Historical Note

Nephrologist extraordinary—Michael Darmady (1906–1989)

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Abstract

Michael Darmady (1906–1989) is now largely forgotten, although he played a major role in several areas of Nephrology in the early days of the speciality, both as a clinician and as a pathologist. His contributions to the early understanding of acute renal failure and of the use of haemodialysis during the 1940s have been particularly neglected. His nephron microdissection work achieved some influence around 1960, but today he is remembered principally for his classical work on the morphology of the ageing kidney, and on being the first to point out the poorer outlook of kidneys transplanted from older donors, in 1974.

Keywords: acute renal failure; experimental polycystic kidney disease; history of haemodialysis; history of nephrology; nephron microdissection; renal morphology in old age; sterilization

Even in his native England, the name of Michael Darmady is not one which will have been remembered by many in 2006, the centenary of his birth. Yet he was an important figure in the earliest days of Nephrology in UK and the wider world, who contributed, perhaps, to a wider range of topics within the speciality than any other single individual, from clinical dialysis on the one hand to renal histopathology and the ageing kidney on the other.

Career [1–7]

Edward Michael Darmady (Figure 1) was born on 10 April 1906 in London, the child of the then secretary of Great Ormond Street Hospital for children, a member of a family originally from the Scottish border country; his father’s name was Stewart Johnson, but he took the name Darmady from another branch of the family. Later, Michael’s parents moved to St Ives, where they were part of the artistic movement there, and where Michael grew up. He was educated at Dover College, then went up to Emmanuel College Cambridge, where he was a choral exhibitioner (scholar)—he had a fine bass baritone voice. He was also a notable athlete, particularly in rugby football and boxing. He graduated BA in 1930, but as Cambridge at that time had no clinical school, like almost all his contemporaries he came to London for clinical training, in his case to St Bartholomew’s hospital in Smithfield, from which he qualified via the conjoint examination of the Colleges of Physicians and Surgeons in 1933. He was

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Fig. 1. Michael Darmady about 1980 (Photograph taken by JA Hewes, Southsea, Hants. Courtesy of the Royal College of Physicians, London).
then appointed house physician (intern) to Lord Horder at St Bart’s, but decided on a career in pathology, becoming a demonstrator in Pathology under Dr Kettle, Dr G Hadfield and Dr LP Garrod there. Then after a period as Assistant Pathologist in Salisbury Royal Infirmary and the Wiltshire County hospitals, he volunteered for the Royal Air Force (RAF) in 1940, becoming a Pathological Specialist with the rank of Squadron Leader.

His wartime experience had a major influence on his work, igniting interest in two subjects which were major features of his career: cross-infection (he had responsibility for RAF personnel with hepatitis, either by infection or by transfusion) and kidney disease, in the form of acute renal injury. On demobilization from the armed forces in 1945, he was appointed pathologist to Portsmouth and the Isle of Wight, and remained in that area for the rest of his career. He obtained his MD in 1946 with his thesis on ‘The relationship of anoxia to traumatic uraemia’ and became a Fellow of the Royal College of Physicians in 1954, as well as a founding fellow of the Royal College of Pathologists in 1963. When the University of Southampton acquired a faculty of medicine he was appointed its foundation professor of Pathology, a post he held until his retirement in 1971.

Darmady was a large man, a trencherman of some repute and a lover of wine, reflected in his physique in later life. As a sportsman he was a county rugby player for Cornwall in the 1920s. He was a regular supporter of the Renal Association and of the UK meetings during the 1950s and later took an active role in the evolution of Pathology as a subject and a speciality within the country as a whole. Later he was President of the UK Association of Clinical Pathologists. He was described by all as modest, gentle, convivial and accessible; he and his wife Mary (Bird) had a happy marriage blessed by three children, one of whom became a paediatrician. A research laboratory is named after him in the Pathology department at the Queen Alexandra Hospital, Portsmouth, and a university pathology prize commemorates him.

Early research

As a pathologist at St Bartholomew’s, Darmady worked on hepatic fibrosis, for which work he received a grant from the UK Medical Research Council (MRC) in 1937 [8]. I have not been able to identify any publications relating to this work, however.

Work on acute renal failure and dialysis

Darmady’s interest in this topic began whilst in the RAF during the second World War. After volunteering for military service in 1940, he was appointed as a pathologist to the RAF hospital at nearby Wroughton (close to Swindon in Wiltshire) later that year. In 1941, attention was re-drawn by Eric Bywaters (1910–2003) and his colleagues to the acute renal damage following crush injury with muscle damage [9], which had been reported by several German authors during the first World War but overlooked since then. Many such patients were reported in both military and civilian casualties during the second World War. At the same time, the similarity of these patients to acute renal failure following severe falciparum malaria, as well as haemolysis from other causes such as the incompatible blood transfusions complicating the introduction of blood banking and transfusion became apparent. Gradually the idea that such patients might have something in common arose [10]: the concept of a general syndrome of ‘acute anuria’, with a similar renal pathogenesis emerged during the middle and later 1940s, even though the relative roles of circulating pigment (myoglobin, haemoglobin) or renal ischaemia in producing the renal tubular necrosis found on histology were debated intensively at the time.

The incidence and awareness of such patients increased rapidly in the mid-1940s, almost certainly the paradoxical result of the better management of the early phases of cardiovascular collapse. This in turn arose from blood transfusions being available from the newly created blood banks, and the widening use of intravenous crystalloid solutions, based on work done in the 1930s on fluid balance by many clinicians and experimentalists [10]. In many severely injured subjects this led to partially-successful resuscitation, which permitted more frequent survival, but also led to oligo-anuric acute renal failure in a minority.

In an application for funds to the MRC in 1946 [7,11], Darmady wrote

my interest in traumatic uraemia was first roused whilst I was a pathologist to [the] RAF hospital, Wroughton. During the invasion of France and Germany [in 1944 and 1945] this hospital was acting as a casualty and clearing station to air-evacuated wounded, and an opportunity was afforded of seeing about 20 cases of acute uraemia following severe trauma. These cases resembled those following crush injury except that in our patients there was not history of crushing accident, nor was there evidence of gross muscle ischaemia. For this reason my colleagues and I felt that the muscle ischaemia was not the primary aetiological factor concerned, and suggested that this was due to derangement of the renal circulation caused by severe shock at the time of wounding

The first eight patients (of whom two survived) with severe limb injury often followed by amputation were reported in the Lancet in December 1944 [12], and a fuller account on 17 in the British Journal of Surgery in 1947 [13].

As a result of his histological observations on the kidneys of many of these patients, Darmady conducted experiments in rabbits, published in 1947 and 1948 [14]. He concluded in 1946 [11] from both his clinical and experimental observations:

Recent work by Trueta [Josip Trueta (1897–1977)] Catalan orthopaedic surgeon who worked on acute
renal failure in Oxford and others has suggested that in shock and following stimulation of peripheral nerves there is such a derangement of the renal circulation, and that it can be overcome by section of the splanchnic nerves. They have recommended a splanchnic nerve block for human cases, and although in one of our patients this treatment was successful, in others it was disappointing...the reason for this failure appears to lie in the fact that the kidney will sustain ischaemia for a limited period only... and summarized his work in a review based on his MD thesis in 1947 [15]. The exact pathogenesis of the oligo-anuria resulting from cardiovascular collapse has been investigated intensively since then, but remains at least in part a mystery even today.

However, Darmady was not satisfied with simply observing such patients. He became aware of the work done by Willem Kolff (b. 1911) in the occupied Netherlands through a doctor at the Swedish embassy in London, who drew his attention to Kolff’s work after seeing Darmady’s paper of 1944 [12]. Presumably the work he was directed to read was Kolff’s paper in Acta Medica Scandinavica from earlier that year [16]. Darmady does not mention the use of dialysis by Nils Alwall (1906–1986) in his 1946 MRC application or elsewhere, probably because it was not published until 1947, and details of Gordon Murray’s (1894–1976) patients, dialysed in Canada from November 1946, again were published only in 1948 [10].

Darmady was dealing, of course, with a group of what came to be characterized later as ‘highly catabolic’ patients, whose serum potassium and urea rose precipitously, in contrast to many of the patients seen in civilian practice, such as following poisoning with mercury, in pregnancy and as a result of incompatible transfusions. In these patients oligo-anuria was often brief, lasting only a few days, often the result of mismatched transfusions. Thus, the so-called ‘conservative’ measures centred around limitation of fluid intake and a regime to promote anabolism based on a high-calorie, low-protein diet supplemented by insulin were often sufficient. This view was strongly advocated in Britain by Graham MacGregor Bull (1918–1987) at the Hammersmith hospital, now supported also by Eric Bywaters and A. Mark (Jo) Joekes (b. 1921), despite their earlier experience using haemodialysis (see further).

Darmady saw that control of his traumatized patients using electrolyte management alone was unlikely, and during 1946, just before and after leaving the RAF, he experimented with the design of a dialyser (‘artificial kidney’) and based his application for funds to the MRC [11] on these preliminary studies. This application was successful, and a dialyser (Figure 2A) was built during 1946 and the early part of 1947, partly from materials obtained from wrecked aircraft at RAF Wroughton, and with assistance from ‘Mr Harrison of Goddard’s Garage [in Salisbury]...the painstaking care with which they have constructed the many apparatuses used in this research’ [17]. This was illustrated and described at a session at the Royal Society of Medicine held on 22 January 1948, during which Ronnie Reid, a urologist in Colchester, Essex described his pioneer work on peritoneal dialysis [18], and Bywaters his first attempts with Joekes at haemodialysis, using a kidney donated by Kolff [19].

Darmady realized immediately the many problems with Kolff’s design using a rotating drum in an open bath, in particular the lack of control over the volume in the extracorporeal circuit, which also required large volumes of blood to prime it. Finally, he noted the problem of evaporation from the open dialysate bath. Therefore, although he retained Kolff’s rotating
drum design, he incorporated two blood pumps which could be geared to operate independently or in parallel, one on the arterial line and one on the venous line (Figure 2B). He made the drum longer and narrower, and partially enclosed the bath in which it lay to cut down evaporation (Figure 2C). Metal was used throughout the machine rather than the wood that Kolff had been forced to use (but which, as a devoted carpenter, he probably preferred). Forty metres of cellophane tubing 25 mm in diameter were used as the blood compartment, with a 20 l dialysis tank [17, 20].

Sadly, Darmady never published his clinical results using this dialyser, and as the views of Bull, Geerd Borst (1902–1975) in the Netherlands and others in favour of 'conservative' management grew in strength in UK, he finally abandoned his dialysis machine. However, it was used on at least 19 patients, of whom we know at least two survived [1]. If needed, he towed the machine in a trailer behind his car around the hospitals in Hampshire, to wherever the patients in renal failure were situated. In 1948 he mentioned also an improved model of flat-plate dialyser in his abstract [20], but whether this was ever used on patients seems unlikely. Thus, Darmady constructed the first dialyser in Britain, as Bywaters and Joekes [19] had used a working machine donated to them complete by Kolff in 1946-47. In fact Darmady was amongst the first half-dozen individuals anywhere to use dialysis for the treatment of acute renal failure [21].

However, haemodialysis was not to be undertaken again in Britain until September 1956, when Frank Parsons (1918–1989) began using the Brigham modification of Kolff's dialyser in the department of Urology in Leeds [10]. Why Darmady abandoned dialysis is not clear, and he never discussed this in print, despite participating in several symposia on the subject with clinicians and pathologists [22]. A major factor is likely to have been the enormous personal effort required in undertaking and supervising dialyses more or less single-handed, which must have interfered with his work and career as a pathologist. By 1949 he may also have become convinced, along with Bywaters and Joekes, that the results simply did not justify the input compared with those obtainable by 'conservative' management.

Realising the need for some means of assessing fluid balance rapidly and easily during dialysis and other situations ("...one urgently requires a machine which will weigh the patient in bed, which is after all the simplest method of judging water loss" he wrote in 1952 [22]), Darmady turned his mechanical skills also to the design of a weighing bed, the first of its kind [23]. This was manufactured by WT Avery of Birmingham, and cost £180 complete (about £5500/8000 € today).

In addition he appreciated very early the need for electrolyte measurements, above all that of plasma potassium, then available only using a slow and tedious precipitation method. Thus, when a flame photometer was first described in 1949 in the US, he designed, built and used one of his own, although he did not publish anything on this subject so far as I can find.

**Nephron microdissection and autoradiography**

Nephron microdissection had been practiced since the earliest days of effective microscopy, in the absence of either tissue sectioning or of stains, for example by Joseph Toynbee (1815–1866) under the supervision of Richard Bright around 1840 [24]. However, in the modern era it was the advocacy of Jean Oliver (1889–1976) in the US [25] that promoted its use. Darmady began microdissection in the late 1940s to investigate the lesions of acute tubular necrosis, as Oliver had before him [25]. In this work, he was ably assisted for more than a decade by Fay Stranack, who performed many of the actual dissections, and they presented a joint paper to the Renal Association on this topic in 1951, although no publication followed. The technique involved maceration of the kidney using a variety of agents (in their case concentrated hydrochloric acid), followed by careful and tedious dissection and teasing out of individual nephrons under a dissecting microscope, using domestic sewing needles mounted into wooden handles. Stranack obtained a PhD for this work in 1960.

One of Darmady's special interests was tubular disorders, to which he applied this technique. In 1953 a study of Fanconi syndrome appeared, describing a 'swan neck' appearance of the early proximal tubule [26] (Figure 3). Because of the large urinary losses sustained by such patients, he studied also those suffering inherited diabetes insipidus, finding that both conditions had shorter proximal tubules than normal [27]. At first the 'swan neck' lesion seemed to be specific for cystinosis, but was noted later by them and others in a variety of types of tubular damage...
and diseases. He studied also, after her death, a patient of Hugh de Wardener’s who had presented with polyuria complicating polyarteritis nodosa [28].

The microdissection technique was applied also to studies of transplanted kidneys, and in combination with Bill Dempster, they published an important early paper in 1955 on the tubular and interstitial changes following homotransplantation in dogs [29], followed by studies in seven human transplants in the early 1960s [30] one of which had survived for 1½ years, which showed how extensive the vascular lesions could be. He also studied nephrons from nephrotic patients, with interesting results in the congenital nephrotic syndrome of Finnish type [31]. A summary of Darmady and Stranack’s microdissection work was published in 1957 [32].

From the middle 1950s, the pair also made a number of studies combining microdissection and autoradiography (then in its infancy) to define the sites of binding of different toxic, physiological and pharmacological agents to the renal tubules. This resulted in a series of papers from 1959 to 1964 [33–37] which showed that different agents affected different parts of the tubule.

Although Darmady attended the landmark meeting of the CIBA Foundation in 1961 on renal biopsy [38] and contributed extensively to the discussions during the meeting, he did not have experience of renal tissue obtained by biopsy at that time and did not give a paper.

Studies of ageing kidneys

If Michael Darmady is remembered at all today, it is probably because of his work on the ageing kidney, rather than his experiments with dialysis or microdissection. Around 1970, prompted perhaps by his studies on kidney development, Darmady began a very basic but necessary study of the kidney changes during senescence in normal individuals. He was well aware of the necessity of avoiding the complication of associated hypertensive changes in his subjects, and selected 105 strictly normotensive individuals from youth to more than 100 years from amongst over 200 post mortems he had performed on subjects who had died incidentally. The histology of their glomeruli, tubules, interstitium and vessels was carefully described, and changes defined as primarily due to age were defined [39]: decrease in length and volume of the proximal tubule, appearance of tubular diverticula and dramatic vascular changes. This paper of 1973 became—and remains—a landmark paper in geriatric nephrology. Some of its messages have been forgotten today, in particular the severe vascular changes which accompany ageing in the great majority of even normotensive individuals.

Following on from this work, he studied for the first time the outcome of kidneys transplanted from donors of various ages [40]. As predicted, outcome was worse with the age of the donor, a topic which has generated much debate right up to the present day, as criteria for donation have expanded under pressure due to the shortage of suitable cadaver kidneys.

Other work in renal disease

During the early 1970s, Darmady published a series of papers using the agent 5,6,7,8 tetrahydrocarbazole-3-acetic acid to induce cystic disease in young and even unborn rats [41–44]. Using this and other agents, it was hoped to mimic the lesions of polycystic kidney disease, and indeed the lesions resembled those of the infantile, recessively inherited form of cystic disease; but interest waned in this area when genetic animal models of inherited cystic disease gradually emerged.

Finally in 1980, together with his pupil and colleague Angus McIver, he wrote his final massive publication, a comprehensive 500-page textbook, Renal Pathology [45]. This book was a late example of a textbook by individuals, rather than by a team of experts edited together. Its contents reflect at many points Darmady’s own experience, and in particular his work using nephron microdissection. However, it appears in retrospect to have had little impact on the renal community in UK or elsewhere, and has been little cited or used since.

Work in cross-infection and sterilization

To pathologists, Darmady’s career is of interest not because of his work on renal structure and disease, but because of his pioneer work on cross-infection and sterilization. From the 1940s to the 1960s, he published a stream of papers on a variety of topics from the prophylaxis against ‘serum’ hepatitis [46] (where his interest in the subject began) using sterilization of needles by dry heat, and avoiding syringes by draining blood into a tube; to sterilization of medical and surgical materials [47], disinfection of bedpans [48] and sterilization of baby feeds [49]. He was responsible for the idea of setting up central sterile supply units from the late 1950s, on the model of his pioneer unit in Portsmouth, and advised the British and later many other governments worldwide on sterilization. He did pioneer studies using infra-red heat in 1957 [50] and radiation in 1961 [51] as new sterilizing agents. He was invited to many countries to help with sterilization procedures, and was a leading figure in the area for many years. In fact, his renal work was more or less a hobby to this, his main professional interest and work. In addition, he published jointly a well-used manual of haematology technique [52].
Envoi

It is sad that Darmady, as with so many pioneers of Nephrology, is largely forgotten only 30 years after some of his best work was published. Almost no-one, for example, cites his landmark work on the use of ageing kidneys for transplantation during the intense debates today on this topic. An examination of the reasons for this would require another paper, but certainly electronic retrieval of papers has not, paradoxically, helped the identification of earlier work, but led to a culture where the newest paper seems always the best. At least the horizon for rapid online search has receded from 1966 to 1950, with easier availability of OLDMEDLINE, but Darmady’s early papers in the 1940s must still be sought in now musty volumes of the Index Medicus and the original journals in basements.

Two other factors are worth mentioning also; first, he did not work in a large centre in the capital or even in a major conurbation, and so his contribution was less immediately visible, despite his extensive participation in committees and leadership roles. Second and perhaps more important, his modest personality and aversion to writing led him to publish only a part of his work in several areas, so that his contribution was known more by repute than through texts, and was thus more easily lost.

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Notes and References

11. Grant application to MRC. Application by Dr EM Darmady…for a grant of up to £200 per annum for technical assistance and current expenses, with up to £75 for non-recurrent expenditure. Darmady papers, held by his family
20. A film of Darmady’s machine in use is now in the Science Museum in London (Dr Ghislaine Lawrence), and a copy is now also filed in the Video Archive of the International Society of Nephrology. This is probably the earliest film of any dialysis machine in action that we possess—Kolff’s film of his dialyser in use dates from 1949. In the precis paper of 1948, abstracts of the three papers given in the session are printed first and separately in English, French and Russian. Darmady (Darmady EM. Abstract. Proc Roy Soc Med 1948; 41: 410) wrote in this abstract: ‘…but the [rotating drum] machine is bulky, and in spite of this careful control of blood flow the cellophane tube may expand and allow accumulation of blood. We have therefore developed a second and more compact machine, in which the cellophane tubing is run through a series of plates, the dialyzing fluid being injected by a series of ports in the centre of the plates. In this way the same sized dialysing surface can be compressed into a machine 18 inches [45 cm] long and nine inches [23 cm] high, and at the same time the volume of blood in the machine cannot be increased.’ This machine is not discussed in the main paper [17], however, which Darmady still described as a ‘precis’
21. Unfortunately we do not know exactly when Darmady first used his dialyser on a patient. The application to the MRC for funds to construct it [14] is dated 15 November 1946; while a copy of the photograph reproduced in the 1948 precis [17] (Figure 2A) and found in Darmady’s papers has, written on the back in ink ‘general view of the apparatus in use’ and the date ‘January 1948’. Thus, it seems most likely that it was first used some time during 1947. Bywaters and Jockes [20] used their machine donated by Kolff clinically from October 1946 (see Ch. 11 of reference [10] for further discussion of early haemodialyses)
References


