Historical Note

The juxtaglomerular apparatus of Norbert Goormaghtigh—a critical appraisal

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The discovery of the unique structural relationships between the early distal tubule of the nephron and the vascular pole of its originating glomerulus and the subsequent demonstration of the functional and clinical importance of this remarkable complex—the juxtaglomerular apparatus—is one of the principal achievements of nephrology. Of the several investigators who made this possible, an immeasurable debt is owed to Norbert Goormaghtigh (1890–1960), who was not only one of its first observers but the only one to persevere in its investigation, to recognize and define the critical relationship of the complex he named the juxtaglomerular apparatus, and in what were clearly prescient insights to foresee correctly many of its functions that were to be documented in the ensuing decades. His discovery, description and deductions of the juxtaglomerular apparatus and its roles are a landmark in the history of medicine. Regrettably, his key part in characterizing and elucidating this distinct apparatus has been confused, often misrepresented, frequently misunderstood and generally forgotten.

Historical background

In order to appropriately evaluate the credit that Goormaghtigh deserves in the discovery of the juxtaglomerular apparatus, it is important to consider his work in the context of the state of the medical sciences, the knowledge of kidney function and the socio-political setting in which he conducted his studies. In the medical sciences, it was the closing years of the era of endocrinology launched in 1891 or a simple filter championed by Carl Ludwig (1816–92) described his eponymous cap-}

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Alfred N. Richards (1826–1966) in the early 1920s [8]. In his studies, Richards used frogs because of the accessibility of the ventral surface of their kidneys to direct visualization. Relevant to the work of Goormaghtigh is the early observation and report by Richards and his associates of the intermittency of glomerular function [9]. In clinical studies of the kidneys, the notion of hypertension as a cause of kidney disease, rather than just a result of kidney disease, was being differentiated by the work of Franz Volhard (1872–1950) and Theodor Fahr (1877–1914), who in 1914 provided their classification of Bright’s disease and characterized the arteriosclerotic (nephrosclerotic) kidney [10]. Thus, by the opening decades of the 20th century, when Goormaghtigh began his studies, it was generally considered that whereas the diseased kidney could cause hypertension, the more common form of elevated blood pressure was a primary form of ‘essential’ hypertension, in which renal involvement was secondary to the hypertension. The cause of elevated blood pressure and the role of the kidney in either form of hypertension remained uncertain and debatable. This was another area directly relevant to the research of Goormaghtigh, who studied the vasculature in hypertension and was the first to propose a link of hypertension to the juxtaglomerular apparatus.

Norbert Goormaghtigh—biography and scholarship

It is on this background in the state of the medical sciences that Goormaghtigh made his major contributions on the juxtaglomerular apparatus in the period between the two world wars, both of which to some extent influenced and shaped his personal life. Born on 14 February 1890 in the North Sea port city of Ostend, in West Flanders, Goormaghtigh graduated in medicine from the University of Gent in 1913. Drafted into service at the break of the First World War (WWI), he served as a surgical pathologist in an English Field Hospital in Hoogstade. It is there that he met and married an English nurse, Mabel Lawrence, in 1917. The Second World War (WWII) was equally defining in his life, when his favoured son was accused and imprisoned in Daschau in 1943. The following year, the Gestapo incarcerated him also, albeit for only a short period. The toll of WWII on his work and productivity is reflected in the diminishing number of his publications (Table 1). His subsequent administrative responsibilities as a rector (1947–1950) of the University of Gent (Figure 1), during a particularly difficult period in its history, further hampered and practically ended his investigative career. Following a series of progressively severe and incapacitating cardiac attacks beginning in November 1957, he died on 2 January 1960 [3–5].

After WWII, Goormaghtigh returned to the University of Gent, where under the tutelage of the professor of microscopic anatomy, Omer van der Stricht (1862–1925), he completed his thesis on the adrenal glands, demonstrating that the zona fasciculata of the adrenal cortex was the source of corticosteroids while its medulla was adrenergic. The following year, in 1922, he was appointed to the chair of Pathology at the University of Gent [3–5]. It is then that he embarked on a productive career of research and training in experimental pathology (Figure 2, Table 1). He was a prolific author and a meticulous experimenter, who was himself directly involved in the work of published studies. He is the single author of 68% of his 113 publications. The rest of his papers, except for two of them, are two authored only, reflecting the fact that he was also an admired teacher and role model who trained and supervised the work of an increasing number of graduates (the second authors of 36 of his multi-authored publications) in the period preceding WWII.

The principal areas of his studies were endocrinology in general and the adrenal glands in particular, carcinogenesis, hypertension and the kidney (Table 1). Of the 39 publications listed under other in Table 1 almost all are on endocrine glands (thyroid, parathyroid, ovaries, insulin). Excluding this category of others, it is evident that most of his publications (27% or 31 articles) were on the kidney and two-thirds of Pathology at the University of Gent [3–5]. It is then that he embarked on a productive career of research and training in experimental pathology (Figure 2, Table 1). He was a prolific author and a meticulous experimenter, who was himself directly involved in the work of published studies. He is the single author of 68% of his 113 publications. The rest of his papers, except for two of them, are two authored only, reflecting the fact that he was also an admired teacher and role model who trained and supervised the work of an increasing number of graduates (the second authors of 36 of his multi-authored publications) in the period preceding WWII.

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<table>
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<tr>
<th>Period</th>
<th>Number</th>
<th>Single author</th>
<th>Adrenal</th>
<th>HBP</th>
<th>Renal</th>
<th>Cancer</th>
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<td>1936–40</td>
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<td>Total</td>
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<td>18</td>
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<td>31</td>
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In the column labelled renal, the numbers in parenthesis indicate publications about the juxtaglomerular apparatus.
of these (21 out of 31) were on the juxtaglomerular apparatus (Table 1). His first renal publication in 1924 is about horseshoe kidneys and not directly relevant to our topic [11]. What is relevant, however, from this early period is his work on hypertension, beginning in the mid-1920s. This work, which had begun on the relationship of hypertension with the adrenal glands [12], then extended to studies of the effect of hypertension on the renal vasculature [13,14]. For his initial studies, he used an experimental model of hypertension induced by the stimulation of the carotid sinus developed in collaboration with the Professor of Pharmacology and Therapeutics at the University of Gent, Cornelle Heymans (1892–1968), the 1938 Nobel laureate in Physiology or Medicine for his discovery of chemoreceptors in the carotid sinus and aortic arch. Later, after Harry Goldblatt (1891–1977) described a reproducible ischaemic model of hypertension in 1934 [15], Goormaghtigh used Goldblatt kidneys to study the sequential changes of the renal vasculature and the juxtaglomerular complex as renovascular hypertension sets in and evolves [16,17].

His first paper on the juxtaglomerular apparatus was written in French, [18], as were three-quarters of his publications (76%, or 86 out of 113). Despite its location in the Flemish northern part of Belgium, the official teaching language of the University was French until 1930, when the changeover to Dutch begun. This is also about the time that the dominant language of the medical sciences began to change to English. This is reflected in the publications of Goormaghtigh (Figure 2). His first paper in English, published in 1934, was on the thyroid gland [19]. The majority (10 out of 13) of his English papers were published during the decade between 1936 and 1945, and most of them (8 out of 10) were on the juxtaglomerular apparatus.

**Norbert Goormaghtigh—the juxtaglomerular apparatus**

It is with this background of considerable experience in the morphology of endocrine glands and the vascular effects of hypertension that Goormaghtigh published his first manuscript on the juxtaglomerular apparatus in 1932 [18]. In this first report, Goormaghtigh acknowledges the work of two of his predecessors in the field. Essentially, in 1925, J. H. C. Ruyter was the first to call attention to the structural peculiarities of unique cells lining the afferent arteriole as it approaches the glomerulus [20]. Ruyter described in mice the changes in the smooth muscles of the juxtaglomerular afferent arterioles, which begin to lose their fibrils and are replaced by one or more layers of larger granular cells with prominent oval nuclei. He characterized them as epithelioid cells, which are variably present in different afferent arterioles, being most abundant in those supplying the cortical glomeruli. He suggested that by swelling these cells could occlude the lumen of the afferent arterioles and thereby regulate blood flow to the glomerular capillaries. He reported observing similar cells in rat kidneys, but explicitly denied their presence in dogs, monkeys, guinea pigs, cats, rabbits and man. Two years later, and independent of Ruyter, Charles Oberling (1895–1960), then working in Strasbourg, reported the presence of similar cells in human kidneys in a brief two-page report published in 1927 [21]. He highlighted their features as identical to the subcutaneous digital glomi described by his then mentor Paul Mason (1880–1959).

In his inaugural paper on the subject [18], Goormaghtigh described in detail the afibrillar cells of the juxtaglomerular arterioles, principally in an 8-year-old girl who had died of scarlet fever. He characterized them as afibrillar granular cells and identified them with those lining the afferent arteriole described by Ruyter. In addition, he identified a second population of smaller, also afibrillar but agranular, spindle-shaped cells in the vascular pole, and highlighted the rich enervation of the entire area. The second type of cells he described were subsequently termed lacis cells because of their interlacing processes separated by basement membrane. Like Oberling, he mentioned the similarity of his findings to the subcutaneous glomi of Masson [22]. Masson had used the term glomus (from the Latin for ball of thread) to describe the subcutaneous plexus of arteriovenous anastomoses (anastomases artéromioveneux) rolled upon itself and embedded in fibrous tissue that blends into the surrounding dermis. The analogy made was not only to shape but also the appearance of the cells lining the glomic arterioles and the abundance of neural fibres supplying these neuro-muscular cells (cellules neuromusculaires) described by Masson, hence the title of Goormaghtigh’s first manuscript ‘Les segments neuro-myo-artériel juxtaglomerulaires des reins’ [18].

Relevant to this background are two other reports by Karl W. Zimmermann (1861–1935) of the University of Berne. In 1929, Zimmermann had mentioned briefly the changes in the epithelial cells of the distal tubule returning to the region of its originating glomerulus, where it makes contact with the afferent arteriole [23]. In this paper he states, ‘In all mammals that I have studied, there is at the junction of the ascending branch of the loop of Henle with the afferent arteriole an increase in the number of epithelial cell nuclei of that side of the tubule. For some time now, in my lectures I...
A. N. Richards, whose studies in frogs had shown intermittent afferent arterial obstruction. This was espoused by that the afferent cells he had described could by swelling on the kidneys. paper and died 2 years later. He never wrote another paper [30]. Zimmermann retired the year following his polkissen subject more than a decade later at which time he felt com- that Goormaghtigh went on to study and elucidate the func- tion of the distal tubule to the vascular pole of its originating glomerulus had been described in 1889 by Camillo Golgi (1843–1926) [24], the 1906 Nobel laureate in Physiology or Medicine, and confirmed in the early 1900s in the elegant reconstrucive models of the nephron developed by Karl Pe- ter (1870–1955), who also noted the distal tubular epithelial cell changes but failed to name them [25]. In a subsequent extensive paper [26], Zimmermann provides further details on the macula densa and the adjacent cells in that location. What Zimmermann described in 1933 was that as the afferent arteriole approaches the glomerulus, the medial cells begin to multiply irregularly, expanding into a vascular sleeve that fills the space between the afferent and efferent vessels and extends into the glomerulus. These are the external mesangial cells, as they have since been identified and as we know them today. Because of their appearance as a cushion supporting the vascular pole of the glomeru- lus, Zimmermann called them polkissen, i.e. polar cushion or pad. Zimmermann does not mention the term ‘enartrine’ for the vasoactive substance [4], but the pathogenesis of hypertension. He is said to have used the term ‘enartrine’ for the vasoactive substance [4], but in his published articles proposes that it is renin. Further, after the description of anuric acute renal failure in trau- matic crush injury in WWII [38], he studied and reported the vascular changes of the juxtaglomerular apparatus in anuric crush syndrome, including those in preserved specimens he had studied in WWI, when stationed in Hoogstade [39,40].

A good example of his analytical and perceptive aptitudes is his paper about the macula densa [33]. In his report, Zimmermann never refers to any functional significance of the structure he named. In contrast, in concluding his observations on the intimate structural relationships of the juxtaglomerular apparatus’ structural compo- nents Goormaghtigh states, ‘The anatomic relationships described above allows eventually for the glomerular circulation to be informed of the changes in its corresponding tubule. In this case then, the epithelial cells (macula densa) would act as a sensory plaque placed at a most important position of the nephron; hence, the possibility of an automatic regulation of the glomerular circulation controlled either by changes in volume or the physico-chemical composition of the urine (tubular fluid) flowing passed the plaque’.
This is as succinct and clear a statement as could be made about tubuloglomerular feedback, as we understand it now. To have been formulated in 1937 at a time that the giants of nephrology of the day considered the juxtaglomerular apparatus mere structural changes due to mechanical stress [41,42] only indicates the considerable insights that Goormaghtigh brought to his power of morphologic observations. His ability to foresee structural–functional correlates and correctly formulate them is stunning, to say the least, and these were far ahead of their time. It was decades later that they were documented and elucidated.

Essentially then, Goormaghtigh literally single-handedly recognized and documented the significance of the critical structural relationship of the juxtaglomerular apparatus and foretold the many roles of his apparatus that were fully documented after WWII. At the time, however, his prescient conclusions were based on histological observations, without any bioassay or biochemical confirmation. As such, they could be influenced, to some extent, by subjective impressions. This reservation is magnified by the fact that the figures illustrating his papers were drawings or camera lucida renderings of his microscopic observations. Goormaghtigh acknowledges this shortcoming in a 1951 manuscript in which for the first time he presents a single photomicrograph in support of his drawings [37]. And with the appropriate humbleness of an experimentalist he questions his own conclusions about renin as being indirect and inferential.

These self-acknowledged limitations notwithstanding, what is most striking in his work is that literally every one of his sagacious deductions has been and continues to be substantiated and documented. Unfortunately, the promise of the important functions of the juxtaglomerular apparatus that Goormaghtigh had promoted became moribund during WWII, as did his own investigative work not only during the war but thereafter as well when he became rector of the University from 1947 to 1950. His last paper on the subject, published in 1956, is on the renal circulation in chronic glomerulonephritis [43]. That is just about the time that the entire subject was being resurrected by the meticulous studies of Phyllis M. Hartroft and her students [28], who began unravelling the line of documentations of the functions of the juxtaglomerular apparatus of Goormaghtigh that continues to the present [44,45]. As shown in Figure 3, following the lull in the period after the war there was an exponential increase in the number of publications on the juxtaglomerular apparatus beginning in the 1960s that peaked in the 1970s and continues at a steady pace to the present. The accrued information from this work on the juxtaglomerular apparatus has had far reaching consequences that have not only expanded our understanding of renal structure, function, pathophysiology and therapeutics but also affected that of the care of patients with acute and chronic kidney disease.

An apologia

The delay in work on the juxtaglomerular apparatus and the confusion in appropriate attribution of its discovery are perhaps best reflected in the magnum opus of Homer Smith, who in his 1950 classic book 'The Kidney. Structure and Function in Health and Disease' devotes barely one page to the subject [41]. The section is titled ‘Polkissen or Juxtaglomerular Apparatus’, which reservedly mentions Goormaghtigh’s findings only to dismiss them by referring to Jean R. Oliver (1889–1976) who ‘finds no suggestion of endocrine nature for the polkissen cells and thinks that they represent structural modifications resulting from the mechanical stresses where the thin-walled arteriole enters the glomerulus. This view is consonant with their hyperplasia in degenerative renal disease’.

This was not the first time that Homer Smith was wrong. He had long resisted the countercurrent mechanism in generating concentrated urine. In that error he lived long enough to see its documentation and wrote a humorous piece in 1959 about an imaginary encounter with Saint Peter at the Gates of Heaven where he admits his error and attempts to justify why he had insisted for so long on drawing the tubule straight [46]. Unfortunately, Smith did not live long enough to write a similar apologetic piece on the juxtaglomerular apparatus. Nevertheless, and in the same general vein, one can imagine a similar scene where Saint Peter inquires of Smith: ‘You were intimately familiar with the early work on the granular cells of Goormaghtigh and summarized it in your 1940 Harvey Lecture [47]. Why did you confuse it by equating it all with the frivolous polkissen term in your book?’ To which Smith answers, ‘I was misled by the two people I admired most, Richards who espoused the mechanical description of Ruyter and by Oliver who denied any endocrine function of the apparatus [41,42], and attributed intermittency of glomerular function to the shunting of afferent flow through the arterioles of Carl Ludwig, “the discoverer of glomerular filtration” [48]. How could I deny the opinion of these three giants of nephrology? In my defence though I must submit the only coloured illustration of my book, its frontispiece to which I refer in the section on the polkissen as “a normal glomerulus, where the structure of the afferent arteriole is clearly visible”. Please note the granular cells of Goormaghtigh I failed to mention in the text. Mea culpa. Mea maxima culpa’. 

Fig. 3. Number of publications per 5-year period listed in PubMed under the search word ‘juxtaglomerular apparatus’ for the period 1951–2004.
The unique structural and functional features of the juxtaglomerular apparatus were recognized, examined, described, characterized and studied by Goormaghtigh, whose name deserves to be associated with it. Bowman and Malphigi earned their eponymous attributions for much less work than what Goormaghtigh did to unravel that of his remarkable juxtaglomerular apparatus. As for terms like polkissen and lacis, or descriptors such as epithelioid or myelopithelioid cells, the sooner they are forgotten and omitted from future textbooks the clearer the story of Goormaghtigh’s juxtaglomerular apparatus will become.

Conflict of interest statement. None declared.

References