THOMAS ADDIS (1881–1949); SCOTTISH PIONEER IN HAEMOPHILIA RESEARCH

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ADDIS AND THE RCPE LABORATORY

In 1887, the Royal College of Physicians of Edinburgh established a laboratory, for research and service, in Lauriston Lane. It moved to Forrest Road in 1896, and closed in 1950. (The Scottish National Blood Transfusion Service headquarters' laboratories occupied the site until late 2000.) Among its most notable early researchers was Thomas Addis (Figure 1), Carnegie Fellow. In 1911 he described the pathogenesis of haemophilia, suggesting – remarkably – that there was 'an anatomical defect in the structure of the prothrombin molecule'.[1] Also in this year, William Bulloch and Paul Fildes confirmed the way haemophilia is inherited.[2] Bulloch (1861–1941, MB and MD Aberdeen 'with highest honours') was Lecturer in Bacteriology at the London Hospital, and Fildes his medical student assistant.

FIGURE 1

Thomas Addis MD, FRCP Edin; b. Edinburgh, 27 July 1881; d. Los Angeles, 4 June 1949. (New York, 1929; courtesy Dr R Melhuish).

Before 1900 haemophilia was poorly understood. Queen Victoria had one haemophilic son (Leopold, born 1853) and two carrier daughters, through whom haemophilia entered the royal houses of Europe.[3,4] Although Victoria never understood her own personal role in the transmission of the disease, haemophilia's 'sex-linked' mode of inheritance emerged during her reign. In 1886 Frederick Treves described a girl with a bleeding tendency.[5] Her parents were cousins, and she and her father had similar bleeding histories; nevertheless he fathered twelve children. Although his descendants claimed he bled to death after an accident at work, this family's bleeding tendency was not severe.

Bulloch and Fildes gave 949 references and 607 'pedigrees' of bleeder families in Europe and the US, excluding the Royals.[2] Although some families were found later to lack factor IX, it is uncertain whether Victoria carried VIII or IX deficiency. Bulloch compiled a Royal family tree from medieval times to 1918 – now at the Royal Society of Medicine. One nineteenth-century German prince – whose parents were cousins – might have been a 'bleeder', but this is unlikely.

Bulloch emphasised the carrier role of asymptomatic mothers, but doubted if any female 'bleeders' were truly haemophilic,[6] even in Treves's family ('pedigree 493'). Inconsistencies in recollected ancestry (giving apparent father-to-son transmissions in early generations of 493) and a mild clinical effect added to an inherent improbability. Later work[7,8] restored 493's family pride; and in 1974 'V8' – a younger sister of Treves's patient – and two of her four sons were all found, at the London Hospital, to have 5% plasma factor VIII activity (one-stage assay).

In the latter part of the nineteenth century, the interaction between fibrinogen, thrombin (fibrin ferment), and tissue extract (thromboplastin) became apparent. In 1904, Paul Morawitz of Heidelberg (1879–1936) hypothesised that, in the presence of calcium, damaged tissues cause thrombin to be released from a freely circulating, inactive and soluble precursor, *prothrombin*, which he (and others) thought to originate from platelets. But William Howell from Johns Hopkins University believed that thrombin came directly from injured tissues or white cells. Howell's concepts developed away from those of Morawitz, particularly after his discovery of heparin.[9,10] Similar 'contra-Morawitz' views were held by others, notably Sahli of Berne. Bulloch and Fildes, however, followed Morawitz's theory, and quoted Addis who had studied patients from 'pedigrees' 500 and 389.

ADDIS'S WORK 1905–9

Addis gained his Edinburgh MB in 1905. After posts in

Dublin and Gloucester, his first Edinburgh attachment was in the University's Physiology Laboratory where, in 1887, William Hunter (1861–1937) had worked on transfusion, mainly intra-peritoneally, in animals.[11] Hunter, who moved to Charing Cross Hospital in London, regarded human transfusion as dangerous, particularly in pernicious anaemia, in which he felt transfused cells aggravated an underlying haemolysis. Significantly for Addis, his reservations were partly shared by G Lovell Gulland (1861–1941), a pioneer of haematology, Professor of Medicine from 1915, and President, RCPE, 1923–6.

Addis's thesis for his MD (1908) comprised principally a methodological investigation of the blood of healthy people. All clotting-time methods then in use took blood obtained by a skin-prick, usually collected into glass capillaries: Addis devised an ingenious alternative to glass capillaries.[12] Although too cumbersome for clinical application, it gave good end-points, revealed the major influence of temperature, and disproved any diurnal effect or changes in clotting following oral calcium chloride or citrate.

In the Royal College's laboratory, JP M'Gowan (1879?–1961; Figure 2) had already adapted a portable glass capillaries-based system of measuring clotting times.[13] Addis added a water bath to control temperature, and in the summer of 1907 or 1908 took his apparatus and method to Gloucester and Bristol where he established that oral calcium and citrate had no effect on clotting in several patients with a recent thrombosis, and that calcium also had no effect on mild bleeding in a haemophiliac after a tooth extraction.[14] M'Gowan's clotting time description was his only foray in this field, but Addis clearly discussed it with him. From Berlin, in 1909, Addis vigorously (but not altogether justifiably) defended M'Gowan against accusations of plagiary from Sabrazes of Bordeaux.[14]

FIGURE 2

Workers at the laboratory of the RCPE, 1910, including T Addis (centre back row); JM Graham (three places to his right); J Ritchie, Laboratory Superintendent (centre, front row); JP M'Gowan, front row on Ritchie's left.

In Gloucester and Bristol, Addis determined the clotting times of 112 people with various disorders except haemophilia.[15] It was found to be short in severe haemorrhage, but therapeutic venesection (of a pint) had no effect. It was prolonged in a uraemic man and in a man with septicaemia; and slightly prolonged in another male patient, although not in his father, both of whom had acute nephritis (they were cousins of the haemophiliac bleeding from his tooth; neither were typical 'bleeders'). Intriguingly, Addis later specialised in nephritis.

In the autumn of 1909 (probably) Addis visited Morawitz in Heidelberg and investigated four people of Bulloch's 'pedigree 389'; this family was well-known to German investigators.[16] Here Addis measured venous blood clotting in ways strikingly similar to those of Lee and White[17] (indeed Lee and White acknowledged this), and learnt the trick of oxalation discovered by Arthus and Pagés in 1890.[18] Addis may not have shared all Morawitz's views – such as the platelet origin of prothrombin or that haemophilia was related to reduced tissue thromboplastin release. They did not, however, co-author any reports: all Addis's publications at that time were solo efforts. Around this time Addis read Mellanby's work,[19] which supported Morawitz's prothrombin theory. Working on cockerel blood, which has a very long clotting time, being defective in factors XI and XII,[20] Mellanby claimed to have isolated prothrombin from crude fibrinogen; but this preparation undoubtedly contained many other clotting factors. Biggs and Macfarlane[21] regarded 'prothrombin' to be a relatively unformed concept until after Bordet and Delange[22] developed the modern basis of its preparation by eluting it from oxalated plasma adsorbed onto insoluble crystalline salts such as barium phosphate. But Bordet and Delange's concepts differed from those of Morawitz; they (correctly) did not agree that their *serozyme* was derived from platelets; but thought (incorrectly) that it had its own precursor – *pro-serozyme* (see also reference 10).

1910 AND CONTROVERSY

Back in Edinburgh, Addis, now MRCP Edin and with access to patients in the Royal Infirmary, added another three haemophiliacs to his series, making it 12 altogether. One was referred by JM Cotterill (1851–1932), President of the Royal College of Surgeons of Edinburgh 1907–10. On another, Addis and TY Finlay compared finger-prick and venous blood.[23] He reported his preliminary results on oxalated venous blood plasma to the Pathology Section of the BMA at their 78th Annual Meeting in July 1910,[24] giving notice of his claim that the fault in haemophilic blood was due to an inherited qualitative defect in the prothrombin. Sahli – who was in the audience – disputed this, claiming that washed normal 'corpuscles' accelerated haemophilic blood clotting, so that the haemophilic defect lay in the patient's corpuscles. Sahli did not take kindly Addis's suggestion that his observations were due to inadequate washing.[24] Addis, undeterred, indicated that

Sahli's reported accelerated clotting of haemophilic plasma by normal washed cells was still slower than the clotting of cell-poor normal plasma.[1]

Sahli's view continued to dominate; the persistence of intact platelets in clotted haemophilic blood was held to indicate that haemophilic platelets were unduly stable – releasing their thromboplastin too slowly – rather than the correct inference that they reflected slow clotting. Minot and Lee (1916)[25] claimed that washed normal platelets did accelerate haemophilic clotting; but their washing procedure (in oxalate-saline) often clumped the platelets, so traces of plasma may have remained, and the platelets may have been damaged.

Addis's definitive report was of a high quality although it merits scant mention in the *History of the Laboratory*.[26] His interpretations – in accordance with Mellanby's concepts of prothrombin – were imperfect, but his experimental designs and observations were exemplary. Venous blood from haemophiliacs was taken into 2% potassium oxalate in a 9:1 volumetric ratio and the supernatant plasma separated; usually by sedimentation for a few hours though centrifugation was sometimes used (the College laboratory had purchased a centrifuge in the early 1900s). Addis timed clot formation after adding small quantities of normal blood derivatives, including 'fibrinogen' and 'prothrombin' prepared by Mellanby's methods, tissue (testicular) extract, etc, and then calcium chloride – usually equivalent to one volume of 2% calcium chloride to ten volumes of oxalated plasma. In this way he anticipated the 'prothrombin time' of Quick[27] and the partial thromboplastin time of Langdell *et al.*;[28] Addis showed that there were no inhibitors and that the component missing from haemophilic blood does not lie in either cells or platelets, but in the plasma. Not surprisingly, he failed to appreciate that this missing component – the 'Anti-Haemophilic Globulin' of the mid-1930s[29, 30] – normally participated in what later came to be called 'intrinsic thromboplastin generation'.[21]

In a related study,[31] Addis showed that native plasma contained complement. This was in contrast to Gengou's theory which held that complement came from white cells, just as Sahli argued that thromboplastin came from white cells. Like Mellanby, Addis used unanticoagulated bird blood which would have been unaffected by clotting or calcium chelation.

In May 1910, Addis conducted some truly remarkable work culminating, on the 20th (the day of Edward VII's funeral), in the first ever transfusion to a haemophilic patient of fresh anticoagulated blood.[32] (In 1840 fresh unanticoagulated blood had been transfused, with difficulty, to a haemophilic boy,[33] and Crile summarised three other cases.[34]) This imaginative enterprise was more questionable and risky than Addis realised: questionable because it was an unprecedented investigative procedure rather than given for treatment (being the culmination of a series of IV injections of various types of sera – for which there were precedents[35]); and risky because he had conducted no pre-transfusion compatibility (blood grouping) tests.

Weil's apparent success with 20 cc of (horse anti-diphtheria) serum, given intravenously pre-operatively to a 40-year-old haemophiliac requiring drainage of a perinephric abscess, is surprising because serum has no factor VIII activity; but he was led to advocate 10–20 cc of serum IV or 20–30 cc orally as a pre-operative measure for haemophiliacs requiring surgery. It mattered not whether the serum was human or animal. Weil's success was probably more due to his patient not being severely affected than to any virtue in the serum.

No-one in Edinburgh at that time knew about blood groups – they were not even mentioned in Crile's 1909 textbook on transfusion[34] (although it did refer, rather dismissively, to sporadic haemolytic post-transfusion episodes). Indeed, they were not recognised outside Landsteiner's immediate circle except by a young New York physician at the 'German Hospital'.[36] Two months before Addis conducted the transfusion, Moss's seminal article on blood 'isoagglutinins and isohaemolysins' came out,[37] but it may well not have been read by Addis until later. Essentially a re-announcement and extension of Landsteiner's discovery of blood groups,[38] it was expressed somewhat obscurely (Moss did not really understand the basis for his observations). No-one in Edinburgh applied Moss's work for several years, even though it was the sort of topic which might have interested M'Gowan (but at the time he was concentrating on an outbreak of distemper in the laboratory's animal house[39]).

Presumably with Weil's claims in mind, Addis also gave his subject 8 cc of 20-hour-old human serum intravenously. Clotting time was accelerated, but less effectively than by blood; nevertheless it seemed preferable because of its much smaller volume and the inconvenience of preparing phosphated blood. Three months earlier, Addis had given 15 cc of 96-hour-old human serum which also accelerated the clotting (of finger-prick blood); but normal or anti-diphtheritic horse serum older than five weeks given intravenously had no perceptible effect. (Therefore his subject probably did not have factor IX deficiency.)

Other concerns about donor blood clotting, and assumed toxicities of anticoagulant oxalate or citrate given intravenously, made him turn to sodium phosphate. From his account 'about 300 cc' of freshly drawn human whole blood (probably his own – and if so, an unidentified collaborator, possibly Finlay, must have taken it), to three parts of which had been added one part of 5% sodium phosphate, was injected intravenously. After the transfusion the patient's recalcified oxalated plasma

clotting time at 20° C (in normal subjects, 13 minutes) fell from 245 to 24 minutes.

Addis only reported these *in vivo* infusions[32] when he was in California developing other interests, and after Ottenberg had described similar investigations of haemophilics transfused with citrated blood.[40] He stated he had intended to 'complete and extend these observations, but this has not been possible'. ABO blood group frequency distribution among Britons would, however, have given a two-to-one chance in favour of compatibility. Citrate was introduced in 1914, principally by Lewisohn who in 1915 reported 18 patients (none with haemophilia) transfused with citrated blood.[41]

Why had the relatively small volumes of (fresher) serum given produced such encouraging results? Such effects were often claimed after Weil's report, and, as animal sera were accessible through 'passive vaccines', even their oral use was recommended. Ottenberg and Libman, however, found IV serum ineffective for controlling haemophilic bleeding, although transfused (unanti-coagulated) blood was efficacious.[42] The apparent but spurious potency of human fresh serum *in vitro* and intravenously would have been through several activated clotting factors and biological 'mediators' (complement, kinins, cytokines), which would have faded with storage. (Claims for oral serum were even more spurious.) Intriguingly, Ottenberg[40] reported that IV infusion of citrate alone also accelerated haemophilic blood clotting *in vitro*. Rosenthal and Baehr[43] attributed this to citrate-induced platelet lysis, citing in support a (mild and irregular) decline in platelet count. They also noted that IV citrate had no effect on ducks. Although they assumed ducks to have few platelets, bird blood is defective in factors XI and XII.[21] If, as seems likely, the transient thrombocytopenia and accelerated clotting were caused at least partly by pyrogens in the citrate solution activating the 'contact factors', a similar qualification must be made for Addis's *in vivo* phosphate anticoagulant. Blood donors giving red cells by apheresis in the 1990s – during which an infusion of (pyrogen-free) sodium citrate and saline accompanied the return of their plasma – had no significant changes in platelet count.[44]

Why did Addis choose phosphate? He gave no explanation but in the 1880s phosphate had been used in Edinburgh to anticoagulate blood prior to transfusion. Addis's phosphate-anticoagulant formula was the same as that used by Cotterill, Duncan and Brakenridge.[45–7] Hunter's reservations on transfusion[11] were echoed in Brakenridge's report. Addis must have learnt of phosphate through Cotterill (Brakenridge died in 1896 and Duncan in 1899). Cotterill's wife died in 1909, but his son Denis (1881–1918) became FRCS Edin in 1910. In 1905, Cotterill gave Addis a career-supportive testimonial. Addis is likely to have heard about transfusions directly from him, thereby later feeling encouraged to try it for himself.

Who was Addis's transfused subject? Although reference 32 gives few clinical details, it is clear from the clotting times and dates that its 'Cases I, II and III' were the 'Cases III, IV and V' in reference 23. Of these two brothers and a cousin Addis wrote[23] that he was indebted to 'Dr Groves of Bristol' who had published their histories and family tree in 1907.[48] They were listed by Bulloch and Fildes, who had consulted Groves, as 'pedigree 500'.[2] Groves describes the man who came to be transfused by Addis in 1910 as a 'well grown, intelligent lad who has had almost every variety of bleeding,' and described his main clinical feature – a Volkmann's ischaemic contracture of his right arm. This had stopped him from gaining work as a tram conductor or on the railways. One gets the impression that although he bled a lot, he was not physically inactive. Bulloch relays how he once landed awkwardly from his bicycle, and both ankles were stiff and painful. Groves names him 'William W' (and his younger cousin 'Harry C'); but Bulloch gives the surnames – Webb and Curtis. William Webb would have been about 20 when Addis transfused him.

However, there are inconsistencies. Case II of reference 23 was described as a mildly affected middle-aged cousin of Case V; but this fits neither Groves's nor Bulloch's charts. There is probably a misprint – Case II was very likely a cousin of Case I (the man bleeding from his tooth, and cousin of the men with nephritis). In both, the haemophilia was mild. Groves also stated that William's younger brother was not a 'bleeder', but Addis found him to be so – presumably the boy's bleeding tendency had not yet become apparent to Groves. Also, Bulloch reported III, IV and V to be residents of Kingswood near Bristol, but Addis conducted the transfusion in Edinburgh.

RECAPITULATION 1906–11

It seems that something like the following sequence took place. In 1906 or 1907, while working at Gloucester, Addis visited Bristol where a new Faculty of Medicine was developing. He met Groves – MD, MS, FRCS and about 15 years his senior. Addis may have seen Groves as a potential mentor. Groves introduced him to the Webb/Curtis family and Addis may have been struck by the cheeriness in adversity of young William – then 16 years old and with a horrendous contracture in his forearm. Addis – susceptible to the suffering of the poor – became interested in clotting disorders; but with few other haemophiliacs available – apart from the mildly affected cousins (I and II) – turned to examine clotting in commoner haemostatic disorders, particularly thrombosis.[14] He went to Edinburgh, obtained his MD in the Physiology Department (he would also have had to pass a clinical examination) and returned to Gloucester in the summer of 1908 to conduct clinical studies with his modification of M'Gowan's apparatus.

In May 1909 he visited Berlin, heard reports of the

haemophilic Hampel family and arranged to visit them. That autumn, in Heidelberg, he investigated four family members with his modified M'Gowan method. He also learnt how to analyse their venous blood, of Weil's work on serum therapy in haemophilia, and of Mellanby's on prothrombin. Returning to Edinburgh in early 1910 he investigated the venous blood of three more haemophiliacs. In May 1910, William Webb and others of his family were in Edinburgh – possibly sponsored by Addis – where with Cases X, XI and XII of reference 23 they provided many venous blood samples for the later stages of Addis's work. Here, Addis gave William various doses of serum intravenously, and 400 mls of phosphated blood, following this up until late June.

In July – more than two months after William's transfusion – he had his altercation with Sahli at the BMA meeting. Sir Clifford Allbutt, Regius Professor of Physic at Cambridge, may well have been there too – he had addressed the Pharmacology Section the previous day (on digitalis). Any favourable impression Addis might have given could have been reinforced when Allbutt visited Edinburgh in October to open the laboratory of clinical medicine at the Royal Infirmary, and to address the Royal Medical Society (on blood pressure). For reasons mentioned, however, Addis kept quiet about the transfusion even though the Chairman at the BMA meeting remarked that 'he was sorry Dr Addis had not drawn conclusions of what occurred *in vivo* from his experiments *in vitro*'.[24] (Did he suspect something?) That autumn Addis finalised his report for publication.[1] He left for Stanford the following spring. Addis never forgot William and regretted not completing his haemophilia work more satisfactorily. When Ottenberg reported,[40] Addis paid belated tribute to William by putting his experiences on record.

AFTERMATH I – HAEMOPHILIA AFTER ADDIS

Back in Edinburgh, Finlay continued Addis's interest. In January 1915, a haemophiliac (probably not William Webb) died under his and Gulland's care after prolonged bleeding from a cut lip, despite many doses of serum, usually given by mouth. Although Finlay thought that the serum (by mouth) helped reduce clotting times, he used Addis's modification of M'Gowan's method.[49] There is no record of venous samples being taken – perhaps access was very difficult. Although JM Graham (Figure 2; 1882–1962; President, Royal College of Surgeons of Edinburgh, 1945–6) was conducting transfusions in the Royal Infirmary that same month,[50] Gulland may still have been unwilling to try it (although by 1918 he was referring cases to Graham). Perhaps Addis would not have done any better; but he might have.

From New York in 1916, Peterson, who referred to Addis, described a miscellany of 34 transfusions with unmodified (i.e. unanticoagulated) blood of which six were to haemophilic boys.[51] Two were transfused and responded well, but the response was less good in the others who received intramuscular injections (presumably venous access was difficult). Unger (1917), also using unmodified blood in 165 transfusions given by syringe (eight to seven haemophiliacs), commented that although haemophilia is not cured by transfusion, for actual bleeding it is 'practically a specific'.[52]

Citrated blood was used by US Army surgeons on the Western Front[53]; several Britons, particularly Geoffrey Keynes (London) and JM Graham (Edinburgh), applied this back in civil practice.[54, 55] War also disrupted Morawitz's transfusion research. He conducted over 200 blood transfusions with potassium citrate in post-war Würzburg,[56] but would have been well placed to promote transfusion for haemophilia earlier. Whether haemophiliacs were included in Würzburg is unstated. In the US, in a neat reprise of Addis, Bulger reported good clinical results after transfusing 300 cc of a mother's citrated blood to her haemophilic son.[57] Like Addis he found that the usually prolonged clotting of the boy's blood and plasma in the absence of added thromboplastin was greatly accelerated after transfusion (whereas with added thromboplastin – the 'Quick's prothrombin time' – it was equally short after *and before* transfusion). Bulger interpreted this as indicating a 'lack of thromboplastin' in the boy's plasma.

Keynes's 1922 masterpiece on transfusion[54] referred – like Bulger – to Addis, to Minot and Lee, and also to four others, on the efficacy of transfusion for haemophilia without further speculation. Graham reported the first successful (citrated) transfusion to a haemophiliac in Edinburgh in 1923[58] – to an eight-year-old, referred by Gulland, who had cut the sole of his right foot on the seashore. Graham's interest in transfusion began in 1913; like Crile, he initially experimented on dogs; but by 1919 he had transfused 23 patients in Edinburgh, the last two receiving citrated blood, many of whom had been diagnosed (not always correctly) with pernicious anaemia. He was well aware of the past use of sodium phosphate (but never tried it himself) and the need for compatibility. This work – the basis of his ChM thesis (1919, with Gold Medal) – was published separately.[50, 59]

In the 1920s, JM Graham recruited several Edinburgh medical students as 'universal donors'.[60] When required, the donor attended a ward side-room; a pint of blood was withdrawn into citrate and transfused immediately. Those benefiting were mostly people with obstetric haemorrhage, pernicious anaemia, and occasional haemophiliacs. Donors received no fees for 'public' patients and continued normal activities – including their obligations on the rugby pitch. When – rarely – a private patient was treated, the donor would get £5.

In 1925 an account from Worksop described a haemophilic youth with a psoas bleed who survived

surgery after intramuscular injections of blood and serum, and two separate blood transfusions (of 'type 4' – i.e. group O).[61] But another report, which gave Addis's work no more credence than that of Howell or of Sahli, compared haemophilic blood to that of embryonic chicks.[62] The same year saw Gulland's comments that it was 'very doubtful whether a sufficient amount of lime can be added' (orally, to accelerate clotting in haemophilia); nevertheless he advocated large doses of calcium chloride (15–30 grains) and serum transfusions, claiming that patients could be freed of haemorrhage for many months by regular IV administration of serum, even 'normal horse serum from manufacturing chemists'.[63] Transfusion was not mentioned; but at a seminar in 1926 Gulland briefly commented, without references, that an 'ongoing study' in haemophilia had shown it to be effective;[64] and Rolleston devoted only 123 words to haemophilia – which he thought was due to a platelet defect – referring just to Minot and Lee,[25] and Keynes.[54]

In 1932 Kugelmass, who followed Howell's theory, described an 'index' based on the 'prothrombin activity', the 'antithrombin activity' and a 'platelet disintegration' factor without describing how these were measured, or mentioning Addis. All of the eight haemophiliacs studied, aged two to 30, had a low index.[65] It increased transiently in three of them following transfusion – no details given – but fresh serum (animal or human, IV or subcutaneous) and IV citrate also accelerated clotting transiently. (He also tried female hormones to alleviate haemophilia.)

Patek and Stetson[29] held Addis's work in high regard. They repeated the investigations of serum on haemophilic plasma, confirming a distinct acceleration of clotting *in vitro* but poor and inconsistent results *in vivo*. The distilled water they used for their reagents may have been less pyrogenic. This was one of many ground-breaking haematology articles from the Thorndike Laboratories; and Minot came to revise his opinion of Addis's work.[66]

AFTERMATH II – ADDIS IN CALIFORNIA

Addis's period in this field was short, unlike Minot who remained in haematology for over 30 years (sharing a Nobel prize for his work in pernicious anaemia). Addis's attitude to work in Britain may have become affected by a lack of recognition and, if Sahli and Gulland were typical, an unsympathetic attitude from some European haematologists. (I infer Gulland's antipathy from his astonishing lack of reference to Addis's work although as curator of the College Laboratory, 1912–15, and prize-winner for his work there, he must have been aware of it.) Whatever, Addis accepted an offer from Dr Ray Lyman Wilbur, Dean of the newly established Medical School in Stanford, California to whom he had been recommended by Allbutt.[67] Addis went in the spring of 1911: a brief hand-written note in the College archives states 'Tom Addis left for California.' He married in 1913 and became naturalised in 1917. He specialised in renal medicine, describing the 'Addis Count' (of white cells in urine as a mark of glomerulonephritis). No sycophant to authority, he was a passionate advocate of clinical skills and the application of laboratory analysis.

Addis's 30-plus year career at Stanford was characterised by an outstanding appreciation from his colleagues and patients, and by his very radical political views, which led him and his wife, Elesa Partridge (born into California pioneer stock), to join the Communist Party. Although his Addis family roots in Britain were with the founders of the Hong Kong and Shanghai Bank – he was related to Sir Charles Addis – he apparently always displayed a distaste for money, often refusing to treat people who offered cash direct; and also finding difficulty in raising funds for his own research. His nephew and niece recall heated arguments with their own banking parents which, however, were always conducted in an atmosphere of mutual fond regard. Tall and distinguished-looking, and reputed to have 'never used money and so was unable to pay for his normal round of drinks', Addis more than held his own on the Californian golf links. (Perhaps both these characteristics were attributed by his rueful partners to his Scottish upbringing – he never lost his Scots accent.)

In his extraordinary book on *Glomerular Nephritis*[68,69] Addis displayed his highly pragmatic research approach, and also great sensitivity to the problems of those unable to pay for hospital fees, or for anything more than basic laboratory costs. In the era prior to antibiotics and corticosteroids, he defied conventional wisdom by pioneering the 'protein-poor-but-not-protein-free' diet, and a very cost-effective laboratory approach. He and his wife, who was also his dietician, were so appreciated by the local police (several police families had benefited from his care) that they extricated them whenever they raided local Communist Party meetings. Their younger daughter studied with the Bolshoi Ballet; and their elder daughter married David Karnowski, an oncologist. Addis's grandchildren are still living in California.

The photographs (Figures 1 and 2) show a well-presented young man; but Addis was of an independent mind, not afraid to indicate errors even by men of the establishment, and prepared to defend colleagues against accusations.[14] In the introduction to his book[68] he emphasised that the work described in it was produced by a team, and no individual contribution – even his own – was paramount: yet the book caries his stamp. Just as clear was his concern for human welfare – expressed in his later politics and very evident in his book. His departure from Edinburgh was a loss to British haematology and to local haemophiliacs. He was, perhaps, a few years too early.

Addis left a political cauldron. At the 'Heart of Empire' was a widening wealth gap. The election of January 1910 in Britain – called because the Lords had rejected Lloyd

George's 'People's Budget' – reduced Asquith's majority, making him dependent on the Irish Nationalists. The king died in May; coalition talk faded; and the election of December 1910 returned a virtually unchanged House. The new year saw laws passed on National Insurance, limits on the Lords' fiscal powers, and £400 a year for MPs. With increasingly violent demonstrations for women's suffrage, and war-clouds over Europe, California might at first have appeared a picnic.

Captain in the US Army Medical Corps 1917–19, and consultant to the Surgeon General 1942–5, Addis's contributions were recognised by the College. In 1942 he was awarded the Cullen prize 'for the greatest benefit done to practical medicine in the previous four years'. He died, aged 67, in the Cedars of Lebanon Hospital, Los Angeles.[70] At least, he escaped the McCarthy era; but he has no detailed obituary – unlike Graham.[71]

ADDENDUM

After this article was submitted for publication, the author located an article by Gulland and Goodall in 1911 which contains a very fair description of Addis's work,[72] rephrasing his conclusions by ascribing the disease 'to an inherited abnormality in the construction of the prothrombin of the blood'. For therapy, however, they still suggested high doses of calcium orally and injections of serum – which Gulland continued to advocate for more than ten years. In 1912 Hutchison, a physician at the London Hospital, also quoted Addis but recommended transfusion, citing two recent successes in the US.[73]

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