Book Reviews

ADDISON ON THE 'SUPRA-RENAL CAPSULES'*
AN ESSAY REVIEW BY KENNETH D. KEELE

ADULATION of Addison and Bright in Britain's medical circles resounds only slightly less loudly than Harveian songs of praise. These men carry a large share of legendary British medicine in their names. Of recent years Harvey's worthiness of such a role has been the subject of several studies; as a result he has, if possible, gained in stature. What of Addison? The question is prompted by the appearance of a reprint in facsimile of Addison's book of 1855 *On the Constitutional and Local Effects of Diseases of the Supra-renal Capsules*. This has been produced as one of the series of Pall Mall classics by Dawsons. Not only is this reprint a treasure of medical history but also of the printer's art, for here is brought to us today an opportunity for appreciating Addison's famous work, not only through his words but by the meticulous reproduction of his colour plates. These present to us, with a dramatic power beyond words, the clinical observations from which Addison set out to make his case. Here is a striking example of fine art wedded to fine science for the purpose of making enter by the eyes a visual image which should enter by the eyes and not through verbal substitutes.

Most of us through our familiarity with the name think we have a clear idea of how Addison reached his description of Addison's Disease of the suprarenals. Very often this very familiarity in fact deceptively masks his fascinating struggle for comprehension of the syndrome presented in this his greatest work. For full appreciation of the publication of this reprint it is essential to sketch the context within which Addison published the work in 1855, a context which lights up not only Addison's own personal outlook on medicine in relation to his momentous discovery, but also the state of medicine during the period of his observations.

Born in 1795[1] at Longbenton near Newcastle and dying in 1860, Addison's professional life saw the rise of morbid anatomy in England. Introduced by Morgagni in 1761 as a systematic procedure for elucidating the relationship between the patient's symptoms in life and changes in the organs found after death, this method of study bore its first revolutionary fruit in Paris in the hands of Napoleon's physicians. Perhaps the most notable of these were Corvisart (1755–1821) with his work on cardiac diseases, and Laënnec (1781–1826) with his contributions on pulmonary and hepatic diseases. Laënnec clearly exerted a powerful life-long influence on Addison, both through his morbid anatomical studies of the lungs and through his introduction of the stethoscope.

Throughout his life Addison showed a particular proclivity for dermatology. Having graduated in Edinburgh in 1815 with a thesis on Syphilis and Mercury, it was not surprising that when he came to London he obtained an appointment as house surgeon to the Lock Hospital. About the same time he worked under the dermatologist Thomas Bateman (1778–1821) who was then preparing his *Delineations of Cutaneous Diseases* for publication (1817). This work consisted of an atlas of

* *On the Constitutional and Local Effects of Disease of the Supra-renal Capsules*, by THOMAS ADDISON, first published in London, 1855. Reprinted in facsimile, 1968, by Dawsons of Pall Mall.

seventy-two coloured plates. Thomas Bateman was mentor to both Bright and Addison, and his influence would seem to be reflected in the accurate and beautiful colour-plates which form such a notable feature of the works of both his pupils. Bateman's influence on Addison is also evident in the younger man's life-long interest in dermatology. Not only is it significant that skin pigmentation is the dominant characteristic of Addison's Disease, but amongst his less known achievements are the description (with Gull) of xanthomata and what he called 'keloid', or localized scleroderma. Addison was also influenced by the great French dermatologist Jean-Louis Alibert (1768–1837) who proudly claimed to be the first to use the painter's pallette in illustrating skin diseases. And it was from Alibert's description of 'cancroide' that Addison separated out the features of his localized scleroderma.

In 1819 Laënnec published his epoch-making treatise on mediate auscultation. In 1826, the year of his death, the second edition appeared. In this Laënnec developed his great theme of the diagnosis, pathology and treatment of chest diseases. Laënnec here laid great stress on the importance of correlating the auscultatory findings with morbid anatomy. In the year 1820 Addison entered Guy's Hospital as a student, and his friend Bright was appointed assistant physician. Four years later he joined Bright as assistant physician at Guy's Hospital. During these impressionable years Addison appears to have become deeply inspired by the outlook and results of Laënnec's work. Already he had shown his meticulous powers of observation as a successful dermatologist in succession to Bateman who died in 1821. Laënnec's example now convinced Addison of the great importance of correlating symptoms in life with morbid anatomical changes after death, and he set about the task of making such correlations with almost fanatical zeal. His intense desire to reach diagnostic accuracy in life gave rise to several stories reflecting his obsession. For example Wilks writes[2] that, 'he never reasoned from a half-discovered fact, but would remain at the bedside with a dogged determination to track out the disease to its very source for a period which constantly wearied his class and his attendant friends. So severely did he tax his mind with the minutest details bearing upon the exact exposition of the case, that he has been known to startle the sister of the ward in the middle of the night by his presence.' Such clinical studies Addison followed up when opportunity arose by many hours in the post-mortem room elucidating the morbid anatomy. So great was his enthusiasm for this aspect of medicine that Addison's interest in treatment was relatively weak, and his biographer records that, 'To those who knew him best his power of searching into the complex framework of the body, and dragging the hidden malady to light appeared unrivalled; but we fear that the *one* great object being accomplished, the same energetic power was not devoted to its alleviation or cure.'

Not only did Addison follow Laënnec in his methods of research, but also in the subjects upon which he worked. The greater part of his writings are devoted to pulmonary disease. Between 1837 and 1847 he read five papers on pneumonia, phthisis and the diagnosis of diseases of the chest. This group of papers, read at the meetings of the Physical Society of Guy's Hospital and the South London Medical Society, played a significant part in the evolution of knowledge of pneumonia and pulmonary tuberculosis. Previous views of the morbid anatomy of pneumonia had looked upon

it as an 'interstitial' disease. Addison carefully described the anatomy of the pulmonary air-cells or alveoli, and demonstrated that the exudate in pneumonia was alveolar and not interstitial. With regard to pulmonary tuberculosis, 'he endeavoured to combat the prevailing idea that tubercle was the sole deadly ingredient in chronic pulmonary disease; and constantly asserted that a large proportion of cases in which persons died of so called "phthisis" tubercles were not present.'

His method of investigating these pulmonary diseases was chiefly by dissection and naked-eye appearances, which he illustrated in his publications with coloured plates. In 1843 Addison writes, 'The best mode of showing these appearances [of tubercles] is to inject the bronchial tubes and cells of a tuberculated lung with tallow coloured with vermilion: when not only the interlobular cellular membrane will be rendered apparent by remaining pale, but the portion of aerial cellular tissue occupied by the minute tubercles will be distinctly seen, and may be examined by means of a microscope with the aid of a reflector, the rest of the lobe presenting a very good example of what is called red hepatisation.'[3] Thus he now carried his analysis of morbid anatomy to injection and began to use microscopic techniques. In this connection it will be remembered that a Microscope Department was introduced at Guy's Hospital in 1835.

The last of these papers on pulmonary disease (1846) comprises a constructive criticism of the difficulties and fallacies attending the use of auscultation and percussion in examination of the chest. It opens with the words, 'Were I to affirm that Laënnec contributed more towards the advancement of the medical art than any other single individual, either of ancient or modern times, I should probably be advancing a proposition which is neither extravagant nor unjust.'[4] Addison leaves us in no doubt as to the identity of his hero-figure. He goes on to point out that, 'Laënnec has sustained more real and serious injury from indiscreet and indiscriminate advocacy than from the most determined hostility.' Then under forty separate headings he discusses the fallacies of physical examination of the chest with a clarity and good sense which reveal those characteristics of the brilliant teacher in which many, including Wilks, have seen the essential greatness of the man.

During these years Addison was also turning his attention to diseases of other organs than the lungs, to fatty degeneration of the liver; to hysteria (which he considered to be essentially the result of uterine innitation), and to diseases of the suprarenal glands.

On 15 March 1849 as reported by the *London Medical Gazette*, Addison delivered a paper before the South London Medical Society describing, 'a remarkable form of anaemia' which, 'had for several years past been with him a subject of earnest inquiry and deep interest.' He then proceeded to describe a group of symptoms:

> an insidious languor and restlessness to which succeed a manifest paleness of the countenance, loss of muscular strength . . . . These symptoms go on increasing with greater or less rapidity; the face, lips, conjunctivae and external surface of the body become more and more bloodless, the tongue appears pale and flabby, the heart's action gets exceedingly enfeebled . . . the appetite may or may not be lost . . . the breathing is painfully hurried by the slightest exertion whilst the whole surface bears some resemblance to a bad wax figure . . . slight oedema perhaps shows itself about the ankles . . . and the patient dies either from sheer exhaustion, or death is preceded by signs of passive effusion or cerebral oppression.[5]

The report continues: 'Dr. Addison gave the details of several cases which had fallen under his own immediate observation. In only two of these did the patients recover.' One of these recovered, 'under the use of brandy, but with the singular result of the hair of one side of the head turning permanently grey . . .' (This is the only mention of pigmentation changes made by Addison in this series of cases).

> In three cases only was there an inspection of the body after death and in all of them was found a diseased condition of the suprarenal capsules. In two, no disease whatever could be detected in any other part of the body. Dr. Addison inquired if it were possible for all this to be merely coincidental . . . He could not help entertaining a very strong impression that these hitherto mysterious bodies—the suprarenal capsules—may be either directly or indirectly concerned in sanguification.

In the discussion of Dr. Addison's Paper, John Hilton, the Chairman, said that he had looked over the preparations in the museum of Guy's Hospital and in every case 'where both capsules were diseased . . . the state of bloodlessness alluded to by Dr. Addison was mentioned, but not when only one was diseased.' Addison during the discussion again emphasized the possibility of mere coincidence between the anaemia in life and the supra-renal changes found at post-mortem.

At this meeting there was no mention of pigmentation of the skin of the patients; no mention of vomiting. All clinical emphasis was laid on a progressive anaemia of unknown cause. In fact the clinical syndrome had the features of Addisonian anaemia, but the disease found at post-mortem was Addison's disease of the suprarenals. That Addison the diagnostician and Addison the morbid anatomist were at odds with each other, confusing the two diseases is a crystal-clear feature of the situation as it existed in 1849.

Let us now turn to see what was Addison's position by 1855 as presented in this famous book on disease of the suprarenals. In his preface Addison declares his method of investigation. He opens thus; 'If Pathology be to disease what Physiology is to health it appears reasonable to conclude that in any given structure or organ; the laws of the former will be as fixed and significant as those of the latter, and that the peculiar characters of any structure or organ may be as entirely recognised in the phenomena of disease as in the phenomena of health'. Addison cites his work on the morbid anatomy of pneumonia in support of this thesis—'When investigating the pathology of the lungs, I was led by the results of inflammation affecting the lung tissue to infer, contrary to the general belief, that the lining of the air-cells was not identical and continuous with that of the bronchi; and microscopic investigation has since demonstrated in a very striking manner the correctness of that inference'.

He ends his preface with the comment that: 'There are still, however, certain organs of the body, the actual functions and influence of which have hitherto entirely eluded the researcher, and bid defiance to the united efforts of both physiologist and pathologist. Of these not the least remarkable are the Supra-Renal Capsules . . .'

Again his method clearly consists of a correlation of symptoms and signs with morbid anatomical changes; 'believing as I now do that these concurring facts in relation to each other, are not merely casual coincidences, but are such as admit of the fair and logical inference . . . that where these concurrent facts are observed we may pronounce with considerable confidence the existence of diseased supra-renals'.

Thus he expresses his search for a significant correlation between the syndrome and a morbid anatomical finding.

He now refers to the paper delivered to the South London Medical Society in 1849 with the significant words, 'For a long period I had from time to time met with a very remarkable form of general anaemia, occurring without any discoverable cause whatever . . . Accordingly in speaking of this form of anaemia in a clinical lecture, I perhaps with little propriety applied to it the term "idiopathic".' He proceeds to describe the anaemia in words very similar to those he used in 1849, noting on this occasion the additional feature that 'after a sickness of perhaps several months' duration the bulkiness of the general frame and the amount of obesity often present a most striking contrast to the failure and exhaustion observable in every other respect.' He mentions microscopic examination of the blood only to say that it was not done.

His post-mortem examination results are now reported in terms very different from those of six years previously: 'On examining the bodies of such patients 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 . . .'. He does suggest that fatty degeneration, 'might have a share in its production.' He makes no mention of the stomach or spleen, and examination of the bone-marrow appears not to have been part of Addison's post-mortem technique. In contrast with his paper of 1849 the suprarenals are not here mentioned. Leaving the negative morbid anatomy of this form of anaemia, Addison writes, 'It was whilst seeking in vain to throw some additional light upon this form of anaemia, that I stumbled upon the curious facts, which it is my more immediate object now to make known to the Profession.' He now proceeds to describe the syndrome of what we recognize as Addison's Disease of the suprarenals. The 'leading features' of this disease he describes as 'anaemia, languor, 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'.

That Addison has not completely shed his previous views becomes evident on reading his clinical description of his twelve cases. Throughout he repeatedly over-emphasizes the feature of 'anaemia'. For example, 'As has been observed in other forms of anaemic diseases . . .' is the opening phrase of his clinical account. His masterly description of anorexia and vomiting includes many signs of 'anaemia' as well as the 'characteristic discolouration' of the skin.

This attitude is interestingly reflected in his search for the morbid anatomical cause: 'We may be led to enquire into the condition of the so-called blood-making organs; but we discover no proof of organic change anywhere—no enlargement of spleen, thyroid, thymus or lymphatic glands—no evidence of renal disease, purpura, of previous exhausting diarrhoea or ague . . .'. And one of the great problems he sees raised by this disease of the suprarenals is: 'how we may at the earliest possible period detect the existence of this form of anaemia, and how it is to be distinguished from other forms of anaemic disorder'.

Sometimes the reader may be pardonably confused as to whether he is reading phrases which refer to pernicious anaemia or suprarenal disease. There can be no

doubt that this truly represents Addison's own position, for he had by no means completely cast off the impression of the clinical and morbid anatomical correlations expressed in 1849. Today we can separate the clinical entities of pernicious anaemia and suprarenal insufficiency but for Addison the two pictures of his anaemia and his suprarenal disease were still seen through a glass darkly. In extenuation of this confusion it is right to note how clinical experience today may still occasionally uncomfortably remind one how surprisingly similar the two diseases can be in their mode of presentation.

Perusal of the twelve case-histories reveals that eight of the nine dated cases were seen by Addison between 1850 and 1855. The second case was diagnosed by Gull (not Addison) in 1851. The fifth case is of particular interest, because it was seen by Bright as early as 1829. The case history, cited from Bright's clinical notes, observes that the patient's 'complexion was very dark' and 'her stomach irritable'. At post-mortem Bright found a left breast abscess, bilateral apical tuberculosis of the lungs, and both 'renal capsules enlarged, lobulated, and the seat of morbid deposits apparently of a scrofulous character'. Addison makes the comment: 'It does not appear that Dr. Bright either entertained a suspicion of the diseases of the capsules before death, or was led at any period to associate the colour of the skin with the diseased condition of these organs, although his well-known sagacity induced him to suggest the probable existence of some internal malignant disease'. The sixth case is undated. Once more we find Addison describing the patient as 'greatly anaemiated', as well as pigmented—this time with vitiligo. The post-mortem report was furnished by Dr. Hodgkin, who noted tuberculosis of both suprarenals. One cannot help being impressed by the meticulous accuracy of each case report so characteristic of the man, such that it enables him to report the unusual association of vitiligo with Addison's Disease—a feature which finds not only record but vivid illustration in his book.

Two questions which one often hears asked about Addison's Disease of the suprarenals should be touched upon; how original was his discovery?—and what sort of reception did it get?

The suprarenals had by no means been ignored before Addison's day. These glands owing to their firm adherence to the surrounding fat are easily separated from the kidney on which they lie, a fact that probably accounts for their eluding such great anatomists as Galen, Leonardo da Vinci and Vesalius. Their first clear description came at the hands of Eustachius who illustrated them in his copperplates in 1564.[6] Jean Riolan named them suprarenal capsules in 1629.[7] Wharton called them suprarenal bodies in 1659,[8] and noted their rich and close connection with the sympathetic ganglia and nerves. The structure and function of the suprarenals failed to arouse much further interest until the beginning of the nineteenth century. In 1839 Bergmann[9] re-emphasized once more the extremely rich nerve supply of the gland. Kölliker[10] endorsed this feature, counting thirty-three nerve trunks to the right suprarenal of man, all destined to end in the medulla of the gland. He considered that the cortical and medullary parts of the suprarenal should be looked upon as physiologically distinct, the cortex as a secreting gland, the medulla as an apparatus appertaining to the nervous system.

Leydig in 1853[11] from his investigations of the suprarenals in mammals, fishes and amphibia agreed with Bergmann and Kölliker regarding the close relationship between the suprarenals and the sympathetic nervous system. He brilliantly suggested that the suprarenals bear the same relationship to the ganglia of the sympathetic nerves as the pituitary gland does to the brain.

Descriptions of pathology of the suprarenals scattered sporadically over centuries are to be found for example in the *Ephemerides Naturae Curiosorum*. It is interesting to note that Bergmann based his hypothesis of the neural function of these organs partly on the observations of his father, a psychiatrist of Hildesheim, and Jacobson, that the suprarenals were found affected in disease of the brain and spinal cord. And Brown-Séquard in 1851[12] had noted that experimental wounds of the spinal cord in animals resulted in hyperaemia of the suprarenals followed by death.

In 1837 Rayer[13] published a collection of cases in which were found haemorrhages, cysts, tumours or tuberculous changes in the suprarenals. But he could not correlate these findings with any consistent clinical or physiological changes and so failed to obtain any insight into their functions in health or disease.

When it is realized that this was the background upon which Addison made his clinico-pathological correlations, the measure of his achievement stands out in clear perspective.

Addison lived at the beginning of the period of experimental physiology. Indeed in that eventful year of the publication of this book, 1855, Claude Bernard also published his epoch-making *Lessons on Experimental Physiology*, so inaugurating the physiological pattern of endocrinology which harmonized with Addison's clinical example of the theme. It is not surprising therefore, that experimental ablation of the suprarenal glands was soon carried out in Paris—and this in 1856 by the erratically brilliant Brown-Séquard[14] after observing with Trousseau a post-mortem on a case of Addison's disease. Brown-Séquard experimented on sixty animals, noting that the average duration of life after complete extirpation of both suprarenals was eleven hours; with removal of one suprarenal, survival averaged seventeen hours. Brown-Séquard was emphatic that in none of these animals was death attributable to haemorrhage, peritonitis, lesions of kidney, liver or other viscera; others took a contrary view.

Trousseau in Paris,[15] contrary to those in London, accepted Brown-Séquard's results, and decided that: 'From facts adduced, we must conclude, with the physiologist [Brown-Séquard] that the suprarenal capsules are organs essential to life, that their extirpation, alteration of structure, or destruction, influence the economy, either by arresting the functions of these organs as haematopoietic glands, or by inducing irritation of the nervous system.' It was Trousseau who in 1856, named this syndrome of suprarenal deficiency, 'Addison's Disease'.

Further cases of Addison's Disease rapidly accumulated; by 1858 some thirty-four had been described in England. Confusion occurred however, when it became appreciated that 'bronzing' of the skin could be present with healthy suprarenals and that bilateral disease of the suprarenals could exist without bronzing of the skin. It was not at that time realized that such tantalizing combinations were merely the opening of further portals into that great new field of endocrinology of which Thomas Addison had found the first clinical key.

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The Worshipful Society of Apothecaries of London: A History, 1617–1967, by W. S. C. COPEMAN, Oxford, Pergamon Press, 1968, pp. xiii, 112, illus., 63*s.* 0*d.*

Dr. Copeman's short history was published to mark the celebrations of the 350th anniversary of the Society's Royal Charter, granted by James I on 6 December 1617. On that day it at last gained the separate incorporation from the Company of Grocers to which it had a just claim as far back as 1525. The author, as much a purist in English as he is a learned medical historian, follows the Society's struggles to assert its rights and proclaim its sincerity of purpose in the face of the acrimonious opposition of the College of Physicians, the Corporation of London, and the Royal Society, many of whose members grouped it in scurrilous tirades with fraudulent quacks and mountebanks.

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