Concluding Remarks

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Up to a few decades ago, the medical community was uncertain, vague and confused about cardiomyopathies (CMPs). By definition, the etiology was unknown [1] and the diagnostic approach was essentially based on the clinical phenotype. The classifications of these diseases, developed to provide order to a complex and rather confused matter, were appropriately considered to be a provisional "bridge between ignorance and knowledge" [2] that would change with the progress of science. The majority of CMP classifications [1, 3, 4] were based (and continue to be based) on the phenotype. However, the classical "hypertrophic-dilated-restrictive" approach has some limitations, considering that in this classification there is a mix of diagnostic criteria: anatomic-morphologic (hypertrophic cardiomyopathy [HCM], dilated cardiomyopathy [DCM]), functional (restrictive cardiomyopathy [RCM]) and anatomic-functional (arrhythmogenic right ventricular cardiomyopathy [ARVC]). In 2006 [5], the American Heart Association suggested an approach that was based mainly on etiology (genetic, mixed, acquired) and considered two groups: primary CMPs (the disease is solely or predominantly localized in the heart) and secondary CMPs (heart involvement is part of a multi-organ disorder).

In the last 20 years, remarkable progress has been made in the knowledge of etiology, pathogenesis, diagnosis and therapy. For example, a genetic background of DCM was considered rare (2%) in the 1980s, while we know now that a familial trait may be present in at least one-third of individuals [6, 7]. Right ventricular CMP (the adipositas cordis or the lipomatosis cordis of the classical pathologists [8]) was unknown as a CMP in the 1980s [1], then in 1982 it was considered to be a "dysplasia" (i.e., an abnormality of development) [9], in 1995 it was accepted as an arrhythmogenic CMP localized in the right ventricle, while in recent years it has been considered to be a disease that involves both ventricles [10–12].

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In the past, our understanding of these disorders was essentially based on two sources: the correlation of clinical findings with morbid anatomy, and long-term follow-up data. However, more recently, genetics and molecular medicine have opened up new horizons, with potentially useful consequences for prevention and treatment of the disorders. The growth of molecular genetics in cardiology has been spectacular since the demonstration in 1989 [13] that HCM was caused by a mutation of the gene encoding cardiac myosin heavy chain. Since then, from a simplified theorem "one disease–one gene", we have been transported into an era characterized by high complexity, with a great number of genes involved. In HCM, for example, more than 15 sarcomere-related genes with hundreds different mutations have been identified. However, if we consider the presence of hypertrophic cardiomyopathy (defined as the presence of increased left ventricular wall thickness or mass in the absence of loading conditions sufficient to cause the observed abnormality [4]) in well-defined syndromes, metabolic diseases and mitochondrial disorders, then more than 70 genes are involved. The same phenomenon has been observed in other CMPs, especially DCM and ARVC, in which the number of causative genes will continue to increase in relation to ongoing research [14, 15].

Genotype–phenotype relationships are not always simple and clear, and the approach and possible interpretations may be complex. Different mutations in the same gene can cause apparently identical phenotypes, as well as be associated with phenotypes that are radically different one from the other. Moreover, apparently identical phenotypes may be the consequence of mutations in different genes (phenocopies). The comparative diagnosis between different forms is important, also from a prognostic and sometimes a therapeutic point of view. Some clinical features of CMPs can also vary within the same family, a phenomenon that indicates that sometimes there is not a clear-cut relationship between the mutation and its clinical consequences [16]. Finally, it should be reaffirmed that the association between the presence of a certain mutation (or mutations) and a cardiac abnormality (or complex of abnormalities) cannot always be considered a cause–effect phenomenon. With respect to genetic testing, the positive predictive value of a test will be the expression of the frequency with which a phenotype is observed in the presence of a specific genotype.

The clinical cardiologist must also be aware that many other factors of genetic and environmental origin may contribute to the variability of the phenotype, a variability that is sometimes very relevant within the same family. One factor causing variability is "incomplete penetrance", i.e., when an individual who carries a mutation does not manifest the disease phenotype, or develops the disease at a more advanced age (age-related penetrance). In CMPs, the penetrance (the proportion of carriers of a mutation affected by the disease) usually increases with the age, but almost never reaches 100%.

Another possible occurrence that may complicate the disease assessment is variable expressivity, i.e., only some aspects of the disease, sometimes minor, are present. In some CMPs, it is a common experience that early reports or

reports coming from referral centers frequently indicate the presence of severe forms of the disease, sometimes with an ominous prognosis, while subsequent findings frequently indicate that the disease is less severe, more common and often benign. For these reasons, the diagnostic criteria, which usually reflect the evident abnormalities of a severe disease, might be absent or less evident in some family members with early stages of the disease. Moreover, some CMPs can be associated with a peculiar symptomatology (e.g., supraventricular arrhythmias) or an involvement of other organs or systems (skeletal muscle, auditory system, etc.), or they might be a component of a syndrome involving multiple tissues and organs. Sometimes, traditional and neglected diagnostic techniques, such as electrocardiography, can be very useful for diagnosis. Electrocardiographic findings should be analyzed and interpreted considering the phenotype and the clinical context. Some electrocardiographic changes (e.g., negative T waves in V1–V3 in adults with ARVC [8], abnormal Q waves in HCM, and various abnormalities in the electrocardiograms of young patients with Duchenne muscular dystrophy [17]) may be the early manifestations of myocardial disease, signaling myocardial involvement well before the onset of clinical symptoms.

The role of the clinical cardiologist in this revolution of medical knowledge is clearly relevant, considering that in genetic studies the approach guided by the patient phenotype is extremely important: this involves a systematic, accurate, competent observation and study of the clinical characteristics of the phenotype of patients, the family history, and the correlation between the clinical findings and genetic data.

This book has been conceived from the perspective of the clinical cardiologist who takes care of his patients and their families, and is confronted with clinical problems that are sometimes difficult and complex. This book is also based on many years of experience, observations, studies and research in the field of CMPs, and on the Trieste Registry of Cardiomyopathies, which was started more than 30 years ago, and which contains data for more than 1,300 patients who have been systematically studied.

The aim of our book is to bring genetics closer to clinical practice, contribute to the construction of a bridge between clinical observation and molecular genetics, help in the identification of a possible specific genetic background, and finally to give support to clinicians in the study of some complex, usually rare syndromes that are frequently characterized by multi-organ involvement, in an attempt to link the experience of the past with the progress of the present.

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