My country may rightly claim the discovery of arrhythmogenic cardiomyopathy (ARVC/D) as a distinct heredo-familiar morbid entity. In 1736 Giovanni Maria Lancisi postmously published in Naples the book “De Motu Cordis et Aneurysmatibus” (1). Lancisi was Professor of Anatomy at the University “La Sapienza” in Rome and personal doctor of the Pope (“Archiatrii Pontifici”). In Chapter V of the book, entitled “De Hereditaria ad Cordis Aneurysmata Constitutione: De Cordis Prolapsu” (on the hereditary predisposition to cardiac aneurysms: cardiac prolapse) he reported some examples of such morbid entities and described the history of a family with disease recurrence in four generations, all featured by signs and symptoms which were in keeping with what nowadays we call AC: palpitations, dilatation and aneurysms of the right ventricle (RV), heart failure, sudden death (Fig.1). Thus, the first description of AC dates back nearly two centuries and half earlier than modern observations.

The first recent pathological description has been done by Laennec, as reported in his bibliography by Saintingan in 1904 (2). In Middlemarch, published in 1871 by George Eliot, the protagonist Dr. Lydate, talking to his patient, says “you are suffering from what is called fatty degeneration of the heart, a disease which was first described by Laennec... it is my duty to tell you that death from the disease is often sudden...” (3).
In 1905 Sir William Osler reported a case of a nearly 40 year old man who died suddenly while climbing a hill (4). Postmortem disclosed a biventricular myocardial atrophy, with a thinning and translucency of the ventricular free walls, that Osler immortalized with the name “parchment heart”. The heart specimen was part of Maude Abbot collection (5). Segall in 1950 reviewed the specimen and republished the case with unequivocal drawings showing paper thin walls (6) (Fig.2).

A controversial case, which was the source of subsequent misconceptions, has been reported by Uhl at the Johns Hopkins Hospital in Baltimore in 1952 (7). He published “A previously undescribed congenital malformation of the heart: almost total absence of myocardium of the right ventricle” in a 8 month old female infant who died due to congestive heart failure and no arrhythmias at the ECG. Here is the description of the heart at autopsy: “Externally the heart appears greatly enlarged... almost the entire dilated chamber (RV) was occupied by a large laminated mural thrombosis which adhered firmly to the endocardium along the anterior wall of the ventricle. Examination of the cut edge of the ventricle wall revealed it to be paper-thin with no myocardium visible... In the RV wall epicardium and endocardium lie adjacent to each other with no intervening cardiac muscle... no fibro-fatty tissue in the RV free wall was observed” (Fig.3). The early age and the peculiar pathological description points to a structural heart disease present at birth (congenital malformation), as emphasized in the title itself. Clinical presentation was neither characterized by cardiac arrhythmias nor by a family history of heart disease. Thereafter, cases in adults with paper-thin ventricular walls have been published with the eponym of Uhl’s anomaly, clearly a misnomer since the parchment heart in adult is the end-stage of a late progressive loss of the myocardium followed by fibro-fatty replacement. On the opposite, the cases reported in the literature under the age of 15 months with the eponym of Uhl’s anomaly, were all featured by heart failure and isolated RV involvement (whether segmental or diffuse) without
arrhythmias, all in keeping with the original description (8-15). The parchment heart cases reported in the adults (including the Osler heart) (6) varied from 17 to 81 years and died either of congestive heart failure or electrical cardiac arrest (16-26).

The University of Padua wrote pages that are milestones in the history of the disease (27). Sergio Dalla Volta in 1961 and 1965 first published similar cases under the name of “auricularization of the RV pressure” to emphasize the behavior of the RV chamber without an effective systolic contraction, with the blood was pushed to the pulmonary artery mainly thanks to the right atrial systole (28,29). Although the patients presented also with ventricular arrhythmias, Dalla Volta pointed more to the hemodynamic features rather than to the arrhythmogenicity of the RV. One of the original patients reported by Dalla Volta underwent cardiac transplantation 30 years later in 1995 at the age of 65, because of congestive RV failure. The left ventricle was normal, whereas the RV was hugely dilated with diffuse paper-thin free wall and complete disappearance of the myocardium (30) (Fig.4).

At the same University of Padua, the pathologist Vito Terribile in 1972 performed the autopsy of a woman with a history of palpitations and congestive heart failure, who died due to pulmonary embolism. The heart showed an extreme dilatation, mural thrombosis and “adipositas cordis” of the RV, and the left ventricular myocardium exhibited areas of “myocardiosclerosis”, all structural findings in keeping with AC (31) (Fig.5).

The interest on the arrhythmic aspects of the disease was attracted by Guy Fontaine from Paris in the ‘70s with the report of non-ischemic ventricular tachyarrhythmias, originating from the RV with left bundle branch block morphology (32). Moreover, he observed in the basal ECG delayed repolarization (“postexcitation syndrome”) at the end of the QRS complex, a feature which he named epsilon wave (33).

Frank Marcus from Tucson, fascinated by this new field of RV electrophysiology, decided to spend a sabbatical year in Paris with Fontaine at the Jean Rostand Hospital (34).
He had the time and opportunity to review the adult cases studied by Fontaine with clinical manifestation of primary RV disease. The result was a milestone paper, which was published in Circulation in 1982 (35). The disease was named “RV Dysplasia” since the histology of the myocardial specimens, resected at surgery for removal of arrhythmic foci, showed anomalous histological features of the RV myocardium consisting of fibro-fatty tissue, which were believed to be the consequence of an embryonic maldevelopment. By observing the presence of aneurysms in the inflow, apex and outflow of RV, they coined the term “triangle of dysplasia”, a pathognomonic landmark of the disease. The same group, with the help of the surgeon Guiraudon, perceived the idea of total disconnection of the RV free wall as surgical treatment of RV tachycardia, by interrupting the reentry into the left ventricle (36).

The early pioneeristic contributions of Marcus and Fontaine stimulated the interest of the electrophysiologists. Andrea Nava in Padua, thanks to the study of families with sudden death and autopsy evidence of AC from Piazzola sul Brenta (a small village close to Padua in the Veneto Region), discovered the heredo-familial nature of the disease, a monogenic disorder with a mendelian autosomal dominant transmission (37,38). Gianfranco Buja reported the occurrence of the disease both in homozygous and heterozygous twins (39).

The risk of sudden death as first manifestation of the disease was proven by the postmortem study of a series of young victims, in the setting of a project supported by the Veneto Region and carried out by Gaetano Thiene.

The first observation consisted of a young doctor, formerly cycle champion, who died suddenly in a tennis court, in a hot afternoon of May 1979 (Fig.6). Fifteen minutes after the starting of the game, he stopped, took his pulse, walked back to the border of the tennis courtyard and suddenly fainted. In his diary, written on October 4, 1978, during preparation of the Internal Medicine examination, the sentence “ventricular tachycardia of left bundle branch block morphology” was found, which retrospectively can be referred to his own ECG.
The girlfriend told that in that day he had suffered of palpitations and did an ECG. It required years to understand that the explanation of cardiac arrest and ventricular fibrillation was the fibro-fatty tissue that had been observed at autopsy in the RV free wall and at apex of the left ventricle and not conduction system abnormalities as first hypothesized (40). This experience confirmed an old concept in Medicine, namely that you see only what you look for and you recognize only what you know.

Among the 60 consecutive cases of sudden death in the young (<35 years) collected in the Veneto project, 12 of whom (20%) were found to be affected by AC. Most deaths had occurred during effort and had presented inverted T wave in the right precordial leads a the basal ECG. The novel findings were promptly submitted to the New England Journal of Medicine, which was reluctant to believe that the disease could be a so frequent cause of juvenile sudden death. Eventually, by providing all the data and illustrations, case by case, the paper was accepted for publication (41) and accompanied by a quite rewarding editorial, signed by Barry Maron, entitled “Right ventricular cardiomyopathy: another cause of sudden death in the young” (42).

A letter to the Editor was then forwarded to the New England by a group of Greek doctors (43), claiming that a very similar cardiac malignant disease was observed in Naxos in the setting of cardiocutaneous syndrome, consisting of AC, palmoplantar keratosis and woolly hair (Naxos disease) (44). They postulated that those patients might belong to families that descended from Venetians, who had landed in Naxos in 1207 (Fig.7). Soon after Domenico Corrado demonstrated that AC was a killer among the athletes, accounting for about 25% of fatalities in the Veneto Region (45), at difference from the United States where hypertrophic cardiomyopathy ranked first.

The report of AC as a major cause of sudden death in the young arose skepticism in the scientific community. Many scientists came to Padua to examine the heart specimens of this
morbid entity (Fig.8). The statement of Sir James Mackenzie is quite relevant: “There are three stages in the history of every medical discovery. When it is first announced, people say that it is not true. Then, a little later, when its truth has been borne in on them, so that it can no longer be denied, they say it is not important. After that, if its importance becomes sufficiently obvious, they say that anyhow it is not new” (46). Meanwhile postmortem observations increased with time, since our Pathology Unit became the only tertiary center for all cases of juvenile sudden death in the Veneto Region.

The interest was then focused on the in vivo recognition of the disease and risk stratification through instrumental investigations: Andrea Nava with electrocardiogram (47), Roldano Scognamiglio with echocardiography (48), Luciano Daliento with angiography (49), Thomas Wichter with 123I-meta-iodobenzylguanidine scintigraphy (50), Luca Oselladore with signal averaged ECG (51), Annalisa Angelini with endomyocardial biopsy (52), Luigi Menghetti with cardiac magnetic resonance (53), Pietro Turrini with QT dispersion (54), Franco Folino with heart rate variability (55), Hari Tandri with contrast enhanced cardiac magnetic resonance (56), Domenico Corrado with electroanatomic mapping (57).

In 1994 an international task force leaded by Bill McKenna put forward the diagnostic criteria, based upon family history of AC and/or sudden death, ECG depolarization/conduction/repolarization abnormalities, arrythmias of RV origin, global and/or regional dysfunction and structural alterations of the RV, and fibro-fatty replacement of the RV myocardium at pathological analysis (58). In the absence of a single gold standard, the diagnosis was achieved by major or minor criteria (2 major, or 1 major and 3 minor, or 4 minor).

A revision of the diagnostic criteria was recently accomplished, by introducing quantitative other than qualitative diagnostic parameters, including cardiac magnetic resonance and genetic testing (59). The application of the diagnostic criteria greatly
contributed to the early detection in young subjects affected by silent AC at the screening for sport eligibility, thus resulting in a sharp decline (nearly 90%) of sudden death during sport activity (60).

As far as the treatment, while curative therapy is still far away in the absence of precise knowledge of the pathogenesis of cardiomyocyte injury, an algorithm for antiarrhythmic drug therapy in AC patients was first introduced by Thomas Wichter (61). Endocardial catheter ablation was performed by Hugh Calkins, although limited by a high rate of arrhythmias recurrence during the follow-up (62). More recently, Francis Marchlinski demonstrated the superiority of epicardial catheter ablation vs the endocardial approach (63).

Prevention of sudden death is now feasible with the introduction of implantable cardioverter defibrillator (ICD). Up to 20-25% of patients survived from cardiac arrest in a follow-up of 48 months, thanks to appropriate electric shocks with cardioversion of ventricular fibrillation to sinus rhythm. ICD implantation is indicated for both secondary (64) and primary (65) prevention.

Other fascinating contributions came from pathobiology and genetics. Cristina Basso, by studying a large series of heart specimens, disclosed that AC is not a congenital heart disorder (i.e. lesion present at birth). It is a genetically determined myocardial dystrophy with acquired cell death occurring with time, mostly during adolescence (66). It was considered a sort of cell suicide, due to apoptosis, as demonstrated through TUNEL and electron microscopy studies by Marialuisa Valente (67). Focal myocardial inflammation was found in nearly 75% of cases, however Fiorella Calabrese ruled out viral infections by enterovirus (68). Thereafter, AC was added in the list of cardiomyopathies in the WHO classification (69). By the way, the disease was reported to spontaneously occur also in animals, both in cats (70) and dogs (71).
In 1994, linkage analysis studies in families with AC, carried out by Alessandra Rampazzo and GianAntonio Danieli, led to identify the first gene locus in chromosome 14 (72). Thereafter, several loci were demonstrated in other chromosomal sites (73), suggesting genetic heterogeneity (multiple genes, similar phenotypic expression). The candidate genes were first searched for in the cytoskeleton, as in Duchenne and Becker muscular dystrophies.

The enlightening inspiration to solve the genetic puzzle came to the scholars of the Naxos disease (Nikos Protonotarios and Adalena Tsatsopoulou), who perceived that desmosomes are in common to heart and skin and that a cell junction defect might explain their cardiocutaneous syndrome. Other researchers, in previous investigations, by studying mice with targeted mutation of plakoglobin, a γ-catenin of the desmosome localized in chromosome 17q21, showed that the knock-out of this gene resulted in devastating cardiac lesions in the embryos, with disappearance of the desmosomes and spontaneous cardiac rupture (74). Based upon these observations, the Naxos group carried out the linkage analysis in their families and identified the Naxos disease locus exactly in the same chromosome 17q21 (75). Thereafter, gene sequencing proved that the molecular defect was a deletion of plakoglobin (76).

At the same time, in Equador, Luis Carvajal Huerta reported another recessive cardiocutaneous disease, characterized by dilated cardiomyopathy, wooly hair and palmoplantar keratosis (77). The gene defect was proven to be a mutation of desmoplakin, another protein of the desmosome (78). A child of the affected family died suddenly, due to arrhythmic cardiac arrest and the heart specimen was sent by the wife of Dr. Carvajal (who meanwhile passed away) to Jeff Saffitz in St. Louis for pathological study. Gaetano Thiene was asked by Dr Saffitz to go to St. Louis and examine the heart. It was a biventricular cardiomyopathy, with extensive left ventricular dilatation and mural thrombosis. The RV disclosed the typical aneurysms in the triangle of dysplasia with translucent thin wall and the
histology showed mostly fibrous replacement (79). Thus, another defective gene of desmosome (desmoplakin) was found to be responsible of a new recessive cardiocutaneous syndrome.

Desmoplakin became immediately a candidate gene also for the dominant variant of AC. The genetic screening in Padua in some of Nava’s families lead to the identification by Alessandra Rampazzo of desmoplakin as the disease causing gene, in the form of missense mutations (80). This proved that both autosomal and recessive AC were desmosomal diseases. Genotype-phenotype correlations, carried out by Barbara Bauce, disclosed that the desmoplakin variant of the disease was featured by extensive left ventricular involvement, as to suggest that the disease, being biventricular, should be better called AC (81). By performing contrast enhanced cardiac magnetic resonance in genotyped AC patients, Sen Chowdhry confirmed that the disease is wider than previously thought, with predominant left ventricular and biventricular forms, besides the classical RV AC (82).

Missense mutation of the gene encoding ryanodine receptor 2, in charge of the Ca++ release from smooth sarcoplasmic reticulum, was associated by Natascia Tiso to a variant of AC with polymorphic ventricular tachyarrhythmias (83). Since the same defective gene was proven by Silvia Priori (84) to be related to catecholaminergic polymorphic ventricular tachycardia first described by Philip Coumel in 1978 (85), the nosographic entity by Tiso was then considered the same as the one reported by Coumel.

All the other genes, which encode for desmosomal proteins, were subsequently investigated in patients affected by familial dominant (non-syndromic) AC, and found to be responsible of the same phenotype: plakophilin-2 by Brenda Gerull (86), desmoglein-2 by Kalliopi Pilichou (87) and desmocollin-2 by Paul Syrris (88), the latter confirmed soon after by Giorgia Beffagna (89). Thus, both dominant and recessive variants of AC were eventually nosographically identified as cell junction (desmosome) diseases (90, 91).
Electron microscopy studies, carried out by Cristina Basso in genotyped patients with AC, revealed abnormalities of the desmosomes. They appeared less numerous, short, pale, fragmented, as to hypothesize that disruption of intercalated disc was the final common pathway of a genetically determined, progressive cell death (92).

The discovery of the defective genes, although limited to 50% of affected families, opened new avenues. Genetic screening, for early diagnosis and detection of healthy carriers as well as reassurance of non-carriers, entails a tremendous impact on primary prevention of arrhythmic complications and life-style, by including sport activity disqualification and genetic counseling for disease recurrence in sibs and offsprings with the dilemma of procreation (93).

Experimental animal models (knock out, overexpression, knock in mice) are opening new avenues to understanding disease pathogenesis and identify targets for therapy (94-97). After plakoglobin, desmoplakin and plakophillin transgenic mice, Kalliopi Pilichou recently generated a transgenic mice with overexpression of mutated desmoglein-2 (97), the same defective gene previously detected in an AC Italian proband (87). The recapitulation of the disease in the mice was quite convincing: dilatation and aneurysms at echo of both ventricles, tachyarrhythmias, sudden death, fibrous replacement of the ventricular myocardium at histology. Interestingly enough, the animals were normal at birth and cell death occurred with time after a few weeks, in the shape of cell necrosis (oncosis) at electron microscopy, thus confirming that the disorder is a genetically determined cardiomyopathy and not a congenital heart disease (98).

Depletion of plakoglobin signal at intercellular junctions was found by Angeliki Asimaki in AC patients, whatever the defective gene, and may be considered a biomarker for the diagnosis at endomyocardial biopsy (99).
Generation of knock-in transgenic mice will contribute to the understanding of the mechanistic events, as to find etiological (not merely symptomatic) therapeutic interventions. Prevention of disease onset and progression will be possible only when the underlying biological and molecular phenomena will be better understood.

European and American teams continue to be committed in the study of the disease. At the turn of the last millennium, following a series of meeting of experts from both sides of the Atlantic Ocean (Fig.9,10), it became evident that the expertise of scientists and clinicians should merge into an “army” for the fight against the calamity of sudden death due to AC. An International Registry was considered mandatory in order to collect study material and concentrate efforts on this rare disorder (100).

It was then decided to apply for grants of the European Commission and the National Institute of Health. Two teams were created, one in Europe coordinated by Gaetano Thiene and one in North America coordinated by Frank Marcus. The two projects started by utilizing a similar database and sharing some Core Labs. The method was somewhat different: the European Registry enrolled patients who were previously diagnosed as well as new entries (101), whereas the North American Registry enrolled only newly diagnosed patients (102). Previously published diagnostic criteria were employed and protocols implemented accordingly. Genetic investigation was an integral part of both studies. Both projects were approved and funded by the European Commission and the NIH for 5 years, thus allowing the starting of a major interdisciplinary study of AC. The results exceeded the best expectations, culminating in the discovery of 5 disease genes, numerous publications in highly ranking cardiovascular journals and new diagnostic criteria. A monograph collected all these achievements (103) (Fig.11).

The progress in the knowledge of AC was possible thanks to an international tight collaboration and loyal competition. We like to quote here the late Lino Rossi’s words “All of
them share the unique merit of a skillful and dedicated engagement in a scientific contest of vital importance which is not comparable to any sports competition; as such, the present overview concludes with the popular saying – who cares who came second? – here intended in an entirely positive, even laudative sense” (104).
REFERENCES

1) Lancisi G. M. De motu cordis et aneurysmatibus. Caput V. Naples, 1736


6) Segall HN. Parchment heart (Osler). Am Heart J 1950;40:948-950

7) Uhl HSM. A previously undescribed congenital malformation of the heart: almost total absence of the myocardium of the right ventricle. Bull Johns Hopkins Hosp 1952;91:197-209


12) Reeve R, MacDonald D. Partial absence of the right ventricular musculature—partial parchment heart. Am J Cardiol 1964;14:415–419

13) Cumming GR, Bowman JM, Whytehead L. Congenital aplasia of the myocardium of the right ventricle (Uhl's anomaly). Am Heart J 1965;70:671–676


22) Haworth SG, Shinebourne EA, Miller GAH. Right to left interatrial shunting with normal right ventricular pressure. Br Heart J 1975;37:386–391


Roberts WC, Ko JM, Kuiper JJ, Hall SA, Meyer DM. Some previously neglected examples of arrhythmogenic right ventricular dysplasia/cardiomyopathy and frequency of its various reported manifestations. Am J Cardiol 2010;106:268-74


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<td>46</td>
<td>Wilson RM. The beloved physicians: Sir James Mackenzie. New York, Macmillan 1926; 177</td>
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91) Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, Moss AJ, Seidman CE, Young JB; American Heart Association; Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and


LEGENDS

Fig. 1  The book of Giovanni Maria Lancisi published in Naples in 1736.

Fig. 2  The drawings of the “parchment heart” of Osler, with paper-thin walls of both ventricles.

Fig. 3  The original picture of the Uhl’s anomaly.

Fig. 4  The heart at cardiac transplantation of one of the patients published by Dalla Volta in 1964. Note the huge dilatation of the right ventricle, both at gross and in vitro magnetic resonance, with paper-thin RV free wall.

Fig. 5  The autopsy report of a case of AC of a patient who died due to pulmonary embolism with adipositas cordis in the RV and foci of myocardial sclerosis in the left ventricle.

Fig. 6  A 26 year old physician who died during a tennis game in May 1979. A ventricular tachycardia, left bundle branch block morphology, had been recorded at the ECG during palpitations. The autopsy disclosed for the first time AC as a cause of sudden death in the young.

Fig. 7  Cartoon of Professor Lino Rossi stressing the connection between Venice and Naxos history.

Fig. 8  Dr Frank Marcus visiting the Patavian group in 1994. From left to right: Gaetano Thiene, Luciano Daliento, Marialuisa Valente, Beth Livolsi (a visiting nurse from the States, belonging to a family with AC), Gianfranco Buja, Frank Marcus, Bortolo Martini, Andrea Nava (courtesy of Dr Martini).

Fig. 9  A meeting in Baltimore in 1999 between American and European groups involved in the study of AC. From left to right - bottom: Jeff Towbin, Arthur Moss, Guy Fontaine, Cristina Basso, Thomas Wichter, Barbara Bauce, Frank
Marcus; top: Kathy Gear, Duane Sherrill, Hugh Calkins, Wojciech Zareba, Gaetano Thiene.

**Fig.10** Meeting in Naxos in 2003 of the European team. From left to right: Barbara Bauce, Guy Fontaine, Cristina Basso, Nikos Protonotarios, Gaetano Thiene, Katarzyna Wlodarska, Andrea Nava, Elzbieta Czarnowska, Thomas Wichter,Loizos Antoniades, GianAntonio Danieli, William McKenna.

**Fig.11** Meeting in Denver in 2007 of the European and American teams for the presentation of the book “Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia – Recent Advances” (103)

**Fig.12** Domenico Corrado, Barbara Bauce, Cristina Basso and Gaetano Thiene. Denver, May 2007
"PARCHMENT HEART" (Osler)
Right ventricle, anterior aspect
Pleura viscerale
Linfonodi
Bronchi
Arterie
Vene
CUORE (gr. 450)
Epicardio
Endocardio
Valvole
Coronarie
Miocardio
Aorta
Arterie polmonare

Diametri: trasversali cm. 15        verticale cm. 11
Spessore ventricoli: V.S. cm. 1,5   V.D. cm. 2,5
Spessore aorte: cm. 1,5

Nuova fibra di collagene nella parete arteriosa

Fig. 5