

Italian Pioneers in Cardioneurology: how some fundamental Italian cardiorenal researches have passed into oblivion

Storia della nefrologia italiana

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ABSTRACT

A historical research was made on papers published by Italian scientists on cardiorenal diseases. The investigated period is between the beginning of the 20th century and the entry of Italy into the Second World War, 1940. 34 papers dealing with the relationship between the kidney and the cardiovascular system were retrieved. All but two articles were published in Italian medical periodicals. The topics covered are varied and range from cardiotoxicity of substances in uremia to the role of renal disease in vascular damage. Some articles are forerunners of later pathophysiological concepts and research technologies. These concern early atherosclerotic vascular damage and the presence of dialyzable cardiotoxic substances in renal insufficiency. Unfortunately, these highly innovative researches have had little diffusion and have fallen into oblivion in Italy and abroad. In conclusion, our research shows that in the first half of the 20th century in Italy there was a lively interest in cardio-renal diseases and that some researchers had produced precursor results of what was confirmed many years later.

KEYWORDS: cardioneurology, cardiorenal studies, Italian scholars, history of nephrology

Introduction

Thanks to the Mario Timio's series of congresses in Assisi, dedicated to *Cardioneurology*, this branch of Nephrology has experienced growing success in Italy and in the world since 1987 [1]. Although the term Cardioneurology apparently was coined in 1991, studies on the relationship between kidney disease and the heart have a much longer history [2–4]. An attempt to define cardiorenal disease was made in 1914 in Philadelphia by the renowned clinician Alfred Stengel (1868-1939). According to this eminent clinician “the term comprises cases of combined cardiovascular and renal disease without such manifest predominance of either as to justify a prompt determination of the one element as primary and important and the other as secondary and unimportant” [5]. This term was also used in death certificates in USA [4]. Among the early studies on cardiorenal syndromes, the best known are those performed in UK, France and USA [3, 4].

In Italy in the first half of the 20th century such definition was not diffused, although the relationship between heart and kidney was the object of several studies. The heart involvement in uremia, in acute and chronic glomerulonephritis and the early atherosclerotic changes associated with chronic renal failure were the topics most frequently dealt with. To our knowledge, these studies remained almost as unknown abroad as at home. Only belatedly through the references of the paper on “The pathogenesis of renal cardiopathy” from the Pisa group published in 1957 some early Italian work on cardiorenal disease has come to light [6].

To what extent the lack of acknowledgment and of citations of early Italian studies in the cardiorenal field can be justified can only be established from a retrospective survey of the early research carried out in this field. We have therefore undertaken this study with the aim of retrieving Italian papers dealing with cardiorenal disease, published in the first half of the 20th century. We subsequently analyzed the retrieved studies and compared them with contemporary international researches.

Material and Methods

We searched the medical bibliographic databases for articles that dealt with kidney pathophysiology and disease written by Italian authors, published between the year 1900 and 1940, entry of Italy into the Second World War. Then many Italian doctors were drafted into the army and stopped their normal activities. Moreover, the war was a turning point for medical research worldwide since because of it changed completely [7].

Therefore, we chose 1940 as the end limit for our research. Among the papers we have therefore selected those that dealt with the relationship between the kidney and the cardiovascular system. The articles in this selection were analyzed for the purposes of this research.

Results

We retrieved 638 papers of Italian authors published in the period 1900-1940. Among these, 34 (5.4%) dealt with the relationship between the kidney and the cardiovascular system. All but two papers were published in Italian journals. The main topics dealt with are shown in chronological order in Table 1.

Representative papers are listed in the references [8-16]. In Figure 1 is shown the cover of the oldest cardiorenal Italian paper we were able to retrieve, published in a French journal. Almost all authors were from internal medicine institutes. Only one was a surgeon [17].

Year	Subject	Bibl Ref #
1911	Urea concentrations and heart function	8
1914	Heart Hypertrophy in unilateral kidney disease	9
1924	Lipid metabolism in GN and uremia	10
1924	CV changes in different kidney diseases	11
1930	Heart failure and the kidney	12
1935	Heart involvement in acute GN	13
1936	Vascular lesions in chronic GN	14
1939	Electrocardiographic changes in Uremia	15
1940	Atherosclerosis, myocardium changes and heart failure in chronic GN	15

Table 1: Cardiorenal topics in Italian researches (1900-1940). GN: Glomerulonephritis. CV: Cardiovascular.

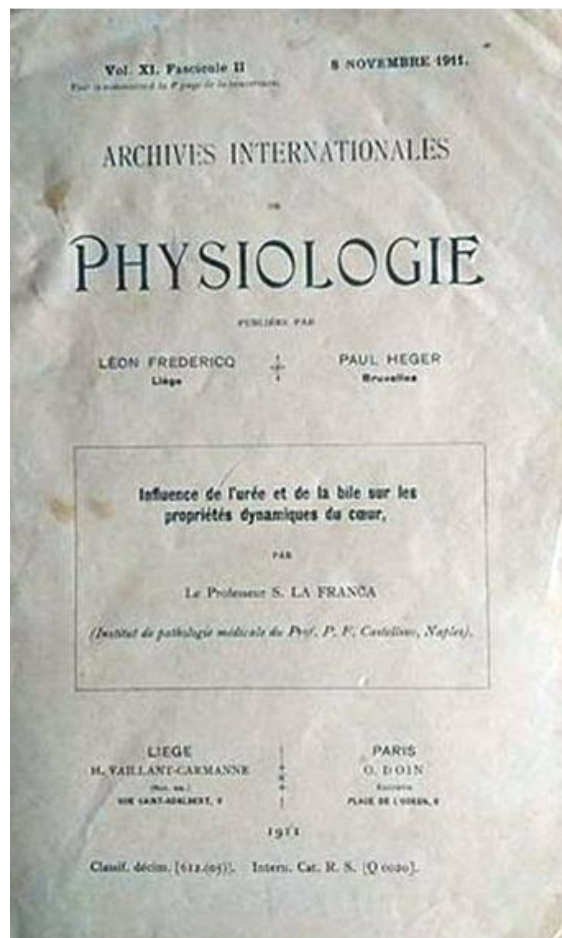


Figure 1: Cover of one of the oldest cardiorenal Italian papers published in a French journal. The subject is the effect of urea on the heart, one of the hottest topics of the period.

Characteristics of researches

Most were clinical studies. Others were clinico-pathological [9, 14, 16]. Only two were based on experiments made in lab with animals [15, 17]. Blood pressure measurement, electrocardiogram, x-ray and blood chemistry were the clinical investigation tools employed. Since early researches much emphasis was placed on the role played by urea or other toxic substances produced by kidney disease on the heart [8, 18]. Later papers generally dealt with single nephropathies in their relationship with heart diseases. An attempt was also made to list individual types of renal diseases with their association with cardiovascular complications [19].

Several papers aimed at discriminating the effects of hypertension on the cardiovascular system from those produced directly by kidney disease [9,13]. The cardiovascular complications

investigated were heart hypertrophy and failure, arrhythmias and electrocardiographic changes, macrovascular and microvascular changes. In none of the retrieved papers pericarditis was a subject of research. Generally, the authors published only one paper on cardiorenal disease. Only one researcher published several papers on this subject, in the period from 1935 to 1940, Fernando Marcolongo (1905-1969) from Turin [13, 16, 20-22].

Discussion

We found that from the beginning of the 20th century to the war, Italian researchers published a fair amount of papers dealing with cardiorenal diseases [18]. The results of some of these studies have maintained their value over time and have proved to be the forerunners of research lines that are still current today. Table 2 summarizes the results of two papers that we believe are the most relevant in this respect.

Year	Research	Bibl Ref#
1939	Study of the effect of serum from uremic patients on guinea pig heart. Dialysis of serum removed its toxic effect on myocardium. First demonstration of dialyzable heart toxic substances in uremia.	14
1940	Demonstration that early coronary atherosclerosis in chronic glomerulonephritis is independent of hypertension and other general risk factors. Clinical and pathological study.	15

Table 2: Outstanding cardiorenal Italian researches (1900-1940).

Generally, the different themes dealt with in the articles we retrieved do not differ from those of contemporary international medical literature, except for pericarditis. This uremic complication, although dealt with in the Italian textbooks of the time, is not present in the articles we have found. Uremic pericarditis, on one hand, was the object of several researches carried out in the US during the same period [23, 24]. On the other hand, it should be emphasized the particular interest shown by some Italian authors towards vascular lesions, which today we would define as atherosclerotic, associated with chronic nephropathies. In some of the papers, the hypothesis that atherosclerotic lesions are a direct consequence of nephropathy is put forward [14]. The most significant and original research on the relationship between vascular lesions and chronic nephropathies is the one carried out by Marcolongo [16]. This study was based on pathological observations, during a period of several years, and the respective clinical characteristics of 44 cases of chronic glomerulonephritis. The conclusions of the study are original and differ from what was generally believed not only in Italy but also in the US at the time and years later [25, 26]. In fact, against common thought, this research suggests a direct role played by nephropathy in the pathogenesis of coronary atherosclerotic lesions. In particular, this research, carried out on young subjects, indicates a particular role of nephropathy in the interrelation between coronary artery disease, hypertension and heart failure. In the sample population studied the other well-known risk factors for atherosclerosis were absent. The short duration of arterial hypertension, resulting from the young age and the short time of the disease, ruled out its role in the pathogenesis of the coronary lesions. Therefore, nephropathy was indicated as the key element in favoring the early development of coronary damage. This, to our knowledge, is the first study identifying a specific role of the kidney in the development of vascular damage. Unfortunately, the well-known studies made in the US, dealing with the same matter, published many years later do not mention this innovative research published in Italy at the time of the start of the Second World War [27, 28]. The only recognition of this innovative research came many years later in the seminal article on renal heart disease from the Pisa group [6]. We attribute the Italian language of the medical periodical and the date of publication, coinciding with Italy's entry into World War II, among the causes of the scarce recognition obtained by this innovative research.

Another research that deserves a particular mention is an animal testing carried out in Genoa [15]. The experiment consisted in studying the effects of the serum of uremic patients, its dialysate or its ultrafiltrate on the heart of guinea pigs. The authors found that the injection of dialyzed sera from the uremic patients did not induce any cardiac changes in the guinea pig. Conversely, the dialysate and the ultrafiltrate of the uremic serum induced a myocardial toxicity which manifested itself with various alterations of the electrocardiogram. To rule out a possible interference of hypertensive substances the experiment was repeated with the serum of a hypertensive subject without uremia. In this case the injection of the ultrafiltrate did not induce any myocardial change. The authors conclude that they demonstrated for the first time that uremic serum contains myocardiotoxic substances. Most interestingly their experiment shows that these substances are removable with ultrafiltration or dialysis. This research introduces for the first time in the scientific world the possible removal of cardiotoxic uremic substances with dialysis. Surprisingly, this discovery was ignored in subsequent years even in well-documented texts such as Cameron's on the history of dialysis or in other more recent historical reviews on cardioneurology [29, 4]. We ascribe to the use of the Italian language and to the time of publication, simultaneous to the war declaration, the cause of this outstanding research going unnoticed.

As far as the author is concerned, it is worth underlining that most of the authors of these early researches have subsequently played an important role in Italian internal medicine before and after the Second World War. Some of them such as Nicola Pende (1880-1970) and Luigi Condorelli (1899-1985) obtained chairs at the most prestigious Italian universities and founded illustrious schools of internal medicine and cardiology. The same observation was previously made for early scholars of nephrology [30, 31]. Marcolongo became professor of internal medicine and was among the founders of the Italian Society of Nephrology [32].

Our investigation of early cardiorenal studies in Italy allows us some brief considerations. The first is that the problem of the complex pathological relationships between kidney and heart was well present in the scholars of the time. Therefore, many researches were conducted on the subject. Some of these, even in the light of subsequent scientific advances, appear to be forerunners of new knowledge. Unfortunately, for a whole series of circumstances related to the troubled period and the use of Italian in the publication, these results were not sufficiently widespread in the scientific community. Consequently, the value of these researches did not obtain the deserved recognition and went soon into oblivion. Other similar forgetfulnesses have been reported recently in the nephrology field [33]. We, therefore, hope with our research that we have drawn historical attention to these forgotten studies.

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