HOF 01-057

本田財団レポートNo.57

「生物学者の科学的責任」

コレージュ・ド・フランス名誉教授　ジャン・ドーセ

Professor Jean DAUSSET
is awarded HONDA PRISE together with all the privileges and honours pertaining thereto,

in recognition of his significant works and activities done as the leader of the "Universal Movement for Scientific Responsibility" in order to clarify the benefits and the harms which may be brought by the advancement of science and technology, as well as to draw people's attention to these issues confronting society, and thus to develop a worldwide drive channeled to harness science and technology for the real benefit of mankind and of our earth.

Biography and Positions

1916	Born in Toulouse, France
1945	M.D., University of Paris
1948	Harvard Medical school
1950-1963	Director of Laboratories, National Blood Transfusion Centre
1958-1968	Associate Professor, University of Paris
1963-1968	Co-Chairman, Institute for Research into Diseases of the blood
1963-1978	Biologiste des Hopitaux, Paris municipal Hospitals
1968-1977	Professor of Immuno-Haematology, University of Paris
1968-1984	Director of Research Unit on Immunogenetics of Human Trasnsplantation, Institut National de la Santé et de la Rechetche Médicale
1969-1984	Co-Director of the "Institut de Recherches sur les Leucémies et les Maladies du Sang", Saint Louis Hospital, Paris
1977-1987	Professor of experimental Medicine, Collège de France, Paris
1978-1984	Co-Director, Oncology and Immunohematology Laboratory, Centre National de la Recherche Scientifique
1982 to present	President of the Universal Movement for Scientific Responsibility (MURS).

He is Currently:

— Honorary Professor of Experimental Medicine, Collège de France, Paris
— President of the Universal Movement for Scientific Responsibility (MURS)
— Expert in Immunology of the WHO
— President of France-Transplant

Honour

He received the 1980 Nobel Prize in Physiology and Medicine for his discovery of antigens (major histocompatibility antiqens) different from blood types in leukocytes and other tissue cells and that transplantations are subject to the differences of the antigens.

Also, he has received various other prizes, including the Koch Foundation Prize (1978), Wolf Foundation Prize (1978) and Légion d'Honneur (1984).

Member

A member of various national academies and international learned societies, such as the American National Academy of Sciences, the Sociéré Française d'Iimmunologie, the British Society of Immunology, the American Academy of Arts and Sciences.

Recent Monographs

"Immuno-hématologie Biologique et Clinique"
Flammarion, 1956
"Iso-leuco-anticorps"
Acta Haematologica, 1958
"Histocompatibility Testing 1972"
in collaboration with J.Colombani; Monksgaard, 1972
"Histocompatibility"
in collaboration with G.D.Snell and J.Nathenson; Academic Press, 1976
"HLA, Complexe Majeur d'Histocompatibiilté de I'Homme"
in collaboration with M.Pla; Flammation, 1985

ジャン・ドーセ氏の受賞は、「科学の責任に関する世界会議」の活動を通じて、科学技術がもたらす恩恵と弊害を明確にし、社会が直面しているこれらの問題に対する人々の関心を高め、科学技術を人類と地球の将来のために活用する世界的な運動を展開してこられた功績によるものです。

●学歴および経歴

1916	フランス、トウールーズ生まれ
1945	パリ大学卒業（医学博士）
1948	ハーバード・メディカル・スクール卒業
1950～1963	国立輸血センター 実験室長
1958～1968	パリ大学医学部 准教授
1963～1968	血液系疾患研究所 副所長
1963～1978	パリ市立病院 病院付生物学者
1968～1977	パリ大学医学部 教授（免疫血液学）
1968～1984	国立保健・医学研究所　人体移植免疫遺伝学部門研究部長
1969～1984	パリ市立サン・ルイ病院　白血病及び血液疾患研究所所長
1977～1987	コレージュ・ド・フランス 教授（実験医学）
1978～1984	国立科学研究センター 腫瘍学・免疫血液学研究所副所長
1982～	科学の責任に関する世界会議(MURS）会長

現在●コレージュ・ド・フランス名誉教授（実験医学）
●科学の責任に関する世界会議(MURS）会長
●WHO免疫学専門委員
●フランス移植学会会長、他

●栄誉

白血球やその他の組織の細胞に血液型とは違った抗原（主要組織適合抗原）が存在し、その抗原の差によって移植の成立が左右されることを発見したことに対し、1980年度のノーベル医学・生理学賞を受賞した他、コッホ財団賞（1978）、ウオルフ財団賞（1978）、レジオン・ドヌール勲章（1984）等多数の賞を受賞する。

●会員

全米科学アカデミー、英国免疫学会、フランス輸血学会アメリカ芸術・科学アカデミー等数多くの国内・国際学会に所属する。

●近年発表の論文、著者

『免疫血液学－生物学的・臨床学的側面』
1956年、フラマリオン社
『同種白血球抗体』
1958年
『組織適合性試験　1972』
J.コロンバニと共著
1972年、ムンクスガールド社
『組織適合性　1976』
G.スネル、S.ナテンソンと共著
1976年、アカデミック・プレス社
『HLA　1985』
M.プラと共著
1985年、フラマリオン社

The Scientific Responsibility of Biologists

Lecture at the Conferring Ceremony of the Honda Prize on 17 November, 1987

Professor Jean Dausset

1. INTRODUCTION

I am very proud to have been chosen as the 8th recipient of the Honda Prize. This honour is directed to me mainly as current president of the Universal Movement for Scientific Responsibility, the spirit of which is in close analogy with that of the Honda Foundation. Indeed the aim of both is to exploit science and technology to the benefit, and not the detriment, of mankind, or, to use a word very appropriately coined by the Honda Foundation —ECO-TECHNOLOGY.

Amazed as we are by daily new technological exploits and saturated with human drama, we realise that we are living in what is probably the most exciting but also the most dangerous period in the human adventure, a unique moment in world history. We cannot tell whether this is a stroke of luck or a privilege, but it is certainly a heavy responsibility to which we cannot remain indifferent.

The epic of life on Earth began more than three billion years ago. In the course of a slow and fabulous biological evolution, vegetable and animal species all emerged one by one. The size of the brain increased progressively and culminated in that of man who appeared at least two million years ago. Of all living creatures, he alone developed, in a surprising fashion, the capacity to foresee, to anticipate, and to relate cause and effect. Only in the course of the past century has he applied scientific reasoning systematically and rigorously.

The scientific and technological revolution is barely beginning. Man himself, a material being, is starting to understand the great forces which dominate matter, and to apprehend the mechanisms of life. He is progressively acquiring a certain mastery over his environment and his own reproduction, and is developing more fully his intellectual capacity and spirituality.

Yet, despite daily enjoyment of the benefits of scientific and technological progress, some of us feel a certain nostalgia for the past — a past that we always tend to idealize. But let us not forget the famines, epidemics, scourges of all kinds which have occurred regularly throughout history. There are many people who fear for the future and who, considering themselves helpless to modify the course of events, retire into passive resignation.

We believe both these attitudes to be irrational. On the one hand, we cannot but rejoice over the progress achieved in the understanding of the world around us. Every new piece of knowledge is liberating; ignorance is the worst form of slavery. We cannot and must not stop the march of science and technology. On the other hand, man must be trusted to find for himself the road to survival. His imagination, ingenuity and aggressiveness (in the best sense of the words) are without limit.

Man must not resign himself to his fate: he is now capable of influencing and orienting his destiny towards a carefully thought-out future.

The times in which we live are unique due to an unprecedented situation. An obvious imbalance has arisen between the rapid material and technological changes crowding in on us, and the slow mental and social changes, resulting from scientific discoveries, these latter changes proceeding according to the rhythm of generations. The malaise that we feel is caused by this lag.

Science and technology should be applied with wisdom. Each advance presents a positive and negative facet. The benefits should be carefully weighed against the risks and adverse side-effects. If the advantages outweigh the disadvantages, we should attempt to minimize, as far as possible, the risks and adverse side-effects involved.

In this complete mutation of mankind, which we are fortunate enough to witness, the responsibility of scientists is enormous.

New knowledge imposes new duties. First of all, scientists should be well aware of the possible practical applications of their discoveries. Second, they should inform the public in the clearest way possible in order to shape public opinion toward the correct utilization of technological progress.

Thirdly, they should point the decision-makers in the right direction after an exhaustive and honest evaluation of the risks and adverse side-effects of science.

To illustrate this situation, let me take three examples from my own discipline.

I am a biologist, and more precisely, an immunogeneticist. Immunogenetics is a discipline which appears very innocent at first sight.

In 1958, I had the good fortune to discover the first tissue antigen in man, belonging to the main tissue system, the HLA system: H for histo (tissue) compatibility, L for leucocyte (since this system was first detected on white blood cells) and A for the first system. Thanks to the enthusiastic work of thousands of research workers, this system has been rapidly elucidated although it turns out to be very complex. This complexity is such that each individual possesses, in fact, his own formula due to the almost infinite number of possible combinations of alleles (which are slight variations of the products of the six HLA genes (figure 1). In fact even for this limited part of the human genome (i.e. 1/1000), it is striking that every unrelated individual is unique.

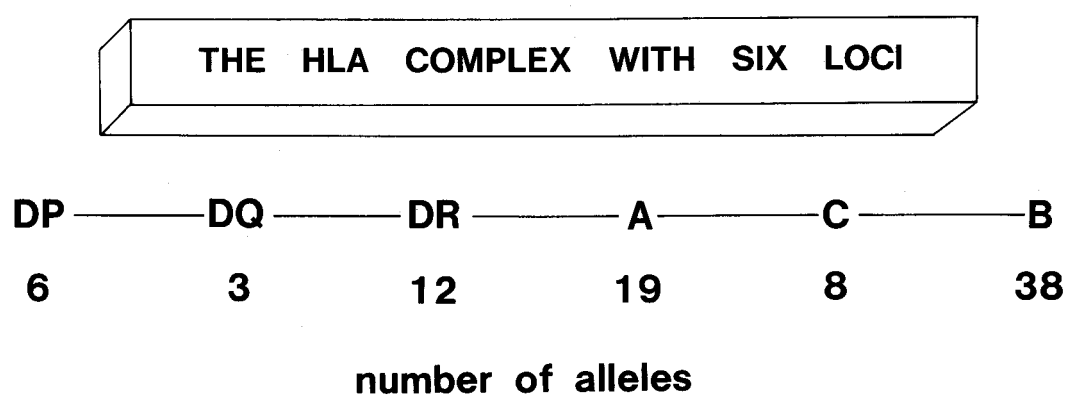


Fig. 1: Diagram representing the Major Histocompatibility Complex in man. The HLA region, situated on the short arm of chromosome 6, carries at least six genes (or families of genes), each of which possesses a large array of individual variations called alleles. Thus the number of possible combinations is almost infinite. (1988)

The unravelling of this complex tissue antigen system leads to an important conclusion that no two individuals are identical, or ever have been or ever will be, except, of course, for monozygotic twins.

Man's uniqueness is undoubtedly a treasure on which is based his liberty and dignity.

This remark is applicable not only to the physical differences but — and probably more important —to culturally acquired differences.

It is essential to understand the vital need of differences not only at the genomic level — to ensure the continuous mixing of genes which permit the permanence of the evolutionary process — but also at the psychological and cultural level. Each culture is a leaven which allows individuals to compare themselves with each another and to compete with one another for better welfare. A new idea, indeed a new concept, has more chance of occurring in a special environment, or in a special culture. If the world were uniform, with one standard culture, as it is tending to become at present, it is to be feared that mankind will become sterile. A cultural, behavioural evolution has to proceed in the same way as the biological evolution. When a new concept or idea arises, it is accepted or eliminated by a comparable selective process.

The difference between human beings is the essential reason for tolerant behaviour. Tolerance in itself is not enough since it implies making a conscious effort to put up with others. Tolerance should be instinctive and not enforced. It should be a pleasure to meet somebody different from oneself, and an occasion to be enriched by these differences. As the French author, Saint-Exupery, so beautifully said in "THE LITTLE PRICE": "If you differ from me, brother, far from insulting me, you enrich me".

The practical implications of the discovery of this exuberant diversity, and more specifically of that of the main tissue antigen system in man, the HLA system, has had a tremendous impact on medicine and surgery.

As the blood group systems opened up the possibility of blood transfusion, so the HLA system has opened the way to transplantation. The benefits to mankind have been enormous. Thousands of organ and bone marrow transplantation have been done following the HLA compatibility rules.

These rules were written after an exhaustive series of skin-graft experiments (figure 2) done on ad-

Fig. 2: Skin grafts (1cm in diameter) performed on the arms of a volunteer. Three skin grafts (black areas) were rejected on the 10th day; in contrast, the other three grafts (pink areas) have still not been rejected.

mirable human volunteers who offered their time and suffered pain for the sake of science. More than 300 skin grafts were performed in Paris, mainly between unrelated individuals but also often among family members. It was obvious that the best donor is the one who shares the maximum number of antigens with the recipient (figure 3). The longest survival was observed after an exchange of skin samples between two HLA identical sibs. The shortest occurred between unrelated individuals who have no common antigen. An intermediary situation occurs between parent and child since half of their HLA type is common to both. In a typical family, shown in figure 4, segregation of the HLA antigens follows the classical Mendelian laws.

The situation found in kidney transplantation is analogous (figure 5). The kidney was the first organ to be transplanted. The best results were obtained when the donors were HLA genetically identical sibs, but most individuals are not fortunate enough to have a volunteer, HLA identical brother or sister (statistically, one chance in four). In these cases, it is necessary to seek a compatible organ from an unrelated individual. Only unrelated cadaver donors are ethically acceptable. In most developed countries, organ exchange organizations have been created, the aim of which is to distribute available organs, attempting to match the donor and recipient as closely as possible.

More important are the histocompatibility rules in cases of bone marrow transplantation. Complete cures for leukaemia or aplasia have now been recorded, but only where the donor was an HLA identical sib. The donor is often a child, even a baby. The results obtained are fabulous, and immunologists and clinicians can be very proud of their role in this achievement.

Until recently, organs and bone marrow were generously donated either before or after death. Hundreds, if not thousands of patients benefit each year from histocompatibility testing. Heart, liver and pancreas transplantations are becoming increasingly numerous. Surgery in the next century will be mainly replacement surgery.

The donation of an organ for transplantation is probably the most exemplary gesture of human solidarity.

Unfortunately this gesture risks being tainted. While the voluntary donation of a mother to her child, or between brother and sister is extremely noble when strongly motivated by powerful sentimental links, the buying of an organ of a non-related individual is, in contrast, shocking. It goes against human dignity, exploits human misery, and opens the door to every kind of exploitation to which those unfortunate individuals who are totally dependent

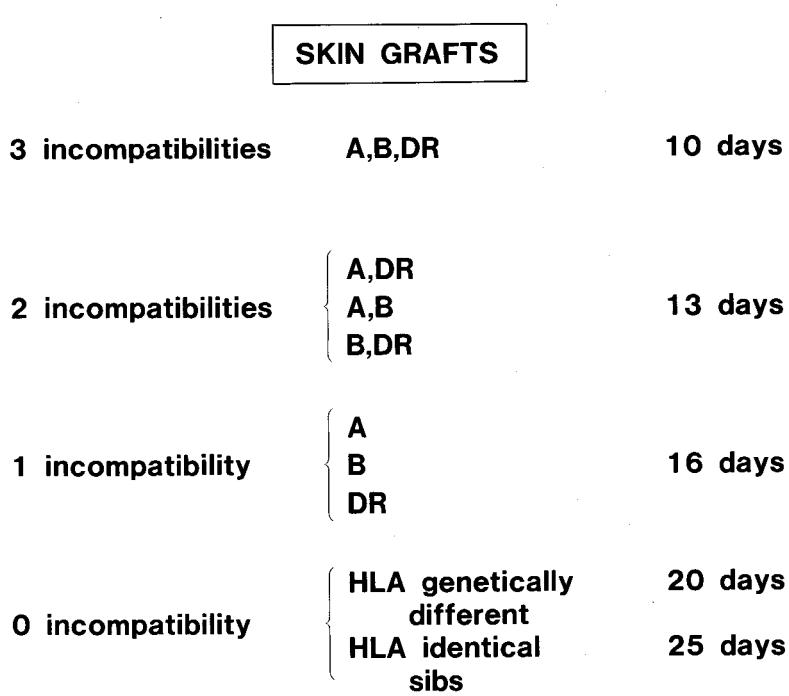


Fig. 3: Results of skin grafts done in situations of varying degrees of HLA compatibility. Survival time increased in direct relation to the number of HLA incompatibilities between donor and recipient. The most favourable circumstances are when the donor is genotypically HLA identical to the recipient (25 days). All these grafts were done in ABO compatibility.

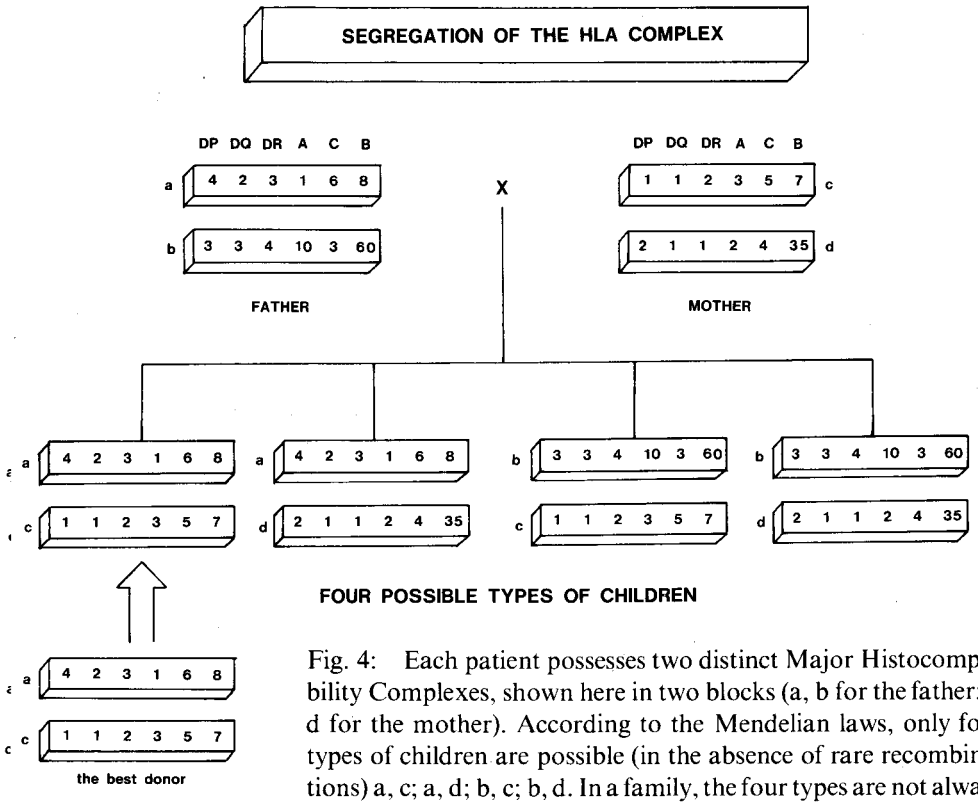


Fig. 4: Each patient possesses two distinct Major Histocompatibility Complexes, shown here in two blocks (a, b for the father; c, d for the mother). According to the Mendelian laws, only four types of children are possible (in the absence of rare recombinations) a, c; a, d; b, c; b, d. In a family, the four types are not always represented and there are often several children with the same combination, said to be HLA identical. The best donor is a sib HLA identical to the patient.

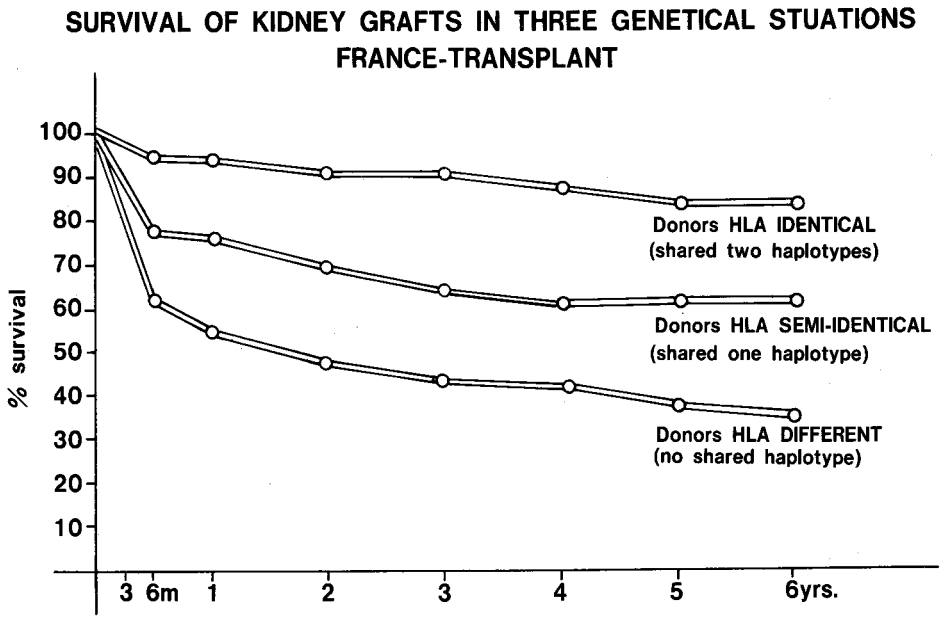


Fig. 5: The difference in kidney survival after 6 years is striking. 90% of kidneys donated by HLA genetically identical sibs always survive. Slightly more than 60% survive when half of the HLA type of the donor and recipient is common to both (i.e. a parent or HLA semi-identical sib). Less than 40% of kidneys survive when the donor is HLA different (either an unrelated or HLA different sib).

on others would be subjected (like prisoners or members of a minority). Equally it opens the door to all types of hypocrisy, as a sale can be easily camouflaged as a disinterested gesture, a so-called "gift". Moreover, it increases inequality in the face of disease.

Organ trafficking is illegal in most countries, and has been formally condemned by the Transplantation Society, the Council of Europe and many other institutions. Yet there are many countries in the world where organ trafficking is being practised, in most cases illegally but nevertheless openly.

Those of us invovled in the field of histocompatibility are committed in conscience to refuse to HLA type or to perform cross-matching when the living donor is not obviously motivated by humanistic feeling. Moral obligation is stronger than the law. If we take this attitude, we will honour ourselves and our discipline.

This first example shows that a tremendously beneficial technical advance can lead to the worst possible consequences, degrading the human spirit, depriving it of the enthusiasm and solidarity which prevailed during the first decade of transplantation.

The second example of the dilemma posed by modern science followed the discovery that HLA antigens are deeply involved in the immune response. They are in fact the initiators of immune response, either by antibodies or killer cells. Indeed, they enable the organism to distinguish between self and non-self. Only foreign structures, when present on the HLA molecules, are recognized as foreign and eliminated. Thus the HLA system plays an essential role in our defence against all kinds of aggression.

The discovery of the tissue groups has had a capital impact on our fundamental understanding of the immune system. The major histocompatibility complex was the key which opened a large array of concepts both of the normal mechanisms of immune defence and the abnormal pathological processes.

Consequently, it was not astonishing to find that numerous diseases were associated with certain HLA antigens (figures 6 and 7).

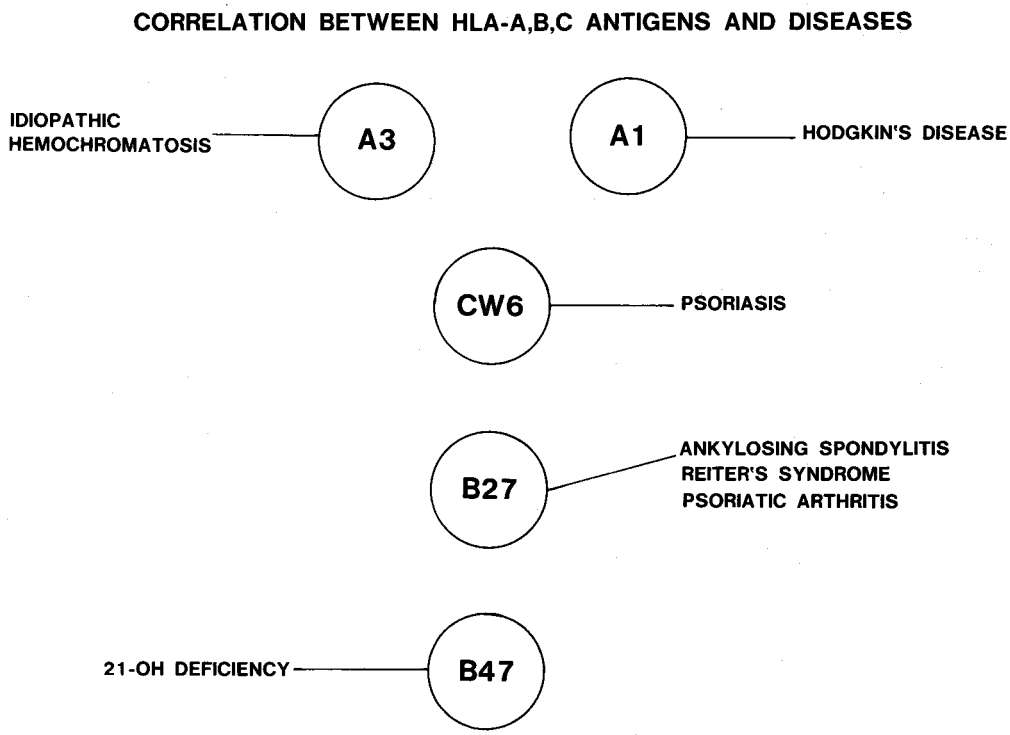


Fig. 6: Correlation between HLA-A, B, C antigens and diseases. The most striking correlation is that of HLA-B27 and ankylosing spondylitis. However there are other important correlations such as A3 and idiopathic haemochromatosis, and B47 and 21-OH deficiency—two diseases linked to HLA due to the presence of deleterious genes in the HLA complex.

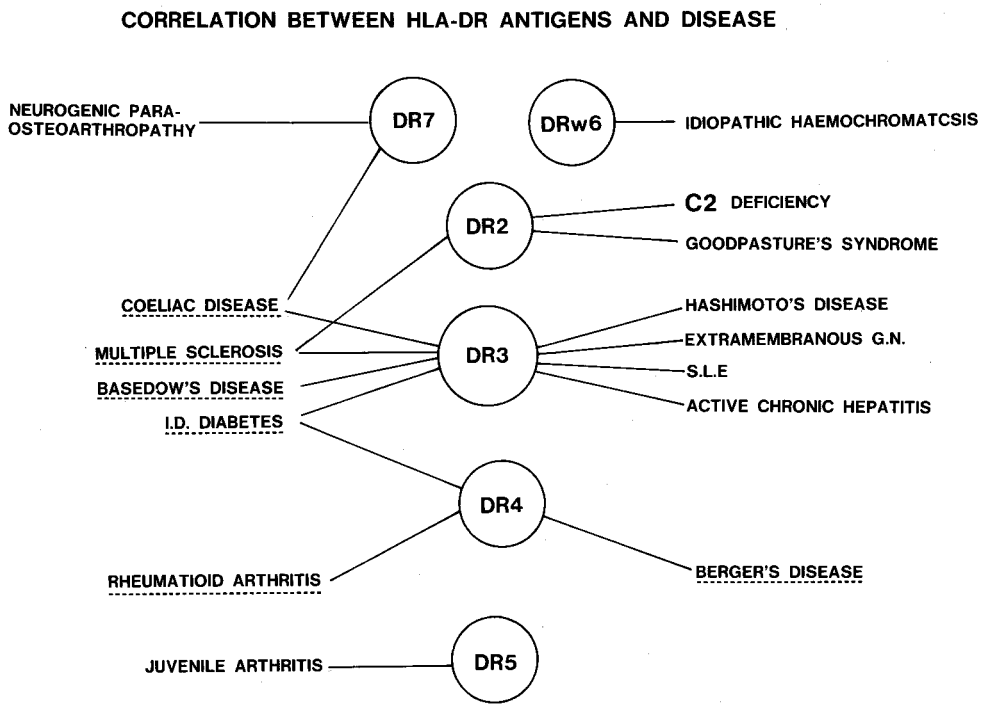


Fig. 7: Correlation between HLA-DR and disease. Many auto-immune diseases, so frequent in our industrial countries, are associated with HLA. These correlations can help in establishing difficult diagnoses and could lead to a better understanding of the physio-pathology of disease.

For example, anyone with the HLA-B27 antigen carries an increased risk of contracting ankylosing spondylitis associated with impaired movement of the lower part of the spine. His risk is 600 times that for someone who does not possess the HLA-B27 antigen. Thus, HLA-B27 is a marker of a special susceptibility — it indicates a particular predisposition to this incapacitating disease.

Likewise, a child who is HLA-DR3 and/or DR4 has a much greater risk of contracting juvenile diabetes than another child who does not bear these antigens.

The detection of susceptible children in families may have important consequences. These children should be closely followed and, at the earliest signs of diabetes, preventive measures (if there are any), or at least early curative treatment, should be instituted.

The list of other HLA associated diseases is now astonishingly long. It comprises many systemic diseases, which although frequent in developed countries, are still not fully understood or effectively treated. These diseases include rheumatoid arthritis, multiple sclerosis, lupus erythematosis, Hashimoto's disease, etc. In fact most, if not all, of the so-called auto-immune diseases are more or less strongly associated with HLA. Thanks to these associations, we are not far from understanding the mechanisms leading to the appearance of these diseases which are probably due to the joint interaction of genetic and environmental factors.

The prediction of susceptibility will not be limited to the association with HLA genes. This approach will be generally applied to many other genetic markers spaced over the 3 billion nucleotides or letters which form the human hereditary material.

In the near future, it will eventually be feasible to detect the gene or combination of genes which determine genetic susceptibility to many multifactorial diseases. These relatively common conditions result from a set of predisposing genes acting in concert with environmental influences, including diseases like rheumatoid arthritis, heart disease, hypertension, or diabetes.

It can be foreseen that medicine in the 21st century will be predictive medicine, allowing disease to be prevented, or at least early treatment to be instituted. Susceptible individuals will be detected by systemic screening of their genetic map.

But this victory will not come without disturbing consequences.

It is, first, obvious that if there is no real treatment, the disclosure of susceptibility, let us say for example, to some form of cancer or disabling disorder may induce a state of unbearable and needless anxiety.

Moreover, the free divulgence of an individual's genetic characteristics can be odiously exploited by the employer or life insurance company.

Here, too, in this second example, the detrimental effect of tremendous scientific progress is purely in the ethical realm and not a technical problem. Genetic knowledge must be used wisely and humanely, and certainly not for economic exploitation.

The third example will be much more general since it concerns the use, and misuse, of the powerful tool brought by molecular biology.

The scientific world is presently discussing the usefulness and validity of completely sequencing the 3 billion letters which comprise the human genome. It is likely that the full knowledge of this sequence will be beneficial both from a fundamental point of view and in practical implications. One day or another, and probably sooner than generally expected, sequencing will be completed. The mystery of gene interaction and regulation will be unveiled.

But it will also allow many undesirable genetic manipulations which, unfortunately, may have already begun without the full knowledge of the genomic sequence.

In my opinion, it will be very useful to introduce a gene into a non-germ line cell of a patient in order to compensate a hereditary defect. On the contrary, no gene should be introduced into an early human embryo or into germ line cells since this character could then be hereditarily transmitted. Any attempt to modify the human genome should be strictly forbidden.

Biologists themselves should declare a moratorium with respect to this process, because of the danger that these techniques will be used for a non medical purpose — for false eugenic engineering, which will recall the worst recent human tragedy, familiar to all of us. Arbitrary negative selection but also arbitrary positive introduction of some genes, arbitrarily decreed beneficial should be strictly forbidden.

The human gene pool should not be modified. It has attained an extraordinary level of evolutionary subtlety and sensitivity. Man will only impair his marvellous mechanisms by tampering with his genome.

These three examples have been given to illustrate the fact that knowledge, on the one hand, and utilization of knowledge, on the other hand, should not be confused. Knowledge is always a victory over obscurity and superstition. Applications are always more hazardous as they bear both beneficial and detrimental facets which should be carefully scrutinized before they are launched on society.

Of course, scientific responsibility overtakes biology and covers every field of science and technology.

The responsibility of science to the future of mankind, and by direct consequence the responsibility of scientists, is becoming evident to the general public.

The Universal Movement for Scientific Responsibility or, in French, le Mouvement Universel de la Responsibilité Scientifique, the abbreviation for which is M.U.R.S., was found 10 years ago when this notion had not yet become obvious. It pioneers this line of thinking.

This movement is a non profit-making organization, with no political, ethnic or religious attachments. It has a strictly scientific approach to the great problems which mankind is presently confront-

ing or will face in the future. It tries to anticipate the consequences of scientific progress. It has, for example, organized a series of conferences, international meetings or gatherings of experts on such importnat subjects as overpopulation, aggressiveness, tolerance, risk evaluation, ageing of individuals and populations, impact of computerization, social impact of parasitism, and so on. It publishes, every 3 months, a journal called "Science and the Future of Man" (les Cahiers du MURS), in which the most interesting lectures appear as well as the conclusions and possible resolutions presented by experts.

The Universal Movement for Scientific Responsibility is endeavouring to accelerate the awakening in scientists, but also in all those who are in positions of authority, and, in fact, in all men, to the consciousness of their immense responsibility.

Time is no more when the scientist could isolate himself in his ivory tower and consider his discoveries as interesting abstractions. The applications of science have an ever greater place in each of our actions, in the satisfaction of our basic needs, whether or not we are conscious of this fact. In the face of an unbalanced and limited world very soon to be overpopulated, the responsibility of scientists becomes more and more burdensome. The scientists, apt in objectively weighing the advantages and risks of scientific progress, are the most able to inform society and mold public opinion with the greatest possible objectivity and clarity.

The public is thirsting for this information. One is struck by the avidity to know and the desire to penetrate into what appears to be fabulous scientific world. This avidity is not idle curiosity; it testifies to the unconscious feeling of a responsibility in which all aspire to participate. It is up to the scientists to break down the cultural barriers and get their message across.

Thus, based on well informed, objective statements of specialists, public opinion will be able to influence those in authority.

The Universal Movement for Scientific Responsibility has taken on the role of promoting this triple dialogue between scientists, the public and the "decision-makers" (figure 8).

New knowledge entails new duties, duties for the investigators, for all those who, because of their functions, their profession, their official position are decision-makers and duties also for those who participate in the education of young people and the crystallization of public opinion.

The process of living is one of constant adaptation which was formerly subjected to blind and unjust evolutionary laws eliminating the weakest. This must no longer be so today. Scientific culture, that is accumulated knowledge, in the different branches of science-sociology and economic as well as physio-chemistry and biology — must exercise extreme vigilance over the future of humanity. Assuming the worst, science must at least assure the survival of mankind, but beyond that, science should lead mankind to pursue the possibilities offered by this extraordinary breakthrough.

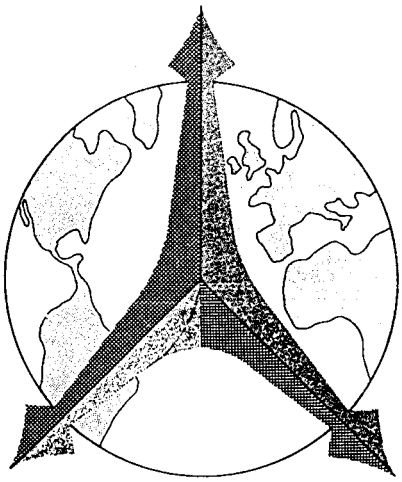
In associating firmly the forces of the spirit, the incalculable forces of will, initiative and solidarity with the physico-chemical and biological forces, humanity must without doubt succeed in overcoming the serious crises in growth which it is undergoing. First of all, we must make sure that the whole of mankind is adequately fed, while preserving the equilibrium of our fragile biosphere upon which man is totally dependent. Then we must improve his quality of life.

This can be achieved only through eco-technology as proposed by the Honda Foundation, working in association with the Universal Movement for Scientific Responsibility, and we are certain that a fruitful collaboration will be instituted between the two. For only a well-informed and determined public opinion can guarantee a wise course for mankind.

UNIVERSAL MOVEMENT
FOR SCIENTIFIC RESPONSIBILITY

DIALOGUE BETWEEN :

SCIENTISTS



DECISION-MAKERS **THE LAY-PUBLIC**

Armed with the informed advice of specialists, public opinion will be able to ALERT those in authority and to INFLUENCE their decision at the right moment.

Fig. 8: The aim of the Universal Movement for Scientific Responsibility is to provoke a "trilogue" between scientists, the lay public and decision-makers. Scientists should inform the general public. Public opinion will thus be able to alert the decision-makers in order than scientific advances are used for the benefit of mankind.