

The early introduction of percutaneous renal biopsy in Italy

GIOVANNI B. FOGAZZI and J. STEWART CAMERON

Divisione di Nefrologia e Dialisi, Ospedale Maggiore, IRCCS, Milano, Italy, and Renal Unit, United Medical and Dental Schools, London, England, United Kingdom

The early introduction of percutaneous renal biopsy in Italy.

Background. Percutaneous renal biopsy, based on the use of an aspiration needle and the patient in the sitting position, was first described by Iversen and Brun in 1951. In 1954, Kark and Muehrcke described the use of the cutting Vim-Silverman needle on patients in the prone position, with a substantial improvement in the rate of success. The 1961 CIBA Foundation Symposium on renal biopsy marked the coming of age of this technique. During the 1950s in Italy, several individuals played a part in promoting and developing percutaneous renal biopsy. Because this pioneer work has received insufficient attention, we describe the contributions of Italians to the early introduction of this technique.

Methods. The Italian and international literature about percutaneous renal biopsy of the period 1951 through 1965 was reviewed. In addition, structured interviews with surviving members of the Italian researchers who first used renal biopsy were conducted.

Results. The first renal biopsies in Italy were performed in 1951 in Pisa by the group of Ernico Fiaschi (1913–1989). In their hands, renal biopsy became a tool to investigate the pathogenesis of renal diseases in particular, while simultaneously using the early application of immunofluorescence and electron microscopy. In 1954, Pietro Leonardi (1914–1991) and Arturo Ruol (born 1924) introduced renal biopsy in Padova; they used this technique extensively and published one of the first monographs on the subject. In 1957, Vittorio Bonomini (born 1928) introduced renal biopsy in Bologna, and in subsequent years used this technique to focus on the study of pyelonephritis.

Conclusions. Our historical research shows that Italian groups were among the first to use and develop percutaneous renal biopsy both as a clinical tool and an investigative tool. This article gives international credit to their work.

*Whatever end man aims at in this world
is not the final end, or it gives not man full happiness.
What was an end becomes a new beginning . . .*
AUZIAS MARCH (1393–1459)

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The introduction of the technique of renal biopsy is one of the major events in the history of nephrology, and its development, together with the appearance of transplantation and the introduction of dialysis, is a major factor in the separation of the specialty from general internal medicine in the early 1960s [1–3]. The “conventional” history of the introduction of renal biopsy has been repeated often [1–3]: After unpublished attempts by Nils Alwall in Sweden in 1944 [4], in 1951, Claus Brun and Poul Iversen of Copenhagen published their landmark article in the *American Journal of Medicine* [5] and described experiences with aspiration biopsy with their patients in the sitting position [6]. However, the success rate in obtaining useful tissue remained low, and it was not until after the description of biopsy in the prone position using the cutting Vim-Silverman needle by Kark and Muehrcke in 1954 that renal biopsy began to be performed elsewhere [7]. Finally, in 1961, the publication of CIBA Foundation Symposium on Renal Biopsy registered the coming of age of a clinically useful and acceptable technique [8].

In fact, the full truth is much more complicated and interesting, with a number of other individuals from various countries playing a major role in the development of the technique [3]. For example, Maurice Payet, a Frenchman working in Senegal, made an intensive study of the localization of the kidney, as Perez Ara had done in Cuba as early as 1949, using both the prone position and a cutting rather than an aspiration needle, while Richard Joske in Australia and Alvin Parrish and Richard Howe in the United States were the first to perform biopsies in their countries.

Some of the earliest and most prominent contributions also came from Italy, where a number of individuals and centers played a part in promoting and developing the technique of renal biopsy during the 1950s. This pioneer work in Italy has received insufficient attention outside that country, probably because it was published in Italian language journals, some of which had only local circulation. Furthermore, even within Italy the memories of this era have largely faded.



Fig. 1. Members of the Institute of Clinica Medica of the University of Pisa in 1952. Fourth from the left is Aldo Torsoli, and fourth from the right is Ernico Fiaschi, aged 39 (courtesy of Professor Aldo Torsoli, Chair of Gastrointestinal Diseases, Università La Sapienza, Roma. Reproduced with permission from *Nephrol Dial Transplant* 14:507, 1999).

Our article reviews early Italian contributions that introduced new techniques to both localize the kidney and obtain the tissue. Percutaneous needle biopsies were performed in Italy as early as 1951, the original technique used being described in 1952 [9] (this paper contains the text of the communication on the technique of renal biopsy presented by A. Torsoli, M. Di Gaddo, and M. Righini at 38° Raduno Gruppo Tosco-Umbro SIRM, Viareggio, 1952), which described the use of a cutting needle with the patient prone for biopsy, only one year after Iversen and Brun's description of the aspiration technique with the patient sitting. Thereafter, intensive work was carried out in several centers, which in only a few years led to impressive results.

Our article is based not only on the published literature, mostly in Italian, but also on recently conducted structured interviews with surviving members of the Italian groups who first used renal biopsy to investigate the diseases. Our research concentrates on the period between 1951 and the first half of the 1960s when, as all over the developed world, renal biopsy became available in many centers throughout Italy as a routine procedure.

THE PEOPLE CONCERNED

The first percutaneous renal biopsies in Italy were performed as early as 1951 in the Institute of Clinica Medica of the University of Pisa, at that time directed by Professor Cataldo Cassano (1902–1998). In the Institute, there was already an interest in kidney diseases, as documented by articles of Professor Cassano himself [10] and by studies based on clearance techniques that had begun already in the late 1940s [11, 12]. Ernico Fiaschi (1913–

1989; Fig. 1) had a pivotal role in this work. He had joined the Institute in 1948 as assistant and, over the years, had collected around him a number of enthusiastic young fellows, including Giuseppe Andres (born 1924), who is now Professor of Pathology at Harvard Medical School, Boston, and of Clinical Pathology at Columbia University, New York; Aldo Torsoli (born 1924), now professor of Gastroenterology at the University La Sapienza, Rome; and Giuseppe Ercoli (1921–1976; Figs. 1 and 2).

The event that rendered transcutaneous renal biopsy feasible was Aldo Torsoli's introduction of the technique of retroperitoneal insufflation into the institute [13]. Thanks to the greatly improved visualization of the kidneys obtained with this technique, Torsoli was able to carry out the first successful and safe needle renal biopsies. In 1952, he described his technique (Table 1) in a local meeting of the Italian Society of Medical Radiology [9], where it raised a remarkable interest in the audience and also obtained an award for his most original contribution [13]. After those first trials, percutaneous renal biopsy started being done on a regular basis by Giuseppe Ercoli, and in 1953, Fiaschi published his first article describing the results obtained by renal biopsy in six patients [14].

In subsequent years, Fiaschi moved to Rome (in 1955), Cagliari (in 1959), and Padova (in 1963) and was joined by new fellows such as Remo Naccarato (born 1933), now Professor of Gastroenterology at the University of Padova; Aldo Fabbrini (born 1926), now Professor of Internal Medicine at the University La Sapienza, Rome, and Luciano Campanacci (born 1930), now professor of Internal Medicine and Nephrology at the University of



Fig. 2. The Institute of Clinica Medica of the University of Pisa. Giuseppe Ercoli (left) and Giuseppe Andres in front of the Institute of Infectious Diseases of the Ospedale Santa Chiara in January 1953. The steps on the left behind doctor Ercoli were often used to sharpen the tip of the Silverman-like needle, which had been made by a craftsman from Pisa (courtesy of Professor Giuseppe Andres, Harvard Medical School, Boston, MA, USA). Reproduced with permission from *Giorn Ital Nefrol* 16:73-78, 1999).

Trieste. All of them developed an interest in the study of renal diseases by biopsy and published several articles that described the renal lesions in a wide spectrum of conditions. These included peripheral vascular disease [15], pregnancy [16], diabetes mellitus [17, 18], hemoglobinuria induced by favism [19], and the nephrotic syndrome. To this latter subject, Fiaschi and his group devoted special interest, which resulted in the publication, in 1959, of a ponderous article [20], which was followed by others. These appeared in the book *La Sindrome Nefrosica* (The Nephrotic Syndrome; Fig. 3) [21-23], which contained the proceedings of the 61st meeting of the Italian Society of Internal Medicine, which was held in October 1960 in Naples.

Table 1. Transcutaneous renal biopsy as done by Dr. Torsoli and his colleagues in the Institute of Clinica Medica of the University of Pisa [9 and 14]. Note how many radiographic checks were performed before proceeding to the drawing of the tissue

- Patient in prone position
- Insufflation of a small amount of oxygen into the retroperitoneal space
- Identification of the right kidney by radioscopy
- Drawing of the projections of the kidney on the skin of the back and right flank
- Injection of 2% novocain into the external area of the lower pole of the right kidney, with the patient in prone position
- Manometric measurement of the perirenal pressure caused by retroperitoneum
- Radiographic check of the location of the anaesthetic needle
- Introduction of the mandrel of the biopsy needle
- Radiographic check of its location and penetration into the kidney
- Replacement of the mandrel with the needle
- Tissue drawing by a cutting needle with a spiral tip designed by Torsoli
- Immediate fixation in 3% formaldehyde
- In case of bleeding injection of small amounts of haemostatic gelatin

ATTI DEI CONGRESSI DELLA SOCIETÀ ITALIANA DI MEDICINA INTERNA

61° CONGRESSO - NAPOLI 17-19 OTTOBRE 1960

I° RELAZIONE

LA SINDROME NEFROSICA

I — CORRELAZIONI FISIOPATOLOGICHE
ED ISTOPATOGENETICHE CON LE GLOMERULONEFRITI

RELATORI:

C. CASSANO (Roma) - E. FIASCHI (Cagliari) - G. A. ANDRES (Roma)

con la collaborazione di

A. ALESSANDRINI - L. CAMPANACCI - G. A. CINOTTI
C. CONTI - A. FABBRINI - A. IPPOLITO - M. G. PICCARDO

II — LA TERAPIA DELLA SINDROME NEFROSICA

RELATORI:

R. PACHIOLI (Modena) - E. CHELI (Modena) - L. CAMPANACCI (Cagliari)



LÙIGI POZZI EDITORE — ROMA
1960

Fig. 3. Cover of the book *La Sindrome Nefrosica*, the major work of the group of Fiaschi.

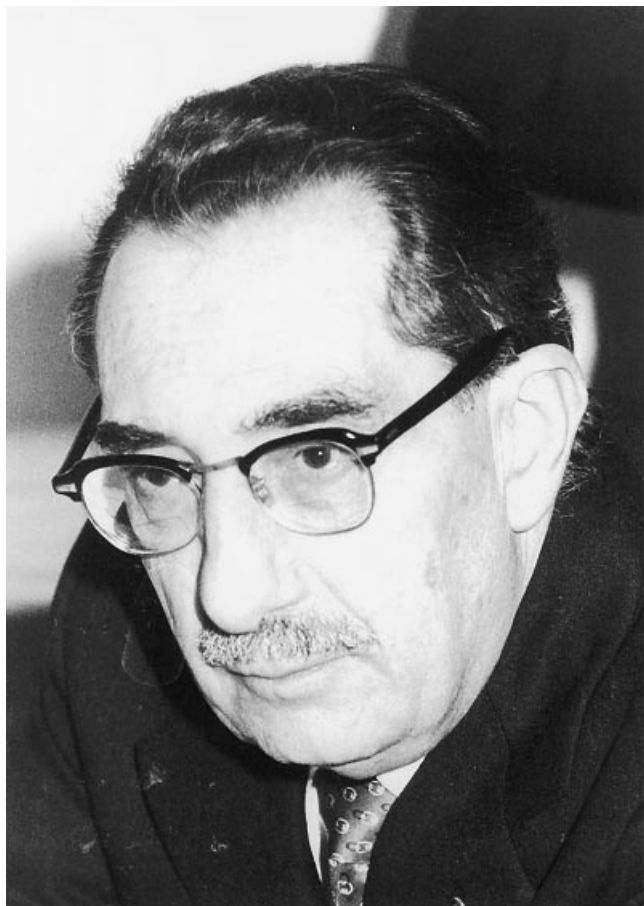


Fig. 4. Pietro Leonardi (courtesy of his son, Andrea Leonardi).

Almost at the same time in which Fiaschi performed his first percutaneous renal biopsies in Pisa, two other doctors started devoting themselves to the same subject in Padova. These were Pietro Leonardi (1914–1991; Fig. 4) and Arturo Ruol (born 1924), now Professor Emeritus of Internal Medicine at the University of Padova, who had been working since the late 1940s in the Institute of Patologia Medica of the University of Padova, directed by Professor Gino Patrassi (1904–1981). Leonardi and Ruol started doing percutaneous renal biopsies in 1953, after reading the first reports about the new technique in the international literature and as a consequence of their interest in renal diseases and pathology. In fact, Ruol had already worked on renal clearances and electrolyte disturbances and had spent a period in Berne in the institute of Professor François Reubi (1917–1997), where both nephrology and renal biopsies were the subject of special consideration [24, 25]. As to Leonardi, he was already familiar with biopsy techniques, having performed some liver biopsies [26].

Over the years, Leonardi and Ruol performed more than 300 renal biopsies and published several articles,

PIETRO LEONARDI - ARTURO RUOL

LA BIOPSIA RENALE TRANSCUTANEA

Prefazione del Prof. G. Patrassi



1961

CASA EDITRICE AMBROSIANA - MILANO

VIA G. BERTACCHI, 8

Fig. 5. Title page of the book of Leonardi and Ruol.

the first of which appeared in 1954 [27]. Most of these articles appeared in Italian journals [28–34], but some others were published in either foreign [35, 36] or important international journals [37, 38]. The large output of Leonardi and Ruol covered many aspects of renal diseases and found its organic arrangement in a book published in 1961 with the title of *La Biopsia Renale Transcutanea* (Percutaneous Renal Biopsy) [39]. This is their major work and is one of the first books entirely devoted to renal biopsy (Fig. 5).

In 1957, Vittorio Bonomini (born 1928; Fig. 6) introduced percutaneous renal biopsy in Bologna, where he is now professor of Nephrology and Dean of the Medical School. This started after Bonomini, who had been working in the renal laboratory of the Institute of Patologia Medica since its foundation by Professor Domenico



Fig. 6. Vittorio Bonomini (center) in 1957 with two students (first and fourth from the left) after discussing their theses on renal biopsy for their medical degree. These two theses are thought to be the first presented on the subject in Italy [40] (courtesy of Professor Vittorio Bonomini, Chair of Nephrology, Università degli Studi, Bologna).

Campanacci (1898–1986) in 1953, had spent one year at Hammersmith Hospital, London, United Kingdom. There he learned how to perform renal biopsies from Robert Muehrcke (on leave from the team of Kark in Chicago, IL, USA), whereas Robert Heptinstall and Priscilla Kincaid-Smith taught him how to evaluate the renal samples [40]. The first article of Bonomini and his group, which also included Pietro Zucchelli (born 1932), another distinguished nephrologist of today, appeared in 1958. This was based on 59 renal punctures in 52 patients with a wide spectrum of renal diseases [41]. It was followed by many other articles that were focused on multiple subjects, including the distribution of sulfhydryl groups in the proximal tubules [42], the relationship between metabolic acidosis and the histological changes of the kidneys [43], the renal findings in hemotologic disorders [44], type II diabetes mellitus [45], and the so-called collagen diseases [46]. However, it was pyelonephritis, defined as the invasion of the renal parenchyma by bacteria, that over the years became the main subject of study of Bonomini and his group [47–52].

DEVELOPMENT OF THE TECHNIQUE: PROGRESS, DIFFICULTIES, AND PITFALLS

As mentioned earlier in this article, the group of Fiaschi was the first to introduce percutaneous renal biopsy in Italy. After describing the technique to obtain the renal samples (Table 1) [9], they had major difficulties in obtaining histological sections of good quality. This problem was solved by taking the samples from Pisa to the Institute of Botany of Florence, where a skillful

technician named Ignesti was able to prepare adequate five-micron sections [12]. Giuseppe Andres acted as courier between Pisa and Florence and was thus introduced into renal pathology [12]. Shortly after these first difficult steps, Fiaschi and his colleagues started applying the newest and more advanced techniques to renal biopsies. These, however, became possible only through the cooperation with other institutions and groups, often outside Italy. Thus, electron microscopy started in 1955–1956 with Remo Naccarato, who used an instrument belonging to the Istituto di Sanità (Institute for Health) of Rome [53], and continued in 1958 at the Department of Pathology of the Karolinska Institute, Stockholm, Sweden, where Giuseppe Andres was spending a period of study [12, 53]. Immunofluorescence started in 1957, through co-operation with Beatrice Seegal, of Columbia University, New York, USA, at the suggestion of Giuseppe Andres [54], who in that period was working at Columbia University in the laboratory of Dr. Robert F. Loeb [12]. The renal specimens were sent to him by the junior members of Fiaschi's group in Rome, who woke up early in the morning to be at Ciampino airport in time to forward the boxes containing the specimens stored in carbon dioxide [53]. This overseas link resulted in the earliest article about immunofluorescence in human renal biopsies [55], which appeared one year before the article of Freedman et al, the one that is usually quoted as the first study published on this subject [56]. Other sophisticated techniques used by Fiaschi and his group included phase contrast microscopy applied to ultrathin sections fixed in osmic acid and embedded in methacrylate to evaluate the fine changes of the glomerular basement

membrane [20, 21] and histochemistry applied to electron microscopy [16].

Technically, Leonardi and Roul were less innovative than Fiaschi's group. They usually performed renal biopsies on patients in the prone position after the kidney had been located by plain x-rays of the abdomen or, less frequently, by intravenous pyelography. Initially, they used the Turkel aspiration needle but subsequently preferred the cutting Franklin-Vim-Silverman needle, whereas later on, they turned to the aspiration Menghini needle, which was smaller and particularly suitable for children and patients with increased risk of complications. With the Franklin-Vim-Silverman needle, adequate samples were obtained in 75% of cases [39], with rare major complications. The samples were analyzed only by light microscopy. For each case, approximately 10 sections were stained with hematoxylin eosin, the remaining being stained with the method of Van Gieson and Azan-Mallory (for collagen), Evans (for amyloid), Turnbull (for iron), Hotchkiss-MacManus (for polysaccharides), etc. [39]. The two doctors analyzed the samples separately and then compared their reports [26]. Electron microscopy was done for only a few cases, whereas immunofluorescence was not done at all [26].

Bonomini also performed renal biopsies with a Franklin-Vim-Silverman needle on patients in the prone position. Adequate samples were obtained in approximately 80% of cases, failures being observed mainly with patients with sclerotic kidneys [49]. Severe complications were rare, being confined to retroperitoneal hematoma in 2 cases out of 372 biopsies [49]. For several years, the samples were analyzed by only light microscopy, based on stains similar to those reported for Leonardi and Ruol [52]. Special stains, such as that for the identification of sulfhydryl groups within the proximal tubular cells, were used for research purposes only [42]. For the study of pyelonephritis, a portion of the renal tissue was often cultured for comparison with the urine culture and the search for glitter cells in the urinary sediment [47, 49]. Electron microscopy and immunofluorescence were started in 1968 and 1970, respectively [40].

Besides the previously mentioned technical advancement and limitations, how was renal biopsy regarded in those years in Italy? There are several examples that demonstrate that the technique was at first regarded with caution and suspicion.

In 1954, a short review published in the first issue of the journal *Minerva Nefrologica* (which by 10 years is the first journal to be devoted exclusively to the study of renal function and disease; *Nephron* was not started as the journal of the International Society of Nephrology until 1963) stated the following:

"The utility [of renal biopsy] is obvious, but one should not forget that an accurate clinical examination, performed together with the help of the modern clearance

techniques, allows us today [to draw] precise diagnostic conclusions in most cases of bilateral nephropathies" [57].

Three years later, in 1957, Bonomini encountered several difficulties in introducing renal biopsy into practice because it was still considered too dangerous for the patient and to produce unreliable results. The size of the specimens was considered to be too small to be representative of ongoing disorders by pathologists, used to autopsy samples.

Still, in 1961, when the nearly final version of the book by Leonardi and Ruol was presented for an important Italian medical award, the Premio Ganassini (Ganassini Award), it obtained a special mention but was not the winning monograph because a member of the judging committee—a surgeon—allegedly considered percutaneous renal biopsy too dangerous for the patient and ethically unacceptable [26].

However, on July 1, 1961, a breakthrough was represented by a symposium on renal biopsy held at the Carlo Erba Foundation in Milano, Italy. This was organized by Professor Gabriele Monasterio (1903–1972) with the aim of demonstrating the utility and safety of the technique (Fondazione Carlo Erba, Comunicato Stampa 166, 1961). The meeting was probably also organized in the wake of the CIBA Symposium on Renal Biopsy, held a few months earlier in London [8], where some Italians were present, but only in an unofficial capacity and without making any presentations. [Although strangely they do not appear in the list of participants, Fiaschi and Andres attended the CIBA Symposium, where they had been invited by one of the organizers, Sir Gordon Wolstenholme, who had noticed during a visit to Fiaschi's ward in Rome that the clinical notes of some patients contained the reports and micrographs of electron microscopy of renal biopsies (G. Andres, personal communication)].

The invited speakers at the Carlo Erba meeting were Ernico Fiaschi, Pietro Leonardi, and Vittorio Bonomini. In addition, there were Professor Angelo Migliavacca (1904–1968), who had done some work with Fiaschi in Cagliari, and Professor Giuseppe Folli (born 1924). The latter had developed a considerable experience of renal biopsies, especially by using electron microscopy, while working as research fellow in Kark's group at the University of Illinois (Chicago, IL, USA) in 1956–1957 [58, 59].

Fiaschi was entrusted with the opening lecture and described the main results of his large experience, which by 1961, was based on 385 biopsies [60]. Leonardi did the same, basing his lecture on his series of approximately 300 biopsies [61]. Bonomini concentrated on the contribution of renal biopsy in the diagnosis and management of patients with pyelonephritis [62]. Migliavacca presented the results of his electron microscopy investigation on pregnant women with renal disease [63], whereas Folli presented an overview of the main ultrastructural

Table 2. Year of introduction of renal biopsy as a routine procedure in the first Italian renal units

Center (Director)	Beginning of regular renal biopsy	Immunofluorescence	Electron microscopy
Torino (A. Vercellone)	1968	1972	1972
Sampierdarena (S. Lamperi)	1965	1982	1965
Genova (A. Tizianello)	1969	1970	1971
Milano (C. Ponticelli)	1964	1970	1969
Milano (G. D'Amico)	1967	1970	1975
Milano (L. Minetti)	1969	1969	1969
Parma (L. Migone)	1962	1968	1962
Brescia (R. Maiorca)	1970	1970	1970
Verona (G. Maschio)	1971	1975	1975
Bologna (V. Bonomini) ^a	1957	1970	1968
Bologna (P. Zucchelli)	1968	1970	1973
Roma (G.A. Cinotti)	1956 ^b	1975	1958
Napoli (C. Giordano)	1960	1978	1978
Bari (A. Amerio)	1965	1970	1965

^a See text for details

^b In Rome renal biopsy was introduced by Fiaschi when he left Pisa. The information contained in the Table was obtained by telephone from the directors of the centers.

lesions in various conditions, especially in the primary nephrotic syndrome [64].

The lectures presented at the symposium were published in 1962 in *Gazzetta Sanitaria* (Medical Gazette) [60–64], a journal that no longer exists. However, they were scattered in different issues of the journal and without any record of the discussion. Thus, the meeting had a lesser impact than expected and did not become a landmark for the Italian nephrologists and pathologists, as instead happened with the proceedings of the CIBA Symposium [8]. However, at the Milano meeting, the discussions were very lively, and the arguments in favor of renal biopsy must have been convincing, because after the symposium Bonomini was called by Professor Luigi Migone to perform renal biopsies in Parma [40].

Then, as everywhere else, the procedure began to be accepted and was used more frequently. However, this process took several years. This is exemplified by the fact that even in the 1970 edition of *Le Nefropatie Mediche* (*The Medical Nephropathies*) [65] of Gabriele Monasterio, a popular book among Italian physicians, only 22 of approximately 110 photographs of renal histology had been obtained by biopsy, whereas all of the others were still from autopsy cases. In fact, percutaneous renal biopsy in Monasterio's Institute started being done regularly only in 1966–1967 thanks to Quirino Maggiore (born 1933), who also was among the first to regularly apply immunofluorescence techniques [66]. This situation was not confined to a single center. In fact, in most Italian geographic areas renal biopsy became a regular procedure only in the middle of the 1960s or later (Table 2). This corresponds to the period that saw both the opening of several renal units and the birth of nephrology as an autonomous medical specialty.

CONTRIBUTION OF RENAL BIOPSY TO THE UNDERSTANDING OF DISEASES AND TO TREATMENT

For Fiaschi and coworkers, from the very beginning renal biopsy was an important diagnostic tool. However, in their hands it was above all a unique means to investigate the nature of renal diseases. The former aspect was already clear from their first article, published in 1953, in which it was stressed that in one case (observation VIII) renal biopsy had revealed discrete renal changes (that is, chronic intracapillary glomerulonephritis associated with interstitial nephritis and tubular damage) while the clinical signs were mild [14]. The research importance of renal biopsy is documented by the whole scientific output of Fiaschi's group, no matter the renal disease studied. However, it is especially the article on immunofluorescence [55] and the articles on the nephrotic syndrome [20–23] that reveal how much renal biopsy contributed in their hands to the understanding of renal diseases. The finding of both streptococcal antigens and gamma globulins in the glomeruli of some patients with glomerulonephritis suggested that gamma globulins could react as antibodies against the streptococcal antigens, which led to the farsighted conclusion that “it seems logical to admit that the inflammatory lesions of the glomeruli are the result of the reaction between antibodies and antigens” [55]. As to the nephrotic syndrome, a large number of important observations were made. Some of these are not acceptable today, but several others remain valid. For instance, if membranous nephropathy can no longer be seen as the late evolution of a proliferative glomerulonephritis, it is still true that in most instances, it is associated with nephrotic proteinuria and that the thickening of the glomerular basement

Table 3. The main renal diseases studied by transcutaneous renal biopsy by Leonardi and Ruol as reported in their book [39]

Renal disease	Number of patients
Acute glomerulonephritis	10
Subacute and chronic glomerulonephritis	45
Nephrotic syndrome	21
Chronic interstitial nephritis	6
Arterial hypertension	13
Collagenoses	10
Renal amyloidosis	5
Diabetic nephropathy	10
Renal diabetes	3
Renal hemosiderosis	6

membrane is due to osmiophilic material lying irregularly on its external side [20–22]. If Fiaschi and coworkers were wrong when they were skeptical about the existence of a nephrotic syndrome without histological changes of the glomeruli, they were absolutely correct in claiming that one could exclude the presence of lesions only by examining the samples by both light microscopy and electron microscopy [20–22]. They also noticed that tubules also could undergo a number of changes in glomerular diseases, which led to the correct observation that “in nephrotic syndrome regressive changes can involve the whole nephron” [20]. Very importantly, they also stressed the importance of chronic interstitial and vascular changes as indicators of poor prognosis [20–22].

Leonardi and Ruol, who studied a wide spectrum of renal diseases (Table 3), used renal biopsy mainly to explain the clinical findings and to properly characterize the renal patients, which is clearly shown in their monograph [39]. Thus, in acute glomerulonephritis, renal biopsy allowed the definition of the spectrum of lesions, the understanding of their prognostic significance, and the differential diagnosis with other types of glomerulonephritis. In subacute and chronic glomerulonephritis, renal biopsy was considered of lesser importance and was associated with a higher risk of complications; however, it could also separate the cases with only sclerotic lesions from those with also active changes. It could reveal disorders, such as amyloidosis or incipient interstitial nephritis, that were unexpected on clinical grounds. For the nephrotic syndrome, renal biopsy made a better classification of renal diseases possible, based on the correlation between the clinical appearance and the pathological findings (Table 4). It also showed that some secondary forms had a typical histological picture. For interstitial nephritis, renal biopsy was considered especially valuable because most of their cases would have been misdiagnosed without it. For hypertension, renal biopsy could help in differentiating primary forms from nephrogenic forms, the latter being associated with well-defined glomerular lesions. For what were then called

Table 4. Classification of nephrotic syndrome based on clinical and pathological findings according to Leonardi and Ruol [39]

Primary forms
Paranephritic nephrotic syndrome
Genuine lipoid nephrotic syndrome
(a) membranous
(b) with only foot process fusion by electron microscopy
(c) with only interstitial lesions
Secondary forms
Amyloidosis
Renal vein thrombosis
Diabetes mellitus
Toxic
Infectious
Collagenosis

collagenoses, special interest was focused on (a) systemic lupus (6 cases), in which it was noticed that severe renal lesions could be associated with mild clinical signs and (b) on acute interstitial nephritis, which could superimpose on glomerular disease. For diabetic nephropathy, it was noticed that the prognosis was good if the Kimmestiel-Wilson lesion was focal. For amyloidosis, it was found that not always there was nephrotic syndrome or renal failure. For renal diabetes, no specific findings were found by light and electron microscopy [37], which was in disagreement with the results subsequently described by Monasterio et al [67]. For hemosiderosis, renal biopsy showed that hemoglobin mainly filled the cytoplasm of proximal tubules and that the tubular lesions were not associated with renal dysfunction [38].

For Bonomini, renal biopsy was important for the study of the correlations between renal functional tests and the renal lesions and to predict the prognosis of a renal disease [41–43]. In addition, renal biopsy was seen as a unique tool to reveal the presence of “pyelonephritis,” especially in cases with normal renal function in which both clinical and radiological signs were often misleading [51]. Moreover, only by renal biopsy was it possible to differentiate the cases of primary pyelonephritis from those with pyelonephritis superimposed on other renal diseases, which showed glomerular or vascular changes not seen in the primary form. For such cases, it was possible to predict a poorer clinical course and the appearance of a more severe hypertension.

Was this large use of renal biopsy important to therapeutic decisions? From what we found in the Italian literature of the period, it appears that this aspect was the least considered. In fact, even though hormonal therapy—glucocorticoids and corticotropin (ACTH)—was well known to Italian physicians in the 1950s [68], this was rarely mentioned in the articles of Fiaschi, Leonardi, and Ruol, and Bonomini. Moreover, when there was mention, it was only in general terms and mainly to describe the results obtained by others [39, 51], rather

than reporting on personal experience. This confirms that in this early period renal biopsy in Italy was used as a diagnostic and investigative technique rather than as a useful tool to make therapeutic decisions.

THE ITALIAN RESULTS IN RELATION TO THEIR CONTEMPORARIES

The analysis of the articles of Fiaschi and his group, Leonardi and Ruol, and Bonomini shows that they were all very familiar with the literature about renal biopsy that was published abroad. It also appears that they carefully analyzed the studies published in the international journals and compared their results with those obtained by others. It also seems that—at least in the beginning—they tried to emulate these foreign articles. For instance, the first article of Fiaschi, Ercoli and Torsoli, which described the clinical and biopsy findings of six patients in detail [14], was very similar in its layout to the article published in 1951 by Iversen and Brun, which gave information about eight patients [5]. Also, the disorders chosen for investigation, that is, the nephrotic syndrome [20–23, 39], amyloidosis [34], diabetic nephropathy [17, 18, 45], and pyelonephritis, reflected the relative high frequency of these disorders in other countries, as in Italy [69–74]. Not surprisingly, also in Italy renal biopsy showed that several conditions could be found in patients with nephrotic syndrome, which led to the classification reported by Leonardi and Ruol (Table 4) [39]. When compared with that of Kark et al, this included a smaller number of distinct forms, even though all of the main groups of disorders were listed [71].

Therapy was not given too much space in Italian articles, even though a role for renal biopsy in identifying nephrotic patients who might respond to a corticotropin (ACTH) treatment had already been suggested in the international literature as early as 1952 [75].

Notwithstanding, there was a good deal of originality from the Italians, as demonstrated by studies on the renal changes associated with favism [19], renal glycosuria [37], hemosiderosis [38], or the distribution of sulfhydryl groups in the tubules [42], which were not dealt with outside Italy. This originality is also found in technical aspects. As shown in Table 1, the technique to obtain the tissue cores described by Fiaschi and his group [11] greatly differed from that of Iversen and Brun [5]. Furthermore, Leonardi and Ruol, after achieving a large experience with the Franklin-Vim-Silverman needle and a 75% success rate [39], a percentage very close to that of Kark et al [76], did not hesitate to swim against the stream by turning to the smaller aspiration Menghini needle with the aim of reducing the complication rate [39]. An original technical aspect was also the early application of immunofluorescence [54, 55]. Compared with the study of Freedman, Peters, and Kark in which only antihuman

Table 5. Milestones in percutaneous renal biopsy in international and Italian literature

Milestone	International literature	Italian literature
First percutaneous renal biopsies	Iversen and Brun 1951 [5]	Torsoli et al. 1952 [9]
First use of cutting needle with patients in the prone position	Kark and Muehrcke 1954 [7]	Torsoli et al. 1952 [9]
First electron microscopy studies	Farquhar et al. 1957 [77]	Fiaschi et al. 1959 [20]
First immunofluorescence studies	Freedman et al. 1960 [56]	Seegal et al. 1959 [54, 55]

gamma globulin serum was used [56], Seegal and Andres also demonstrated the presence in the glomeruli of streptococcal antigens, which allowed them to hypothesize that an antigen-antibody reaction was taking place. Electron microscopy too came early [20–22], shortly after the publication of the articles of Farquhar, Vernier, and Good [77] (Table 5) and with a similar application to a large spectrum of diseases and similar findings.

However, interpretation of the results obtained by the Italians was not always the same as that given by groups elsewhere. For instance, the osmiophilic material observed by electron microscopy on the external aspect of the glomerular basement membrane in membranous nephropathy was considered by Fiaschi et al as a product of secretion of epithelial cells [20, 22]. This contrasted with the view of Movat and McGregor [78], who correctly considered this material as the result of accumulation of proteins deriving from the circulation. Moreover, at variance with the view of others [79, 80], Fiaschi et al doubted the existence of “minimal change” disease because in their experience, glomeruli were always altered [20, 22]. For Bonomini, who observed some cases with nephrotic syndrome and normal glomeruli, the lesion in such cases instead might reside in the tubules, which were always abnormal, a hypothesis that also had supporters outside Italy [81].

Were the Italian contributions and views known outside Italy? Several studies indicate that they were not. Fiaschi's 1953 article was sometimes quoted during the 1950s, for instance by Kark et al [76] or by Parrish and Howe [82], but without comment or discussion of the original technique and results in the text of any of the articles. Furthermore, the Italians were neither officially invited to CIBA Foundation Symposium on Renal Biopsy, which was held in 1961 in London, nor was any Italian mentioned in the “List of Authors” in the book of the proceedings of the symposium [8]. The most likely explanation for this exclusion of a large body of work is that the bulk of scientific output appeared for many years in only Italian language journals not always even of national significance, which did not circulate abroad.

In a time in which the languages in nephrology were English and to a lesser extent French, this certainly limited the contacts with the leading foreign centers and the recognition of the Italian contribution. Moreover, at that time, Italy was not regarded abroad as a country from which advances in biomedical sciences could regularly be expected. Today, Italian nephrology is well acknowledged internationally, the deserved result of a large output of scientific articles, as well as clinical investigation in international journals. In addition, today the world is a "global village" in which contacts and exchanges are easy, but that was not so in the 1950s and early 1960s.

With this article we hope to recapture certain historical facts and ideas, for Italians and for the international community of nephrology, and also give credit to a number of pioneers who helped form our specialty in the 1950s and early 1960s.

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Reprint requests to Giovanni B. Fogazzi, M.D., Divisione di Nefrologia e Dialisi, Ospedale Maggiore, IRCCS, Via Commenda 15, 20122 Milano, Italy.

E-mail: croffi1@polic.cilea.it

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