ESHG

Mauro Baschirotto Annual Award in Human Genetics

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The Speech of Acceptance by Professor Maroteaux

Thoughts of a Geneticist

Pierre Maroteaux,
Paris

The award Müller-Baschirotto Prize in Barcelona was the occasion for a human geneticist reaching the end of his career, and who has lived in times of tremendous progress in genetics, to express a number of his thoughts. Whereas the map of human chromosomes is now outlined to a large extent, classical genetics, as taught back in the fifties, still only knew 48 chromosomes in man! In the field of bone pathologies, the confusion was great. Most micromelic dwarfisms were classified as achondroplasias, whereas diseases manifesting by increases in bone density were considered as osteopetroses. A disorder known as Fairbank's disease in England was called 'dysplasie polyépiphysaire' or 'polyostéochondrite de Turpin et Coste' in France and 'Müller-Ribbing-Krankheit' in Germany. In

Prof. Pierre Maroteaux receives the Mauro Baschirotto Award, consisting of a plaque in a golden ring that was specially designed by the goldsmiths of the City of Vincenza (Italy), from the hands of Prof. Romano Tenconi (Padua, Italy) who represented the Baschirotto family.

During the opening ceremony of the 25th Annual Meeting of the Society, in Barcelona on May 6, 1993, the Mauro Baschirotto Award was presented to Prof. Pierre Maroteaux. Nominations for the 1994 Award signed by two members of the Society can be sent to the Secretary General Prof. J.J. Cassiman (Leuven) or to the President of the Scientific Program Committee Dr. C. Van Broeckhoven.

spite of the progress accomplished, a huge unexplored area remains, leaving us a future with hopes and fears which will also have to be shaped by our own convictions.

My Hopes

Three of them might be emphasized: The first concerns the improvement of our techniques of investigation. Today, for instance, we have at our disposal MRI examinations which enable us to prevent a number of neurological complications of bone diseases. In achondroplastic infants, this technique may allow early detection of a risk of bone marrow compression related to a narrowing of the foramen magnum although the neurological examination may be normal, except for the very frequent hypotonia at this age. An intervention will protect the child from long-term complications.

We may also hope that our better knowledge of some oncogenes will enable us to predict malignant degeneration of bone disorders like hereditary multiple exostoses, in which it is by no means exceptional.

Our second hope is to be able to locate genes inducing diseases whose etiopathogenesis is still completely unknown. My collaborator, M. Le Merrer, and I have already defined one location for hereditary multiple exostoses and are seeking that for achondroplasia. The isolation and sequencing of the genes thus located should permit one to clarify the pathophysiology of these diseases.

Finally, we are also entitled to think that gene therapy will become available for humans in the near future, at least for the treatment of some metabolic diseases. Work presently conducted on a murine model of beta-glucuronidase deficiency by J.M. Heard and O. Danos at the Institut Pasteur in Paris seems very promising. Introduction of the human gene into the fibroblasts of the diseased animal by means of a modified retrovirus and inclusion of the fibroblasts in organoids reimplanted into the peritoneal cavity yield results similar to those obtained with bone marrow transplants in humans. The risk is much lower and it is not necessary to have an HLA-identical donor. It is thus not chimerical to hope that such treatments can be envisaged fairly soon for mucopolysaccharidoses.

My Fears

In spite of these perspectives, one should not ignore certain worrying problems. The first concerns what one could call the 'dehumanisation' of some human geneticists. Fascinated by their technical possibilities, they sometimes consider them a game. They take pride in having been able to detect such and such hereditary trait in a child before its birth, but they do not always measure the consequences of this finding. This child's life may indeed become endangered by this discovery which cannot always prejudge the future. The manifestation of some genes may be varied or of late onset – towards the 4th or 5th decade. Should one eliminate a child because of the threat of polycystic kidney disease after the age of 40 or 50 years? What will its therapeutic possibilities be in half a century?

Yet another fear is motivated by the prescription of multiple examinations which are not always necessary, or the performance of useless or very heavy therapies. Once the diagnosis of chondrodysplasia is confirmed by skeletal X-rays, is it really necessary to start complex, perfectly superfluous metabolic investigations?

Genetic engineering, which has made growth hormones readily available, has led to their abuse. It is prescribed in achondroplasia although it does not significantly influence the

evolution of the disease. Surgical lengthening of the long bones is also often proposed in this disease or in other chondrodysplasias. Such interventions are not free of complications, and should only be undertaken when bone shortness is associated with epiphysial lesions. Presently, in the Hôpital des Enfants-Malades (Paris), we never offer it before adolescence, when the patients are able to make the decision themselves: the majority refuse this therapy.

Nonetheless, my greatest fear is the absence of protection of the fetus and even of the new-born being rejected by its family or society. The discovery of achondroplasia in utero often entails late interruption of the pregnancy (up to 38 weeks in a case we know) and much remains to be said about the misdiagnoses that lead to such interruptions when the child bears no skeletal dysplasia at all.

Today, even minor malformations of the hands and feet, like ectrodactylia, polydactyly, talipes, can be detected by ultrasound examinations: this often leads to requests for pregnancy interruption that are ethically unacceptable.

My Convictions

The first is modesty in the face of the gaps in our knowledge, even if dramatic progress was accomplished in genetics. In our speciality we are confronted with numerous, still unclassifiable cases. We understand neither their genetic pathophysiology nor do we know their prognosis. We also do not understand why the same gene can manifest quite differently in various members of the same family. Recklinghausen's disease is a good example: some affected individuals only have some café au lait spots, whereas others suffer from a form which causes particularly severe skeletal malformations or complications.

Another of my convictions pertains to the necessity, in the field of constitutional diseases, of an excellent human relationship. This high-quality communication should extend itself not only to the affected individuals but also to the parents. For instance, if a child is born with achondroplasia, the modalities of the evolution of the disease must be explained to them, stressing the positive aspects – the normal intellectual development of the child is one of them. On the other hand, if the statu-
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ral deficit cannot be corrected, it will also be necessary to insist on the fact that it will nonetheless be possible to help this child and to prevent certain complications. The doctor must not abandon these parents after telling them that their child's adult height will be around 1.25 m. Unfortunately, I have sometimes observed such a behaviour, which may lead to rejection and feelings of guilt.

Finally, I am deeply convinced of the spiritual dimension of human beings, which confers them their dignity and renders them unique in Nature. If it is the geneticist's task to endeavour to ameliorate human evolution, this task must be accomplished in the respect of this dignity. We shall even add that it should be pervaded by the climate of love which, for me, presided at the creation of man.