Addison, pernicious anemia and adrenal insufficiency

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In 1849 Thomas Addison described the clinical entity now known as pernicious anemia. In 1855 he reported several cases of adrenal insufficiency, or Addison's disease. Considering the importance of these works, there remains a great deal of confusion about them. Contrary to what many historians have written, a review of Addison's original publications demonstrates a firm appreciation of the distinction between pernicious anemia and adrenal insufficiency, based particularly on the discoloration of the skin in these conditions. Three major sources of possible confusion for historians who are attempting to understand Addison's views include Addison's early attempts to link pernicious anemia with disease of the suprarenal capsules, Addison's redefinition of pernicious anemia in his monograph on adrenal disease, and several confusing statements made by Wilks and Daldy in the first reprint of Addison's monograph.

En 1849 Thomas Addison décrivait l'anémie que nous appelons maintenant pernicieuse. En 1855 il devait rapporter plusieurs cas de la maladie qui porte son nom, l'insuffisance surrénalienne. Au contraire de ce qu'ont écrit certains historiens, on se rend compte à la lecture des publications princeps d'Addison que celui-ci, loin de confrondre ces deux maladies, était conscient de leurs différences, particulièrement en ce qui a trait à la coloration de la peau dans l'une et l'autre. Qu'est-ce qui a pu dérouter l'historien cherchant à comprendre les concepts d'Addison? C'est d'une part que celui-ci avait d'abord essayé de relier l'anémie pernicieuse à une atteinte surrénalienne et que, par la suite, c'est dans sa monographie sur les maladies surrénaliennes qu'il a voulu redéfinir l'anémie pernicieuse. Et c'est d'autre part certaines affirmations équivoques de Wilks et Daldy dans leur première réédition de l'ouvrage d'Addison.

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In 1849, at a meeting of the South London Medical Society, Thomas Addison presented several cases of a syndrome that was characterized by pallor, weakness and a progressive decline in health that culminated in death. This report is considered to have been the first clinical description of pernicious anemia, then termed "idiopathic anemia".[1] In 1855 Addison published his famous monograph, titled "On the Constitutional and Local Effects of Disease of the Supra-renal Capsules",[2] describing for the first time the entity now known as Addison's disease.

A great deal of confusion remains about whether Addison's monograph is merely an expansion of his 1849 report or if it indeed describes a separate disease entity.

Several authors are of the former opinion. For example, in his "Introduction to the History of Medicine", Fielding Garrison[3] stated:

> In 1849 Addison read a paper before the South London Medical Society, in which he described pernicious anemia (twenty years before Biermer) and disease of the suprarenal capsules (melasma suprarenale). These clinical notations were afterward expanded at full length in his great monograph On the Constitutional and Local Effects of Disease of the Supra-renal Capsules.

White and MacDonald[4] agreed with Garrison:

> "On the Constitutional and Local Effects of Disease of the Supra-renal Capsules" was published in 1859 [sic] and followed upon clinical observation of eleven patients whose case histories are fully documented. A briefer account had previously appeared in 1849 in the London Medical Gazette.

Statements similar to these, as well as other interpretations, can be found elsewhere.[5,6] Consider, for example, the following:[7]

> [Addison's disease] was described in a paper which he read before the South London Medical Society in 1849. In his introduction to "The Constitutional and Local Effects of Disease of the Supra-renal Capsules", he describes a condition far more prevalent and of greater clinical importance than what we now call Addison's disease. This condition is pernicious anemia.

According to this author, the first description

of Addison's disease was published in 1849, before that of idiopathic anemia.

White and MacDonald[4] stated that the patients described in Addison's monograph "did not all have Addison's disease but . . . some had pernicious anemia". This statement suggests that the two diseases were mistakenly reported together by an obviously confused Addison.

After reviewing Addison's original publications one is forced to conclude that none of the authors I have cited is correct. Hale-White[8] is one of the few who seems to have correctly understood the relation between the two reports. It is obvious that Addison did not confuse pernicious anemia with adrenal insufficiency and that he did not describe the same disease in both reports. On the contrary, he made it clear that in idiopathic anemia the skin becomes "more and more bloodless" and bears "some resemblance to a bad wax figure". Nowhere did he refer to any other discoloration of the skin in that condition. Also, despite Garrison's and Medvei's statements to the contrary,[3,9] Addison did not use the term "melasma suprarenale" in his 1849 paper on idiopathic anemia.

Addison's monograph does begin with a redefinition of idiopathic anemia, which he used to explain his reasons for becoming interested in the suprarenal capsules. According to Addison it was "whilst seeking in vain to throw some additional light upon this form of anaemia" that he "stumbled" upon the facts that he related in his monograph.[10] Unfortunately, he did not mention the all-important fact that his patients with anemia had demonstrated disease of the adrenal glands.

Addison's purpose in writing his monograph was to describe the condition now known as Addison's disease, which is characterized not by pallor but, rather, by a pronounced darkening of the skin (Fig. 1). As a matter of fact, Addison made it clear that he considered this darkening of the skin necessary in making the diagnosis: "the great distinctive mark in this form of anaemia is the singular dingy or dark discoloration of the skin".[11] He also added that "the more decidedly the discoloration partakes of the character described, the stronger ought to be our impression as to the capsular origin of the disorder".[12]

Having noted these facts, we must consider how it is that so many writers and historians have been misled regarding Addison's publications on adrenal disease. I have discovered at least three areas of possible confusion.

The first and perhaps most important cause of misunderstanding was Addison's own early attempt to link idiopathic anemia to disease of the suprarenal capsules. Addison was greatly impressed by the fact that all three patients with idiopathic anemia for whom autopsy was performed demonstrated bilateral suprarenal disease: the first had malignant adrenal destruction, the second atrophy and the third hypertrophy.[13] He thought this relation important enough to record it in italics in his 1849 paper.[1] Even that paper's title, "Anaemia-disease of the suprarenal capsules", emphasizes the possible relation between these two conditions.

Following Addison's presentation a cause-and-effect relation between adrenal disease and idiopathic anemia was immediately championed by Dr. John Hilton,[13] the then president of the South London Medical Society. In a discussion of Addison's paper Hilton made the interesting statement that a review of preparations in the museum of Guy's Hospital had shown in every case in which both adrenals were diseased the "state of bloodlessness alluded to by Dr. Addison". Addison himself took pains to go on record as stating that the two conditions may have been only coincidentally related.[13]

Although in retrospect we may say that the finding of diseased adrenal glands in pernicious anemia was one of the most fortunate coincidences in the history of medicine, leading as it did to Addison's original interest in the adrenal glands, it has also served to confuse not only many of Addison's medical contemporaries but also many future generations of medical historians.

The second feature that has served to blur the distinction between Addison's earlier paper and the subsequent monograph is his redefinition of idiopathic anemia in the latter. Although Addison

Fig. 1—Sketch of James Wootten, Addison's first patient, showing skin discoloration seen in adrenal insufficiency. (Reproduced from reference 2.)

went into a fair amount of detail, no new facts were added to what had already been published in 1849. However, this inclusion was no doubt the source of Major's confusion when he stated that the monograph contained the original description of pernicious anemia.[7]

By the time Addison's monograph was published in 1855 there were some indications that he no longer considered adrenal disease the probable cause of idiopathic anemia. First, he did not mention the suprarenal glands in the monograph directly in connection with this malady, although he had stressed such a relation in his earlier paper. Second, later in the monograph he made the following statement:[14]

> On examining the bodies of such patients [with idiopathic anaemia] after death I have failed to discover any organic lesion that could properly or reasonably be assigned as an adequate cause of such serious consequences.

Again no mention is made of the suprarenal glands. Perhaps, then, it is safe to assume that in 1855 (perhaps on the basis of autopsy studies of additional cases) Addison believed that adrenal disease seemed less likely a cause for idiopathic anemia than it had in 1849.

This leads us to the third possible cause of confusion for modern medical historians: the preface to the reprint of Addison's monograph found in a volume of his collected writings edited by Wilks and Daldy.[15]

This volume of Addison's collected works, published by the New Sydenham Society in 1868, has become a standard reference source, since it is much easier to obtain than Addison's original monograph. In the preface to the last section of the book there is an extremely confusing view of Addison's earlier paper and its relation to the monograph.

We are first told that Addison introduced disease of the suprarenal capsules to a local medical society in "an attempt to elucidate the nature of a malady which he had styled 'idiopathic anaemia' ". This statement is true, but it is put forth in such a manner as to make the reader believe that Addison had actually described Addison's disease in the earlier paper. This false impression is strengthened by the statement that patients with idiopathic anemia exhibited "various shades of alteration in the colour of the skin".

Nowhere in Addison's original paper is reference made to any skin shading, only to its pallor. The source of this statement is therefore a mystery. Since Wilks was so closely involved in Addison's research[16] this statement is doubly mystifying and is at variance with what is to be found in Addison's original report.

In the same preface we are told that because no other cause for idiopathic anemia was observed Addison considered the cause of that malady to be disease of the suprarenal capsules but that anemia and morbus addisonii are really not "pathologically connected; . . . in the one case the patient is pale . . . [and] in the other . . . a brownish hue". So again it seems that all patients with idiopathic anemia are considered pale, and the two diseases are clearly separated.

The final reversal of this position appears in a discussion of "the true morbus addisonii", Wilks and Daldy noting its slow acceptance by the medical community:

> Nearly a quarter of a century has elapsed since the original paper was read before the South London Medical Society; yet even now it does not find a place in the nosology of some writers, although the evidence of its distinct and essential nature as a malady *sui generis* is conclusive.

This alternate "lumping" and "splitting" on the part of Wilks and Daldy when discussing idiopathic anemia and Addison's disease is perplexing to the modern reader, as it certainly must have been to their contemporaries.

But this was not the only occasion in which Wilks demonstrated a seeming carelessness in differentiating these two conditions. The following misleading statement is quite similar and can be found in a history of Guy's Hospital that Wilks wrote with Bettany:[17]

> [Addison's] book appeared in 1855. . . . It may be mentioned that five years before this publication he read a paper on the subject at the South London Medical Society, a short account of which may be found in the *Medical Gazette* of March 15, 1849.

We can only guess at Wilks' reasons for making these statements. Perhaps he meant only to indicate the early date at which Addison became interested in the adrenal glands. But whatever the reasons, his writings are some of the earliest and probably the most consulted references to present an unclear picture of Addison's studies. They have no doubt, because of the early date of their publication and authoritative nature, been the source of at least a portion of the current misunderstanding surrounding Addison's works.

I have attempted to demonstrate how the works of Thomas Addison on pernicious anemia and adrenal insufficiency have been misunderstood by modern historians, and I have presented at least three possible factors that may have led to this confusion. It is hoped that by my doing so, the modern physician will avoid the same mistakes and come to a clearer appreciation of that great medical genius Thomas Addison.

References

1. Addison T: Anaemia-disease of the suprarenal capsules. *Med Gazette* 1849; 43: 517–518
2. Addison T: *On the Constitutional and Local Effects of*

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to his practice and to his exercise routine over the next 6 weeks. Sequelae 15 months later included occasional slight loss of balance and low weight.

Discussion

Torten[1] noted the absence of a pathognomonic syndrome and the presence of misconceptions that hinder the diagnosis of leptospirosis in humans. Gutman and coworkers[2] emphasized this problem in their account of a patient with leptospirosis that was signalled by an ocular disorder. Avery[3] and Hart and colleagues[4] described the behavioural and social consequences of missed diagnoses, and Cheng[5] specified leptospiral arteritis as a major cause of cerebrovascular disease.

The use of rapid, accurate methods for detecting leptospires in blood and urine along with the IHA test for early antibodies can facilitate diagnosis. However, the immune response to leptospiral infection is highly variable, and, therefore, serologic testing alone should not be depended upon to establish the diagnosis. Culture of blood and urine samples with commercially available albumin-polysorbate-80 medium is now practical and should always be done in patients at risk of leptospirosis. Treatment with doxycycline is indicated because of its specificity, its ability to penetrate into the cerebrospinal fluid and the anterior chamber of the eye, and its long half-life (16 hours) in the body.[6]

The potential for exposure of Canadians to leptospiral infection increases with the amount of time spent with livestock. The risk of this debilitating disease, with its serious sequelae, merits much concern: public health authorities should obtain survey data, veterinarians should caution clients and coworkers and try to control the sources of infection, and the medical profession should recognize leptospirosis as a zoonosis indigenous to Canada.

References

1. Torten M: Leptospirosis. In Steele JH (ed): *CRC Handbook Series in Zoonosis*, vol 1, CRC Pr, Boca Raton, Fla, 1979: 363–421
2. Gutman I, Walsh JB, Knapp AB: Cotton-wool spots as a sign in leptospirosis. *Ophthalmologica* 1983; 187: 133–136
3. Avery TL: Leptospirosis and mental illness [C]. *NZ Med J* 1983; 96: 701
4. Hart RJC, Gallagher J, Waitkins S: An outbreak of leptospirosis in cattle and men. *Br Med J* 1984; 288: 1983–1984
5. Cheng M-K: A review of cerebrovascular surgery in the People's Republic of China. *Stroke* 1982; 13: 249–255
6. McClain JBL, Ballou WR, Harrison SM et al: Doxycycline therapy for leptospirosis. *Ann Intern Med* 1984; 100: 696–698

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Disease of the Supra-renal Capsules, Samuel Highley, London, 1855
3. Garrison F: *An Introduction to the History of Medicine*, 4th ed, Saunders, Philadelphia, 1929: 422–423
4. White IR, MacDonald DM: Thomas Addison, MD. First dermatologist at Guy's Hospital. *J Am Acad Dermatol* 1982; 6: 426–430
5. Long ER: *A History of Pathology*, Dover, New York, 1965: 98
6. Upstairs, downstairs at Guy's: Addison, Bright, and Hodgkin. *Hosp Pract* 1977; 12 (5): 119–131
7. Major RH: *Classic Descriptions of Disease*, 3rd ed, CC Thomas, Springfield, Ill, 1978: 290–294
8. Hale-White W: Thomas Addison, M.D. *Guy's Hosp Rep* 1929; 76: 253–279
9. Medvei VC: *A History of Endocrinology*, MTP Pr, Hingham, Montana, 1982: 225–244
10. Addison T: *On the Constitutional and Local Effects of Disease of the Supra-renal Capsules*, Samuel Highley, London, 1855: 4
11. Ibid: 7
12. Ibid: 8
13. Hilton J: Discussion of Dr. Addison's paper on anaemia. *Med Gazette* 1849; 43: 562–563
14. Addison T: *On the Constitutional and Local Effects of Disease of the Supra-renal Capsules*, Samuel Highley, London, 1855: 3
15. Wilks & Daldy (eds): Prefatory remarks on disease of the supra-renal capsules. In *A Collection of the Published Writings of the Late Thomas Addison, M.D.*, New Sydenham Society, London, 1868
16. Bishop PMF: Dr. Addison and his work. *Guy's Hosp Rep* 1955; 104: 275–294
17. Wilks S, Bettany G: *A Biographical History of Guy's Hospital*, Ward, Lock Bowden, London, 1892: 223–234

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21. Stevenson DD, Simon RA: Sensitivity to ingested metabisulfites in asthmatic subjects. *J Allergy Clin Immunol* 1981; 68: 26–32
22. Schwartz HJ: Sensitivity to ingested metabisulfite: variations in clinical presentation. *J Allergy Clin Immunol* 1983; 71: 487–489
23. Habenicht HA, Preuss L, Lovell RG: Sensitivity to ingested metabisulfites: cause of bronchiospasm and urticaria. *Immunol Allergy Pract* 1983; 5: 243
24. Schwartz HJ, Chester EH: Bronchospastic responses to aerosolized metabisulfite in asthmatic subjects: potential mechanisms and clinical implications. *J Allergy Clin Immunol* 1984; 74: 511–513
25. Stevenson DD, Simon RA: Sulfites and asthma [E]. Ibid: 469–472
26. A growing concern over sulfites. *Chem Week* 1983; Nov: 16
27. Sulfite update. *FDA Drug Bull* 1984; 14 (3): 24
28. Twarog FJ: Metabisulfite sensitivity in asthma. *Allergy Proc* 1983; 4: 100–103
29. Yang WH, Purchase ECR, Rivington RN: Positive Prausnitz-Küstner reaction in metabisulfite sensitive subjects [abstr]. *J Allergy Clin Immunol* 1985; 75: 373
30. Delohery J, Castle W, Simmul R et al: Metabisulfite and SO_2 reactivity in asthmatics [abstr]. *J Allergy Clin Immunol* 1984; 73: 136
31. Jacobsen DW, Simon RA, Singh M: Sulfite oxidase deficiency and cobalamin protection in sulfite-sensitive asthmatics (SSA) [abstr]. Ibid: 135

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