FINAL REPORT

regarding

Elsie DEVINE (Ref No. BJC/16)

PREPARED BY

Dr C.R.K. Dudley

Consultant Nephrologist and Senior Clinical Lecturer

The Richard Bright Renal Unit, Southmead Hospital, North Bristol NHS Trust,

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AT THE REQUEST OF

Hampshire Constabulary

Date of report

20 March 2005

CONTENTS

1. SUMMARY OF CONCLUSIONS

Mrs DEVINE was an elderly, "frail" lady who had a plasma cell dyscrasia manifested by the presence of an IgA lambda paraprotein and amyloidosis. In addition, she had the nephrotic syndrome and progressively deteriorating renal function probably as a consequence of renal amyloid. In the 9-12 months prior to her final hospital admission, she had suffered with chronic memory loss and had become unable to look after herself. She was admitted as an emergency to hospital with an acute confusional state for which no cause other than multi-infarct dementia and severe renal impairment could be found. After a period of stabilisation, her clinical condition worsened with severe renal failure and worsening agitation and restlessness. Although it may have been possible to stabilise her condition with relatively simple measures, this would not have materially changed her prognosis as death was inevitable. She was treated appropriately in the terminal phase of her illness with strong opioids to ensure comfort and calm, to enable nursing care and to maintain her dignity.

2. INSTRUCTIONS

I was asked to prepare this report on the instructions of Detective Sergeant Code A of Hampshire Constabulary based at Fareham Police Station, Quay Street, Fareham, Hampshire PO16 0NA.

3. ISSUES

I was asked to consider the following issues:

3.1 Beyond all reasonable doubt, was Mrs Devine dying due to her failing renal condition?

3.2 If Mrs Devine was beyond all reasonable doubt dying of renal failure, would any simple measures that were available and appropriate have had any reasonable chance of making a difference?

3.3 Would the acute confusional state that Mrs Devine developed be in keeping with dying from renal failure?

3.4 At the time when Mrs Devine's renal function declined, would a better assessment have identified appropriate treatment options that would have had a reasonable chance of stabilising or improving her situation?

3.5 Would the acute confusional state be untypical of someone dying of renal failure?

3.6 A comment on the use of strong opioids to "calm, keep comfortable and enable nursing care" in someone dying of renal failure who is not in obvious pain.

4. BRIEF CURRICULUM VITAE

I am a full time NHS Consultant in Renal Medicine at the Richard Bright Renal Unit, Southmead Hospital, North Bristol NHS Trust and an Honorary Senior Clinical Lecturer at the University of Bristol. I have been in post since January 1995. I hold post-graduate qualifications in General Internal Medicine. I am included in the Specialist Register of the General Medical Counsel. I am experienced in all aspects of renal medicine and renal transplantation, and confirm that I have experience relevant to this case. A copy of my brief curriculum vitae is available in the appendix of this report.

5. DOCUMENTATION

This Report is based on the following documents:

(1) A copy of Mrs Elsie DEVINE'S medical records

(2) A copy of a statement made by Dr Judith STEVENS (statement number S237), Consultant Nephrologist, Portsmouth Hospitals National Health Service Trust

(3) A copy of a statement made by Dr. Tanya CRANFIELD (statement number S254), Consultant Haematologist, Haematology Department, Michael Darmady Laboratory, Queen Alexandra Hospital, Cosham, Portsmouth

(4) A copy of a statement made by Dr Jane BARTON (no statement number), General Practitioner, Forton Medical Centre, White's Place, Gosport, Hampshire and Clinical Assistant at Gosport War Memorial Hospital from 1988 to 2000

Detective Sergeant Code A provided all these records in a single lever arch file. The quality of some of the photocopied medical records was poor and difficult to read and in places was unreadable. Similarly, the size and quality of the copy of the drug treatment charts is such that these could not be read clearly (e.g. page 277).

The copy of the medical records has been paginated. In my report reference to the relevant page number from the medical records is given in parenthesis.

6. CHRONOLOGY/CASE ABSTRACT

SEQUENCE OF EVENTS PRIOR TO ADMISSION TO HOSPITAL

Mrs DEVINE an 87 year old lady, was referred to Dr LOGAN (Consultant Physician in Geriatrics) on the 9th March 1999 because of increasing ankle swelling and abnormal blood tests including a creatinine of 130 µmol/l (normal laboratory range for females given as 45 – 90 µmol/l). In the past a diagnosis of mild to moderate congestive cardiac failure and hypothyroidism (under-active thyroid gland) had been made. At the time of referral she was taking a combination of a "water tablet" (diuretic) known as Co-amilofruse 5/40 one or two a day and Thyroxine 100 micrograms a day. She was seen on the 1st April 1999 in the Elderly Medicine Clinic by Dr RAVINDRANE, Specialist Registrar to Dr LOGAN. A number of investigations were performed which revealed the nephrotic syndrome which is a condition whereby excessive amounts of the blood protein albumin leak through the kidney into the urine resulting in a low blood albumin level. As a consequence fluid retention occurs, characterised by swelling of the ankles as in Mrs DEVINE'S case. Her kidney function had also deteriorated with her creatinine rising to 151 µmol/l. An ultrasound of the kidneys had been performed (page 375) and was reported as showing both kidneys to be slightly small, the right measuring 8.7 cm and the left 8.4 cm. No other abnormality was identified and a chest x-ray was normal. Blood tests also revealed the presence of an IgA lambda paraprotein quantified at 5.9 g/l. Her urine however tested negative for Bence Jones protein (often found in a condition known as myeloma).

Following a clinic visit on the 15th April 1999, Dr LOGAN referred Mrs DEVINE to Dr TANYA CRANFIELD for a further opinion on whether the paraprotein was associated with a haematological malignancy such as myeloma with the nephrotic syndrome related. In his referral letter he noted that Mrs DEVINE was *"moderately frail but very bright mentally"*.

Dr CRANFIELD assessed Mrs DEVINE in the clinic on the 13th May 1999. She went onto perform a bone marrow biopsy and aspirate which revealed no evidence of myeloma and although plasma cells were prominent they made up only 6% of the nucleated cells present. There were no lytic lesions on a skeletal survey although this did show generalised osteoporosis. On the basis of these investigations Dr CRANFIELD felt that there was insufficient evidence for a diagnosis of myeloma to be made (page 70). She referred the patient to Dr JUDITH STEVENS, Consultant Renal Physician in view of Mrs DEVINE'S deteriorating renal function and for an opinion on the cause of the nephrotic syndrome.

Dr JUDITH STEVENS reviewed the patient in a clinic on the 8th June 1999 (page 60). Dr STEVENS' opinion was that *"in view of the small kidneys this is likely to be long-standing glomerulonephritis rather than a new problem"*. Glomerulonephritis is a condition resulting in damage to the filtering units of the kidneys usually associated with blood and protein loss in the urine. A modification in Mrs DEVINE'S diuretic tablets was suggested. In her letter she noted, *"she is a rather frail old lady"*.

The patient was further reviewed by Dr CRANFIELD in a clinic on the 28th July 1999 (page 50). In that letter she noted that Mrs DEVINE'S leg swelling was much better controlled on the increased dose of diuretic tablets. She noted that further laboratory staining of the bone marrow biopsy revealed the presence of amyloid. She also noted that the patient's kidney function had worsened further with her creatinine rising to 192 µmol/l.

Mrs DEVINE was reviewed again by Dr STEVENS in a clinic on the 7th September 1999 when Dr STEVENS noted that the oedema (swelling) extended up to the patient's knee. A further increase in the dose of diuretic medication was recommended.

SEQUENCE OF EVENTS FOLLOWING ADMISSION TO QUEEN ALEXANDRA HOSPITAL

Mrs DEVINE was admitted to the Queen Alexander Hospital, Cosham, Portsmouth on the 9th October 1999. The referral letter from Dr P. SMITH, a general practitioner at the Health Centre, Osborne Road, Fareham, reported that for 2 days she had been confused, aggressive and wandering (page 38). The copy of the medical records provided to me from the day of her admission are illegible but from the discharge summary (page 24) and the remainder of the medical records (from page 158) I can determine that she was treated for a possible urinary tract infection and given intravenous fluids. She remained very confused and aggressive and had a mental test score of 3/10 reflecting significant cognitive impairment. A creatinine of 201 µmol/l was noted. This indicates advanced renal failure (calculated creatinine clearance of 14 mls/min; chronic kidney disease stage 5).

Because she continued confused and aggressive, refusing medication and physically harming staff, she was treated with Haloperidol, an anti-psychotic sedating drug (page 160).

On the 14th October she was seen by Dr TAYLOR, Clinical Assistant in Old Age Psychiatry, who recorded that since January of that year Mrs DEVINE'S family had noticed a decline in

her memory and was no longer able to look after herself (page 28). She concluded that it was likely Mrs DEVINE had dementia with an acute episode of confusion secondary to urinary tract infection. Mrs DEVINE scored 9/30 on a mini-mental state examination reflecting definite cognitive impairment. Because of Mrs DEVINE'S son-in-law's ill health and requirement for treatment in London, her daughter was no longer able to care for her. A recommendation that she be referred to the social services for residential care in a home that had experience in dealing with memory problems was made (page 29). A CT scan of the head was performed with sedation on the 18th October and was recorded as showing involutional and ischaemic changes only (signs of atrophy and impaired blood supply due to blockage of small arteries) (page 168). The patient was assessed by Dr JAYAWARDENA, Locum Consultant Physician in Geriatrics on the 19th October who thought her suitable for a rehabilitation programme and made arrangements for her care to be transferred to Gosport War Memorial Hospital (pages 26 and 171). On the 18th October her creatinine is recorded as 201 µmol/l (page 171).

SEQUENCE OF EVENTS FOLLOWING ADMISSION TO GOSPORT WAR MEMORIAL HOSPITAL

On the 21st October 1999, Mrs DEVINE was transferred to Dryad Ward, Gosport War Memorial Hospital under the care of Dr REID, consultant-in-charge. The plan recorded in the notes by Dr BARTON at that time was for the team to get to know Mrs DEVINE, assess her for rehabilitation potential and probably place her in a rest home in due course (page 154). She was noted to be mildly confused, mobile, able to wash with supervision and dress herself as well as being continent (page 154). A mini-mental state examination of 9/30 was recorded. Elsewhere in the notes it is recorded that Mrs DEVINE was quite confused and disorientated (P155). I am not able to identify from the signature in the notes by whom this entry and others elsewhere were made. However, Dr BARTON identifies these entries in her statement as being made by Dr REID. Mrs DEVINE'S creatinine is recorded as 187 µmol/l on the 22nd October and as 200 µmol/l on the 9 November 1999 (page 349). By the 15th November, the patient's condition had apparently deteriorated and Dr REID notes that she had become very aggressive at times and very restless requiring the use of thioridazine, an antipsychotic drug used to calm restless patients (page 155). The patient was receiving treatment for a suspected urinary tract infection although a mid-stream urine sample (MSU) had revealed no growth. A referral back to Dr LUSZNAT was requested and made the following day (page 155). On that date (16 November 1999) laboratory results revealed a marked deterioration in Mrs DEVINE'S kidney function as demonstrated by a rise in creatinine to 360 µmol/l (page 349).

She was seen on 18th November 1999 by a locum staff psychiatrist who noted that the patient had deteriorated and had become more restless and aggressive again (page 156). She was placed on the waiting list for Mulberry ward.

On the 19th November, Dr BARTON'S entry in the notes records *"Marked deterioration overnight. Confused and aggressive. Creatinine 360. Fentanyl patch commenced yesterday. Today further deterioration in general condition, needs sc analgesia with midazolam. Son seen and aware of condition and diagnosis. Please make comfortable. I am happy for nursing staff to confirm death"*(page 156). The nursing notes on 19th November record that the patient's condition had deteriorated markedly over the previous 24 hours and that she had become extremely aggressive refusing all help. Chlorpromazine had been given intramuscularly (an antipsychotic drug used to calm restless patients) and a syringe driver consisting of 40 mg diamorphine and 40 mg midazolam had been commenced at 09.25 (page 222 and 223). Mrs DEVINE died on the 21st November 1999.

7. TECHNICAL BACKGROUND / EXAMINATION OF THE FACTS IN ISSUE

Mrs DEVINE had progressive renal failure and the presence of the nephrotic syndrome would indicate that there was damage to the filtering units within the kidney. It is possible that this was due to an unrelated glomerulonephritis (non-specific term for "inflammation" within the glomeruli or sieving units) as suggested by Dr STEVENS. However, it is more likely that it was directly related to the underlying IgA lambda paraprotein.

IgA is one of 5 classes of antibody protein (immunoglobulin) produced by plasma cells within the bone marrow and lymph glands. Different plasma cells produce different types of IgA antibodies resulting in a mixture within the blood referred to as polyclonal (derived from many different clones of plasma cells).

Occasionally for reasons that are poorly understood, a plasma cell divides and multiplies to an aberrant degree resulting in an abnormal collection of identical plasma cells producing the identical antibody type (in this case IgA lambda). Using biochemical techniques, the excessive amount of anomalous identical antibody type can be identified in the blood. As this protein is derived from one individual clone of plasma cells it is referred to as a monoclonal immunoglobulin or paraprotein.

Such an expansion of monoclonal plasma cells is abnormal. At one extreme, the number of abnormal plasma cells proliferating in the bone marrow is excessive (> 10%) and suppresses

the other normal plasma cells as well as destroying the bone itself (lytic lesions), causing an elevated plasma calcium level. This is a malignant condition known as multiple myeloma and untreated results in death. At the other extreme, the number of abnormal plasma cells is low, the number of normal plasma cells is maintained and the bone is not destroyed. The significance of the abnormal clone is uncertain and the patient remains well without treatment for many years. This condition is known as a monoclonal gammopathy of uncertain significance (MGUS). Between these two extremes is the condition of smouldering multiple myeloma, which has some but not all the features of multiple myeloma but probably represents an early stage of this condition. This group of conditions is known as plasma cell dyscrasia (reference 1).

A component of the monoclonal immunoglobulin known as the light chain may "join together" and become deposited particularly in the walls of blood vessels. This condition is known as amyloidosis and can be identified from a biopsy of an affected tissue or organ. In the setting of a paraprotein, amyloid can be thought of as a malignant condition with a prognosis similar to that of multiple myeloma (reference 2). Within the kidney, amyloid is deposited in the sieving units (glomeruli) damaging them resulting in protein leaking into the urine and kidney dysfunction.

Further examination of Mrs DEVINE'S bone marrow biopsy demonstrated the presence of amyloid (page 50). It is more likely than not that the cause of Mrs DEVINE'S nephrotic syndrome and renal impairment was due to the deposition of amyloid within the kidney rather than a *"long-standing glomerulonephritis"*.

On the 20th January 1999, Mrs DEVINE'S creatinine was 130 µmol/l (page 96) with a normal laboratory range for females given as 45 – 90 µmol/l. Using the Cockcroft and Gault formula her calculated creatinine clearance, a measure of glomerular filtration rate, was 22.3 mls/min (normal range usually 80-120 mls/min). This value reflects moderate to severe renal impairment (DOQI Stage 4 reference 3). Over the course of the year there was a progressive rise in her creatinine reflecting a progressive deterioration in renal function. By the 7th September 1999 it had risen to 203 µmol/l (creatinine clearance 14 mls/min) (page 357). During her admission to Queen Alexandra her creatinine varied between 161 and 201 µmol/l (page 349). During her admission to Gosport War Memorial Hospital it varied between 187-200 µmol/l. On the 16th November her creatinine had risen to 360 µmol/l reflecting a marked deterioration in renal function (creatinine clearance 7.8 mls/min) signifying severe renal

failure. It is probable that an unidentified infection was responsible for the deterioration in the patient's general condition and renal function. Intravascular volume depletion ("dehydration") associated with inappropriate diuretic use is less likely given the stability in the patient's weight (see weight chart page 250). Fluctuation in weight over a short period of time is a good indicator of changes in body fluid status.

Mrs DEVINE was admitted as an emergency to hospital with an acute confusional state for which no cause other than multi-infarct dementia and severe renal impairment could be found.

8. OPINION

8.1 Beyond all reasonable doubt, was Mrs Devine dying due to her failing renal condition?

In my opinion, beyond all reasonable doubt, Mrs DEVINE was dying from a combination of amyloidosis, progressive renal failure and dementia. It is probable that the acute deterioration in her condition noted on the 15th November was precipitated by an unidentified infection.

8.2 If Mrs Devine was beyond all reasonable doubt dying of renal failure, would any simple measures that were available and appropriate have had any reasonable chance of making a difference?

It is difficult for me to comment on her diuretic therapy as I cannot read her drug chart clearly. However, the patient's weight chart shows no marked change in weight to suggest significant fluid depletion. In my opinion, any simple measures such as stopping diuretics, the use of intravenous fluids and/or antibiotics were unlikely to have had any significant effect on the eventual outcome. Although her clinical condition may have improved or stabilised for a few days, a further deterioration culminating in her death was inevitable.

8.3 Would the acute confusional state that Mrs Devine developed be in keeping with dying from renal failure?

Mrs Devine appeared to have a chronic confusional state (dementia) which had acutely worsened, resulting in her admission to the Queen Alexandra Hospital. During this admission and after her transfer to Gosport War

Memorial Hospital, her confusional state fluctuated. This chronic confusional state with episodes of exacerbation was likely to be due to a number of factors including progressive renal failure on a background of multi-infarct dementia.

8.4 At the time when Mrs Devine's renal function declined, would a better assessment have identified appropriate treatment options that would have had a reasonable chance of stabilising or improving her situation?

Mrs Devine's renal function declined progressively over the course of 1999 with a further acute deterioration in the final phase of her illness. As stated above, although simple measures such as stopping diuretics, the use of intravenous fluids and/or antibiotics may have improved or stabilised her clinical condition for a few days, further deterioration culminating in her death was inevitable. Treatment options such as dialysis would not have been appropriate given her age, frailty and general medical condition.

8.5 Would the acute confusional state be untypical of someone dying of renal failure?

Death from renal failure is usually characterised by increasing drowsiness leading to coma. However, in a proportion of patients, renal failure is characterised by an acute confusional state (reference 4) and such an observation would not be untypical in a patient with terminal renal failure particularly when a previous chronic confusional state exists.

8.6 Comment on the use of strong opioids to "calm, keep comfortable and enable nursing care" in someone dying of renal failure who is not in obvious pain.

Strong opioids are commonly used in the terminal care of patients dying with renal failure who are agitated and restless to ensure comfort and calm, to enable nursing care and to maintain dignity.

9. LITERATURE/REFERENCES

Reference 1 Kyle RA. Diagnosis and differential diagnosis of multiple myeloma. UpToDate Version 13.1 2005 http://www.uptodate.com/

Reference 2 Kyle RA. Primary (AL) amyloidosis and light and heavy chain deposition diseases. UpToDate Version 13.1 2005 http://www.uptodate.com/

Reference 3 Table 10 Stages of Chronic Kidney Disease from Part 4 Clinical Practice Guidelines, DOQI, National Kidney Foundation http://www.kidney.org/professionals/kdoqi/guidelines_ckd/toc.htm

Reference 4 Cohen, LM, Germain, M, Poppel, DM, et al. Dialysis discontinuation and palliative care. Am J Kidney Dis 2000; 36:140.

10. EXPERTS' DECLARATION

1. I understand that my overriding duty is to the court, both in preparing reports and in giving oral evidence. I have complied and will continue to comply with that duty.
2. I have set out in my report what I understand from those instructing me to be the questions in respect of which my opinion as an expert are required.
3. I have done my best, in preparing this report, to be accurate and complete. I have mentioned all matters which I regard as relevant to the opinions I have expressed. All of the matters on which I have expressed an opinion lie within my field of expertise.
4. I have drawn to the attention of the court all matters, of which I am aware, which might adversely affect my opinion.
5. Wherever I have no personal knowledge, I have indicated the source of factual information.
6. I have not included anything in this report which has been suggested to me by anyone, including the lawyers instructing me, without forming my own independent view of the matter.
7. Where, in my view, there is a range of reasonable opinion, I have indicated the extent of that range in the report.
8. At the time of signing the report I consider it to be complete and accurate. I will notify those instructing me if, for any reason, I subsequently consider that the report requires any correction or qualification.
9. I understand that this report will be the evidence that I will give under oath, subject to any correction or qualification I may make before swearing to its veracity.
10. I have attached to this report a statement setting out the substance of all facts and instructions given to me which are material to the opinions expressed in this report or upon which those opinions are based.

11. STATEMENT OF TRUTH

I confirm that insofar as the facts stated in my report are within my own knowledge I have made clear which they are and I believe them to be true, and the opinions I have expressed represent my true and complete professional opinion.

Signature: Code A Date: 20/3/05

Appendix 1: Brief Curriculum Vitae

Name Christopher Richard Knox Dudley

Date of Birth Code A

Current Appointment

Jan 1995 - Present Consultant Renal Physician
The Richard Bright Renal Unit
Southmead General Hospital
Westbury-on-Trym
Bristol BS10 5NB

Senior Clinical Lecturer
University of Bristol

GMC Number 2579799

Medical Education	1976-1982	St Thomas's Hospital Medical School, University of London
Degrees and Qualifications	July 1979	BSc Biochemistry (Hons)
	June 1982	MB BS (Distinctions in Surgery and Pathology)
	June 1985	MRCP
	Oct 1993	MD (University of London)
	May 1999	FRCP

Membership of Societies

The Renal Association
The British Transplantation Society
The American Society of Nephrology

Publications

More than 30 original articles and reviews published in peer reviewed journals, more than 20 abstracts reflecting presentations at international meetings, book chapters in the Oxford Textbook of Medicine.(3rd and 4th Edition) and The Concise Oxford Textbook of Medicine, author of the Transplantation chapter in the UK Renal Registry Report since 2000 and 14 invited lectures including satellite meetings at International Meetings.

Appendix 2: References

Reference 1 Kyle RA. Diagnosis and differential diagnosis of multiple myeloma. UpToDate Version 13.1 2005 http://www.uptodate.com/

Reference 2 Kyle RA. Primary (AL) amyloidosis and light and heavy chain deposition diseases. UpToDate Version 13.1 2005 http://www.uptodate.com/

Reference 3 Table 10 Stages of Chronic Kidney Disease from Part 4 Clinical Practice Guidelines, DOQI, National Kidney Foundation
http://www.kidney.org/professionals/kdoqi/guidelines_ckd/toc.htm

Reference 4 Cohen, LM, Germain, M, Poppel, DM, et al. Dialysis discontinuation and palliative care. Am J Kidney Dis 2000; 36:140.