Medicina Historica 2019; Vol. 3, N. 3: 156-169

Original article: history of medicine

The young Nicola Pende and the ambiguous adrenal gland: at the origins of Italian endocrinology

Liborio Dibattista
Department of Humanities Studies, University of Bari "Aldo Moro", Bari, Italy

Abstract. The thesis of Niccolò Pende, supported in 1903, bore the title: The alterations of the adrenal gland after resection of the splanchnic nerve. Studies on the adrenal glands were the main gate through which the Apulian clinician became one of the first scholars in the world to attempt a systematic organization of the endocrine glands and their functions. Six years after graduating, the treatise on the physiopathology of the adrenals placed Pende on the attention not only of the Italian medical class, but also of the newly formed American magazine *Endocrinology* and of Sir E. Schaefer himself. The idea of a close correlation between the nervous system and endocrine glands constituted the guiding idea by following which Pende built the systematic building of Italian endocrinology; however, it also constituted the limitation that prevented him - for example - from grasping the exact distinction between the functions of the cortex and medulla of the adrenal glands. The present contribution aims to underline the precisely ambiguous role that preconceived ideas play in the construction of scientific hypotheses.

Key words: Nicola Pende, endocrinology, adrenal gland, preconceived ideas

Introduction

When does a new scientific discipline come into being? When a medical speciality detaches itself from the corpus of general medicine to take upon itself the right to claim as separate and distinct not only Subject, Methods and Epistemology but also University Chairs, Sector Journals, Institutes, Schools? Is it possible to pinpoint a moment, a place, a figure that marks a caesura between a before and an after? Certainly, depending on the criteria cited by the historian to respond to these questions, different milestones may be identified: if one favours internal history, the history of ideas and concepts, the answer will be borne out by the reading of articles, treatises and, perhaps, by awareness on the part of coeval scientists – as I. B. Cohen would have said. If the material examined consists of the minutes of academic committees, financial reports, juridical summaries, scientometric criteria, then the so-named external history may or may not invalidate the conclusions reached by the first method. But unexpected factors may intervene, linked with the historian's sensitivity, his belonging to a national community or to a collective of thought. In this brief essay we shall examine, with criteria prevalently internal, the affirmation – wholly Italian – of the seminal role played by Nicola Pende in the birth of endocrinology, with specific reference to the episode that lay at its origin, seeking to point out how – setting out from an obscure physiopathological subject, the function of the suprarenal glands – he built up a coherent body of knowledge which, at least in Italy, has led to acknowledgement of the Apulian physician as founder of the discipline.

Nicola Pende was born in Noicattaro (Bari) on 21/04/1880. Having attended the Liceo-Ginnasio Cirillo in Bari he enrolled at the Faculty of Medi-

cine in Rome where his teachers were Giovan Battista Grassi, Amico Bignami, Ettore Marchiafava and Luigi Luciani. In the laboratory of Michele Bufano he became acquainted with the experimental and biochemical methodologies that were to become so useful in his research activities. Graduating in 1903, he remained in Rome until 1909, when he obtained the post of assistant at the Institute of Pathological Medicine, University of Palermo. Giacinto Viola taught here, the second leading light of Italian constitutionalist medicine after Achille De Giovanni. Viola took Pende with him to Bologna after the war – in which the latter had been an army doctor in Bari, Rome and Padua – and as early as 1921 he returned to Sicily as head of Clinical Medicine at the University of Messina. In 1923 he was at the centre of a troublesome series of events for the position of full professor between Parma, Sassari and Messina, which ended up with a sudden call for a competition in Cagliari *ad personam* . But Pende was too late to take the position in Sardinia because meanwhile the Minister for Education, Gentile, called him to Bari , as first Rector of the then forming Università Adriatica Benito Mussolini. Here too Pende remained only a few months, being called to menage the Medical Clinic of the University of Genoa, where he founded the first Institute of Human Biotypology and Orthogenesis. In 1925 he took the chair in Rome for Medical Pathology and Clinical Methodology, and in December 1933 became senator of the Kingdom. In 1938 his signing of the Manifesto of Racial Laws led in 1944 to the order of forfeiture of the position of senator, a provision that was quashed four years later. Restored to the chair in Rome, he remained until 1956.- He died on 8th June 1870 in Rome.

Rome 1912

If the paper read at the XXII Congress of Internal Medicine in Rome was the one wholly published in the proceedings, then the moderators who sought to cut him short for exceeding the time limit could not, at bottom, be reasonably faulted. Sixty-seven very densely written pages suggest the duration of Pende's intervention, entitled "Internal secretions in relationships with clinical science". Certainly the task «entrusted him by his illustrious masters, to give *rapidly* and with a *critical spirit* a balanced account of positive endocrinological facts» (1) was onerous, and it may be that Pende (1880-1970) had in mind the address to the *British Medical Association* (2) with which Sir Edward Albert Sharpey-Schaefer had inaugurated the study of internal secretions as a physiological science – as well as clinical – seventeen years earlier (3, 4). But his masters, Edoardo Maragliano (1849-1940) and Achille De Giovanni (1838-1916), intervened in order that the thirty-two year old clinician might finish reading his paper. According to his son Vito Pende, on that occasion the great clinician Augusto Murri (1841-1932) exclaimed: «Behold a new sun rising!»

Effectively, Pende – who at the time was assistant to Giacinto Viola (1870-1943) at the Institute of Medical Pathology in Palermo – took upon himself the role of systemiser of «endocrinology which seems to us today rather a *true new science,* of the kind that reform, dominate and orient the medicine of an entire age» (1). Of this new science Pende attempted not only a complete summary but also put forward – in the final pages of his paper – a theory that was a «brief, general and unitary synthesis». Presented modestly as a draft, as a working tool, point of departure and meeting (1), the theory in reality concluded a decade of avant-garde – at least in Italy – experimental and clinical studies on the subject. For all that it was fleeting, this provisional theory contained a thread that would run through the whole scientific career of the Apulian clinician: the synergy between the *endocrine* and *nervous* systems, in particular the sympathetic section of the autonomous nervous system. The 1912 theory proposed the existence of a tropho-regulator system of the organism, consisting of the two cited systems and maintained in constant equilibrium between two antagonistic neuro-hormonal groups: accelerators and retarders of matabolism. Without entering into the details of this theory, it is worthwhile underscoring how it already clearly contains that which, in the decades to come, must have been Pende's correlative psycho-neural-endocrinology:

> Since the sympathetic nerve is connected to the psychic centres, we understand in what way a psychic trauma or a cerebral lesion may produce an

> endocrinal syndrome, Basedow's syndrome for example, if we admit the secreting influence of the sympathetic nerve on the hormone producing organs. On the other hand the facts, which we have already analysed elsewhere, demonstrate a great influence of hormones on psychic functions: which explains the onset of psychic syndromes due to a primitive hormonal disruption… our hypothesis may be applied to growth disorders, to metabolic disorders, the diseases of the visceral nervous system, and lastly to the pathogenesis of the highly complex syndromes of the endocrine glands. It perhaps allows us to orient ourselves even in the solution of the problem of determinism of morphological types and individual temperaments (1).

It seems to us that one of Pende's powerful, original and definitive ideas should be pointed out here. Victorius C. Medvei, author of a monumental history of endocrinology, places the beginnings of neuroendocrinology in 1936, with the *Croonian Lecture* by Francis H. Marshall (1878-1949) (5). On that occasion the British physiologist, a pupil of Schaefer, underlined the role, in the overall female reproductive hormonal balance, of the hypothalamus and of the nervous system in general.

Even more than being useless, in the history of science it is sickening to raise or lower the bar of a discovery, of an idea, along the axis of time, almost as if it were among the historian's most important duties. Even though this concept had peak moments in the 19th and part of the 20th century. And in any case, to understand how an idea, a research programme, a scientific paradigm took place at different times and in different places is not idle, above all when that programme of research was fertile and its various declensions took on different connotations, precisely in relation to the historical, social and political situation in which they were lived.

In Pende's case, that "determinism of individual types and temperaments" would lead in subsequent years to the theory of Biotypology and Orthogenesis on the one hand and, on the other, to his controversial idea of "race" which has weighed so heavily on the historical image of the Apulian physician. In Rome, in 1912, his ideas on the subject were already fairly clear. Referring to Charles Richet (1850-1935) who two years earlier advocated a "physiology of the individual", Pende expressed his wish:

> We hope for the conquest of what must be the goal and aspiration of future physiology and pathology, which is to say, the substitution of a physiology and pathology of the individual for the physiology and pathology of the species (1).

Moreover, in 1912 he asked to further backdate the origin of the idea of the neuroendocrine: «On this concept of the neuro-glandular concatenation we have been insisting for several years ... we maintain that these two systems, endocrine and sympathetic, are to be considered as a unitary apparatus: the endocrine-sympathetic apparatus» (1).

In truth this idea had been adumbrated precisely in his first scientific work, his degree thesis.

Rome 1903

Nicola Pende, Nicolò as he signed his first works, graduated at the age of twenty-three in Rome at the Institute of General Pathology, headed by Amico Bignami (6, 7), with a thesis entitled: *Alternations of the suprarenal gland after resection of the splanchnic nerve*. Amico Bignami (1862 - 1929), together with Ettore Marchiafava and Giovanni Battista Grassi, established the Italian road to the etiopathogenesis and anatomopathological study of malaria. There are traces of this research tradition in Pende's earliest scientific productions (e.g.: *Il liquido cefalo-rachidiano in alcuni casi di perniciosa malarica* published in 1906 in the medical section of the journal "Il Policlinico"). In Rome Bignami from 1900 led, as adjunct professor, the Institute of General Pathology where, over and above malaria, he carried out research on the nervous system, the haematopoietic system and, what is of interest here, work on the internal secretion glands in their reciprocal relationships and with the vegetative nervous system. A brief extract from the Pende's thesis appeared, on 28th November 1903, in the Practical Section of the Journal "Il Policlinico" (8), in which Pende claimed credit as

first experimental pathologist of the suprarenal glands and their innervation: `study of the alterations that the suprarenal capsules undergo due to lesions of the nerves with which they are so abundantly provided, had not to my knowledge been attempted theretofore in any way by experimental pathology». Details of the experimentation in question would be supplied in the monograph of 1909 (9). Here, instead, the pathologist restricted himself to giving brief outlines of the experimental methodology in order to establish some fundamental concepts:

a) resection of the splanchnic nerve induces atrophy of the suprarenal medulla and this is the cause of the loss of production of Schaefer's "prodigious active principle". The conclusion was icastic, but somewhat hurried: «It is therefore appropriate to conclude in favour of the existence of regulatory nerves of trophism, independent of regulatory nerves of vasoconstriction, of the suprarenal capsules. But trophic nerves of glandular elements cannot but be secretory: therefore in the splanchnic and in the celiac plexus, together with the vasodilator nerves of the capsules demonstrated by von Biedl and with the vasoconstrictors demonstrated by my researches and by the recent plethysmographic research of Laiguel and Hallion, there are also the secretory nerves of the suprarenal capsules, nerves which heretofore had been merely presumed».

b) a hypothetical nervous aetiology of Addison's disease, caused therefore by resection of the splanchnic;

c) a feedback mechanism mediated by the same nerve for the compensation of pressure imbalances;

d) lastly, a hypothesis of specific secretion by the adrenal cortex "in connection with phenomena of reproductive life".

Rome 1552 - London 1855

Although published only in 1714, the *Tabulae Anatomicae* by Bartolomeo Eustachio (1520-1574) had remained unprinted in the Vatican Library since 1552. In these works the Roman anatomist illustrated the *glandulae renibus incumbentes* of which, in 1563 (10), he claimed to be the discoverer. Nonetheless, neither Eustachio nor a long procession of anatomists after him clearly put forward a function for the suprarenal glands.

This was the case with Casserio (1561-1616), Spigelio (1578-1625), Thomas Wharton (1612-1673) and Morgagni (1682-1771). Caspar (1585-1629) and Thomas Bartholin (1616-1680), father and son, were among the first to state that the *capsulae atrabiliariae* had a central cavity in which a mucus, precisely, of black bile, was secreted. Jean Riolan the Younger (1580-1657), basing his view on observation of the greater relative size of the glands during foetal life in comparison with adult life, hypothesised that their function was linked to embryonic growth, and this theory still had lasting echoes in Pende's day. Other Authors hypothesised functions linked to the position of the suprarenal capsules, and therefore with a regulatory secretion of the excretory function of the kidney (Joseph Lieutaud, 1703-1780), or as anastomotic deviator shunt of arterial blood incoming to the kidneys (Giuseppe Ippolito Pozzi 1697-1952).

Confirming this unsolvable knot, as early as 1716, the Academy of Sciences of Bordeaux established a competition aimed at clarifying the function of the suprarenal glands. Two years later, Charles de Montesquieu (1689-1755) pronounced thereon in *Discours sur l'usages des glandes rénales suivi de quatre résomptions.* Therein, the future author of *L'ésprit des lois* ran rapidly through both the historical hypotheses – such as that of the Bartholins, father and son – and those, some more original than others, put forward on the occasion of the prize.

> Most of the [competition] participants had only the merit of heartfelt, noble emulation, while others, more fecund, were no more fortunate: but these vain efforts are rather to be seen as proof of the obscurity of the subject and not of the sterility of those who dealt with it.

Thus there was a proposal that the suprarenal capsules secreted a substance which, on reaching the kidneys, induced the formation of a kind of its own bile; others hypothesised the function of filtration of the pararenal fats, or of further filtration of blood issuing from the kidneys. Yet others hypothesised a contractile function like the cardiac function for expulsion of

a dense liquid; in any case, Montesquieu's conclusion was disarming:

> From all this we see that the academy will not have the satisfaction of awarding the prize this year and that this day is not as solemn as it was hoped to be… in spite of the experiments and the dissections which have been put before your eyes, we have become aware of the difficulty in all its breadth and have learnt not to wonder about the purpose not having been achieved. Perhaps one day chance will do that which all these researches have been unable to (11).

The good fortune invoked by Montesquieu would have to wait more than a hundred years, three hundred from Eustachio's discovery, before the suprarenal glands began to reveal their secret. And nearly all the histories of endocrinology that do not wish to go back to the Venus of Willendorf (one of the many Palaeolithic Venuses with exaggerated female attributes, almost certainly apotropaic of fertility, acrobatically interpreted as steatopygia by medical historians who are interpreters of a scientific historiography of days of yore) date the first clinical accounts of dysendocrinism to 1855 and the work of Thomas Addison (12). Addison (1795-1860), while studying "idiopathic" anaemia in 1849 – what would later take the name of Addison-Biermer's disease or pernicious anaemia – had proposed therein an etiopathogenic role played by the suprarenal glands, having found in several cases the lesion of these organs as the only anatomopathological evidence.

> It was whilst seeking in vain to throw some additional light upon this form of anæmia, that I stumbled upon the curious facts, which it is my more immediate object now to make known to the Profession; and however unimportant or unsatisfactory they may at first sight appear, I cannot but indulge the hope, that by attracting the attention and enlisting the cooperation of the Profession at large, they may lead to the subject being properly examined and sifted, and the enquiry so extended, as to suggest, at least, some interesting physiological speculations, if not still more important practical indications. The leading and characteristic features of the morbid state to which I would direct attention, are, anæmia, general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach, and a peculiar change of colour in the skin, occurring in connexion with a diseased condition of the "supra-renal capsules. (13).

In fact the eleven cases of Addison, which presented the symptoms that later became the classic ones of the disease, all evidenced grave damage to the suprarenal capsules, due in six patients to tuberculosis, and in the rest prevalently to primary or secondary carcinomas. Six years later he published his monograph on the disease to which Armand Trousseau gave the name, precisely, Addison's disease (14). Six of Addison's eleven patients evinced tubercular lesions of the suprarenal glands. In the same year, while at the *Collège de France* Claude Bernard explained what he meant by internal secretions, C. E. Brown-Séquard began his experimental researches which were to lead him to putting forward a theory that took a long time to die, since Pende was still combating it in his monograph of 1909: the theory of the detoxifying role of the suprarenal glands themselves. Brown-Séquard experimented by removing the suprarenal capsules, thus causing the death of his animals – cats, mice, dogs, guinea-pigs – in an Addisonian crisis: in the space of 24 hours, after rapid death throes, the animals succumbed. So the capsules, connected in Brown-Séquard's view to the spinal centres, were indispensable to life, probably because they removed from the body a not better defined toxic substance whose remaining in circulation also explained the darkening of the patients' skin, a "melasma", presage of death (15). Still in 1856, Vulpian pointed out a "special matter" in the medulla of the suprarenal and in the veins of the organ, coloured by iron perchloride, a matter he considered responsible for the function of the glands (16).

Schaefer's "prodigious principle"

Not all scholars accepted Addison's disease as a definite nosological entity. For example, in Italy in

1863, R. Mattei in the *Sperimentale* denied its identification, perhaps due to a theoretical conservatism as supposed by R. S. Lavenson in an overview of acute suprarenal insufficiency of 1908 (17). The suprarenal glands eluded the understanding of physiologists and clinicians in the difficulty of pinpointing separate functions for the medullar and cortical: while Addison had pointed out a condition which only in the 1920s must have been correctly ascribed to the collapse of the production of substances produced in the cortical, the substance identified as agent physiologically produced by the suprarenal was the one identified by Oliver and Schaefer in 1894: a prodigious principle capable of causing sudden and considerable rises in pressure, both in the clinic and in experiments on animals. Schaefer had correctly identified the origin of his prodigious principle – which Abel and Crawford would shortly isolate, giving it the name of epinephrine (18, 19) – in the medulla of the suprarenal gland:

> Injection of a large dose of extract of the cortical substance has little or no effect, whereas extract of even a minute dose of decoction of the medullary substance produces the ordinary physiological results to a *prodigious* degree. We conclude therefore that the active principle of the extract is contained entirely in the medulla, the very small effects which we have sometimes got from extracts of cortex being probably to be explained by post-mortem diffusion of the medullary juice, or other accidental contamination (20).

But as for Addison's disease, the British physiologist noted only that extracts of diseased suprarenal gland had no physiological effect at all. The suprarenal remained ambiguous between hypertension and melasma. Even twenty years later, in his treatise on the endocrine organs, Schaefer initiated his chapter on the physiology of the suprarenal cortex as follows: «Little is known about the function of the cortex». Taking as given his clear distinction from the medullar on bases both histological and embryological, the only biochemical singularity was its considerable lipidic content and the only physiological annotation was related to a probable association with the sexual glands. However, «there is no evidence that any kind of active autacoid substance is produced by the cortical cells» (21). Whereas the medulla contained Vulpian's chromaffin bodies and the excitation of the splanchnic nerve induced the secretion of epinephrine by the medulla. Here – it was 1916 – Schaefer cited our man: «Pende found that section of the splanchnic nerves leads eventually to atrophy of the medulla» (21). The relationship between this fact and death by bilateral adrenalectomy remained an enigma: in witness of just how ambiguous the function of the suprarenal was, Schaefer hypothesised that adrenalin and melanin were substances in competition for a substratum, so the suppression of the production of adrenalin by medullary deficit induced hypersecretion of melanin.

Nicola Pende's Contribution

Schaefer's citation of Pende referred to the latter's degree thesis. Had Pende made no further contribution to the question? In fact in 1909 he had published a monograph on the suprarenal apparatus (9), a voluminous treatise that summed up the question from the viewpoint of international literature explored in a detailed manner and – even more importantly – laid forth the Apulian clinician's experimentations and the conclusions he hypothesised with regard to the physiological and clinical aspects of those glands.

On the subject of Addison's disease:

> Today the pathogenetic question of the disease is found more or less in the terms in which Addison himself, the creator of suprarenal pathology, put it in 1855… we do not yet know the clinical determinism of melanoderma…

And, on the subject of himself:

> I carried out a series of researches with the purpose of isolating, as much as is possible with experimental methods, the function of each of the two portions of the suprarenal gland, that is, the cortical and medullar… with a third series of researches aimed at studying the morphological physiological relationships between suprarenal apparatus and the other internal secretion

> glands… following the avenue disclosed and already so felicitously trodden in Italy by De Giovanni and his school (22).

Adrenalin – produced by the medullary portion of the gland – had already been isolated and described, and Pende hypothesised that the product of the cortical was a lecithin, which certainly had no relationship with blood pressure:

> I wanted to carry out research on the action of cortical extract on blood pressure in man, injecting in several subjects, subcutaneously, the watery glyceric extract of cortical substance from horses or oxen, isolated with maximum care from the medullary portion… pressure remained always unmodified (22).

Whereas the cortical extract «rapidly produced the return of forces and, what was even more impressive, the reappearance of menstruations» (22), so Pende hypothesised an important role played by cortical substance in "organic metabolism".

The clinician thus became physiologist and experimented intensely on animals (usually cats and dogs): having devised a technique to prevent the laboratory animal from dying immediately after removal of the suprarenals, he made a sort of surgical Addison (hypocorticosurrenalism) and, therefore, was able to verify how organotherapy with suprarenal cortical extract could attenuate asthenia, weight loss and cachexia and delay death. Moreover – let us not forget that the word "endocrinology" was coined in 1909 by Pende – great attention was paid to the relationships between the suprarenal ad other internal secretion glands, since this was the thread running through his entire research: the living organism is governed by a *consensus partium*, a harmony, which is embodied in the correlations between the endocrine glands, between this system and the autonomous nervous system and, again, of the latter with the neuraxis, finally reaching integration with the psyche. In Pende's intent, present right from these first writings and, with the years, increasingly consolidated, the constitutions of Viola and De Giovanni would be transformed into the harmonious somatopsychic unity of the tetrahedron. There are different pendian declensions of this platonic pyramid. The biotypological pyramid that distinguishes the aspects under which the living individual presents himself to the physician's examination: the morphological aspect, the humeral-functional aspect, the characterological-moral aspect and the intellective aspect. Another, more oriented towards constitutional harmonies is as follows: Hippocratic harmony, that is, the relationship between instinctual vegetative structures, substantiated by the vegetative nervous system and the endocrine glandular system and the affective and rational dimensions, having their fulcrum in the encephalic structures and in particular the diencephalon and hypothalamus; Thomistic harmony, the reciprocal give and take between biological I and spiritual I which found its fundamental material in the structures of Hippocratic harmony and thence was raised to the synthesis of psyche and body, constituting the indivisible unity of the human person. Christian personalism and medical personology; interpersonal harmony, that is, the agreement of solidarity resulting from altruism, foundation of human fellowship; and lastly, the harmony of Christian splendour that is the vertical dimension of this "regulated sympathy among bodies", the true philosophical leitmotif of Pende's work. But the tetrahedron recurs often in his copious literary production, in other forms which it would be tedious to recall here.

Against those who maintained the uniqueness of the active suprarenal principle, identified as adrenalin, and who therefore ascribed the deficiency thereof as being the cause of Addison's disease, Pende efficiently set forth a series of bibliographical and experimental evidence that centred above all on the difficulty of isolating *in vivo* the two portions of the suprarenal gland:

> Since 1895, Cybulski and Szymonowicz had maintained that the whole Addison syndrome, like the syndrome of experimental suprarenal insufficiency, might be simply explained with the abolition of the function of the medulla-suprarenal gland, a function which in those authors' view could be summarised in maintaining normal the functional tone of the vasomotor, cardiac and respiratory nerve centres and of the centres of muscle tone (23).

But, Pende points out, on the minuscule glands of a cat it is not possible to carry out an emptying of the medulla without also destroying the cortical and then:

> if the emptying is fatal, as is removal of the two capsules, this would appear to depend rather upon suppression of the cortical than the medullar, still largely represented by the paraganglia (22).

Pende had almost resolved the ambiguity of the suprarenal; it is a pity that a few lines on he added:

> We believe that the medullar substance and the cortical of the capsules constitute, at least in the higher animals, an anatomical and functional unity of which [*sic*] cannot be split by either the physiologist's knife or pathological processes (22).

and claimed that the experiences of Biedl (24) who had supposed that ablation of the cortical alone was responsible for the laboratory animals' death had need of being subjected to further controls.

However, a further experiment by Pende demonstrated that it is precisely the cortical which keeps the animal alive:

> I now made the following experiment: in kittens, I first removed the right capsule; after about a month I severed all the nerves of the other capsule. After this second operation, the results of my recent experiments being recorded, I supposed that atrophy of the medullar portion should occur more or less belatedly. On a third occasion, about three months after the second operation, I wholly removed the left capsule; I then expected to see the symptoms of cortical insufficiency added to those of medullar insufficiency (22).

And in effect things went as predicted: only after the third period did cachexia, deep asthenia and death occur. Loss of the medullar function was compatible with life, while that of the cortical function was not. We shall not go into detail about the clinician's further experiments; in 1909 Pende would have solved the problem but for his insistence on considering the two parts of the suprarenal gland connected "in the sense that the medullar cells cannot perhaps carry out a function efficient for the organism's life if not in the presence of a certain quantity of actively functioning cortical cells" (22). Why, when he had come so close to identification of the active principle of the cortical, did Pende insist on keeping together the role of the medullar in the genesis of suprarenal insufficiency both chronic and acute? We do not know and may only hypothesise that the vast literature on adrenalin, on "Schaefer's prodigious principle", prevented the young clinician from assigning a wholly new and independent role to his "lecithin" of the cortical. Moreover, his success in demonstrating the role of the autonomous nervous system in the production of adrenalin must have contributed to keeping the role of the medulla at a higher level. For all his life as a scholar Pende would assign a special place among his contributions to medical science precisely to the resection of the splanchnic nerve and the consequent lowering of blood pressure; and, for a long time, "Pende's operation" would remain on the rolls of surgical procedures as an anti-hypertension intervention (26, 27). But probably the idea that prevented him more than any other from seeing what was practically there before his eyes – i.e. the autonomous role of the cortical – was exactly that preconceived idea, that pre-inductive thought which according to William Whewell is indispensable for "holding together" empirical facts but which Claude-Bernard exhorted scientists to be ready to abandon when they went against the facts. Which is to say the idea that in the living organism *tout se tiens* and, therefore, not only the psyche with the central nervous system and this in turn with the vegetative and the latter with the endocrine glands, but also "within" the gland itself, medullar, cortical and glandular nerves constitute a coordinated, anatomical-functional unity. This is what happens when an idea in itself original becomes an obstacle to grasping the facts. To keep together cortex, medulla and suprarenal nervous system, Pende hypothesised a wholly new metabolic cycle: the cortical synthesised the lecithin, setting out from the toxic products of replacement of the nervous cell, with lecithin in turn utilised in the anabolic process of the nervous system. So an alteration of the cortico-suprarenal glandular function was

simultaneously translated into both an insufficiency of the "primary neuro-dynamogenic material", with consequent asthenia, aboulia, apathy, and into a poisoning of the nervous system itself (Pende thus recovered by another way the hypotheses of Brown-Séquard) due to insufficient removal of toxic catabolites (22).

Thus both the cortical and medullar had a role in the metabolism of the nervous system. The concept was resumed and developed in the fourth chapter of the text, dedicated to the *Physiopathology of the suprarenal syndromes*. Here, after dealing with the two rival pathogenetic doctrines (the "sympathetic", that is, that lesion of the sympathetic was the cause of Addison's disease, and the "glandular", which held that it was caused by a medullar or cortical excretive defect), Pende put forward "his" hypothesis (22) which considered the suprarenal gland as indeed composed of three districts, cortical, medullar and nervous, but integrated, "indissoluble links of the same chain". So at the heart of the pathology there was a "lecithinogenous" defect of the cortical and an "adrenalinogenous" defect of the medullar, both under the influence of the vasomotor and vaso-secretory nerve centres (25). Coherently, melanoderma was ascribable to an injured sympathetic innervation and therefore to an injured medullar secretory function operating on the complex functional mechanism that regulates, through the chromatophore cells, the normal pigmentary tone of the skin (22). Here too Pende was deceived by the ambiguous suprarenal: skin pigmentation was indeed due to hyperfunction of the cells that produce melanin… but this had been related to the absence of a hypothetical inhibitory mechanism mediated by the sympathetic and by adrenalin.

Having "created" a syndrome, it would often be found by Pende in clinical contexts. This was the case - for example – of the "Pende's hyperthymic syndrome".

In the first half of the twentieth century, more than a million young Italians were found affected by a new disease: Pende's hyperthymic syndrome. According to the Apulian clinician, it was a case of hyperfunction of the thymus gland that caused a pathology analogous to Froehlich's adiposogenital syndrome: «For many years I have found that in the sphere of infantile growth, many youngsters – who are fat and tall from birth and have very small genitalia – in spite of being teenagers, look like big babies in their appearance, faces and temperament. These children are greedy, heavy water drinkers, lazy, and characterised by a persistent mental infantilism. Their serious anomaly of growth is due to a hyperfunction of the thymus gland». Thus wrote Pende in an unpublished manuscript (30). This undated manuscript can be probably dated to the last ten years of the clinician's life, owing to a reference to his return from Barcelona, where supreme honours had been rendered him in about 1965. In it, Pende wrote questions and answers, defining himself "the master of endocrinology and orthogenetic world medicine". Unfortunately. this Pendian contribution has also passed into the field of obsolete history, with the aggravating factor that the therapy envisaged by Pende – radiation of the thymus with X-rays – caused adenoma and carcinoma of the thyroid in a great number of these poor children. (28, 29).

The same determination Pende showed for the triadic etiopathogenesis of Addison's disease: in a clinical case sent to the journal *La riforma medica*, the clinician, at the autopsy, found all the signs of the aforementioned syndrome. The tubercular patient had died after showing the signs of Addison's disease; however, both the medullar and cortical of the suprarenals appeared little altered histologically, although "the two main suprarenal glands present, with regard to the cortex, a considerable deficiency in lipoid granulations" (31). The main lesion instead regarded the solar plexus, with a "hypertrophic sclerosis of the semilunar ganglia". In fact:

> Pende has already developed elsewhere the concept which considers Addison's syndrome as a disease of the entire suprarenal apparatus (cortical tissue, medullar tissue and sympathetic tissue); without such a unifying concept it is not possible to explain either the genesis of various symptoms of the disease or the anatomopathological finds so different from case to case (31).

So going back to the 1912 paper at the Congress of Rome, one clearly understands which clinical and physiopathological experiences fortified Pende in the concept that

> it is demonstrated for certain glands, such as the thyroid and the suprarenals, that the nervous system regulates the secretion thereof, by means of secretory and vasomotor nerves. This results from my own experiments, and those of Pellegrino and of Biedl… on the suprarenal glands (1).

Pende's endocrinology

Two years after the Rome paper, Pende began publication of the first edition of his monumental treatise *Endocrinologia. Patologia e Clinica degli organi a secrezione interna.* Although his then chief, Giacinto Viola, warned in the preface of the immaturity of some of the author's views (25), he in any case had to acknowledge that Pende's undertaking to write this treatise was extremely difficult, as demonstrated by the fact that his predecessors north of the Alps had discussed only particular aspects thereof (von Biedl only physiopathology; Wilhelm Falta only clinical aspects) (32). On the other hand, the importance of the treatise was borne out by the authoritative American journal *Endocrinology* (25) which, the year after publication, recognised that

> This is the largest and most comprehensive book on endocrinology that has come to our attention, transcending in size the well recognized monograph of Biedl (while the two volumes of the second German edition of the latter cover 1226 pages, nearly 300 pages are devoted to a bibliography). In going through Professor Pende's book it is very clear that he has given special study both in the laboratory and in current literature of all countries, and we regret very much that this book has not yet been translated from Italian.

A new medical specialisation was on the point of being established: Pende's treatise was not yet dogmatic – as Augusto Comte would have said – and he therefore had to:

1. resort to historical method, because it was a young science (33),
2. bring together everything that had been said and written in those years, compiling a huge bibliographical review,
3. unite a mass of experimental facts – his own and others' – in the attempt, effectively successful, at supplying an account as wide-ranging and profound as possible, of the knowledge of a subject which he himself had contributed to naming, precisely in his 1909 treatise.

For this reason a caveat in the introduction put the reader on his guard about the fact that the concepts set forth were to be understood as working hypotheses and not as endocrinological canons. In fact when many years later Pende was called upon to draw up the item "Endocrinology" for the Encyclopaedia Treccani, he would recover much of his introduction, continuing to distinguish the functions of the endocrine organs as "morphoregulating", "chemioregulating" and "neuroregulating", to which he added a "psychoregulating" function. The basic concept is that the endocrine system, together with the nervous system, is the structure of fundamental integration of the living organism. This integration envisages that psyche, central nervous system (for the life of relationships), the autonomous nervous system (for vegetative life) and endocrinal system should work in close coordination for the constitution of harmonious individual unity. In particular, just as the autonomous nervous system implements balance between accelerating functions (the sympathetic) and retarding systems (the parasympathetic), so does the endocrinal system, in its various glandular sectors, provide for the production of excitant-catabolic and excitant-anabolic hormones. We shall not go any deeper into the construction of the new science that Pende, at thirty-six, is entrusting to these pages, except to point out that it harks back to a noble genealogy in the constitutionalism of Viola and Achille De Giovanni, where it declares that:

> Our school therefore distinguishes two main and antithetical morphological types that represent the two forms of opposed deviation from the average morphological type: the long-limbed or micro-splanchnic type in which excessive development of the extremities dominates over the relatively deficient development of the trunk (microsplanchnia); and the short-limbed or megalosplanchnic type in which excessive development of the trunk (megalosplanchnia) dominates over the

> relatively deficient development of the limbs. The two types correspond to the third and first morphological combination, already distinguished by De Giovanni.

And it was from here that the ephemeral science of Biotypology and Orthogenesis would extend, which was to constitute the acme of Pende's production in the years to come.

As for the ambiguous suprarenal, the *Endocrinologia* devotes more than one hundred and thirty pages to it in which the author recovers all the scientific literature on the subject and, above all, claims the importance of his experiments (of 1909) on the question of innervation of the medulla and on the absence of capsules induced in animals.

In comparison with the 1909 text, Pende is now convinced that cortical and medullar produce different substances, the latter adrenalin, whereas the cortical perhaps produces not only lecithin but cholesteryl esters, in a word «cortical lipoids that actually represent products of secretion…. We can have no doubt about it, especially for reasons of analogy with what is also demonstrated today for the secretions, also of a lipidic nature, of other endocrine glands (genital gland etc.)» (25). The fact is – Pende is well aware of this although he himself is a victim thereof – that the physical action of these compounds is "obscured" by the comparison with adrenalin, for which an antagonistic action is hypothesised (hypotensive?) or, as suggested by Pende, an action aiding the adrenalin. Certainly the cortical secretion is seen to be in relationship with the processes of replacement and with the genital organs (25): «the clinical cases of hyperplasia or of cortical adenomas, coincident with early puberty and with phenomena of pseudohermaphroditism… the parallelism between hyperfunction of the genital endocrine gland and hyperplasia of the cortex render it more than probable that there exists a physical collaboration between it and the sexual glands» (25).

Pende's experiments were, coherently with the dictates of the "foetid Bernard kitchen" (34), experiments of destruction, capsular emptying, removal of part of the gland, then a whole gland, then both, rescission of the related nerves, experiments of grafting and implantation *à la* Voronoff (the Russian physician who, became very famous in the 1930s for his transplants of monkey glands in humans with view to achieving rejuvenation and the recovery of sexual potency) (35), organotherapy with homo- and allospecific glandular extracts. And if all the numerous authors who had dealt with the subject to date (1909) had not succeeded in obtaining engraftment of the complete capsule (but only the medulla), «I believe I have drawn attention to the fact that with appropriate technique, both medullar and cortical tissue may be equally engrafted» (25). Indubitably one of the merits of these works is, precisely, the personal and original synthesis between clinical practice and physiology, between sickbed and laboratory, to which may be added Pende's total mastery of the vast coeval literature on the subject.

As for the ambiguous suprarenal, for Pende it would remain as such, blocked as he was by his demand for functional unity of the gland. Experimental progress notwithstanding, even in 1925, Pende reaffirmed the impossibility of clearly separating the cortical from the medullar functions

> Can we now distinguish clinically the symptoms of hyposuprarenalism in hypocortical and in hypomedullar symptoms? A clear separation, for the reasons already mentioned of the mutual anatomical and functional relationships between the two tissues of the gland, is not possible (36).

Between 1927 and 1937, lastly, the role of the cortical of the suprarenal gland would be clarified, and acetate hydrocortisone would be synthesised (37).

In an article of 1945 (38) Pende would once more claim to be the founder of endocrinology:

> Endocrinology is a term I introduced in 1909 – and its synonyms are hormonology, incretology and science of the internal secretions of the endocrinal glands… in 1916 the first two great treatises on endocrinology come out, my own and that of the Englishman Schaefer. But as early as 1909 my monograph on the suprarenal apparatus and the parasympathetic organs was published, and in 1912 at the Congresso della Società Italiana di medicina interna in Rome, I summarised, in an

official paper, the basics of clinical endocrinology, which after forty years have remained more or less unchanged (38).

The court of the history of science

Was Pende's ambiguous suprarenal the lucky beginning of a discipline and, at the same time, a headstrong ideological error?

> One must avoid a possible equivocation when proposing the image of the court to characterise the function and meaning of a history of science which does not forbid itself scientific judgements of value. Judgement in this field is neither a punishment nor an execution. The history of the sciences is not the progress of sciences in reverse, that is, a prospect of the milestones of goals achieved, of which the truth of today would constitute the vanishing point. The history of the sciences is an effort to render understandable the extent to which certain notions or attitudes or methods, now outdated, were in their own day an advance, and consequently in what way does the outdated past remain the past of an activity for which we must preserve the name of science (39).

The idea of regulated 'sympathy' among organs dated back at least to Galen who, in the *De usu partium* had described part of anatomy from the organic nervous system: and he attributed to the wealth of anastomosis of this system, and therefore to the wide network of communications it established for circulation of the vital and animal spirits, the function of connecting mutually distant parts of the body, in such a way as to justify 'the suffering together' – for example – of the urinary tracts and stomach in renal colic. Meaning the *consensus partium*, the 'sympathy' between organs. Even earlier, Plato had underscored that there were several principles bearing government of the body, in particular the irascible and the concupiscible principles, the less noble, had been relegated – one to the chest, the other to the belly – to control the visceral and organic functions (40). In the early 19th century François Xavier Bichat, in the *Recherches* and even more so in the *Anatomie générale*, having defined life as a grouping of the functions that resist death, he divided these functions into two great systems:

– *la vie animale* or of relationships, including the functions necessary to maintain the living being in relationship with the external world, therefore the conscious and voluntary sense-motory context in a broad sense;

– *la via organique*, understood as the life of the organs, or vegetative life, including the functions of nutrition and reproduction. Obviously this was not of his own invention, being traceable to origins in the writings of Galen and Plato, but Bichat made a system of it and corroborated it, thanks to the great extent of his anatomical-autoptical observations. Furthermore, he assigned a "seat" to the Galenic spirits: animal spirits were localised in the cerebrospinal system while the vital spirits, vegetative life, the life of the organs, found its seat in the ganglionic system. Moreover, Bichat claimed the (moderate) independence of the two lives and the two systems. In the sense that the system of organic life (ganglionic) was wholly independent (autonomous) with regard to the system of the life of relation (cerebrospinal) (41). Subsequently Brown-Séquard was the first to suggest a close relationship between the autonomous nervous system and the humours secreted by the glands that poured their products into the circulatory torrent (42). The young Pende had tied himself to this idea and the experiments of his degree thesis, resumed between 1903 and 1909, had increasingly convinced him of the functional holism between these systems. This idea, certificated by the endocrinal effects of nerve resections, outlined a vast and original research project which saw, in the nascent science of hormones, the field in which to play for more than fifty years, in Italy and abroad, the role of initiator and founder of a school. As we have said, a fertile idea, but one which, like all a priori systematic ideas that adjust empirical observations and experimental facts to their Procrustean bed, in the case of the suprarenal it locked the Italian physician on the ambiguity of a cortical forcedly tied to the medullar and to the sympathetic nerve ganglia. Pende's experimentation therefore surpassed and was itself surpassed: the science of Nicola Pende opened the great chapter of Italian endocrinology and ended up miserably in an obstinate eugenic

project for which he paid with scientific, political and moral ostracism. Endocrinology today is a scientific discipline whose history is ratified, while biotypology and orthogenesis have wound up in the cellar of obsolete histories (43), of interest in our times only to enthusiasts of “alternative”, “holistic”, “homeopathic” medicines and the like, who effectively acknowledge Pende – alas – among the noble founding fathers.

References

1. Pende N. Le secrezioni interne nei rapporti con la clinica. XXII Congresso di Medicina Interna. Roma: Colombo - Tipografia della Camera dei Deputati;1912.
2. Schaefer E. Address in Physiology: On Internal Secretions. Lancet 1895; 2:321-4.
3. Borell M. Setting The Standards For A New Science: Edward Schäfer and Endocrinology. Med Hist 1978; 22:282-90.
4. Biedl A. Innere Sekretion: Ihre physiologischen Grundlagen und ihre Bedeutung für die Pathologie. Berlin: Urban& Schwarzenberg; 1910.
5. Medvei C. The History of Clinical Endocrinology. A Comprehensive Account of Endocrinology from Earliest Times to the Present Day. New York: The Parthenon Publishing Group; 1993.
6. Bignami A. Pende N. Il liquido cefalo-rachidiano in alcuni casi di perniciosa malarica. Roma: Il Policlinico; 1906; 13:189-99.
7. Fichera G. Sulla ipertrofia della ghiandola pituitaria consecutiva alla castrazione. Bull R Acc med Roma 1905; 31:91-133.
8. Pende N. Le alterazioni surrenali in seguito alla resezione del plesso celiaco e del simpatico. Contributo alla fisiologia delle capsule surrenali. Il Policinico 1903; 57:1793-6.
9. Pende N. Patologia dell’apparecchio surrenale e degli organi parasimpatici. Roma: Società Editrice Libraria; 1909.
10. Eustachius B. De glandulis quae renibus incumbent. In: Opuscula Anatomica. Venetia; 1536: 39-40.
11. Montesquieu C. Discours sur l’usage des glandes rénales 1718. In: Laboulaye É, editor. Œuvres complètes de Montesquieu. Paris: Garnier; 1879:16-24.
12. Addison T. On the constitutional and local effects of disease of the suprarenal capsule. London: Samuel Highley; 1855.
13. Addison T. On Anaemia: disease of the suprarenal capsules. London Medical Gazette 1849; 43:517-8.
14. Trousseau A. Capsules surrénales (Maladie bronzée d’Addison). Archives Générales de Médecine 1856; 8:478-81.
15. Brown-Séquard CE. Recherches expérimentales sur la physiologie et la pathologie des capsules surrénales. Compt-es rendus hebdomadaires des séances de l’Académie des sciences 1856; 43(8; 10):422-5; 542-6.
16. Vulpian FA. Note sur quelques réactions propres à la substance des capsules surrénales. Comptes rendus hebdomadaires des séances de l’Académie des sciences 1856; 46:663-5.
17. Lavenson RS. Acute insufficiency of the suprarenals. Arch Intern Med 1908; 2(1):62-73.
18. Abel J, Crawford A. On the blood-pressure raising constituent of the suprarenal capsule. Bull Johns Hopkins Hosp 1897; 8:151-7.
19. Takamine J. Adrenalin the active principle of the suprarenal glands and its mode of preparation. Am J Pharm 1901; 73:523-31.
20. Oliver G, Schaefer E. The physiological effects of extracts of the suprarenal capsules. J Physiol 1895; 18(3):230-76.
21. Schaefer E. The endocrine organs. An introduction to the study of internal secretion. London: Longmans, Green and Co; 1916.
22. Pende N. Patologia dell’apparecchio surrenale e degli organi parasimpatici. Roma: Società Editrice Libraria; 1909.
23. Cybulski N. O Funkcyi nadnercza. Gazeta Lekarska 1895; 12:299-308.
24. Biedle A. Innere Sekretion: Ihre physiologischen Grundlagen und ihre Bedeutung für die Pathologie. Berlin: Urban& Schwarzenberg; 1910.
25. Pende N. Endocrinologia: patologia e clinica degli organi a secrezione interna. Milano: Vallardi, 1916. Reviewed in: Endocrinology 1917; 1(4):466-7.
26. Donati M. L’indirizzo biologico in chirurgia. Minerva Med 1928; 11(8):1-23.
27. De Bonis G. The cure of essential hypertension by Pende’s operation. Gazzetta Sanitatia 954.
28. Pende N. La mia sindrome di ipertimismo costituzionale dei fanciulli e degli adoloscenti, Radiologia 1945; 2:359-71.
29. Dibattista L. Nicola Pende (1880-1970) and his “Big Lazy Children”. Parable Of A Clinical Syndrome. Med Secoli 2014; 26(1):269-91.
30. Pende N. Nuove conquiste della medicina italiana nel campo della crescenza infantile. Intervista col cattedratico di patologia clinica di Roma, il Senat. prof. Nicola Pende. MS, Bib. Noj. FP, 72-1-2. Noicattaro: Archivio Biblioteca Comunale; 1965.
31. Pende N. Morbo di Addison con integrità istologica apparente delle glandule surrenali e con ipertrofia di glandule surrenali accessorie. La riforma medica 1913;40:1-25.
32. Falta W. Die Erkrankungen der Blutdrüsen. Berlin: Springer; 1913.
33. Comte A. Cours de philosophie positive. Paris: Librairie Larousse; 1936.
34. Bernard C. Introduction à l’étude de la médecine expérimental. Paris: Collège de France; 1859.
35. Hamilton D. The Monkey Gland Affair. London: Chatto & Windus; 1986.
36. Pende, N. Le sindromi surrenali. XXX Congresso della Società Italiana di Medicina Interna. Roma: Luigi Pozzi; 1925.
37. Steiger M, Reichstein T. Desoxycorticosterone (21-oxyprogesterone) aus 5-3-oxydatio-Kohelen-saeure. Helv Chim Acta 1937; 20:1164-79.

38. Pende N. Origini ed evoluzione dell'endocrinologia. In: Endocrinologia e Scienza della Costituzione – Archivio fondato da G. Viola e Nicola Pende 1945; 20(3):166-82.
39. Canguilhem G. L'oggetto della storia delle scienze. La Ragione Cieca. Milano: Jaca Book; 1982.
40. Plato. Timeo: Opere Complete VI, It. translation by G. Giannantoni. Roma-Bari: Laterza; 1979:428-30.
41. Dibattista L. Il movimento immobile. La fisiologia di E.J Marey e C.E. François-Franck (1868-1921). Firenze: Olschki; 2010:203-27.
42. Calabrese, F. From Organized Bodies to Integrative Actions: Brown-Séquard Humoral Theory. History of Science. Bari: University Aldo Moro; 2009.
43. Bachelard G. Activité rationaliste de la physique contemporaine. Paris: P.U.F; 1951.

Correspondence:
Liborio Dibattista
Department of Humanities Studies
University of Bari "Aldo Moro"
Bari, Italy
E-mail: liborio.dibattista@uniba.it