us prefer cautious options. This is how one might formulate a precautionary principle for uncertain times, as a guide for rational action and response to the question: how far can we go without going too far?

Innovative therapies are obliging us (in the moral sense) to face the dizzying prospects open to bold researchers. Should they be encouraged or condemned? Uncertainty is an inherent characteristic of medicine. According to Charles Naylor, one of the fathers of evidence-based medicine, the practice of medicine takes place in a no man's land with an 80% grey zone. If it were necessary to wait for absolute certainty before taking action, medicine would have disappeared a long time ago!

Until very recently, one distinguished two principles of action with respect to risk: the principle of prevention and the principle of precaution. Prevention is more akin to control, because it refers to an event that has occurred before or whose consequences can be predicted with certitude before the fact, calling to mind the old adage: let us not repeat the mistakes of the past. A number of ecological

[3] Ibid.

catastrophes can or could be avoided by applying the principle of prevention and thus, for example, forbidding rotten tankers to go to sea or run too near our coasts.

Precaution is a trickier concept, because it introduces the factor of uncertainty in between cause and effect. If an event has never yet happened, it may nevertheless be possible to imagine the consequences of its occurrence; and yet, one must still concede a degree of uncertainty. However clear it may be that the cause produces the effect, it will be difficult to predict the magnitude of that effect before the advent of the catastrophe. The principle of precaution confronts us with an immeasurable risk: one may fear it, but one cannot evaluate it. And anyway, it may never materialise!

While it may be bothersome for decision-makers, the principle of precaution is an even greater stumbling block for the legal profession. It does not fit into the classic logical scheme of error and blame that presupposes knowledge, i.e. some kind of certitude, if only of a relative or temporary nature. In some sense, precaution is not subject to blame, unless the effects ultimately confirm the initial hypotheses, i.e. until that which was uncertain becomes fact. The projection over time which lies at the foundation of the precautionary principle forms the horizon for the decision-makers. If to govern is to act, this does not mean action without a view to the consequences; in fact, it means exactly the opposite.

The relationship between precaution and the sciences is even more at odds. To paraphrase Karl Popper, bodies of scientific knowledge are relative constructs, and the sciences are continuously re-forming themselves. The concept of precaution in the sciences is linked to the question of the epistemology of the relativity of knowledge. In medicine, the problem is compounded, since possible consequences may endanger the lives of others.

Development risk

During recent years, an extreme – not to say extremist – form of the precautionary principle has appeared on the scene in the form of so-called "development risk." This risk is addressed in question form by the European Union directive of 1985 dealing with responsibility for defective products: may a provider, who has an objective responsibility for the consequences of the faults of a product that he has put into circulation, be exonerated from this responsibility in the event that he could not have foreseen the existence of said defect?

This novel concept, doubtlessly inspired by the contaminated blood affair[4], raises serious questions that implicate the very practice of medicine. From an epistemological point of view and leaving legalities aside, we know that science progresses more through changes in its paradigms than through an accumulation of knowledge; we also know that scientific progress increases our powers and capacities without, however, reducing the uncertainty that it generates. Under these conditions, what should be our attitude towards medical precautions?

A posteriori, "development risk" seems more like a diabolic surprise than a probable, let alone foreseeable risk. Ever since the French Revolution, the French legal tradition has always refused to sanction after-effects. Since the Declaration of the Rights of Man in 1789, the legislation governing penal responsibility has been founded upon the conviction that laws may not be applied retroactively.

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[4] Editor's note : The author refers to the distribution of HIV-contaminated blood products prepared in France in the early Eighties. At that time, the pharmaceutical industry used to pool blood sources for transfusions. When the danger of the virus finally entered public and governmental awareness, four basic questions arose: How to handle transfusion processes in the future? What to do with existing products? Who is to be held accountable for the damage incurred? What should be done collectively for people who became infected?

Article 8 of the French Civil Code: "Nothing is punishable except by virtue of a law established and promulgated prior to the misdemeanour and lawfully applied." Analogously, Article 2 states: "The law only covers the future; it has no retroactive impact."

The concept of development risk is completely new in that it holds us responsible not only for effects that we did not intend and all that we undertook to avoid them, but also for unpredictable effects that we should have envisaged anyway. Is such a thing as medical innocence still possible or even conceivable on these terms?

So what should we do now? Refrain from all therapeutic activity, avoid all socio-medical decisions? Of course not, for many reasons, e.g. because the urgent need for treatments and research make it impossible to wait, and for the simple reason that the very definition of responsibility implies choice, including decision-making on medical, economic and political matters. To be responsible means to choose, not to abstain. That said, "development risk" is coming dangerously close to the limits of decision-makers' possibilities. On the other hand, the patients themselves must resist the temptation to applaud systematic accusation of the medical profession in years to come.

The Law can be the objective ally of patients confronted e.g. with unacceptable medical paternalism or an equally cruel silence on the part of the authorities. However, the Law can also be a false friend. What would society have to gain by systematically questioning medical analyses and treatments *a posteriori*, when it is impossible for anyone, including legal experts, to judge whether they were wrong or simply insufficient at the time the decisions were taken and measures put into operation?

Responsibility

By virtue of its new technologies, medically assisted procreation begins a new chapter of medical responsibility, unexpectedly reintroducing the subjective dimension into the patient-doctor relationship with full force.

Thanks to the representation of medical progress in the media, many sterile couples, whose cause for suffering is legitimate, no longer see sterility as an unalterable fact of nature. In their view, doctors not only possess (or could possess) the necessary knowledge, but they have a (moral and legal) obligation to act. The desire for a child veers away from the objective of reproduction within the context of society and towards a more narcissistic form of personal self-fulfilment. This impulse culminates in the desire for a perfect child, which it is becoming possible to program and to which medicine is in some sense an accomplice.

Should medicine necessarily comply with this logic of imperative demand?

Conclusions

A triple-layered security fence should be put in place to contain the mirage created by the idea of unlimited scientific progress, with doctors in the role of demi-gods:

1) An epistemological security fence: we urgently need to define or redefine what is normal and what is anomalous, not just in scientific terms. Is abnormality necessarily synonymous with pathology? In other words, we urgently need to rethink the relationships between individual and supra-individual norms and to ask ourselves the ultimate question with respect to our Hippocratic heritage: what philosophy of medicine do we want to promote at the dawn of a new millennium?

2) An ethical security fence: interference with human life at its most intimate is not without ethical consequences. It is one thing to correct nature; however, the wish to improve upon it is more emblematic of our ability (and desire?) to act as demi-gods. Beware the temptation of the perfect

model, the child with no fabrication defects or formal faults! At the beginning of the 20th Century, the French doctor and Nobel Prize winner Alexis Carrel proclaimed the birth of the new man and the obligation of a civilised nation to reproduce its best elements...

3) A political security fence: the desire to turn medicine into an exact science must be examined collectively. In the medical field as in others, scientific activity must not remain the exclusive domain of specialists. The issue of medically assisted procreation affects future generations. It must be included as an integral part of the civic debate of nations, continents and the entire world. There is a growing cost, in both human and economic terms, attached to medically assisted procreation and innovative techniques. They require political choices that entail far-reaching choices for the entire society.

It is up to us – citizens X, Y and Z – to create new forums for consensus!

Agricultural Research in France

Orientation Document for INRA: 2001-2004

(Institut National de la Recherche Agronomique/
French Institute for Agronomy Research)

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Together with the President of INRA, Bertrand Hervieu, and all members of the management team, we have been working on and finalising the orientation plan for our organisation. This document draws the conclusions of numerous internal and external discussions, and sets our strategic plans for 2001-2004. After different groups within the Institute had reviewed the document, the orientation plan was approved by the Board of Directors in December, 2000.

Preparing the INRA of the future

This orientation plan is essential to INRA. A major organisation such as ours needs a clear, consensual vision of its future and missions. Indeed, in recent years, and notably with the decline in the perceived importance of the agricultural world in French society, the future of agronomic research has seemed uncertain. However, fields of research such as sustainable agriculture, food and its effect on human health, the environment and land use remain central to the needs of society. By consciously investing in research areas, INRA is striving to meet society's expectations in a way which will renew its legitimacy and establish its unquestioned and unique position within the national research system.

Such a project is fundamental to the missions of our Institute. Although its principal objective is to produce high quality knowledge in its areas of competence, validated by the scientific community, INRA must also play its part in training young scientists to conduct research, as well as in disseminating and exploiting the results obtained and providing scientific expertise. We must also remain fully aware of the expectations and fears of our fellow citizens: debating our choices within the Institute and with society at large, explaining our approaches and informing the public of the scientific results we achieve.

Through the changes we must make, we will be preparing the INRA of the future.

The six challenges we face

Within its area of scientific competence, INRA currently faces a major challenge: the industrialisation of biology. The rise of "high throughput" biology is profoundly modifying investigative techniques in the life sciences. It is also palpably reducing the distance between fundamental research and resulting fields of application. Unless INRA decides to abandon all long-term ambitions in this area, it must rapidly increase its ability to produce large quantities of data on the structure, variability and functioning of numerous genomes amongst plants, animals and microorganisms.

A second, similar challenge relates to advances in computer technologies, particularly in the field of data processing. These developments open up new approaches to the study of complex systems and phenomena. It is now possible to consider multiple levels of organisation and conduct analyses on the basis of different spatial and temporal scales, thanks to data integration and modelling tools which

take better account of reality. These advances are particularly important in the environmental sciences, the development of unified and integrative biology and epidemiology.

In addition to these scientific needs, INRA must meet three challenges arising from recent evolutions in the expectations of society. Consumer demands in developed countries have underlined the imperatives inherent in food production, in terms of not only quality and diversity but also safety. In the same way, environmental questions are of crucial importance today. They directly involve agronomic research and address its ability to approach extremely complex problems in a systematic fashion. More than ever before, people are questioning the benefits of technical advances, and expressing a growing need for interaction and understanding. We can respond in several ways, and to achieve this, INRA must review the organisation of its forecasting and expertise functions, develop its risk analysis systems and make this information available to government decision-makers, while at the same time training and encouraging researchers to become involved in the science-society debate.

The sixth challenge is one of scale. We must be ready to act as a driving force behind the structuring of European research efforts. Implementation of the European Agricultural Research Area is particularly crucial to our future, and INRA aims to play a resolutely central role in this project. Problems of a specifically European nature must be considered, amongst which some of the most important are multifunctionality, product quality and the sustainable management of resources, particularly water. Furthermore, because of their scale and the scientific challenges involved, some biological research programmes require investment which must be considered on a European scale. In the same way, long-term structures such as environmental watch networks or experimental platforms could be developed and implemented in the context of strengthened European cooperation.

Responses in terms of scientific priorities

To meet all these challenges, INRA intends to organise its scientific policies around certain priorities which result from the confrontation between the internal dynamics of the research world and the needs and expectations of today's society. Clearly, these priorities do not cover all the research activities that INRA proposes to conduct with its partners over the next four years. They involve disciplines which are emerging or seeing renewed development, to which INRA aims to make a major contribution at both the French and European levels.

The first of these priorities is on research involving the integrated study of terrestrial or aquatic, cultivated, forest or natural ecosystem functioning, the protection of resources and the management of rural areas. The overall strategy established by the Institute lays particular emphasis on four areas of investigation: the management and protection of physical resources, the exploitation and preservation of biological resources, the management of agrarian and forestry systems and public policy relating to the environment and rural areas.

The second priority is the development of integrative biology, creating structures which are organised to ensure the competitiveness of research teams. The scientific challenges for plant research range from genotyping to risk assessment and innovation management. Preservation of genetic resources, diversification of production methods, respect for the environment and food quality are areas where plant genomics will be making a significant contribution. In animal research, integrative biology affects practically all fields acknowledged as priorities for animal production. Its overall development within INRA will be promoted through major efforts in the areas of sequencing and post-sequencing.

INRA's field of competence has been broadened over the past ten years to include human nutrition and links between diet and health, and this scope should increase further in the years to come. INRA has adopted an ambitious policy of increasing the resources devoted to this area. This approach has been justified by the numerous imperatives which have emerged in connection with both the

quality and the biological safety of foods. The study of prion-related diseases, a crucial problem in animal health, is now extending to food and human spheres, notably because of the question of interspecies transmission. Reinforcing our resources in this area will constitute a central part of the national research effort.

A principal characteristic of research programmes in genomics, and more generally in integrative biology or the study of environmental systems, is the enormous growth in the amount and diversity of data produced, and the levels of scale involved. Their management, exploitation and interpretation constitute a challenge which cannot be dissociated from the development of biological and environmental sciences. One of INRA's priorities is therefore to strengthen its competence in bioinformatics, ensuring a geographical scope which will cover the principal poles of research in genomics.

Finally, the relationship between scientific information and application merits particular attention from INRA: most of the work carried out by our Institute involves the promotion of innovative processes and aims to initiate joint projects which will enable the transformation of society, as well as the production of scientific or technical knowledge. Applied social sciences have thus become a strategic tool for INRA, particularly with a view to the analysis and management of risks. However, these new questions must not allow us to neglect development of the agricultural sciences. Although new objectives such as innovation, the environment or consumption are emerging, a better understanding of the imperatives of the agricultural and rural world remains important, particularly in the context of problems linked to multifunctionality and sustainable development.

Reorientation of our resources

The priorities outlined above will necessitate reorienting INRA's resources. Funds may be maintained or adjusted in certain fields of research. Greater emphasis will be placed on areas concerning human nutrition (40% increase in manpower), the development of generic strategies in the life sciences (alliances and the deployment of new resources) and the social sciences (25% increase in manpower). In contrast, the means allocated to systems development and production factors will be reduced (-15%) and transferred to other, higher priority areas.

Responses through renewed, more diversified partnerships

Openness within the scientific community and dialogue with society are now more than desirable; they are a necessity, compelling us to renew our links with our social partners and enhance the influence of our Institute. It is clear that INRA currently faces numerous scientific challenges, most of which can only be met by means of multiple partnerships, either with French public research or higher bodies of education. The many combined research units established in cooperation with higher education institutions (ultimately, nearly half of INRA the units should function in this way) bear witness to our determination to establish closer relationships with these partners.

Especially mindful of its role in contributing towards the construction of a European Research Area, international policy has become an crucial part of INRA's general strategy for openness. The development of skills is only possible today through an active and central presence in the international scientific community. Analyses of the international debates on agricultural, food, health and environmental questions flow into the strategy of our Institute. The growth of partnerships with our European and international colleagues will enhance our presence at the heart of the scientific community.

New links must also be forged with the agricultural world. The notion of multifunctionality is increasingly recognised in official national and European texts. In France, the recent Agricultural

Orientation Law redefined the context of future French agricultural policy. Such changes have incited agricultural research to produce the knowledge, concepts and methods required by the authorities and professionals to implement the decisions taken and monitor their application, and prepare for future challenges -- in particular, the coming European and international negotiations.

Socio-economic partnerships and the exploitation of research results are characterised by various types of transfer, ranging from the diffuse exploitation of results to patent policy. INRA must meet several objectives in this area: participate actively in economic development and contribute to job creation, produce knowledge and protect it from unauthorised appropriation, while at the same time developing expert skills and making them as widely available as possible. INRA intends to apply a policy of protecting its public research activities, notably through patent applications. In liaison with the authorities and partners concerned, it must undertake a structural review of the ethics concerning researchers and experts and the rules of scientific expertise.

Within this dynamic context of renewed partnerships, particular attention will be paid to the role that INRA and its research can play in resolving the problems raised by the citizens we serve. More broadly, strengthening the links between science and society and the participation of scientists in general debates are fundamental issues, not only for INRA but also for the society of the future. Some research objectives actually become social questions. For example, agricultural production models, preservation of the environment and applications of genomic research are the subject of considerable questioning and debate, requests for clarification or even scientific controversy. Through its work on the environment, agriculture and food, INRA has a central role to play in highly sensitive areas involving all sectors of the community.

In conclusion...

In addition to these major changes, we must start preparing and discussing the INRA of 2020 with our partners. While the orientations we have chosen for the period 2001-2004 reflect our determination renew our scientific practices, ensure a strong presence within the scientific community and revise our partnerships with other sections of society, we must also think further ahead and start thinking now about a more distant future.

The renewal of 45% of INRA staff between now and 2010 should bring in new skills and forms of organisation. The depth of our knowledge and experience in agricultural, food and environmental research provides us with a unique standpoint that can play an important role at a time when broadly based reflection and understanding is essential. The future of INRA is being shaped with renewed enthusiasm for the life sciences at the service of all.

For more information on INRA Research Institutes and Programmes visit the website:
http://www.inra.fr

Science and Technology Policy and the Strategy of Life Science in Japan

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1. Organisational reform

In January 2001, in connection with the reform of the central government, the Council for Science and Technology Policy (CSTP) was established under the Cabinet Office of Japan. The council is chaired by the Prime Minister and consists of 14 members, including cabinet members and eight professionals from academia and industry.

The council has effectively formalised the Prime Minister's leadership in determining science and technology policies, including e.g. the allocation of R&D funding and human resources, and the prioritisation of research areas. Since its creation, the CSTP has been developing ties among academia, industry, and legislators as well as between Japan and other countries. It is also developing close cooperative relationships with the newly established Council on Economic and Fiscal Policy of the Cabinet Office and the Ministry of Finance.

The entire council has been meeting monthly, compared to the previous council which met only once or twice a year. Through these meetings, the Prime Minister and other members frankly engage in serious discussions, and high-ranking members are developing a keener interest in science and technology affairs.

2. Science for the 21st Century - a new commitment

During the 20th Century, the driving force of the world system shifted from military power to industrial and financial power. In the 21st Century, this driving force will become knowledge, and the world will be a knowledge-driven society.

The World Conference on Science, convened in Budapest, Hungary, in 1999, chose as its theme "Science for the 21st Century — A New Commitment." More than two thousand scientists, engineers, congresspersons, business people, journalists and administrators came together and deliberated. A declaration was issued that is likely to have long-term impact. It emphasised not only the spirit of "science for knowledge, knowledge for progress" which characterised science in the 19th and 20th centuries, but also "science for peace," "science for development" and "science in society and science for society," as a new commitment for the 21st Century.

In the new century, we need not only "a policy for science" but also "science for policies." Scientific knowledge and insights are indispensable tools for coping with socio-economic issues such as global warming, the energy and food crisis, the population explosion, epidemics, etc..

3. New basic plan for science and technology: towards a knowledge-based society

In 1995, the Diet of Japan adopted the Fundamental Law of Science and Technology. On the basis of this law, the CSTP has formulated a number of important policies and guidelines. Firstly, the Cabinet approved the second five-year Science and Technology Basic Plan in March 2001. This plan calls for Japan to take a stance to promote the "creation of new knowledge and contributions to the world community," "sustainable socioeconomic development through knowledge and stronger

competitiveness," and "upholding safety and security through knowledge and achievement of a high standard of living."

The end of the Cold War and the spread of information technologies have ushered in fierce global economic competition. This competition is spreading from the economy to scientific research and education. The time lag between basic research and its application is growing ever shorter, and research programs based on the linear model of innovation are outdated. It is important to take account of the chain-linked model, i.e., feedback between basic research and application, and collaboration between universities and industries.

The Basic Plan also sets the challenging goal of allocating ¥24 trillion (US$200 billion) in public funding to R&D over the next five-year period. This corresponds to an increase of around 38% as compared to the previous period. This expresses the government's firm intention to spend 1 percent of the nation's GDP in the last year of the 5-year plan on R&D-- equivalent to the investment of other advanced countries. Back in the 1980s, when Japan's economy was at its highest, the public investment in R&D and higher education had unfortunately been too low.

Since a large amount of public money is going toward R&D today, it is crucial to use these funds efficiently. Structural reform of the research system must be undertaken to make Japan's science and technology system flexible, open and more competitive. The Basic Plan emphasises four areas: promotion of non-committed basic research, assigning strategic priority to needs-oriented R&D, collaboration between academia and business, and reform of the university system.

4. Basic research, the four areas of priority and an interdisciplinary approach

(1) Promotion of basic research and the interdisciplinary approach

It is important to conduct high-quality non-committed basic research in a broad range of fields. Recognising this, the second Basic Plan targets the budget size of competitive research funds for basic research, doubling it within 5 years from \300 billion to \600 billion, and includes measures for reforming the evaluation of research and distribution of research funds.

We are convinced of the importance of an inter-disciplinary approach, combining traditional disciplines such as physics, chemistry, biology, mathematics, computer science, and in some cases social sciences and humanities. Research activities and groups that have until now been separated into their respective disciplines and departments must be consciously integrated to enable path-setting breakthroughs in knowledge and nurture future diverse technological development.

(2) Science-innovation links and publication ethics

Today, basic research plays an important role not only in the advancement of knowledge, but also for technological innovation. The science-innovation linkage indicator was developed in 1990s to show the flow of knowledge between science and industry. It is based on the average number of scientific papers cited for patents issued in the United States, organised by country of origin. This indicator is especially high in the life science area. Innovation increasingly draws on scientific research in new industries such as biotechnology. Fig.1 reveals the rapidly increasing gaps between the indicators for Japan, the United States and the United Kingdom since the mid- 1990s. The CSTP is aware of this trend and aims to stimulate knowledge transfer from universities to industries.

Publication and dissemination of basic research results have been the rule of modern science. However, as the distance between basic research and products on the market narrows, this has affected the objectivity, fairness and openness of the review of scientific papers. It is important to mediate in the conflicts of interests which will arise between intellectual property rights and the public availability of knowledge, especially in the 21st century, when knowledge becomes the engine of society.

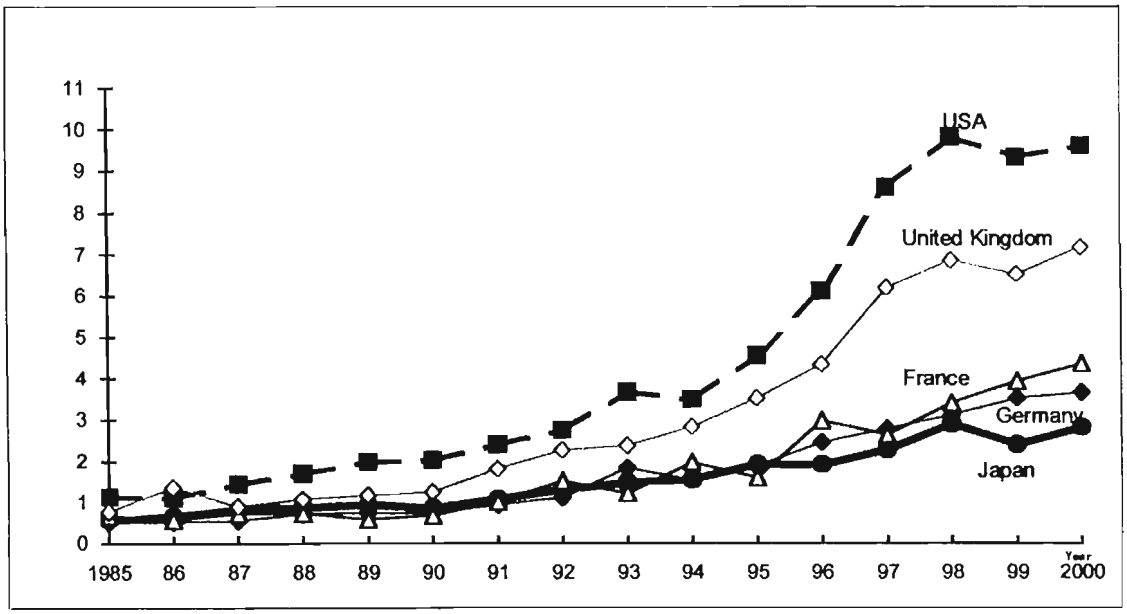

Figure-1: Science-innovation linkages in some G7 countries (Life Science)

(3) Four priority areas

In terms of responding to socio-economic needs, the Basic Plan gives priority to allocating budgetary and human resources to four key areas: life sciences, information technology, environmental science, and nano-technology/material science. These areas are expected to play a crucial role in improving the quality of life, developing new industries and ensuring the security and safety of society.

Focusing its resources on these four key areas, the CSTP shows researchers and administrators how to organise research projects to make them more productive within the context of the overall innovation cycle. Management of technology and innovation becomes more important than ever in the new century.

5. Strategic plan for the life sciences

In the 1990s, the biological sciences transformed into precise, quantitative sciences (Fig. 2). Human genome sequencing was almost completed, and single molecular observation and manipulation technology were developed dramatically. Innovations have also been made in computer science and visualisation technology. Based upon these advances in knowledge and engineering, it may be possible for us to model, design and predict the structures and functions of complex biological systems.

The CSTP published its next five-year strategic plan for the life sciences in September 2001 (Fig. 3). The important points stressed are as follows:

(1) Post genome research and disease diagnosis in an aging society

- Identifying 200,000 SNPs in human genes, Japan has taken the lead in this field.
- Using bio-informatics to improve analysis of SNPs with respect to diseases and drug effectiveness is the main challenge in developing tailor-made medical treatments.
- New developments can be expected in the field of medical regeneration.
- Measures are needed to improve the system for promoting translational research which applies basic science discoveries to clinical trials.

(7) Reforming the research system, cultivating and securing talented personnel

- Basic research in post-genome, gene therapy and regenerative medicine has progressed remarkably. Clinical research must be promoted by reforming the system.
- Since the Biodiversity Treaty was enacted, countries have been keeping biological genetic resources to themselves. As the importance of biological genetic resources increases, it is necessary to reform the system for collecting and overseeing them.
- It is essential to nurture and secure talented persons. Persons are needed in the fields of bio-informatics, bio-statistics, epidemiological statistics, clinical research coordination and intellectual property right. A flexible inter-departmental system is indispensable to developing new tools for biological research and medical applications.
- It is important to transfer research discoveries to society and business. Research to verify the safety of medical technologies and genetically modified organisms (GMOs) is important. Measures should be adopted to secure social acceptance of bioethics in the field of new medical technologies. The scientific examination system for effectiveness and safety must be improved.

6. Collaboration between academia and business

The Japanese economy lost steam at the beginning of the 1990s and is still in poor condition. One of main factors of the economic down-turn is the hollowing-out of Japanese manufacturing industries in the face of rapid economic globalisation. This can only be resolved through structural reform of the Japanese socio-economic system to make it more knowledge-based rather than dependent on public works. Such reforms will make Japan more competitive and attractive as a place for doing business and will draw foreign investment, business people and researchers.

Japan progressed from the catch-up era to the self-created stage in science and technology as well as in the economic field. Since we are in front now, we must carve our own path; this requires creativity and originality. For this, we must utilise the intellectual resources of the universities for the benefit of society and industry. We are in an age requiring that academia and business work together and create a common knowledge base.

The CSTP has been strongly advocating business-academia collaboration. The 1st and 2nd Business-Academia Collaboration Summits in Tokyo in November 2001 and 2002, and the 1st Conference and Exhibition in Kyoto in June 2002 took place successfully. Participants were able to exchange ideas and get to know each other better. They recognized that Japan's economies should be developed through university-industry collaboration rather than by relying upon demand generated by public works projects.

Some promising districts of academic-industrial collaborative clusters in field of bio-technology are developing in Japan, centring around Tokyo, Kyoto, Osaka, etc.

7. Reform of the R&D system and the national university system

The principles of the Japanese socio-economic system, characterised by the seniority system, lifetime employment and decision-making by consensus, functioned effectively during the catch-up era after World War II. Now that Japan has become one of the front-runners in a globalised economy, these should be replaced by the principles of competitiveness, creativity and openness.

In an age of mega-competition, individual ability is becoming more important than the order and stability of the group. The CSTP has instituted extensive reforms of the R&D system, such as reforming the evaluation and funding system, increasing the mobility of researchers, and increasing grants to young and promising researchers.

University reform, one of the main components of the current administration's reform package, is now underway. Japan is planning to make all national universities independent agencies in April 2003, so that they can meet social needs and become more creative and open.

There are four ideas underlying such university reform. First, the competitive principle should be introduced into academic activities. Second, national universities should be independent from bureaucratic control; a non-civil-servant-type employment system will be introduced. Third, an environment should be created where younger researchers can fulfil their creative potential. And fourth, a new and flexible management system should be established. Japan is also studying how the rigid seniority and career system within universities can be reformed.

8. Science and society, wisdom and governance

(1) Explosion and control of knowledge

The explosive progress of science and technology in the 20th Century brought prosperity and enriched the quality of life for mankind. At the same time, we must recognise that this progress can pose an enormous threat to human society and the global environment.

The quality of our future depends upon science and technology. It will be a key tool for tackling the multifarious problems that face the world in the 21st Century, such as global warming, the population explosion, safety and terrorism, supplies of energy, food and fresh water, human cloning and epidemics.

To proceed with foresight, society will require a new science and technology discipline geared to analyse, assess, and respond appropriately. We must recognise the need for human wisdom integrating humanity and knowledge. Human wisdom must be exercised to exert proper control, since progress in science and technology is expected to accelerate even more in the 21st Century.

Since Japan commenced its modernisation efforts in the latter part of 19th Century earlier than any other non-Western country, it has acquired extensive experience in harmonising Western science and technology with a traditional culture and social system. Japan should use its experience to devise strategies by which the various peoples of the world can thoroughly enjoy the benefits of modern science and technology while maintaining their own cultures and values.

As science and technology hold true value only if accepted by society, it is crucial that they be understood, evaluated, accepted and supported by the public. Bearing in mind the concept of "science in society and science for society," forms of interactive communication between science and technology and society must be established.

(2) Governance of science in the 21st Century

International networks of scientists were established in Europe in the latter part of the 19th Century, forming the basis for the "explosion of knowledge" in the 20th Century. Within this framework, independent control and management systems developed within the scientific community and were accepted by society. In spite of two World Wars and a change in the world system during the 20th Century, society exerted only minimal external control over scientific activities, with priority given to the development of science and technology. Until now, this system has been maintained, based, on the one hand, on the respect, trust and support for scientists on the part of society, and on scientists' sense of social responsibility, on the other.

Recent rapid developments and knowledge integration in the life sciences, information technology and nano-technology harbour the potential to have tremendous impact on human life, health, dignity and society, and the entire Earth, to an extent that is difficult to predict. In recent years, not only governments but also various other sectors have begun to participate in public decision-making concerning science and technology. Accurate management and control, including law and ethics, may be exerted from outside the scientific community. In the 21st Century, it is essential to establish a new system of governance to control the mutual relationship between science and society.

Websites of Government Agencies, Research Institutes and Associations in the Field of Life Science in Japan

http://www.cao.go.jp/cstp/
Council for Science and Technology Policy, Cabinet Office

http://www.mext.go.jp/
Ministry of Education, Culture, Sports, Science and Technology

http://www.mhlw.go.jp/
Ministry of Health, Labour and Welfare

http://www.maff.go.jp/
Ministry of Agriculture,Forestry and Fisheries

http://www.meti.go.jp/
Ministry of Economy,Trade and Industry

http://www.jetro.go.jp/
The Japanese External Trade Organization

http://www.jpo.go.jp/index.htm
Japanese Patent Office

http://www.riken.go.jp/
RIKEN (The Institute of Physical and Chemical Research)

http://www.nig.ac.jp/
National Institute of Genetics

http://www.aist.go.jp/index_j.html/
National Institute of Advanced Industrial Science and Technology (AIST)

http://ss.abr.affrc.go.jp/
National Institute of Agrobiological Sciences

http://www.jba.or.jp/
Japan Bioindustry Association

http://www.jbic.or.jp/
The Japan Biological Informatics Consortium (JBIC)

http://www.jpma.or.jp/
Japan's Association of Pharmaceutical Industries

http://web.staff.or.jp/
Society for Techno-innovation of Agriculture, Forestry and Fisheries

http://www.jhsf.or.jp/
The Japan Health Sciences Foundation

http://www.kazusa.or.jp/
Kazusa DNA Research Institute

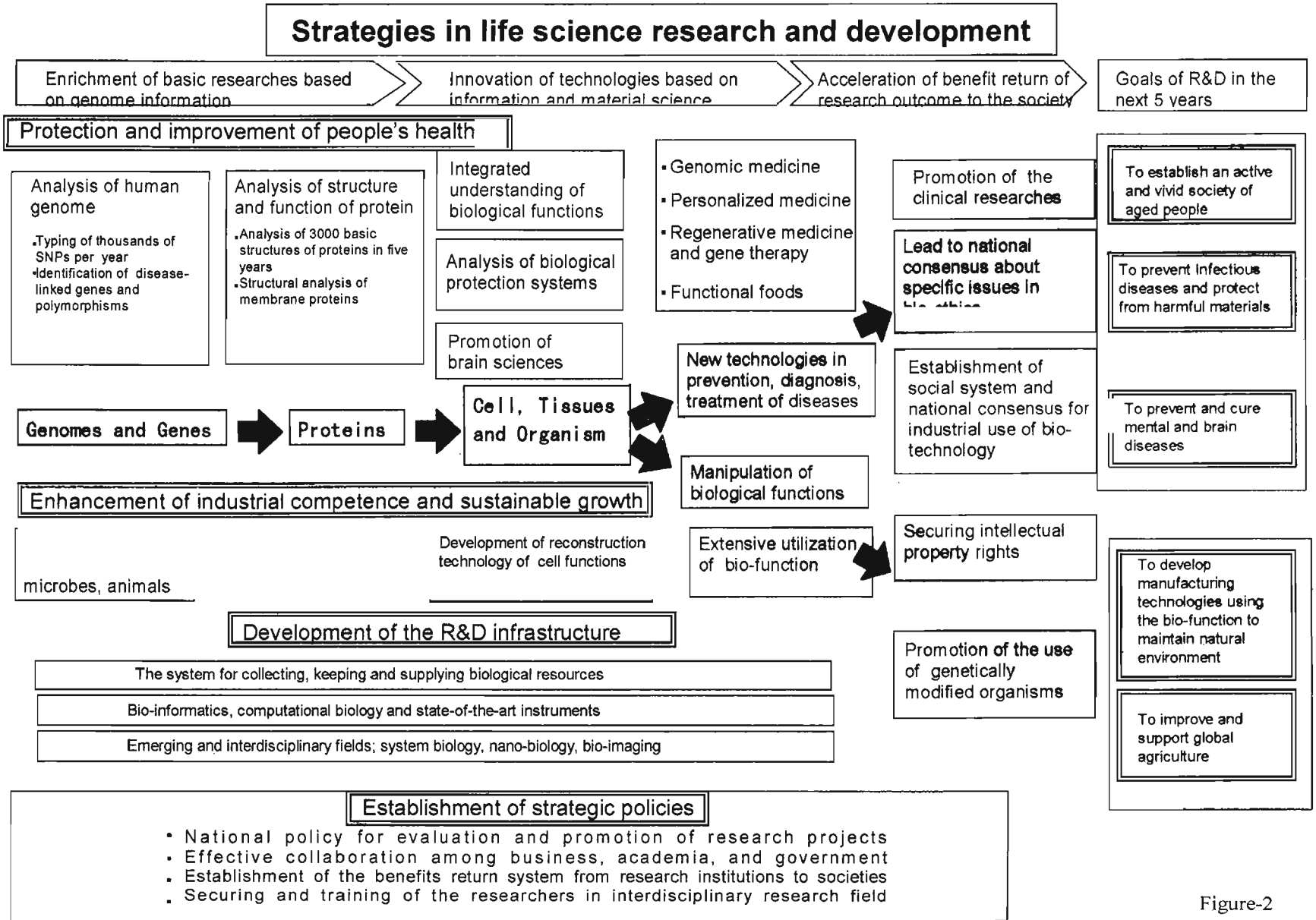
Strategies in life science research and development
Enrichment of basic researches based on genome information
Innovation of technologies based on information and material science
Acceleration of benefit return of research outcome to the society
Goals of R&D in the next 5 years
Protection and improvement of people's health
Analysis of human genome
.Typing of thousands of SNPs per year
.Identification of disease-linked genes and polymorphisms
Analysis of structure and function of protein
.Analysis of 3000 basic structures of proteins in five years
.Structural analysis of membrane proteins
Integrated understanding of biological functions
Analysis of biological protection systems
Promotion of brain sciences
▪ Genomic medicine
▪ Personalized medicine
▪ Regenerative medicine and gene therapy
▪ Functional foods
Promotion of the clinical researches
Lead to national consensus about specific issues in
Establishment of social system and national consensus for industrial use of bio-technology
To establish an active and vivid society of aged people
To prevent infectious diseases and protect from harmful materials
To prevent and cure mental and brain diseases
Genomes and Genes
Proteins
Cell, Tissues and Organism
New technologies in prevention, diagnosis, treatment of diseases
Manipulation of biological functions
Enhancement of industrial competence and sustainable growth
microbes, animals
Development of reconstruction technology of cell functions
Extensive utilization of bio-function
Securing intellectual property rights
To develop manufacturing technologies using the bio-function to maintain natural environment
To improve and support global agriculture
Development of the R&D infrastructure
The system for collecting, keeping and supplying biological resources
Bio-informatics, computational biology and state-of-the-art instruments
Emerging and interdisciplinary fields; system biology, nano-biology, bio-imaging
Promotion of the use of genetically modified organisms
Establishment of strategic policies
• National policy for evaluation and promotion of research projects
• Effective collaboration among business, academia, and government
• Establishment of the benefits return system from research institutions to societies
• Securing and training of the researchers in interdisciplinary research field

Figure-2

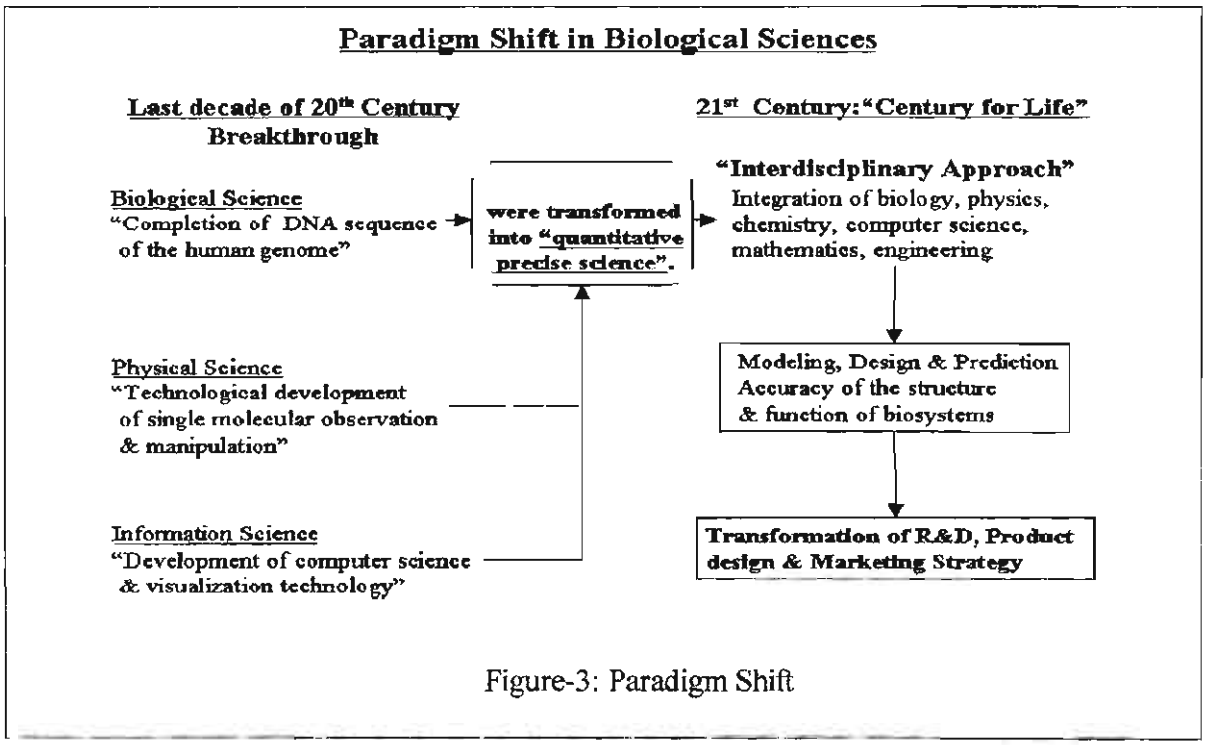

Figure-3: Paradigm Shift

PROFILE

Tokindo S. Okada

The Great and Fashionable Conductor
of the Biohistory Philharmonic Orchestra

Professor Tokindo S. Okada, who is the Director General of the JT Biohistory Research Hall in Osaka and has served as Vice-President of IUBS, is about to retire from the Director's position this coming spring. Becoming 75 years old, he has made up his mind for retirement, although his colleagues all hope earnestly to work with him for more years.

The Biohistory Research Hall, that has been in operation for ten years with Tokindo-san, is a unique organization established in 1993 as "a concert hall for science," where people can enjoy high level performance of science as a novel type of intellectual pursuit. The visitors are introduced into the history of life and the relationship of all the living creatures based mainly on studies with genomes. They are introduced also to the stable but ever-changing genomes that have been passed from parents and ancestors, tracing back to the origin of the genome, or the origin of life. In the BRH, we have attempted to share ideas between people and scientists: how human has become human and how ant has become ant, and how we recognize both similarities and differences between human and ant in the code of the genome.

As Tokindo-san has an unusual love for salamanders, his room in the BRH is full of pictures and ornaments of charming salamanders together with beautiful butterflies. Members of the BRH sometimes wondered whether Tokindo-san's genome has higher similarities to the genomes of salamanders than the average *Homo sapiens*, like us. We all respect him as the true biologist who has both a sympathy for living things and the passion for elucidating the rules of Nature.

In the Biohistory Research Hall, not only research results but also processes of research are shared with the general public through a variety of innovative presentations utilizing videos, exhibitions, music and other kinds of artistic media.

Tokindo-san is an enthusiastic lover of classical music. He is always keen to find novel works all over the world and enjoys introducing them to his friends, occasionally with a proud air. He says that he has never received formal education or training in music but is able to enjoy music from the heart. So he believes all the people can become familiar with science, or lovers of science, if they are exposed to good performers, as with music. Thus, he has been the conductor of the so-called Biohistory Philharmonic Orchestra of Science.

Tokindo-san often coordinated the BRH concert by combining performances of the Symphony Orchestra (the professional one!) and his lecture on scientific research. Among these, the most impressive one was the concert of "*Cantus Arcticus Op.61,*" Concerto for Birds and Orchestra, by Einohuhani Rautavaara (1972), in which the composer used the song of numerous birds as a chorus part. It gave the audience a great impression as a presentation of the harmony of human culture and Nature.

More than a few members of IUBS have visited the Biohistory Research Hall and enjoyed the performances, and they considered his activity as a model one in Biological Education in the 21st

Century. The BRH is proud of this, as IUBS has great responsibilities and is playing an effective role in biological education in developed and developing countries, especially in such domains as biodiversity, ecology, genetics and molecular biology.

Biohistory is a kind of a comprehensive intellect based on biology and the everyone's simple questions about life. So the members in BRH always try, with Tokindo-san, to offer perspectives on an integrated view of life based on an understanding of life from discoveries in modern biology. As noted, we focus on evolution, development and ecosystem, leading the organisms to changes over a lapse of time under various circumstances. In this sense, the interests of the IUBS BioEd project and the BRH overlap, and therefore, we expect that Tokindo-san will continue to be an indispensable person both for IUBS and BRH. We are eager to continue these efforts, maintaining our role as member of the philharmonic orchestra for sophisticated, biology-based performances under the perpetual conductor, Tokindo-san.

Keiko Nakamura
Deputy Director General, JT Biohistory Research Hall

Tokindo Okada : A prominent citizen of the world of science

Professor Okada, on the occasion of his retirement from professional life, played on the world stage of science. An internationally recognized, prominent biologist, researcher and educator, Professor Okada's contributions to the International Union of Biological Sciences extended over two decades. He was elected President of the International Society of Developmental Biology (ISDB) in 1985, Member of the IUBS Executive Committee (1988), and Vice-President (1991-1997). His invaluable contributions played an important role in founding the IUBS Scientific Programme "Reproductive Biology and Aquaculture" (1988-2000) and promoted IUBS activities in the West Pacific-Asia region.

Talal Younès
Executive Director, IUBS

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Biology in India

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The biological sciences occupy an important position in teaching as well as research activities in India. However, like every thing else in this country, there is enormous diversity, not only in the research areas pursued, but also in the pattern and contents of the various teaching programs. Given such diversity, there are no well-defined goals or policies for the nation as a whole. The present article seeks to provide some insight into the present status and future possibilities of teaching and research in various sub-disciplines of biology in India. It reflects the author's perspective and is neither comprehensive nor representative of any "national policy."

Biology teaching: present trends

Instruction in Biology/Life Sciences starts at the primary school level when the young children begin to understand the properties of living beings and their diversity. Biology constitutes a significant component of the Science curriculum and is studied by all students till the middle school level. At the secondary school level (9^{th} and 10^{th} standards), Biology becomes an independent subject. The process of canalisation starts at the higher secondary level (11^{th} and 12^{th} standards) with a largely (though not absolutely) irreversible selection of future choices. Students who desire to prepare for a career in medical practice usually select biology as one of their subjects at the higher secondary level.

Generally, those unable to enter the medical stream after school opt for admission to the B.Sc. (Bachelor of Sciences, 3 years) programme in biology-related subjects that is offered by almost all the universities in the country, either directly or through their affiliating colleges. At the B.Sc. level, subjects like Botany, Zoology, Microbiology, etc. are most common. Some universities also offer Biochemistry, Physiology, Genetics, Biotechnology, etc. at the B.Sc. level, although in most, these subjects are offered only at the M.Sc. level. Very few places treat Biology or Life Sciences as a whole at the B. Sc. level. In most cases, the students who opt for biology-related subjects at the B.Sc. level cannot study Physics or Mathematics, etc. at the same time, although Chemistry is usually allowed.

The 3-year B. Sc. degree is followed by a 2-year M.Sc. (Master of Science) course, which is an essential pre-requisite for a Ph.D. The Masters programmes are generally confined to the major sub-divisions like Botany, Zoology, Microbiology, Physiology, Biochemistry, Genetics, Biotechnology, etc. A limited number of universities also offer M.Sc. in Marine Biology, Aquaculture, Fisheries, Entomology or Biophysics, etc. A few universities offer M. Sc. in "Life Sciences" or "Biological Sciences." In some of these, the student can opt for a greater emphasis on "animal" or "plant" sciences.

Following the M.Sc., students who so desire can undertake research for a Ph.D. degree at a university department or other research institution (the research institutions cannot give their own degree and thus need to be affiliated to a university). Generally, the Ph.D. involves only research, although several places require a minimal amount of course work in addition to research.

In recent years, a number of universities have initiated integrated programs for M.Sc. or Ph.D. degrees. The integrated M.Sc. programme (5 years) starts after the higher secondary level and takes the student through to a M.Sc. degree, while the integrated Ph.D. programme (5 years) starts after the

student has completed the B.Sc. After two years of course work (equivalent to M.Sc.), the next three years are devoted to Ph.D. research.

The range covered in the most commonly available courses in Botany or Zoology at B.Sc. as well as at the M.Sc. levels extends from so-called "classical" botany or zoology to "modern" biology, although considerable variations in emphasis are manifest in the syllabi of different universities. An increasing number of students in recent years have shown preference for "modern" biology and opt to study subjects like Biotechnology, Genetics, Molecular Biology, etc., rather than the traditional Botany or Zoology. The range of laboratory exercises carried out by the students varies vastly but remains limited, in a majority of cases, due to constraints in resources.

It is a general perception that a holistic teaching of biology has suffered in recent years, mostly due to the fact that "Molecular Biology" appears more highly "respected" and attractive for the future career. Furthermore, since the teaching of "classical biology" topics like taxonomy, anatomy, etc. has become increasingly "dry" and restricted to the classroom, fewer students enjoy such subjects (Lakhotia, 1991). Consequently, the quality of research in areas related to basic biology, biodiversity, etc. remains less than satisfactory. Additionally, since the university system in general fails to attract talented "molecular biologists" due to their relatively poor infrastructure, the overall quality of academic manpower has perceptibly declined in the universities, and this is compounded by the fact that fewer of the brighter students now want to go for higher studies in the basic sciences.

Biological research in India: patterns, policies and funding

In addition to the more than 250 regular and "deemed" universities, a large number of autonomous research institutions have been established in India, mostly by governmental agencies like the Council of Scientific & Industrial Research (CSIR), the Departments of Science & Technology (DST), Biotechnology (DBT), Atomic Energy (DAE), etc. Each of these has its own specific research objectives. A number of state governments have also set up research institutes in life science related areas. The CSIR has the largest chain of national laboratories spread across the country, a good number of which are biology oriented. In recent years, several privately owned research institutions have also come into existence.

With such a large network of universities and research institutions, biological research encompasses a vast range of topics in India. Research in organismic or "classical" biology is largely confined to the university system, while most of the biologically-oriented research institutions place greater emphasis on molecular biology/cell biology and biotechnology-related research. Since research in molecular biology and related fields is more finance-sensitive, the university system generally lags behind in these areas, as compared with the various research institutions, where the laboratories are generally better equipped. In most places, research work is mainly carried out by students pursuing their Ph.D. degree. The culture of post-doctoral research fellows has still to be established.

Most of the universities have little money of their own to support research. The University Grants Commission (UGC) and the Department of Science & Technology (DST) have programs whereby identified departments in different universities can get additional funding for general development and/or research in specific areas. However, in order to carry out in-depth research, the individual faculty members need to get external funding for research projects. Multiple sources of funding exist. Agencies like DST, DBT, DAE (BRNS), CSIR, UGC, DRDO, etc. all support biological research, basic as well as applied. Although different funding agencies have identified their own thrust areas for priority support (the respective websites listed in Table 1 may be visited for details), each of them continues to support a "good" research proposal in almost any area of biology. Thus the Department of Biotechnology (Govt. of India), which was created in the 1980s specifically to promote biotechnology in India, also maintains programs to support basic molecular biological

research. Likewise, the Defence Research & Development Organization (DRDO, Govt. of India) also supports basic as well as applied biological research. Each funding agency has its own peer review system to screen proposals and approve the quantum of funding. Projects are generally supported for three years. In addition to individual projects, several agencies also provide more substantial grants for the establishment of major facilities, etc. Several such "national facilities" (for example, facilities for NMR, DNA and protein sequencing, confocal microscopy, micro-array analysis, etc.) have been created across the country. These facilities have worked with varying degrees of success. Private/industrial support for research is not yet substantial.

Future of biological sciences in India: challenges

Public interest in biology has greatly increased in recent years, thanks to the much discussed developments in genomics and biotechnology. Molecular biology/biotechnology and environmental studies/ecology/biodiversity have attracted the attention not only of policy makers but also of young persons and prospective biologists. India is perhaps one of the few countries that have a separate agency to promote research and applications in biotechnology, in addition to regular teaching programs in Biotechnology at the undergraduate and Master's levels. Likewise, bioinformatics has been vigorously promoted, and a number of distributed informatics service centers have been set up across the country by the DBT.

While the increased interest in molecular biology/biotechnology is visible in better quality training, research and other products, progress in the areas of environmental studies/ecology and biodiversity has not been as notable. This is due in part to the fact that good experts in these areas are no longer readily available, because of the general dislike among students, teachers and researchers for taxonomy/morphology and anatomy. As a consequence, a holistic approach to biology is missing.

An incomplete understanding of the biological system also impairs optimal realisation of the benefits of the significantly improved training and research in molecular biology/biotechnology. Biotechnology is currently taught as an independent subject even at the B.Sc. level, unfortunately also in places where neither the teachers nor the laboratories are adequately equipped for the job. Similarly, there is considerable euphoria over the great advances in genomics/proteomics, etc., but once again, in the absence of a good understanding of biology (especially genetics, cell biology and higher level biological organisation), the anticipated "quick" benefits of these technologies have often remained elusive.

As in many other countries, fewer students are now interested in teaching and research as career. Many of those who study biology-related subjects at B.Sc. and M. Sc. levels do so in the hope of entering the biotechnology industry, which is unfortunately still not established in the country. Moreover, given the poorly equipped teachers and laboratory facilities, training of such students is, in many cases, less than satisfactory, and this adds to their frustrations. If this situation continues, the increased interest in biology may wane. To sustain this interest in biology and reap its benefits, there is an urgent need in the country to reorient the teaching programs in biology. We need a judicious mix of the "classical" and "modern" biology. At the same time it is essential to revamp higher education, specially the university system.

The general lack of interest on the part of the younger generation in a career in science is compounded by the "brain-drain." The relatively good training in molecular biology is encouraging more and more of the brighter younger scientists to "go West." Very few return to the country to undertake productive academic activities. The other type of "brain-drain" occurs within the country itself: away from the university system and toward research institutions and national laboratories. There are a variety of avoidable and unavoidable reasons for this intra-national brain drain that has already resulted in a serious decline in the quality of academia in the university system.

Some efforts have been initiated in recent years at different levels to address the above mentioned factors of limitation. There is an increased awareness of the need for an integrative approach in teaching and research in all areas of biology. With a view to initiate a wider appreciation of a holistic approach to biology, the Indian National Science Academy organised a 2-day seminar on Integrative Biology in March, 2000, with participation by scientists and technologists representing different disciplines (Lakhotia, 2000, 2001). The Indian Institute of Technology (IIT) at Kanpur, a premier institution primarily devoted to engineering and technology, has started a new Department of Biological Sciences and Bio-engineering to promote various realms of biology (and not just biotechnology). Some universities (e.g., the Banaras Hindu University) are planning to initiate new courses in Biology at the undergraduate level so that those studying Physics, Mathematics, etc. can also have the option of studying Biology. The Indian Academy of Sciences, Bangalore, has initiated an ambitious "Project Lifescape," involving a large number of teachers and students at undergraduate and post-graduate levels, to address the challenge of monitoring biodiversity for conservation, sustainable use and control. This project has already resulted in a network of collaborating biology teachers in different parts of the country. With a view to improve the quality of biology teaching across the country, the University Grants Commission (a regulatory body for higher education in the country) has recently proposed new sets of syllabi in different areas of biology for adoption by the universities, with appropriate modifications as locally required.. While these are welcome signs, such efforts need to be initiated and sustained on a much wider scale.

The ordinary citizen of today is increasingly aware of the need to maintain the environment and biodiversity, of the potential benefits of biotechnology/genetic engineering, etc. There is also an increasing awareness about genetic disorders, their diagnosis and possible cure. All these concerns ensure that Biology will continue to be a major discipline for teaching and research in India in the coming decades. However, young teachers and researchers do not generally find the university system attractive enough for their careers. This has a long-term detrimental consequence. The various academic bodies and governmental agencies need to work together to tackle the socio-economic and other factors that are adversely affecting the university system. At the same time, the enthusiasm for molecular biology/biotechnology, considered as the cure-all tool for understanding life and exploiting its properties for betterment of mankind, must not be allowed to undermine the importance of other areas in biology. The rich floral and faunal diversity of the Indian sub-continent remains largely unexplored. This deficiency must be addressed with equal vigour, not only for the sake of knowledge in itself, but because comprehensive knowledge of this biodiversity is bound to provide new insights into evolution, ecology, development, etc. In addition, and perhaps more significant from the currently favoured point of view of business potential: a good knowledge of the flora and fauna is essential for a rational development of the traditional medical systems.

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Table 1. Web sites of major funding agencies, some research institutions and universities in India

Organization/Agency/Institution	Website
Dept. Science & Technology (DST), Government of India, New Delhi	http://mst.nic.in/dst
The University Grants Commission (UGC), New Delhi	www.ugc.ac.in
Council of Scientific & Industrial Research (CSIR), New Delhi	www.csir.res.in
Board of Research in Nuclear Sciences (BRNS, DAE), Dept. Atomic Energy, Government of India, Mumbai	www.barc.ernet.in/webpages/brns/brns1.html
Dept. Biotechnology (DBT), Government of India, New Delhi	www.dbtindia.org
Defense Research & Development Organization (DRDO), Government of India, New Delhi	www.drdo.org/labs/dls/index.shtml
Indian Council of Medical Research (ICMR), New Delhi	http://icmr.nic.in
Indian National Science Academy, New Delhi	www.insa-india.org
Indian Academy of Sciences, Bangalore	www.ias.ac.in; http://www.iisc.ernet.in/academy
National Institute of Oceanography, Goa	www.cmmacs.ernet.in/nal/icast/csir/nio.html
Wild Life Institute of India, Dehradun	www.wii.gov.in
Tata Memorial Centre, Mumbai	ww.tatamemorialcentre.com/research.htm
International Center for Genetic Engineering & Biotechnology, N. Delhi	www.icgeb.res.in
Centre for Cellular & Molecular Biology, Hyderabad	www.ccmbindia.org
Centre for Biochemical Technology, New Delhi	www.cbt.res.in
Tata Institute of Fundamental Research, Mumbai	www.tifr.res.in
National Centre for Biological Sciences, Bangalore	www.ncbs.res.in
Natl. Centre for Cell Science, Pune	www.nccs.res.in
National Institute of Immunology, New Delhi	www.nii.res.in
Centre for DNA Fingerprinting and Diagnostics, Hyderabad	www.cdfd.org.in/
Bose Institute, Kolakta	www.boseinstitute.org
Indian Institute of Science, Bangalore	www.iisc.etnet.in
Dept. Biological Sciences & Bioengineering, Indian Institute of Technology, Kanpur	www.iitk.ac.in/bsbe
Jawaharlal Nehru University, N. Delhi	www.jnu.ac.in
Hyderabad University, Hyderabad	www.uohyd.ernet.in
Delhi University, New Delhi	www.du.ac.in
Madurai Kamraj University, Madurai	www.dbtindia.nic.in/btis/dics/mku.htm
Pune University, Pune	www.unipune.ernet.in
Banaras Hindu University, Varanasi	www.bhu.ac.in
for a list of Universities in India	www.educationinfoindia.com

Modeling and Simulating Biological Processes in the Genomic Era

An account of a multidisciplinary seminar held in Autrans (France) in March, 2002.

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Introduction

The global project of high-throughput biology may be summarized as follows. After genome sequencing comes the annotation using the techniques of 'classical' bioinformatics. It then becomes important to interpret the annotations, to understand the interactions between biological functions, and to predict the outcome of perturbations, while incorporating the results from post-genomics studies. This stage can only be achieved through modeling and simulation of biological processes and should be tightly coupled to experiments at the bench.

This scientific development is necessarily a long-term trend for the following reasons.

• (Post-) genomics is characterized by the massive accumulation of molecular data, allowing in principle to generate predictions of a more quantitative nature than before. Modeling / simulation is the tool of choice to test quantitative predictions that involve a great number of objects and their interactions. Since we ultimately challenge our understanding of biological phenomena by prediction testing, simulation is going to play a major and increasing role in the progress of the biological sciences.

• Simulation becomes irreplaceable when it is difficult or impossible to experiment on live material for economical, technical or ethical reasons. The predictive outcome of a successful simulation guides the *in vivo* experimentation, thus reducing its cost ; the *in vivo* experimental results validate or falsify the initial model : this is how the synergistic loop between these two types of experimentation can be primed.

• Ambitious modeling / simulation attempts stumble on fundamental obstacles, including the lack of proper definitions for such basic biological notions like information, function, organization, and the difficulty of defining the domain of observability / falsifiability of a model. Overcoming these obstacles requires a long-term effort.

• The now recognized relevance of mechanical processes in the control of biological functions at different levels (DNA accessibility, endomembrane morphogenesis, signal mechano-transduction,

cytoskeletal and cell adhesion remodeling...) can hardly be analysed without considering physical models and associated simulations based on mathematical descriptions.

Two dozen researchers with various scientific backgrounds started in January 2001 to face these challenges in a stimulating year-round workshop that was initiated and supported by genopole® in Evry, France. Some of these scientists were initially more familiar with the field of modeling / simulation, while others were involved in various aspects of (post-) genomics. After 14 months of work, they held near Grenoble a small multidisciplinary seminar which brought together 60 participants. The following is an attempt to capture some of the evanescent spirit of this seminar, and we apologize for any involuntary mis- or under-representation of particular aspects.

Lectures

This four-day seminar comprised morning lectures of general interest and afternoon workshops on specific topics. The lectures can be placed into one of four categories – physico-chemical approaches, metabolic modeling, interaction networks and miscellaneous.

Physico-chemical approaches

The talks of Jacques Prost, Jean-Baptiste Fournier, Camille Ripoll and Yves Bouligand had physico-chemical approaches to the dynamics of intracellular structures as a common theme. Different sorts of modeling and simulation also played a large part in their work.

Prost insisted on the importance of the mesoscopic scale as one of the relevant scales in biological descriptions. He brought together mathematical modeling and physical experimentation in explaining how bacteria such as *Listeria monocytogenes* travel within and between human cells by locally polymerising actin using a bacterial protein, ActA. He showed how ActA-coated beads could move in a similar way and discussed symmetry breaking and persistence lengths. In the field of intracellular transport, he showed how motor proteins travelling along microtubules could tug tubes of lipids.

Fournier developed a physico-chemical model based on long-range elastic interactions to explore how the curvature of membranes by proteins influences their distribution. He applied this numerical model to the recruitment of dynamins by clathrin coats during endocytosis. There is a general principle here that may underpin the behaviour of many proteins that are integral or peripheral to the membrane.

Ripoll applied physico-chemical theories about the condensation of counter-ions onto linear, negatively charged, cytoskeletal structures to explain a whole range of disparate findings about calcium control of cellular processes. He proposed that condensation and decondensation of ions orchestrate kinases and phosphatases which in turn feed back on structures. This potentially provides a powerful integrative mechanism.

Bouligand took us through the history of liquid crystals in biology and showed us how cholesteric liquid crystals form *in vitro* and *in vivo*. He discussed how liquid crystals in DNA may affect the transcription of genes and the replication and partitioning of chromosomes. One of the many questions his talk raised is whether genome sequences could be used to determine which regions are in a liquid crystalline state.

Metabolic modeling

The next group, Athel Cornish-Bowden, Jean-Pierre Mazat, Christophe Chassagnole and Julie Fiévet, focused on metabolism – and the necessity of using metabolic control analysis to exploit experimental data by computer-modeling.

Metabolism is what cells do, Cornish-Bowden reminded us, and attempts to exploit genomic data that ignore metabolism are doomed. African sleeping sickness is caused by *Trypanosoma brucei* which has its glycolytic enzymes compartmentalised in a glycosome. To identify targets for drug therapy, he used metabolic simulations to determine which of the glycosomal enzymes would be good candidates and which would be useless.

Mazat showed how computer-modeling might be used to create and investigate a virtual mitochondrion, with the prospect of better understanding mitochondrial diseases. The first steps involve using the kinetic parameters of enzymes to predict metabolic fluxes within mitochondria which vary according to cell type. Many mitochondrial DNAs have now been sequenced and he held out the prospect of deriving metabolic maps from genetic ones.

Chassagnole modeled how pollutants such as heavy metals affect the flux through the threonine pathway. He determined the control points and showed that the multiple effects of these pollutants can only be understood by modeling the whole pathway.

Fiévet gave a different dimension to metabolism by introducing constraints due to molecular crowding and the cost of protein synthesis. She introduced the concept of combined response coefficient which takes into account the necessity for cells to evolve a particular distribution of enzymes to optimise the flux through a given pathway.

In these presentations of metabolic modeling, there was little joy for proponents of the genome or proteome as the source of all wisdom – the emphasis was placed on control coefficients and on an integrative understanding of pathways.

Interaction networks

Cellular life is all about patterns of interactions. Interpretation of these patterns were proposed by Derek Raine, Jacques Ricard, Marcelline Kaufman and Jacques Demongeot.

Raine gave us the history of power laws, self-organised criticality and small world networks in metabolism and gene regulation. He derived a parameter related to information entropy to assess the complexity of a network based on the ratio of the clustering or cliquishness to the average path-length between two elements. He examined gene expression during the cell cycle of *Caulobacter crescentus* in terms of this complexity parameter.

Ricard told us more about information. He pointed out that metabolic networks may contain more information than genetic ones. He argued that in metabolic networks the nodes could usefully be considered to be the reactions themselves. Then, beginning with Shannon's theory of information, he derived expressions for metabolic networks in which the values correspond to either integrated systems or emergent systems.

Kaufman took us through the logical analysis method for determining the dynamics of regulatory networks that include gene-protein and protein-protein interaction networks. This essentially discrete approach has been developed to allow asynchronous events in a network to be analysed. This approach permits multi-stationarity states and periodicity to be predicted relatively easily from complex experimental data.

Demongeot continued in the vein of logical analysis by discussing interaction matrices which represent how, for example, one gene regulates another. He raised the problem of the relationship between the number of steady states of the system and the number of regulatory circuits in the interaction matrix. Whilst these analytical techniques should prove suitable for interpreting the wealth of transcriptome data now available, Demongeot showed us that these data are far from perfect and presented a statistical method that helps improve them.

The preceding four talks were all of relevance to the interactions occurring in large intracellular networks, an understanding of which is critical if we are to exploit genome sequencing and the transcriptome.

Miscellaneous

The last series of talks, by Pierre Auger, Yannick Kergosien and Vincent Schächter, were more general.

Auger began by arguing that a progression up through the levels in biology is accompanied by a reduction in the time required for the units to interact and by an increase in the size of the units. This allowed him to apply an aggregation method to hierarchical biological systems and so obtain a simple model in which only a few global variables are important.

Kergosien explored the relationship between adaptation and branching using a simple robust algorithm that is of general relevance to epigenesis or to other situations where multidimensional tree graphs are drawn. He showed us how repeated, abortive attempts at branching might precede a major branch point.

Finally, Schächter gave us a salutary tour of the problems associated with trying to make sense of biological data. These ranged from serious problems with the quality of the experimental data to the inadequacy or limited applicability of models. Schächter's talk highlighted the importance of developing better and more integrative models and simulation techniques.

There was no shortage of candidate methods of simulation presented at the meeting on different occasions (posters, discussions) by the multidisciplinary audience. These ranged from multi-agent systems and cellular automata to L-systems, P-systems, MGS and SiliCell.

Workshops

Each of the four year-round workgroups convened an afternoon workshop devoted to its topics. Two of them, on Hyperstructures and on Endomembrane dynamics, revolved around biological models that are representative of a wide class of processes and are challenging for modeling/simulation. The other two workshops, on Observability and Organization, dealt with conceptual innovations in the overall methodology of biological modeling.

Hyperstructures

Biological objects are often "constructive dynamical systems" whose structures evolve as a consequence of their internal dynamics, which in turn is affected by the overall structure. Because very few tools are presently adapted to tackle constructive dynamical systems, they constitute fascinating challenges for modeling/simulation.

A typical case of a constructive dynamical system in cells would be hyperstructures, defined by Vic Norris and Michel Thellier as supramolecular assemblies that may comprise heterogeneous elements such as protein, lipid, ion, RNA, DNA. They appear during the operation of a particular cellular function and dissociate when the function is no longer required. Some of them are stable cellular substructures. Many of them are dissipative structures that only exist during active, energy-consuming functioning. Such hyperstructures may form if the affinities among their constituents change during functioning to provide higher stability of the whole. The concept of hyperstructure provides an intermediate level between the molecule and the cell and interconnects various remote scientific fields. Because this concept is not easily amenable to experimental testing at the bench, computer simulation is needed to investigate hyperstructure properties and to test whether the concept is coherent. A three-dimensional model of a metabolic hyperstructure has been created. It demonstrates that it is possible to find simple general rules to generate hyperstructures whose existence and stability depend on a flux of material.

The discussion that followed resolved some issues related to the materiality of hyperstructures, their typical time scales and thermodynamic properties. The concept of hyperstructures has the virtue

of emphasizing the dynamics in structural assembly/disassembly, and the multiplicity of functions for a given protein. The major criticisms bore on the very heterogeneous nature of hyperstructures, and the lack of experimental work in this field, which requires caution in the choice of an appropriate formalism that would not automatically generate the expected result.

Endomembranes

In cell biology, the secretory process in eukaryotic cells also corresponds to a constructive dynamical system, as it appears to autonomously generate new structures as a result of its molecular dynamics. François Képès reviewed the only documented case of a membrane-bounded intracellular compartment whose very existence strictly depends on its continued functioning, as for non membrane-bounded dissipative structures. Indeed, the Golgi apparatus of baker's yeast appears at steady-state as a continuously renewed set of transitory membrane-bounded structures that self-mature, rather than as a permanent entity. On the basis of this case and of recent advances in related molecular studies, a detailed model was proposed, that encompasses the birth of a yeast Golgi element and bridges its molecular and morphogenetic aspects. This model was extended to three successive evolutionary "inventions", from bakers' yeast to a methylotrophic yeast, to plant, and then to animal cells: stacking, stabilizing and aggregating the primary Golgi elements.

During the discussion, it was clearly stated that there are other possible mechanisms that may explain the morphogenesis observed in the Golgi apparatus. On the one hand, Jacques Prost pointed out in his talk (see above) that membrane bending can be caused not only by self-assembly of molecular coats, as in the clathrin-mediated vesiculation, but also by the action of microtubules or motors that can pull the membranes. On the other hand, it is known that asymmetric bilayers can easily undergo a bending process, due to forces depending on local curvature. It those forces can accentuate the curvature, a sufficiently large random fluctuation can start a bending process. Moreover, the morphogenesis can be explained by several mechanisms, each intervening at a specific time. It would therefore be interesting to determine the time scale of the migration described in the physico-chemical model presented by Jean-Baptiste Fournier (see above). Jean-Marc Delosme suggested that an order of magnitude may suffice to have an idea of the range of validity of this model in the morphogenesis of the Golgi apparatus.

Observability

For a variety of reasons, one may not be able to observe enough about a biological system to immediately determine whether a property holds; this is the notion of "observability". In Popperian terms, to be able to refute a property, one must be able to construct experiments which bring the model system in some desired state that provide enough information for conclusive validation or refutation; this is the notion of "operability" (basically the notion of "controllability" in systems theory). As Gilles Bernot reminded us, one would like to deal with properties that display both operability and observability.

The case study proposed by Janine Guespin is the hypothesis that there may be populations of *Pseudomonas aeruginosa* bacteria that keep on producing mucus in the lungs of cystic fibrosis patients because of a stable, epigenetic change that occur in the course of the infection. A formalism must be selected and a model of the object under study must be constructed using that formalism. The formalism used for the case study was adapted from that presented by Marcelline Kaufman (see above). It uses multivalued logical variables and a simple temporal logic, and has been modified to explicitly allow the notion of future. A model consists in modes of relations between components or parameters whose number is typically sufficiently large that one cannot readily figure out its behaviors. The model, together with statements about model behavior, may be viewed as a means of describing a complex hypothesis. Separating model and statements about the model (such as feedback

loops in the model for the case study and a statement about which loop is functional) makes things cleaner, albeit all are hypotheses and could be merged into the model.

A number of participants found these notions hard to understand, and the rest of the discussion was mainly devoted to clarifying the logical model and the way in which it could be made observable.

Organization

This workshop is about theoretical tools for simulation and analysis in genomics. Simulation corresponds to a corpus of tools which simulate the behavior of biological process. Analysis corresponds to tools for the finding of structural and dynamical properties from a topological representation.

During the session, Jean Louis Giavitto summarized the advances achieved by the workgroup. Christophe Godin introduced tools for the simulation of plant growth. Franck Molina presented work on the definition of a language dedicated to the design of ontologies. Finally, Franck Delaplace showed how emergent properties could be analysed in biological networks. These talks and the general discussion emphasized the relationships between models and computational frameworks, and between biological complexity and languages.

Conclusion

Among the messages that we took away, a couple were particularly strong. Firstly, to be successful in exploiting the results offered by the investment in the genome, a truly integrative modeling has to take into account physical chemistry of the sort presented at the seminar. In the theatre of the cell, these principles provide the script that a host of molecular actors have learnt over the aeons to interpret. Secondly, the gap between biological and physical approaches to complex systems is being bridged. New concepts are being generated and those interested in integrative simulation now have the exciting task of learning to exploit them. Thirdly, the dialogue between simulation and bench experimentation has been initiated and should be emphasized in the near future.

Further reading

An Autrans seminar book was edited by Patrick Amar, François Képès, Vic Norris and Philippe Tracqui. It contains the meeting abstracts, original papers and courses that relate to the above topics, and detailed accounts of the workshops. It is available from Dr. Hélène Pollard, Directrice Genopole-Recherche (Helene.Pollard@genopole.com).

Acknowledgments

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IUBS – SCOPE

African Renais-Science Conference: a vision for life and environment sciences in Africa

Held on 25 – 29 March, 2002
Durban Botanic Gardens Visitors Complex, NBS Education Center, Durban, South Africa

This conference was convened by Professor H. Baijnath, under the auspices of the National Research Foundation of South Africa, National Botanical Institute, IUBS and SCOPE. Support and infrastructure were provided by the Durban Botanic Gardens and the Natal Herbarium.

The scientific community of South Africa and some neighbouring countries (Angola, Lesotho, Malawi, Namibia, Nigeria) seized the opportunity to assemble and hold a forum on the advances of biological and environmental sciences, their relevance to the problems and expectations of the people of the southern part of the African continent, the status of the research field in Africa, and the ways to build research capacity in the region. The attendance (some 100 persons) comprised researchers and academics as well as students and managers of biological resources or environmental programmes.

Following the impulse given by Prof. Baijnath, presentations and discussions kept a very open tone and did not avoid conflictual topics or extended scientific and political debates. The conference was indeed initiated in the furrow traced by two on-going international initiatives concentrating on the African continent: the Millennium Project of the American Council for the United Nations University funded by UNDP and the Millennium Africa Renaissance Plan launched by South Africa, Nigeria and Algeria. The conference was not intended to applaud these initiatives but to assess what progress was being made, what challenges lie ahead for African countries and to what extent biological and environmental sciences might contribute towards relieving Africa from its present difficulties and miseries. The conference offered the scientists a round of preparation for an African contribution to the World Summit on Sustainable Development (Rio+10, Johannesburg, August-September 2002).

A set of objectives was given by Professor Baijnath to the participants:

- share expertise and build partnerships between participants and with international institutions to address problems and needs relevant to Africa;
- inform key individuals and institutions in Africa about IUBS and SCOPE programmes;
- strengthen national and regional expertise and networking activities;
- increase interest and awareness of young scientists and students in scientific national and international programmes;

with the ultimate goal to help improve quality of life for people in the region.

The conference was opened with a lecture by Professor Tobias, entitled: Africa, the cradle of Humanity. Over three days, speakers and participants addressed the following topics:

- African biodiversity and trans-frontier conservation in Africa;
- sustainable land use and development in Southern African savannas;
- African seeds and the Millennium Seed Bank;
- bioliteracy and education;
- education and dreaded diseases in Africa;
- emerging environmental issues and urban waste management;
- firewood, indigenous resources and land uses;

- HIV/AIDS epidemic and the African crisis;
- integrative biology;
- long term ecological research;
- the genome projects;
- water resources in Africa.

By the end, when Professor Baijnath chaired an overall summing-up session, five major recommendations had emerged:

1 - The necessity, in Africa as everywhere else in the world, to promote a scientific perspective based on the progress and doubts of advancing knowledge and not on *a priori*, definitive and finally obscurantist attitudes and dogmas.
2 - The necessity to promote bioliteracy, education and capacity building at all ages (from childhood through adulthood) and at all levels of social activities and compartments.
3 - The necessity to promote health education and status, environmental awareness and efforts to move up from poverty to sustainable development.
4 - The necessity to promote a dynamic management of biological, land and water resources through diversified and evolving strategies.
5 - The necessity to invest with more determination in national, regional and , interdisciplinary research collaborations and networking operations. Convincing and successful examples are given already by Sabonet and BioNet, by Kew Botanical Gardens in the UK (Millennium Seed Bank and Plant Genomes Project) and by SCOPE (Towards Sustainability) and IUBS (Integrative Biology and Bio-Education) programmes.

The outcome of this conference was published as a book (see Publications Review page), which was presented at the World Summit on Sustainable Development in Johannesburg.

Jean-Claude Mounolou, Past-President, IUBS
& Véronique Plocq-Fichelet, Executive Director, SCOPE

The Third World Academy of Sciences Prizes

The TWAS Prizes, which were launched in 1985, are among the most noteworthy prizes in science in the developing world. The Academy has recently expanded the fields in which the prizes will be given, and we are now encouraging individuals and scientific organizations of excellence to submit nomination forms. Prizes will be granted in the following fields: biology, chemistry, mathematics, physics, agricultural science, earth sciences, engineering sciences and medical sciences. Each prize carries a US$10,000 award and a plaque highlighting the recipient's major contributions to his or her field.

The prizes usually are given at major event - for example, the TWAS General Meeting - where recipients are asked to present a lecture in honour of receiving the award. For additional information about the TWAS Prizes, please contact:

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website: www.twas.org

Report of the 23rd International Ornithological Congress

11-17 August, 2002, in Beijing, P.R. China

The 23rd International Ornithological Congress was held in the Beijing International Convention Centre on August 11-17, 2002. It is a new century for the Ornithological Congress in a new country, a new continent, and a new millennium. About 800 participants came from all over the world, as well as 120 Chinese delegates from different research institutes, universities, museum of natural history, zoos, and nature reserves. The Local Committee organised three pre-congress birding tours: Shanghai-Chongming Island, Hong kong-Mai Po Marshes, and Beijing-Little Dragon Gate Reserve; six post-congress birding tours were also scheduled: South of Yunnan-Xishuangbanna, Lhasa-Tibet, Sichuan-Wolong National Nature Reserve, Heilongjiang- Zhalong Crane Reserve, Shaaxi- the Crested Ibis Reserve, Happy Island-North Beach of Beijing. There were also many exhibits displayed: the Mesozoic Era Bird Fossils in China, Bird Photos in Northeast, Special Bird Stamps of the Chinese Endemic Species, as well as Bird academic publications.

The scientific program committee put together a promising program of ten plenary lectures, a China evening, a special evening debate on the origin of birds, forty symposia, each one with five speakers, 20 round table discussions, and over 500 contributed oral papers and poster presentations.

1. Plenary Lectures
   The congress had 10 plenaries, each opening the morning and afternoon sessions, respectively. Plenaries at the start of sessions help to motivate delegates to come together and enjoy top-level review contribution on different subject of ornithology.
2. Symposia
   A total of 68 symposia proposals were submitted, out of which 40 were finally selected, taking into account an international representation of speakers, gender and topic. It was also requested that the convenors of a symposium be from different countries.
3. RTD
   RTD's are used for a variety of tasks, such as new methods and techniques in a variety of fields, updating on ongoing projects, proposed new lines of research, etc. We decided to have brief summary reports published in the congress proceedings. A total of 20 RTD's was scheduled.
4. Oral Papers
   Out of a total of 678 contributed papers, 397 submissions for oral papers were received. 200 of these were selected and grouped by subject into a total of 25 oral sessions.
5. Posters
   Poster papers are a very important type of presentation, which can often reach a wider audience than symposia and oral presentations. All poster presentations were accepted, provided the abstracts met the requested format.

Moreover, there were three satellite workshops: the International Crane Workshop, held on 9-10 August; the International Pheasant Workshop, held on 15 August, during the day break of the 23rd IOC; and the 9th International Grouse Workshop, held on 18-24 August.

In summary, this congress is another milestone in the history of Ornithological Congresses. As the hosts of the 23rd IOC, we wish to warmly thank the IUBS for kindly sponsoring the 23rd IOC in Beijing.

Secretariat, CCIUBS (10 September, 2002)

Biology International N° 43 (December, 2002)

OBITUARY

YAN Shaoyi (1932 – 2002)

Professor Shaoyi YAN (1932 - 2002), IUBS Executive Committee Member, President of the Chinese Committee for the International Union of Biological Sciences, Member of the China Committee for the International Council of Scientific Unions (ICSU-China), CAST, Beijing, and former Director of the Institute of Developmental Biology, Chinese Academy of Sciences, passed away in Beijing on March 9th, 2002, at the age of 70. His untimely death is a tragic loss not only to CCIUBS, but also to the biological field in China.

Yan's long and illustrious career in developmental biology was well founded in his early education at home and abroad. He graduated from Shandong University, Qingdao, China in 1953, and in 1992, he received a Doctor of Science at Hokkaido University, Japan. From 1953 to 1960, he worked in the Department of Experimental Zoology, Institute of Oceanography, CAS, Qingdao. His teacher was the noted Professor T.C. Tung (1902 – 1979). It was at Tung's suggestion that he focused his efforts on establishing the Institute of Developmental Biology in the Chinese Academy of Sciences, founded in 1980, with the partial support of the Rockefeller Foundation, New York, USA, and the United Nations Fund for Population Activities. One of the first examples of the implementation of China's 'Open Door' policy in science, the Institute has provided China with a new research base for developmental science.

One of the great challenges for developmental biology is to understand the molecular basis of the interaction between the nucleus and the cytoplasm. Yan discovered a series of nucleus transplantations in fish in various combinations: inter-variety, inter-genus, inter-subfamily, inter-family, inter-order, as well as inter-class. The results showed that, the more distantly related the species used in the combinations, the greater the developmental incompatibilities in the NCHs. The history of developmental biology has been considerably enriched through Yan's efforts. His achievements and contributions to developmental biology were appreciated and recognised both in China and abroad.

Yan was an ardent advocate and supporter of the work of IUBS in China and served as the leading member of CCIUBS since its founding in 1986. In addition, Yan published over 50 papers and articles, as well as 10 books, and was awarded many honours, e.g. from the Chinese Academy of Sciences in 1978 and 1987; and from the Ministry of Agriculture in 1990. The State Council PRC presented him with the (lifetime) Scientist's Diploma in 1992.

Yan's warm and generous personality and farsighted manner won him friends wherever he went. The quality of his scientific work has left its mark upon the history of biological science as an academic field. The passing of Shaoyi Yan signifies an irreparable loss to his grieving family, to CCIUBS, and to the wider circle of the IUBS family. IUBS has lost a prominent personality who accompanied, contributed to and promoted the Union's work for more than two decades. We will miss his support and influence.

XU Weishu, Secretary General, CCIUBS, Beijing, China

PUBLICATIONS REVIEW

COENOGENETICS
Genetics of Biotic Communities

By Uladzimir K.Sauchanka. CPL Scientific Publishing Services Limited, 2001 (201 pages).

A sequel to *"The Genosphere: the genetic system of the biosphere,"* by Uladzimir K. Sauchanka, published in English in 1997 (translated from Russian edition of 1991), this new book *"Coenogenetics"* focuses on the biotic community or biocoenosis as a natural system where the real evolution takes place and which is now becoming the centre-point for research and conservation efforts.
The author presents an integrative and interdisciplinary approach to the biological processes at work in biotic communities and develops further perspectives for genetics in the post-genomic era. The biotic communities are a dynamic system of plants, animals and microorganisms and their non-living environment interacting as a functional unit. The genetic system of such a biotic community or genocoenosis includes the interrelated and interacting genepools of different cohabitating species. The monograph embraces a broad concept of biological diversity at different levels of biological organization and may be interesting to all life scientists, but especially for researchers in the overlapping fields of genetics, ecology and evolution.

Nicolas Flay

JOHANNESBURG
Sommet Mondial du Développement Durable 2002 : Quels enjeux ? Quelle Contribution des Scientifiques ?

Edited by R. Barbault, A. Cornet, J. Gouzel, G. Mégie, I. Sachs & J. Weber. Published by Ministère des Affaires Etrangères. Direction générale de la coopération internationale et du développement, 2002 (206 pages).

This volume comprises a set of contributions by French academics addressing the key issues related to sustainable development, published in French on the occasion of the World Summit held on 29 August-4 Sept., 2002, in Johannesburg, South Africa. It includes chapters on the socio-economic challenges of sustainable development, managing plant genetic resources, biodiversity conservation and management, fisheries and the conservation of marine resources, desertification at the cross-roads between environment and development, climate changes, and the opportunity that this Summit represents for the world.
An English version is available online: http://www.adpf.asso.fr.

REBIRTH OF SCIENCE IN AFRICA
A Shared Vision for Life and Environmental Sciences

Edited by Himansu Baijnath & Yashica Singh. Published by Umdaus Press, South Africa, 2002 (246 pages). Orders: umdaus@succulents.net or afr.renais@nbidbn.co.za

Papers in this volume were presented and discussed at the "African Renais-Science Conference" held on 25-29 March, 2002, in Durban, South Africa, which was co-sponsored by the National Research Foundation, the National Botanic Institute, and Durban Botanic Gardens, South Africa, and IUBS and SCOPE.
Twenty papers are included, illustrating how advances in the biological and environmental sciences constitute the basis for socio-economic development. The papers provide key information on the status of Africa's abundant natural resources and practical measures for their sustainable utilisation. A call is made for the popularisation of science in view of promoting awareness of the role of science in health and environmental problems.
The book is of relevance to resource managers and rural planners, health care workers, students, programme designers and global funders. It provides insights over a large spectrum of topics for all those involved in the environment and its diversity.

THE VENICE LAGOON ECOSYSTEM
Inputs and Interactions between Land and Sea

Edited by P. Lasserre and A. Marzollo. Published in MAB Series, Volume 25 of UNESCO and The Parthenon Publishing Group, 2000 (508 pages).

Coastal lagoons, which comprise about 13% of the world's coastline, have long been closely interlinked with human societies in many parts of the world. The Venice Lagoon Ecosystem Project was carried out in the early 1990s as a collaborative research project co-sponsored by UNESCO, the Government of Italy, the Municipality of Venice and a series of research institutes and universities from Italy and elsewhere. The Project aims were to provide a quantitative understanding of the major flows involved in the coupling between pelagic and benthic processes and to relate this understanding to the increased eutrophication in the Lagoon of Venice. The research integrated *in situ* and experimental studies and modelling, focusing on a well-defined salinity gradient in the northern basin of the lagoon. Topics addressed include the biogeochemical cycling of organic carbon and trace metals, the interactions between lagoon sediments and degradation of organic matter, the processes which regulate the coupling of nutrient dynamics, oxygen and metal concentrations, and the effects of contaminants on macroalgae, molluscs, fish and other biota. The results reported in this book are important for the decisions regarding the future development of the Venice Lagoon. Its scientific approaches and insights are also of interest to the scientists, decision-makers and planners working on coastal lagoon ecosystems in other parts of the world.

TOURISM, BIODIVERSITY AND INFORMATION

Edited by F. di Castri & V. Balaji. Published by Backhuys Publishers, Leiden, 2002 (501 pages).

This volume is based upon the papers and discussions that took place at the Port-Cros International Symposium on "Placing Tourism in the Landscape of Diversities: a Dialogue between Nature and Culture" cosponsored by SCOPE, UNESCO, CNRS-France and Total Foundation.
Addressing the key issues of tourism and biodiversity in the global information society, the book comprises 7 Sections and 28 Chapters devoted to: (1) the evolution and interactions of the information society, tourism and biodiversity; (2) the main geographic regions: islands and coastal zones and their hinterlands; and (3) a discussion of the three main conceptual foundations underlying this book, i.e., conservation biology, sustainable development and information technology. The last Section addresses the impact on tourism produced by the terrorist attacks of September 11, 2001.

Useful Books on Hymenoptera, Pollination, Pollinators and their Protection and Use

Reviewed by
Peter G. Kevan, Department of Environmental Biology, University of Guelph, Guelph, Canada

The international Convention on Biological Diversity stressed the importance of pollinators in agroecosystems and in nature as providing an essential ecosystem service. There is now international concern over the potential demise of pollinators and pollination services and what that may mean in terms of human food and fibre security and prices, as well as long term impact upon ecological communities through effects on plant reproduction. The concerns embrace managed and wild pollinators in ecosystems ranging from tropical rainforests to urban gardens. The seven books noted below are noteworthy for their contents and the intended readership.

In 2000, the regional government of Tuscany published "**Apie impollinazione.**" Compiled by Mauro Pinzauti, this book of 307 pages is in Italian and comprises 18 independently authored chapters. All are practical in approach. Chapters are devoted to concerns of the pollination and fertilization of plants, with special reference to Tuscany. The roles of nectar and pollen in the entomological and botanical phases of pollination processes are discussed. As may be expected much of the book is entomological and addresses beekeeping with honeybees, bumblebees, leafcutting bees including the genus *Heriades*, orchard mason bees, while mentioning the importance of other pollinators.

Pinzauti, M. (ed.) 2000. *Apie impollinazione.* Edizioni delle Giunta Regionale: Region Toscana. Via di Novolini 73?a, 50127 Firenze, Italy.

Also in 2000, the German book "**Bienen, Hummeln, Wespen im Garten und in der Landschaft**" was published. Written in German by Helmut and Margrit Hintermeier, this 132-page book is about honeybees, bumblebees, solitary bees, wasps and hornets. It provides accounts of the natural histories, nesting and foraging habits of these bees, and stresses their ecological importance. Pollination and predation are thoroughly discussed. Techniques for encouraging these insects are described, including some practical beekeeping, trap nesting for solitary bees, and on how to house hornets. This book is written for the informed and curious naturalist, but professional entomologists and beekeepers can find much of interest.

Hintermeier, H and M. 2000. *Bienen, Hummeln, Wespen im Garten und in der Landschaft.* Obst- und Gartenverlag, Postfach 15 03 09, 80043 München, Germany. ISBN 3-8759-098-X

The Institut National de la Recherche Agronomique published **Hazards of Pesticides to Bees** in 2001. It is the outcome of the 7th International Symposium of the International Commission on Plant-Bee Relations, Bee Protection Group, held in Avignon, France in 1999. For anyone concerned with the subject, This 308-page book contains 27 papers covering a wide range of relevant issues. Toxicity tests and sublethal effects are well covered, as are non-pesticide approaches to pest control, as they may affect bees. There is a section of five papers on bumblebees and pesticides. Metabolites, residues, and bee poisoning incidents (from Europe) are discussed. An interesting set of five papers concerns methodology and introduces behavioural approaches to assessing pesticide hazards. The EPPO (European and Mediterranean Plant Protection Organization) guidelines are presented with a special view to their "side-effects on honey bees."

L. P. Belzunces, C. Pélissier, G. B. Lewis. 2001. *Hazards of Pesticides to Bees.* INRA Editions, Les Colloques No. 98. Institut National de la Recherche Agronomique, 147, rue de l'Université, 75338 Paris Cedex 07. ISBN 2-7380-0966-2

Also directly related to agriculture and practical issues in pollination is the book "**How to Manage the Blue Orchard Bee as an Orchard Pollinator**" by Jordi Bosch and William Kemp of the USDA in Logan, Utah, published in 2001. This slender book of 88 pages thoroughly covers the subject area. The life cycle and foraging ecology of these bees, called BOBs, are described. Chapters are devoted to artificial nesting materials, rearing BOBs, how to deploy them as efficient and low-temperature pollinators in commercial orchards, and on how to encourage and protect them from pesticides and pests.

Bosch, J. and W. Kemp. 2001. *How to Mange the Blue Orchard Bee as an Orchard Pollinator.* Sustainable Agriculture Network, National Agriculture Library, Beltsville, MD 20705-2351. ISBN 1-888626-06-2. Order: sabpubs@uvm.edu.

The Natural History of Bumblebees: A Sourcebook for Investigators by Carol Kearns and James Thomson is a useful addition to the literature. Published in 2001 at 130 pages, it provides insights into how to study these interesting insects. The accounts of their life cycles, foraging behaviour, parasites and predators, of their importance for

The references provided are quite extensive and allow users ready access to the scientific literature. The photographic field guide is not as useful as it might have been, but covers each species, with face-on, oblique over the back, and lateral illustrations to assist in identification. The range maps provided with the photographs should be used with caution as they are, admittedly "very broad."

C A Kearns and J D Thomson. 2001 *The Natural History of Bumblebees: A Sourcebook for Investigators* . The University Press of Colorado, 5589 Arapahoe Avenue, Suite 206C, Boulder, CO 80303. ISBN 0-87081-621-7 (paper) 0-87081-565-2 (cloth)

Also in 2001, another book that deals with trees and pollinators was published: "**Árboles Melíferos Nativos de Mesoamérica**" by Henry Arce, Luis Sánchez, Judith Slaa, Pablo Sánchez-Vindas, Alberto Ortiz, Johan van Veen, and Marinus Sommeijer. The book, in Spanish at 207 pages, is a compiled guide to the melliferous trees of Costa Rica. Each tree is depicted by colour photographs or two that illustrate flowers, fruits, and growth form. The descriptions provide succinct and interesting information on habitat, seasonal flowering patterns, propagation, use, and general ecology. Three important chapters stress the diversity of tropical bees that depend on the floral resources provided by the trees they describe, the floral relations of the bees as pollinators, and the importance of protecting and conserving bees and pollination system for the mesoamerican forests. Although this book focuses on trees as honey plants, it can serve as an guide to the common trees of Costa Rica, and the ecological lessons have general applicability, beyond that which the title might suggest.

H G. Arce, L A Sánchez, J Slaa, P E Sánchez-Vindas, A Ortiz M, J W van Veen, and M J Sommeijer, 2001. *Árboles Melíferos Nativos de Mesoamérica.* Centro de Investigaciones Apíolas Tropicales, Universidad Nacional de Costa Rica (PRAM-CINAT-UNA-UU), Heredia, Costa Rica. ISBN 9968-870-00-5.

Most recently, in 2002, the much anticipated book "**Pollinating Bees: The Conservation Link Between Agriculture and Nature**" has been published. This book, at 313 pages, is a compilation of papers that were delivered as part of an international workshop on the Conservation and Sustainable Use of Pollinators in Agriculture, with Emphasis on Bees, held in São Paulo, Brazil in October 1998. This workshop was part of the international initiative, spearheaded from Brazil, with respect to pollination and the Convention on Biodiversity. After dedication to the late Professor Soichi Sakagami, and celebrations for Professor Charles Michener and Padre Jesus Moure, the book includes 26 chapters written by internationally recognized experts, presenting a thorough treatments of: The Main Issues in Pollination and Bee Conservation; The State of the Art in Bee Conservation for Agriculture and Nature; Methodology for Pollinator Diversity and Abundance; and Neotropical Crop Pollination. The final part of the book presents an abbreviated version of the São Paulo Declaration on Pollination that has led to various activities in line with the Convention on Biodiversity around the world. This book is a valuable reference for conservation and protection of pollinator diversity. It stresses pollination as an ecosystem service upon which human well-being and natural productivity depend, and delves into the issues of conservation of species, spaces and ecosystemic processes. The lessons go beyond pollination, pollinators, and bees to illustrate the integrated nature of life on earth.

Kevan, P. G., V. Imperatriz-Fonseca, G. W. Frankie, C. O'Toole, R. Jones, and C. H. Vergara (eds) 2002. *Pollinating Bees: The Conservation Link Between Agriculture and Nature. Proceedings of the Workshop on the Conservation and Sustainable Use of Pollinators in Agriculture, with Emphasis on Bees, held in Sαo Paulo, Brazil in October 1998.* Ministry of Environment, Secretariat for Biodiversity and Forests, Brasília, DF, Brazil. cid@mma.gov.br

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The International Union of Biological Sciences is a non-governmental, non-profit organisation, established in 1919. Its objectives are to promote the study of biological sciences, to initiate, facilitate, and co-ordinate research and other scientific activities that require international cooperation, to ensure the discussion and dissemination of the results of cooperative research, to promote the organisation of international conferences and to assist in the publication of their reports.

The membership of the IUBS presently consists of 44 Ordinary Members, adhering through Academies of Science, National Research Councils, national science associations or similar organisations, and 80 Scientific Members, all of which are international scientific associations, societies or commissions in the various biological disciplines.

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BULGARIA - Bulgarian Academy of Sciences
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