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Hippocrates and rheumatology

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The cover of Clinical and Experimental Rheumatology this year has been dedicated to Hippocrates, the "Father of Western Medicine". Therefore, in our last issue for this year we felt it would be appropriate to discuss Hippocrates' contributions to the history of rheumatology.

Hippocrates, as is well known, embodied the transition from pre-history to the history of medicine and the dawn of what may be referred to as "rational" medicine (1). Still, although the practice of medicine was no longer reserved for priests, a lingering sentiment that physicians belonged to a privileged class remained. It is interesting to note that the Hippocrates oath included the vow to teach the art only "to one's sons and the sons of one's teacher", thus excluding all of those who did not belong to the profession "by right of birth". Furthermore, some of the Greek physician's teachings, such as his theory of the four bodily humours, reflected traditional dogmatic concepts rather than scientific fact.

All the same, there is no doubt that under the influence of the philosophers of the Ionic school with their interest in the natural sciences, Hippocrates developed an approach based on direct observation of the symptoms displayed by the patient rather than on pre-conceived notions; he was in a sense the founder of what we consider today as the medical sciences. The Hippocratic texts represent, in fact, the first written accounts in which it is possible to identify specific illnesses known to modern physicians without resorting to complicated or imaginative interpretations. In many cases they illustrate the depth of understanding that may be reached solely on the basis of scrupulous observation and reasoning. The rheumatic diseases, because of their clear symptomology, offer particularly fascinating examples of Hippocrates' powers of observation and deduction.

The rheumatic condition for which the pioneering nature of Hippocrates' scientific approach is best known is without a doubt **gout**. His three celebrated aphorisms (2) – that gout never develops in men before puberty or in women before menopause, and is never seen in eunuchs – are cited in every modern textbook that covers gout. It is remarkable that Hippocrates was able to deduce these facts solely on the basis of clinical observation when we consider that: (i) the existence of uric acid was unknown to him, having been discovered by Scheele in 1776 (3); (ii) the condition of hyperuricemia was not detectable before A.B. Garrod invented his famous "thread test" in 1848 (4); and (iii) the variations in uric acid levels as a function of age and sex, upon which the morbidity in gout depends, were conclusively demonstrated only during the well-known Tecumseh epidemiological study conducted in 1955-1960 (5).

Today we know that Hippocrates' first two aphorisms are true only in the case of primary gout; other forms (such as secondary gout or gout associated with an enzyme deficit) may be observed, albeit rarely, in children (6,7) or in women of child-bearing age (7,8). Today it not possible to confirm the veracity of the third aphorism, although in 1965 a physician in Hong Kong reported a probable case of gout in one of the last eunuchs of the Chinese imperial court (9). In 1534 Dominicus Burgauer wrote an extensive – but incorrect – exegesis on these aphorisms, affirming that the disease was exacerbated by melancholy and by excessive indulgence in love-making after meals, and for this reason it was absent in eunuchs and those who did not engage in sexual activity (10), whereas today we know that these epidemiological factors are actually linked to the influence of the gonadal hormones on uric acid metabolism.

Hippocrates' observations on the subject of gout are not limited to these three aphorisms. For example, he noted that the pain tended to become exacerbated in the spring and autumn months, and correctly affirmed with regard to its prognosis that elderly patients, patients with periarticular concretions (probably tophi, although not all historians of medicine agree that Hippocrates identified these correctly), and those who lead a sedentary life have little hope of recovering, whereas there is reason for optimism in the case of younger, physically active patients with-

out tophi who are fortunate enough to "meet an intelligent physician". Less comprehensible is his assertion that constipation is a negative prognostic factor.

In 1956 Feigenbaum (11) discovered in Hippocrates' *Third Book of Endemic Disease* the description of a condition which, without excessive strain on the imagination, could be identified as **Behçet's disease** (BD). The official identification of BD dates to 1937 when Hulusi Behçet (12), a Turkish dermatologist, described three patients who shared the classic symptoms of oral and genital ulcers and recurrent iritis. Unlike the Greek oculist Benediktos Adamantiades (13), who six years previously had reported an analogous case, Behçet realized that this constituted a syndrome which had never been described before.

As Feigenbaum observes, in just a few lines Hippocrates traces the principal characteristics of the disease: an ophthalmopathy that may develop into blindness, oral aphtosis, genital ulcers, papulo-pustulolis and carbuncles (ἄνθρακες in Greek), probably a reference to erythema nodosa. Only such a brilliant clinician could have defined the disease so precisely, and the sole criticism that Feigenbaum had to make was that Hippocrates included the disease in his book of endemic diseases whereas it is actually a rare and sporadic syndrome. It may be noted, however, that at the time Feigenbaum was writing no more than perhaps a hundred cases of BD had been reported in the literature and its peculiar geographic distribution had not yet been clearly understood. We now know that BD is quite common in Turkey and the Middle East, and Hippocrates lived on the Cyclades island of Kos just a few kilometers from the Turkish coast, an area where BD might well have already been endemic in his time.

A few years ago, in a lecture delivered at the VIII International Conference on Behçet's Disease (14), I reflected on the reasons why a disease so clearly described by Hippocrates should then have "disappeared", only to reappear more than 2000 years later in the same site – the cases described by Adamantiades and by Behçet were observed in two cities located a few hundred kilometers from Kos, overlooking the Aegean Sea. To identify a multi-systemic disease such as Behçet's (or SLE), two conditions are necessary: advanced medical knowledge and the possibility of observing a significant number of cases. Both of these conditions held true for Hippocrates, but within a few centuries Greek civilization had declined and the epicenter of medical culture shifted to western Europe and eventually to North America, where Behçet's disease is extremely rare. Only in recent times, with modern media and the globalization of scientific culture, has this medical knowledge progressively extended to countries where Behçet's disease is endemic (indeed Behçet pursued his medical studies in Germany).

Another rheumatic disease that was certainly observed and described by Hippocrates was **scleroderma**. In his treatise *On Epidemics*, Hippocrates writes that he treated a patient from Athens whose skin was so hard that "it was not possible to raise it in folds." The French physician Elie Gintrac (15) has been credited with coining the term scleroderma (which literally means "hard skin") in 1847, although it had already been used a decade earlier, in 1836, by Giambattista Fantonetti of Pavia (16). That a description of this disease can be found in the Hippocratic texts should come as no surprise, given the Greek physician's remarkable powers of observation and the unmistakable clinical picture of the disease. Even today the "pinch test" remains the principle semiotic examination used to detect cutaneous scleroderma.

If we analyze Hippocrates' description more closely, we could venture to make a more specific retrospective diagnosis. He states that the thickening of the skin was associated with severe pruritus of the testicles, and that the patient eventually died of hydropsy. Might we conjecture that this patient was suffering from Reynolds syndrome, a rare form of scleroderma associated with primary biliary cirrhosis that was first described in 1971 (17), in which pruritus constitutes an early manifestation and renal failure with ascites a possible outcome? This interpretation must remain purely speculative, but Hippocrates deserves full credit for his accurate description of scleroderma.

Although still the subject of debate (18), it appears quite probable (19) that Hippocrates also identified what today is referred to as **rheumatic fever**. He on this occasion used the word "arthritis", but it must be kept in mind that until relatively recent times there was a great confusion between the terms arthritis, gout and rheumatism. While we find "arthritis" and "podagra" ["gutta" being a late Latin synonym for podagra (20)] in Greek medical texts, "rheumatism" as a term for joint diseases dates to no earlier than the Middle Ages (21). In his book *On Diseases*, it is not difficult to recognize among the conditions described by Hippocrates that of rheumatic fever; we read in fact of an illness "that strikes above all young people, which is accompanied by fever and in which acute pain involves first one joint, then another," an unequivocal description of the classic pattern of "migrating pain".

Furthermore, in his book of *Aphorisms* Hippocrates cites arthritis among the complaints that are typical of the rainy season. We cannot but concur with his evaluation of the prognosis: the patient must avoid both extremely hot and extremely cold temperatures and should eat moderately to avoid relapses. If he follows this advice the pain should disappear within six months – a perfectly reasonable lapse of time in an age when salicylates and cortisone did not yet exist. He adds that only the patient's recovery will demonstrate the disease prognosis.

The references to rheumatic conditions in the works of Hippocrates do not stop here, even if the connection may be somewhat tenuous on occasion. Hippocrates, for example, does not specifically discuss **hip osteoarthritis**, but there is a clear reference to the condition in his book *On Joints*. Regarding hip dislocations, he notes that in some patients outward luxation of the femurs may be present from birth, but that in others it may be "due to the effects of disease", probably hip osteoarthritis. In

the latter case the muscular mass is better conserved and the deficit will be manifested prevalently on the internal (medial) side at the level of the abductors.

Hippocrates' account of **sciatica** contains instead a mixture of exact description (he delineates pain radiating from the base of the spine to the external malleolus and down to the joint of the first toe, as in the L5 syndrome) and pure speculation based on unproven (and, at the time, undemonstrable) assumptions, as when he suggests that the disease is a consequence of inflammation and the draining of bile into the veins.

Léca (22) surmised that Hippocrates was aware of the syndrome of **enteroarthritis**, based on a passage from his book *On Epidemics*: "... [a patient] with intestinal pains on the right side was afflicted by arthritis and his pain diminished, but after the arthritis passed, the pain returned." This passage is difficult to interpret, and it would certainly be going too far to suggest that Hippocrates had also deduced the fact that [as, for example, in Crohn's disease (23)], the arthritic symptoms are not always correlated with the flares of intestinal disease.

Scott (24) has proposed that the description to be found in a Hippocratic text of "less severe pains, that are distinguishable from podagra and that are not accompanied by swelling" might perhaps be interpreted as a reference to **fibromyalgia** – a tenuous thesis at best. Even less probable is the hypothesis of Hebra and Kaposi (25) that Hippocrates also described the condition known to us as **lupus erythematosus**, calling it "herpes esthiomenos".

Hippocrates' grasp of medicine was so far-reaching that it could be said that even the lacunae in his writings represent a contribution to the history of this science. Such a case may be made for diseases on the subject of which the Greek physician has left no written evidence. One of the still unresolved problems in the history of the rheumatic diseases concerns the antiquity of **rheumatoid arthritis**. The clinical signs of this disease – stiffness and joint deformity – are so evident, it seems unlikely that such an acute observer as Hippocrates would not have taken note of any patients who presented with these symptoms. This inference lends support to those who argue that the condition is one of relatively recent date (26), or one that up until recent times was confined to areas far from Europe (27).

Nevertheless, many of us have searched for references in the Hippocratic texts that might be linked to the clinical picture of rheumatoid arthritis. For example, Léca (22) cites a passage which describes: "an arthritis that is manifested generally around the age of 35 years" in which "there is often a brief interval between involvement of the hands and involvement of the feet" and "both become similarly bony and stiff", even though he admits that "a slight stretch of the imagination" is necessary to interpret this as a description of rheumatoid arthritis. However, it is difficult to believe that this isolated citation could have represented the first description in the Western medical literature of rheumatoid arthritis when no further unequivocal mention of the condition can be found for the next 2000 years.

References

1. AA.VV.: *Storia della medicina*. Rome, Antonio Delfino Editore, 1984.
2. HIPPOCRATES: *Oeuvres Completes d'Hippocrates* (translated into French by E. Littré), Paris, Baillière, 1839-61.
3. SCHEELE CW: Examen chemicum calculi urinarii. *Opuscula* 1776; 2: 73.
4. GARROD AB: Observations on certain pathological conditions of the blood and urine in gout, rheumatism and Bright's disease. *Trans Med Chir Soc* 1848; 31: 83-98.
5. MIKKELSEN WM, DODGE HJ, VALKENBURG H: The distribution of serum uric acid values in a population unselected as to gout or hyperuricemia. Tecumseh, Michigan, 1955-1960. *Am J Med* 1965; 39: 242-51.
6. DEITRICK JE: Association of congenital hemolytic icterus and gout. *Internet Clin* 1940; 3: 264-77.
7. SERRE H, SIMON L: La goutte sécondaire. In *Rapports au XXXIVe Congrès Français de Médecine*, Paris, Masson, 1963; 3: 113.
8. PASERO G, CIOMPI ML: Goutte tophacée chez une jeune femme. *Acta Reumatol Portog* 1974; 2: 125-8.
9. MCFADZEAN AJS: A eunuch takes gout. *Br Med J* 1965; i: 1038-9.
10. COPEMAN WSC, WINDER M: The first medical monography on the gout. 'On whether it is possible to cure the gout or not'. *Med Hist* 1969; 13: 288-93.
11. FEIGENBAUM A: Description of Behçet's syndrome in the Hippocratic Third Book of Endemic Disease. *Br J Ophthalmol* 1956; 40: 355-7.
12. BEHCET H: Über rezidivierende Aphtöse durch em Virus verursachte Geschwüre am Mund, am Auge and an den Genitalien. *Dermatol Wschr* 1937; 105: 1152-7.
13. ADAMANTIADES B: Un cas d'iritis à hypopion récidivant. *Ann Ocul* 1931; 168: 271-278.
14. PASERO G: The history of Behçet's disease. *In* BANG D, LEE ES and LEE S (Eds.): *Behçet's Disease.* Seoul, 2000; 565-8.
15. GINTRAC E: Note sur la sclérodermie. *Rev Med Chir (Paris)* 1847; 2: 263.
16. FANTONETTI GB: Della chorionite o sclerostenosi cutanea di Forget. *Giorn Progr Patol Terap*, Venice 1847; 602.
17. REYNOLDS TB, DENISON EK, FRANKL HD, LIEBERMANN FL, PETERS RL: Primary biliary cirrhosis with scleroderma, Raynauds' phenomenon and telangectasia. New syndrome. *Am J Med* 1971; 50: 302-12.
18. MASSELLBF: *Rheumatic Fever and Streptococcal Infection.* Boston, Harvard University Press, 1997.
19. QUINN RW: Did scarlet fever and rheumatic fever exist in Hippocrates' time? *Rev Infect Dis* 1991; 13: 1243-4.
20. DELPEUCH A: *Histoire des maladies. La goutte et le rhumatisme*. Paris, Carré et Naud, 1900.
21. PARISH LC: An historical approach to the nomenclature of rheumatoid arthritis. *Arthritis Rheum* 1963; 6: 139-58.
22. LÉCA AP: *Histoire Illustrée de la Rhumatologie.* Paris, Dacosta, 1987.
23. WRIGHT V, WATKINSON G: The arthritis of ulcerative colitis. *Br Med J* 1965; ii: 670-5.
24. SCOTT JT: Historical. *In* SCOTT JT (Ed.): *Copeman's Textbook of the Rheumatic Diseases*, 6th ed. Edinburgh, Churchill-Livingstone 1986: 3.
25. HEBRA F, KAPOSI M: *On Diseases of the Skin, Including the Exanthemata* (translated by W.Tan). London, Fagge and Hilton, 1874.
26. SHORT CL: The antiquity of rheumatoid arthritis. *Arthritis Rheum* 1974, 17: 193-205.
27. ROTHSCHILD BM, WOODS RJ: Symmetrical erosive disease in archaic Indians: the origin of rheumatoid arthritis in the New World? *Semin Arthritis Rheum* 1990; 19: 278-4.