Nephrol Dial Transplant (1999) 14: 794–804

Nephrology Dialysis Transplantation

Letters and replies

Spurious hepatitis B surface antigen detection in adult haemodialysis patients following vaccination

Sir,
We read with considerable interest the letter by Riley *et al.* [1] on the spurious hepatitis B surface antigen detection in a haemodialysis patient. We would like to make the following comments.

We agree with the authors that cases of transient post-vaccination HBsAg positivity needs to be fully acknowledged to prevent misdiagnosis, anxiety and confusion. However, we disagree with Riley *et al.* [1] on several points: transient detection of hepatitis B vaccine following immunization has been previously described in dialysis patients [2] and was the finding that we observed in 12 adult haemodialysis patients. Therefore, hepatitis B surface antigenaemia in adult haemodialysis patients is a frequent problem that we identified in about 30% of the patients who have been vaccinated against hepatitis B viral infection (Engerix B). The final comment concerns the duration of antigenaemia. Although it was more frequent after 2–4 days of vaccination, it has been described after 20 days [2] and in our experience the maximal time of clearance was 11 days. Thus, to prevent misdiagnosis, dialysis patients must not be screened for hepatitis B surface antigen for at least 12–21 days after vaccination.

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Reply

Sir,
Until our patient developed this problem with hepatitis B surface antigenaemia following immunization which required cancellation of transplantation, we and the staff of the Transplant Unit were unaware that this problem could develop. Although we performed a full literature search and asked the companys involved for drug information there appeared to be no previous publication of this problem in dialysis patients. Of course we now read with considerable interest the report of Janzen L *et al.* We would agree that the problem of hepatitis B surface antigenaemia following immunization in dialysis patients appears to be a much more common problem than in the general population. We are intrigued as to any relationship between this and the poor response to hepatitis B vaccine in such patients. Furthermore, although this problem has now been reported on two occasions we still wonder how well reported this information is to the wider renal community. Such a finding in clinical practice can cause a major upset to the patient and to the running of a dialysis unit which could be avoided if the knowledge were more widely available. We thank our colleagues for this letter and the correction regarding the previous literature.

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Note by the Editor-in-Chief

The Editor-in-Chief is embarrassed that both Dr Esparza and Dr Rutherford fail to carefully read *NDT*, since a similar observation has been published by Brodersen *et al.*
Brodersen HP, Beckers B, Köhler H, Dahlmanns C, Kruska L, Larbig D. 'The test for hepatitis B surface antigen is transiently positive after vaccination with recombinant vaccine' *Nephrol Dial Transplant* 1997; 12: 2756–2757

Renal haemodynamic responses to a chicken or beef meal in normal individuals

Sir,
In a paper concerning 'Renal haemodynamic responses to a chicken or beef meal in normal individuals' Simon *et al.* [1] found a rise in glomerular filtration rate (GFR) after protein stimulation. This finding is in accordance with all of the pertinent literature. They conclude that this might be valid also in patients with chronic renal disease although conceding that caution must be used if data obtained in normal subjects are extrapolated to pathological conditions. In order to show that such extrapolation is not even valid in all nephrologically normal individuals, we would like to draw your attention to our dynamic renal function test studies in normal subjects and in patients with essential hypertension who had normal serum creatinine and no history of any renal disease [2].

In nine healthy controls GFR and effective renal plasma flow (ERPF) (ml/min/1.73 m^2) rose significantly tested pairwise from 118.2 ± 13.9 to 139.5 ± 30.9, $P = 0.023$ and from 503.2 ± 75.6 to 558.3 ± 96.2, $P = 0.013$, respectively. Four patients with mild hypertension and mean arterial pressure (MAP) of 106 ± 3 mmHg (duration $= 13.8 \pm 10.3$ years) showed a rise in GFR (73.9 ± 14.7 to 83.6 ± 17.4, $P = 0.034$) after stimulation, whereas six patients with a MAP of 119 ± 3 (duration $= 17.5 \pm 13.7$ years) developed a paradoxical decrease in GFR (113.3 ± 18.7 to 103.0 ± 14.3, $P = 0.037$). The ERPF showed non-significant change in the first group of patients (277.8 ± 52.6 to 323.9 ± 42.8), whereas the second group revealed significant increase in ERPF (430.7 ± 134.5 to 502.3 ± 113.1, $P = 0.013$).

In order to detect such unexpected dynamic GFR response, the traditional renal clearance determination based on constant infusion to a steady state generally may not be sufficient

to perceive acute short-term changes in renal function after protein stimulation [3]. Therefore, we suggest a technique of modern computer-based assessment of kinetic experiments as used in our studies to find altered dynamic renal functional responses in individuals regarded as normal by traditional nephrological standards [4,5].

This technique permits the judgement of reactivity of the renal vasculature to the influence of protein intake or drugs. The influence of reactive oxygen species (ROS) such as the superoxide anion radical [6] and radicals derived from them can induce hypertension caused by a rise in vascular resistance [7] and especially preferential vasoconstriction of the afferent arterioles of the glomeruli [8]. This phenomenon may explain to the paradoxical acute fall in GFR after protein load [9] mentioned above in hypertensive, but otherwise normal individuals.

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Reply

Sir,
Dr Zitta raises an important point. It is well known that the renal haemodynamic responses to protein challenge are not homogeneous in all individuals and in different renal diseases. Particularly, in patients with essential hypertension there are conflicting reports whether these patients present, or not, an elevation of glomerular filtration rate following a protein challenge [1,2]. In the clinical set, the beneficial effect of protein restricted diet to preserve renal function in patients with chronic renal insufficiency is also erratic [3]. Both physiological and clinical studies are important to clarify the mechanism of variable renal responses to protein challenge, and more importantly to identify the subset of patients with chronic renal failure that could benefit of a low protein diet.

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Letters

Henoch–Schönlein nephritis. Adverse effect of treatment with intravenous immunoglobulin

Sir,
We describe a patient with Schönlein–Henoch Purpura (SHP), and membranoproliferative glomerulonephritis (MPGN), with indicators of poor prognosis, such as renal insufficiency and nephrotic syndrome.

The patient was treated with immunoglobulin (Polyglobin N) which contains 10% maltose as stabilizing agent. Following this therapy he developed haemolysis and rapid deterioration of renal function. A renal tubular regeneration was shown in the second kidney biopsy, performed on the 13th day after this treatment.

Case. A 48-year-old man was admitted to the hospital with purpura and swelling of the legs. He had been in good health until 20 days prior to consultation when he noticed mild cold symptoms and swelling of both ankles. Allopurinol was prescribed elsewhere. In the following days he complained of abdominal pain, arthralgia, purpura, and haematuria.

At the time of admission, his blood pressure was 140/80 mmHg and his pulse was regular, serum creatinine was 1.4 mg/dl, Hb was 15.4 g/dl, haematocrit 46%, white blood cell count was 10 470, platelet count 236 000/μl, and serum uric acid was 9.5 mg/dl.

On the fifth day of hospitalization, his serum creatinine had increased to 2.6 mg/dl, and serum protein was 5.3 g/dl (albumin 2.8 g/dl) and proteinuria 4.6 g/day. Subsequent investigations, (antinuclear antibodies, anti-DNA, antineutrophil cytoplasm antibodies, hepatitis B, hepatitis C, and human immunodeficiency virus antibody) remained negative or normal. No cryoglobulins were detected. Serum immunoglobulin G (IgG) was 912 mg/dl (normal range 690–1400),

IgA 403.1 mg/dl (normal range 88–410) and IgM 59.3 mg/dl (normal range 34–210), and C3 and C4 were 101.3 mg/dl (normal 75–140), and 33.5 mg/dl (normal 10–34), respectively. A skin biopsy demonstrated leukocytoclastic vasculitis with IgA deposits in the arterial walls.

Light microscopy of the first renal biopsy specimen disclosed 10 glomeruli, all of which showed a marked endocapillary proliferation and thickening of capillary walls. Massive subendothelial, mesangial and subepithelial deposits were seen by electron microscopy. Immunofluorescence studies disclosed granular IgG, IgA, C3 and fibrinogen deposits in the mesangium.

The patient was treated with a course of pulse intravenous methylprenisolone, 500 mg/day for three consecutive days followed by oral prednisone 1.5 mg/kg/day, as well as a low sodium diet and 40 mg/day furosemide.

The patient was discharged on this therapy. At discharge, his serum creatinine was 2.3 mg/dl, serum protein 4.4 g/dl (albumin 2.2 g/dl), and proteinuria 8.04 g/24 h with persistent haematuria.

One month later the patient was admitted to the hospital as he noted progressive swelling of his legs and bloody urine. Purpura and arthralgia were absent. On physical examination he had marked bilateral oedema in the lower extremities. Laboratory data showed 12 g/dl haemoglobin, 36.7% haematocrit, creatinine 4 mg/dl, protein 4 g/dl (albumin 1.6 g/dl), and proteinuria 5 g/24 h; urinalysis confirmed 3+++ haematuria. Prednisone was continued and treatment with intravenous immunoglobulin (Polyglobin N) was added at a dose of 400 mg/kg body weight for four consecutive days, infused over 12 h. He also received 120 mg/d furosemide, and 20 mg/d enalapril.

On the third day post-infusion, haemoglobin was 7.3 g/dl, haematocrit 20.6%, platelets 100 000/μl, reticulocyte count 50 800/μl, and LDH was 789 IU/l (normal range was 240–480). Serum creatinine increased daily, and on the seventh day post-infusion, creatinine had increased to 7.4 mg/dl. Urine output was not decreased. At this time, 13 days after infusion of immunoglobulin, a second renal biopsy was performed and disclosed 11 glomeruli, two of which were sclerosed. All glomeruli showed mesangial proliferation accompanied by polymorphonuclear leucocyte infiltration. The glomeruli appeared similar to the previous biopsy, i.e. without crescents, but regeneration of the tubular epithelial cells was present. Immunoflurescence microscopy revealed that membranous deposits of IgG, not IgA were present. Subendothelial and subepithelial deposits were seen with electron microscopy.

At this point, the steroid dose was tapered and withdrawn within 3 months and diuretic treatment was stopped. Thirty eight days after the second admission, creatinine and proteinuria had decreased to 6.02 mg/dl and 4.8 g/24 h, respectively, and continued to do so. The patient remained hypertensive, requiring three drugs to control blood pressure (angiotensin converting enzyme inhibitor, calcium blocker and beta blocker).

One year later, there has been no relapse and the patient is in better clinical condition. Proteinuria was 0.27 g/day, serum creatinine level 2.2 mg/dl, serum proteins 7.4 g/dl, albumin 4.1 g/dl, white blood cell count 7330 cells/μl, platelet count 318 000/μl, and haemoglobin value was 13.2 g/dl; he needs two drugs to control blood pressure.

MP-like GN is an infrequent presentation of HSP and is associated with a different outcome [1]. Specific treatment should be considered only in patients with marked proteinuria and/or impaired renal function during the acute episode.

The patient described here had a MP-like lesion [1], with nephrotic syndrome, haematuria and renal impairment. Based on the clinical data indicating a poor prognosis, he was treated with pulses of methyl prednisolone without improvement in renal function and proteinuria.

Due to the sequence of events, we thought that our patient had a severe form of nephritis which did not respond to the doses of prednisone and, therefore, treatment with immunoglobulin was begun [2,3]. In spite of this, renal function deteriorated and haemoglobin measured as haematocrit decreased with signs of haemolysis. The haemolysis was noted by day three post-infusion, and was self limited. Several cases of clinically significant Coombs positive anaemia have been reported after IVIG infusion [4].

Acute renal failure (ARF), associated with immunoglobulin administration has been reported [5,6]. Its pathogenesis is currently unknown, however, it is likely to be multifactorial. No clear risk factors for the development of IVIG associated ARF are apparent in the cases reported, but patients with renal insufficiency, nephrotic syndrome and old age may be predisposed to acute renal injury with IVIG therapy [5].

The stabilizing agent used in the intravenous immunoglobulin preparation plays an important role in the renal pathology. The histopathological lesion seen on most renal biopsy specimens from patients with associated renal insufficiency are identical to those of sucrose nephropathy. In the majority of cases, the IVIG used was Sandoglobulin, which contains sucrose (5–8). The histological changes of the renal biopsy include swelling and vacuolization of the epithelial cells of the proximal tubule with preservation of the brush border and swelling and vacuolization of the epithelial cells of the glomeruli have been observed in a few cases [7].

Another pathological mechanisms could be abnormal glomerular haemodynamics due to an elevated plasma oncotic pressure. The expected risk of osmotic induced changes are probably higher with sucrose and maltose containing products because of their higher molecular weights. Other factors such a decrease in glomeruli-tubular feedback, and intrinsic afferent vasoconstriction may contribute to renal dysfunction.

In this case, the development of rapid renal insufficiency and haemolysis could be the effect of IgG infusion containing maltose, along with factors, such as previous renal insufficiency and nephrotic syndrome. In view of increasing use of immunoglobulin preparations in nephropathies, it is important to know the adverse effects of the different immunoglobulins available for use, the resulting histological lesions, and the factors which increase the risk of side effects associated with their use.

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cANCA positivity in a case of IgA glomerulonephritis (IgAGN) with necrotizing lesions

Sir,

Necrotizing lesions have been described in glomerulonephritis with IgA mesangial deposits (IgAGN) [1–3], but their significance is still controversial. We observed a case of IgAGN with necrotizing lesions. Associated Wegener's disease was supported by laboratory examinations and by clinical follow-up.

Case. P.M., a 49-year-old man, presented in July 1997 because of renal failure and recent onset of haematuria.

The patient was a commercial agent and had a history of ethanol intake >100 g/day.

Laboratory investigations disclosed: serum creatinine (SCr) 1.7 mg/dl, proteinuria 6 g/day, haematuria (20 RBC/hmf), total proteins 6 g/dl, albumin 3.5 g/dl, IgG 898 mg%, IgA 307 mg%, IgM 116 mg%, RBC 4 310 000/mm^3, Hb 13.7 g%, Plts 257 000/mm^3, SGOT 20 U/ml, SGPT 34 U/ml, gamma GT 91 U/ml, C3 161 mg%, C4 41 mg%. Aslo, rheumatoid factor, ANF, anti-DNA antibodies were negative or normal. Hepatitis B and C markers were negative. Cryoglobulins were absent. Echographic examination showed modestly enlarged and hyperechogenic liver. Rx examination of the sinuses was normal.

There were no systemic symptoms or signs suggesting a systemic disease: no fever, arthralgia, petechiae, abdominal pain, asthma.

Histologic examination showed 18 glomeruli. Six (33%) had global glomerular sclerosis, two (11%) florid crescent formation and two necrotizing areas of the tuft (Figure 1a and b). Mesangial stalk, glomerular basement membrane and capillary lumina were normal. Granulomas were not present. IgA and C3 fractions were found in mesangial areas and occasionally in glomerular basement membrane.

Because of these lesions, IgG-ANCA were looked for: the test was positive and specificity for proteinase 3 was documented both with ELISA determination (27 U/ml; normal value <5 U/ml) and with immunofluorescence (cANCA). CRP was positive as well (26 mg/l). Moreover, ^{111}In-granulocyte facial scanning, a sensitive test for upper respiratory tract involvement in Wegener's granulomatosis [4], was positive. Lung CT was negative. The patient was given 3×1 g methylprednisolone pulses followed by oral prednisone 1 mg/day and cyclophosphamide 2 mg/kg/day.

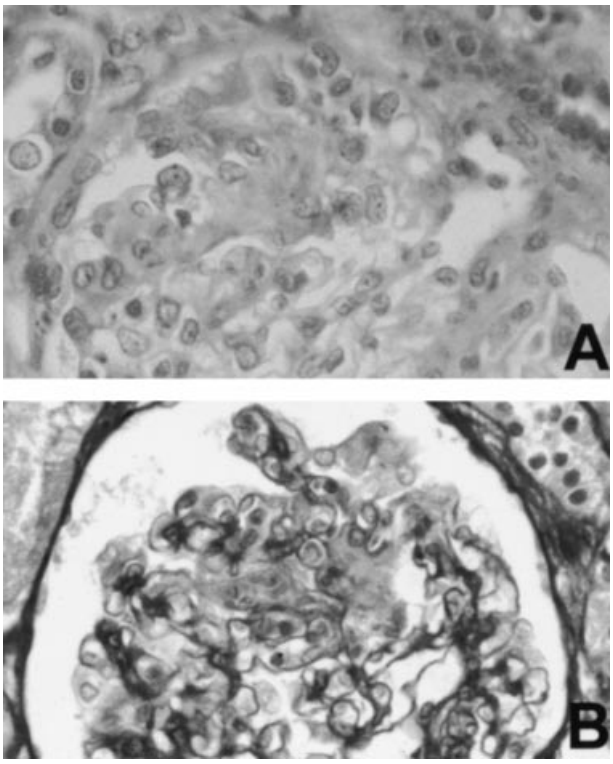

Fig. 1. (**A**) A glomerulus with small cellular crescent (PTAH $\times 250$). (**B**) A glomerulus demonstrating a segmental area of fibrinoid necrosis (AFOG $\times 240$).

In December 1997 scintigraphy and ANCA had become negative, SCr was 1.8 mg%, proteinuria 4 g/day, urinary sediment unchanged.

Comment. In this case, IgAGN was clinically suspected because of the urinary abnormalities and the history of alcohol intake. The diagnosis was confirmed by histology.

In a few cases of IgA nephropathy ANCA have been detected. They are due to an increased IgA binding to neutrophil cytoplasmic extracts, but not to purified ANCA antigens [5]. So our patient's ANCA could not be due to non-specific trapping. Moreover, in order to rule out non-specifically positive cANCA, further investigations were performed to exclude Hodgkin lymphoma, tuberculosis, HIV infection and myeloma, conditions associated with false positive ANCA [6].

The patient was treated with steroid pulses, followed by oral prednisone and cyclophosphamide, which determined a significant response, as a few months later the parameters indicating vasculitis activity were negative (^{111}In-granulocyte facial scanning, ANCA, CRP). SCr was 1.8 mg/dl, due to the presence at biopsy of severe sclerotic changes, proteinuria 4 g/day, urinary sediment was unchanged.

The literature reports some cases of IgAGN associated with leucocytoclastic vasculitis [7,8]. Martin *et al.* have published the case of a patient presenting with overlap syndrome between Henoch–Schoenlein purpura and microscopic polyangiitis with positive pANCA [9]; Ramirez *et al.* have described IgG-ANCA presence in a patient with IgAGN who thereafter developed rapidly progressive GN [10]; Allmaras *et al.* have reported the case of a rapidly progressive IgAGN with anti-myeloperoxidase antibodies which could

represent an overlap between microscopic polyangiitis and IgAGN [11]. Recently, cases of Wegener's disease with superimposed IgAGN have been reported.

The possible association between IgAGN and an IgA-independent vasculitis could be relevant in the genesis of necrotizing lesions in IgAGN.

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Ecstasy-induced renal vasculitis

Sir,

We were interested by the report by Bingham and colleagues [1] because of its many similarities with a case of ecstasy-associated renal vascular disease reported by ourselves [2]. In both cases, ingestion of 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') appeared to be related to the development of severe acute renal failure with, on renal histology, fibrinoid necrosis of the renal arterioles and consequent glomerular ischaemia and infarction. Both patients were hypertensive, severely so in our case, and both failed to recover renal function.

The subsequent clinical course of our patient is of interest. He remained dialysis-dependent for 5 months, following which there was progressive improvement, but not normalization, of renal function. Four years later, he has serum creatinine of 183 μmol/l, and has hypertension controlled with lisinopril and nifedipine in full dose. Over the past 2 years, he has developed cutaneous changes of scleroderma, with telangiectasia and severe Raynaud's phenomenon. Autoantibodies, including ANCA and Scl70, are consistently negative. He has also become hypothyroid, requiring thyroxine replacement therapy. He continues to use cannabis, but probably avoids other drugs.

From these two cases, it would appear that renal vasculopathy is a rare but severe complication of ecstasy ingestion. Cerebral vasculitis [3] has been reported more frequently than renal vasculitis in association with the abuse of various substances, including amphetamines. Although some older reports [4] may have included hepatitis B-associated polyarteritis, it would appear that vasculitis can be caused by amphetamines, cocaine, heroin, and possibly other drugs. The pathogenetic mechanisms are unknown, but clearly it is necessary to enquire of a history of substance abuse in any patient presenting with unexplained acute renal failure, malignant hypertension, or renal vasculitis.

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Mycophenolate mofetil for primary biliary cirrhosis and sclerosis cholangitis?

Sir,

Recently, Ermisch and colleagues have reported the case of a pediatric renal transplantation patient whose liver function improved after triple immunosuppression therapy which included Mycophenolate mofetil (MMF) [1]. The patient of Ermisch and colleagues had biliary cirrhosis secondary, presumably, to a history of a hepatoblastoma which itself may have been secondary to an extensive medical history including congenital bilateral hydronephrosis. The observation by Ermisch and colleagues of the improvement in liver function following treatment which included MMF may have significant implications beyond the obviously welcome clinical benefit in their patient. Indeed, MMF has recently been used successfully in a number of autoimmune diseases including uveitis, pemphigus vulgaris, systemic vasculitis, IgA nephropathy and bullous pemphigoid [2–5]. Perhaps MMF might be useful in treatment of primary biliary cirrhosis and sclerosing cholangitis, either primary or secondary. If MMF were efficacious, it would be a welcome addition to the

therapeutic armementarium for these diseases which can often necessitate transplantation.

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Preliminary survey of the occurrence of anaphylactoid reactions during haemodialysis

Sir,

A number of published reports have described anaphylactoid reactions (AR) in patients dialyzed with polyacrylonitrile high flux (AN69) membranes and who were receiving angiotension-converting enzyme (ACE) inhibitor treatment [1,2]. Because of these reports, FDAs Centre for Devices and Radiological Health (CDRH) issued a safety alert on March 6, 1992, entitled, 'Anaphylactoid reactions associated with ACE inhibitors and dialyzer membranes' to all dialysis facilities [3]. Despite additional reports of ARs in patients dialysed with other types of dialyser membranes or receiving apheresis and plasmapheresis, fewer than 10 reports were received in response to the FDA Safety Alert [4,5]. Because of the growing public health significance and possible under-reporting of reactions, we initiated a preliminary study of dialysis centres to estimate the frequency at which ARs occur during dialysis treatments and to further understand any contributing factors.

Subjects and methods. Two of the US Health Care and Finance Administration's (HCFA) 18 ESRD networks participated in this study. Each network conducted a survey during October 1993. Head nurses of all the dialysis facilities within these regions were asked to recall any anaphylactoid reactions that occurred between April 1 and September 30, 1993. Anaphylactoid reactions were defined as 'all incidents involving two or more of the following symptoms occurring within 20 min of starting dialysis: abdominal cramps, nausea, vomiting, or diarrhea; shortness of breath, tightness of chest, wheezing or bronchospasm; facial swelling, angioedema or laryngeal oedema; hypotension (>20 mmHg drop in systolic blood pressure); flushing or warmth; numbness or tingling of fingers, toes, lips, or tongue'. A case report was filled out detailing patient demographic characteristics, the sequence of events and therapy, the prescribed dialysis treatment, concurrent medications, and history of anaphylactoid reactions. There was a 100% response rate from the dialysis facilities. Additional information gathered included the percentages of patients using various dialyser types, patients on single use or reuse of dialysers, and patients using high flux, high efficiency, or conventional dialysis.

The networks provided aggregate information about numbers of patients, cross-classified by age, sex, race, and renal diagnosis according to ICD9 codes as of the midpoint date for the calculation of 6 month AR prevalence rates for the entire population and simple subsets. In addition, one network provided the numbers of patients at each facility as of December 31, 1992, and December 31, 1993, and the figures were averaged to estimate the population on July 1, 1993. These facility-specific counts were necessary to make simple population estimates of the specific exposures to the different dialysers, calculated by using the percentage of use of the different types of membranes and the numbers of patients for each facility. Analogous calculations were made for single *versus* reuse of membranes and dialysis flux levels.

Crude odds ratios (OR) with exact binomial 95% confidence intervals (CI) [6] were estimated to compare risks of AR in different subsets. Multiple logistic regression analysis was used to calculate the OR and 95% CI, controlling for the independent effects of age, sex, race, and diagnostic category [7]. The final model included information on 68 case individuals and 19 392 controls. Finally, we examined the distribution of cases reported to have been using ACE inhibitors.

Results. Seventy one cases of AR were reported during the preceding 6 months in a population of 20 228 patients, a rate of 3.5 (95% CI of 2.7, 4.4) per 1000 and an annual prevalence rate of 7.0 per 1000. Significant (OR and (95% CI)) risk factors for AR were: female gender, 1.7 (1.1, 2.8); age <50, 2.0 (1.3, 3.3); and cystic kidney disease (compared to diabetes), 3.6 (1.02, 10.5). After controlling for the joint effects of age, race, gender, and cause of renal failure in the logistic model, age 20–49 years (compared to $\geqslant 70$), 3.7 (1.8, 7.6); age 50–69, 2.1 (1.0, 4.1); female gender, 2.1 (1.3, 3.5); and glomerulonephritis (compared to diabetes), 2.3 (1.1, 4.9) and cystic kidney disease, 3.2 (1.1, 9.0) were significantly related to increased risk of ARs.

Dialysis with a polyacrylonitrile membrane was the only statistically significant risk by membrane type, but the association must be interpreted with caution since it was derived from only one patient. Choice of flux level was not statistically significantly related to AR. In contrast, the single or first use of a membrane was associated with anaphylactoid reactions, 2.7 (1.1, 6.6). Patients treated with ACE inhibitors numbered 14 or 20% of ARs. This number was too small to allow any other meaningful conclusions to be drawn regarding overall risk or interactions with other factors.

Comment. This study was designed to provide preliminary estimates of the prevalence of anaphylactoid reactions and clues to risk factors for the purpose of designing additional investigations of their occurrence and causes. It is noteworthy for several reasons. First, we found that the head nurses in these treatment centres could recall a substantial number of ARs (seven episodes per 1000 patients per year) during the 6 months preceding our survey. Thus, if this number is reasonably accurate a dialysis programme with 50 patients, a typical number in these networks, would expect to encounter an AR during dialysis once every 34 months. This rate is in contrast with a previous study by the CDRH, where the annual rate of 'hypersensitivity reactions' reported in 1982 and 1983 to dialyser manufacturers was estimated to be 3.3 per 1000 patients for hollow fibre dialysers and 0.3 per 1000 patients for flat plate dialysers [8]. The difference in these two rate estimates may be due to under-reporting, changes in treatment or other factors that warrant further study.

Second, we found a number of patient characteristics associated with increased risk of AR. Similar to Pegues [4] and Villarroel [8], we observed that younger patients were at higher AR risk and report for the first time that women were at more risk. Further, our data also suggest for the first time some increased risk of AR among patients with polycystic kidney disease and glomerulonephritis.

Third, our data are consistent with the possibility that ACE inhibitors may increase risk of AR. In the absence of information about use in the general (non-case) population, we could not calculate specific estimates of risk of AR among ACE users. Thirteen of the 14 patients reported to have an AR were using the short-acting type of ACE inhibitors, consistent with the speculation that short-acting ACE inhibitors may be associated with increased risk.

Fourth, we found an association between AR and first use of a dialyser. This association could reflect a number of different exposures, including bacterial and endotoxin levels of dialysate, dialysate composition, frequency and duration of dialysis sessions, sterilization modes, flushing, and concomitant medications, data on which would all be necessary in a definitive study of the causes of anaphylactoid reactions during dialysis.

Finally, we did not find any compelling association between membrane type and AR. Although AN69 membranes were not used in any of the dialysis facilities in this study, anaphylactoid reactions were still reported in patients on ACE inhibitors on different types of dialyser membranes.

The limitations of our study are those of any observational investigation and should be noted. Although we achieved an accounting of ARs for the entire haemodialysis population in two networks, the survey relied on nurse recall and the number of actual anaphylactoid reactions may have been over- or under-reported. However, there is no reason to suspect that the nurses' memory would be different for individuals with the characteristics (women, younger patients, cause of renal failure, and frequency of dialyser use) we found to be associated with increased risk of AR and thus our observations are unlikely to be due entirely to recall bias. The second major limitation of this study is the inadequate information about medication use.

The observations derived from this preliminary study certainly warrant rigorous studies of ARs. One major hypothesis to pursue is that the accumulation of bradykinin, a potent vasodilator with hypotensive properties, could cause the acute anaphylactoid reactions we observed. Several studies reported elevated bradykinin levels at various times during dialysis in patients on different dialyser membranes [9]. Previous studies have found that bradykinin accumulated in patients treated with ACEI because of decreased kininase formation and degradation of bradykinin. Finally, a recent sheep study found that polyacrylonitrile dialysis membranes and ACE inhibitor each exerted independent and additive effects on bradykinin levels [10]. Future studies should examine the respective roles of membrane type, ACE inhibitors, and other factors in stimulating bradykinin-meditated ARs.

Notes. The work was conducted in the Epidemiology Branch, Division of Postmarket Surveillance, Office of Surveillance and Biometrics, Centre for Devices and Radiological Health, FDA. Dr Torrence is currently the National Programme Leader for Epidemiology and Veterinary Clinical Medicine for the Department of Agriculture. Dr Daley was a Public Health Service Epidemiology Training Programme Fellow; he is currently in the Epidemic Intelligence Service, National Centre for Environmental Health, Centres for Disease Control and Prevention.

These views are those of the authors and are not to be construed as the official stance of their employers.

We would like to thank the Health Care Financing Administration (HCFA) and especially the Mid-Atlantic Renal Coalition and the Southeastern Kidney Council for their participation. We especially thank Nancy C. Armistead, Executive Director for the Mid-Atlantic Renal Coalition and Mary S. Wilczynski, Medical Review Coordinator, Lois B. Walker, Director for Data Management, and Jenna Krisher, Executive Director, for the Southeastern Kidney Council, Inc. We also thank our Food and Drug Administration colleagues, Heidi Jolson, MD, for help with designing a predecessor data instrument, and Thomas P. Gross, MD, for facilitating an early phase of the study.

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From malaria to transplantation: the evolution of treatment for the nephrotic syndrome in a single patient

Sir,

Up until the introduction of corticosteroids the treatment of the nephrotic syndrome was symptomatic, and the disease was associated with a high morbidity and mortality. It was however well recognized at the time that in patients with refractory nephrotic syndrome, remission, or even cure, could occur immediately after the recovery from an acute febrile illness. In the context of the predominantly paediatric population the febrile illness was frequently measles. This led to speculation that controlled induction of a febrile illness may allow successful treatment of resistant nephrotic syndrome.

In two papers appearing in the same issue of *The Lancet* in 1952, Gairdner [1] and Byrne [2] described the successful use of malaria for the treatment of the nephrotic syndrome. It was perceived that malaria represented a safe, reversible way to induce pyrexia. Following these reports the Malaria Reference Laboratory supplied infected blood or mosquitoes to many hospitals specifically for the induction of malaria in nephrotic patients. Either benign tertian (usually *Plasmodium vivax*) or quartan (*Plasmodium malariae*) malaria was used to induce disease which was allowed to proceed for up to 3 weeks, before treatment with chemotherapy.

We describe the case of a patient in whom remission was achieved with malaria treatment in the 1950s but subsequently developed progressive renal impairment and underwent renal transplantation.

Case. A 19-year-old woman presented in 1953 with severe nephrotic syndrome with oedema extending to her abdomen. Her serum urea was normal (type II nephritis of Ellis in the classification of the day). The oedema was resistant to treatment with bed rest and urea-containing drinks. Therefore malaria was induced by the application of jars containing mosquitoes to each thigh, which were covered in a blanket to simulate darkness and the mosquitoes allowed to feed. Rigors followed some days after and continued for 14 days after which the malaria was treated with proguanil and mepacrine. In view of the subsequent course of the disease the infection was probably benign tertian malaria. Shortly after the treatment the nephrotic syndrome went into remission and the patient was discharged home.

Four weeks after this remission the oedema recurred and the patient was readmitted to hospital. She again developed rigors after admission and a diagnosis of recurrent parasitaemia was made and the patient received a second course of proguanil and mepacrine. The second episode of rigors is probably related to inadequet treatment of the hepatic phase of benign tertian malaria by the combination of proguanil and mepacrine. The second episode of parasitaemia related fever was again associated with clinical remission, and the patient remained oedema free for 10 years. During this time she had three successful pregnancies which were all complicated by hypertension. After the third pregnancy (1964) the nephrotic syndrome recurred and the patient was hospitalized for 6 months. During the admission she developed a high fever following the administration of intravenous frusemide, which was attributed to a drug reaction. After this pyrexial episode the oedema resolved and the patient remained oedema free for a further 3 years.

She had a fourth relapse in 1967 which was treated with cortisone. This was poorly tolerated due to marked masculinization, but resulted in remission. Following this the patient remained oedema free, but with persistent proteinuria and declining renal function. A renal biopsy in 1967 showed glomerulosclerosis and chronic interstitial damage. After an episode of acute pancreatitis in 1979 she entered end-stage renal failure and was commenced on haemodialysis and subsequently peritoneal dialysis. In the intervening period she had developed tuberculous cervical lymphadenitis, treated with chemotherapy, and biopsy proven primary biliary cirrhosis.

In 1981 she received a cadaveric transplant with immunosupression consisting of prednisolone and azathioprine. At present she remains on dual immunosupression with a slow decline in transplant function with a current creatinine of 270 μmol/l.

Comments. The observation that febrile illness could induce remission in the nephrotic syndrome was based largely based on remissions induced by measles infection [3]. However, in addition to inducing fever, measles infection impairs T helper and cytotoxic cell function resulting in an immunocompromised state and susceptibility to concurrent infection [4]. Reduced CD4 and CD8 numbers have been described in measles induced remission of the nephrotic syndrome [5].

In 1955 Gairdner and Schute [6] reviewed 65 cases of malaria treatment of the nephrotic syndrome. In 51 cases of pure nephrosis (Ellis type II) complete remission (loss of oedema for over 3 months) was achieved in 14 and partial remission in a further 11. The majority of remissions were achieved in (11/14) were in children under the age of 15 years. In addition, the presence of impaired renal function or hypertension (Ellis type I) predicted a poor response with no patients obtaining complete remission in the presence of renal impairment. Although none of these cases underwent renal biopsy it is likely that the underlying disease in the group responding to therapy was minimal change disease.

It is possible that the shift in immune status induced by malarial parasitaemia is responsible for the induction of remission by altering CD4 and CD8 +ve T cell function. Therefore the patients treated with malaria, such as the case we describe, represent early, successful attempts at immunotherapy for glomerular disease.

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High incidence of left atrial thrombus in renal transplant recipients

Sir,

Recipients of renal allografts have increased incidence of thromboembolic complications [1,2]. Coagulation abnormalities resulting from steroid and cyclosporin therapy are assumed to be, at least in part, responsible for thrombosis of superficial and deep leg veins, renal vein and haemorroidal veins, and for pulmonary embolism. However, to our knowledge, there are no studies evaluating the incidence of thrombosis in the left atrium in these patients. When one of our patients developed transient attacks of right arm paresis without ultrasound evidence of carotid artery disease and normal transthoracic echocardiogram, we decided to carry out a transoesophageal echocardiogram (TEE) and found her to have a left atrial thrombus.

The findings prompted us to study by TEE a cohort of 27 asymptomatic patients in the transplant clinic of the University Hospital who met the following criteria: (i) transplanted between 5 months and 3 years before with stable renal function; (ii) steady dosage of triple immunosuppression (prednisone, azathioprine, cyclosporin) and no medications known to alter the coagulation; (iii) normal sinus rhythm, no prior history of atrial fibrillation or mitral valve disease (by standard transthoracic echocardiography); and (iv) willingness to participate in the study.

TEE was done with sedation and topical anaesthesia with zylocaine 2% spray, using Sonos 1000 Hewlett-Packard echocardiographic equipment with a 5.0 MHz biplane probe (Hewlett-Packard Medical Products Division, Andover, MA). The left atrial appendage initially was viewed in the horizontal (0°) plane, followed by visualization of the vertical (90°) plane, and posterior and anterior rotation of the probe until the aorta and the coronary sinus were visualized. The TEE was carried out by an experienced cardiologist, and a left atrial thrombus was reported when a well-circumscribed mass of uniform consistency and of different texture from that of the atrial wall was identified.

Five patients out of the 27 studied (18.5%) had thrombi in the left atrium. All were asymptomatic during the period of observation, except for one patient who complained of transient episodes of slurred speech; she was placed on warfarin treatment for 3 months, her symptoms disappeared and a repeat TEE showed the thrombus had disappeared.

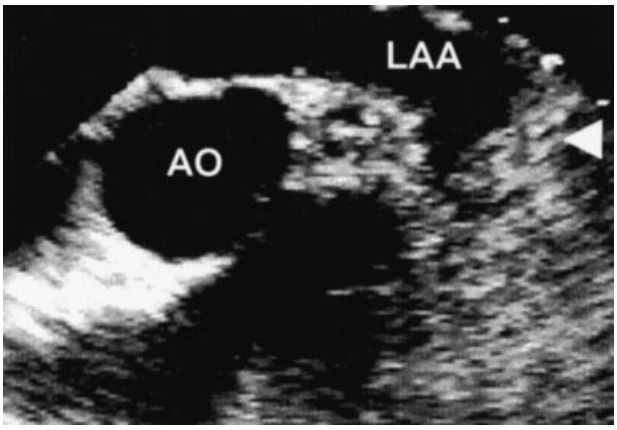

Fig. 1. TEE in a male patient of 18 years of age, transplanted 7 months previously from a cadaveric donor. Basal short-axis view in the horizontal plane to show a left atrial appendage with a thrombus in its cavity. AO, aorta; LAA, left atrial appendage; arrowhead, thrombus.

Table 1. Comparison between the patients with and without left atrial thrombus

	Thrombosis in left atrial appendage	
	Present ($n=5$) A	Absent ($n=22$) B
Sex (F/M)	1/4	9/13
Age in years (range)	31.2 (28–47)	36.1 (20–49)
Weight (kg)	79.8±22.7	69.8±17.3
Months after transplantation	17±9.14	20.7±11.6
Aetiology of ESRF		
HBP	1	6
Chronic GN	3	6
SLE	1	3
Other	–	7
Cadaver (C)/live (L) donor	3/2	16/6
Immunosuppresion:		
Cyclosporin (mg/kg/day)	0.45±0.17	0.65±0.41
Prednisone (mg/kg/day)	0.24±0.07	0.21±0.04
Azathioprine (mg/kg/day)	0.70±0.23	0.67±0.18
Other drugs:		
Ketoconazole (mg/day)	200	200
CysA blood levels (mg/dl)	231.2±92.3	230.2±87.32
Serum creatinine (mg/dl)	1.70±0.52	1.56±0.59
Serum cholesterol (mg/dl)	234.8±35.4	245.3±60.6
Fibrinogen (150–450 mg/dl)	421.0±81.9	335.5±100.8
Protein C (70–140%)	90.2±18.3	81.7±20.6
Protein S (65–140%)	65.3±11.2	74.2±40.9
Anti-thrombin III (80–120%)	110.0±17.0	126.1±27.9
Factor VIII C (60–160%)	80.8±23.9	81.8±28.8

GN, glomerulonephritis; ESRF, end-stage renal failure; SLE, systemic lupus erythematosus; HBP, renal failure associated with severe essential arterial hypertension. The normal values of the coagulation studies are shown in parentheses. The diseases listed as 'other' include hereditary nephritis (two patients), membranous glomerulonephritis (one patient), polycystic kidney disease (two patients), idiopathic crescentic glomerulonephritis (one patient) and interstitial nephritis (one patient).

As shown in Table 1, there were no differences in the group with (group A) and the group without (group B) left atrial thrombi with respect to age, gender, clinical characteristics and immunosuppressive therapy. Coagulation studies were also comparable.

There were no significant differences in vascular access procedures in the patients with and without left atrial thrombus. Before a permanent vascular dialysis access was made, the patients had jugular (24 patients) or subclavian vein (three patients) double lumen catheters for haemodialysis. The catheter tip was placed in the central vena cava. When the patients were in chronic dialysis they had autologous radiocephalic (26 patients) or ulnar arteriovenous fistulae (one patient). Before, during and after transplant surgery, central veins were not catheterized.

All the patients were receiving 200 mg daily of ketoconazole, to decrease cyclosporin A requirements, a cost-reducing strategy reported before [3]; as noted above, cyclosporin blood levels are, in fact, within the therapeutic range. To our knowledge, ketoconazole does not cause alterations in the coagulation system.

TEE is the most accurate non-invasive method of diagnosing left atrial thrombi [4]. Figure 1 is a representative example in one of our patients. Using this method of detection in high risk populations, left atrial thrombi are found in 5.2% [4] to 29% [5] of the patients with mitral valve disease or atrial fibrillation. Our studies indicate that renal transplant recipients without predisposing valvular heart disease or arrythmias have comparable rates of this complication. Furthermore, the incidence of silent left atrial thrombi found by us exceeds the incidence of other thrombotic complications reported by others [1,2] and should be suspected whenever transient ischaemic attacks or embolic episodes occur is transplanted patients.

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Multiple solid malignacies in a renal transplant patient

Sir,

In graft recipients, only specific types of tumours, such as lymphoma (early on after transplantation) and skin carcinoma or cervical carcinoma (later on) are noted with greater frequency than in the general population [1,2]. The true rate of solid organ carcinoma formation relative to what is observed in the general population is uncertain. The development of multiple, non-cutaneous solid tumours in transplant patients is infrequent. We describe the case of a renal transplant patient with four different types of malignancies and discuss their possible relationship with smoking as a common risk factor.

A 64-year-old male who began haemodialysis in June 1993, because of nephrosclerosis received a cadaveric renal transplant 5 months later. He had smoked approximately 40 cigarettes/day for 39 years. The family history is negative with respect to carcinoma formation. The donor was a 17-year-old female, who died of cranial trauma, was free of disease, with normal thoracic radiography, abdominal sonography and blood and urine analyses. Immunosuppression consisted of prednisone (0.5 mg/day), azathioprine (1.5 mg/day) and cyclosporin (7 mg/day). The post-operative period was unremarkable.

Two months after transplantation the patient developed dysphonia. Examination revealed a tumour on the laryngeal side of the epiglottis, and surgery was performed. Histological diagnosis was verrucous carcinoma of the epiglottis (Figure 1A). Azathioprine and prednisone were suspended and cyclosporin was adjusted to the lowest therapeutic range (mean dose: 2.7 mg/kg/day). In spite of recommendations, the patient continued to smoke. Repeated biopsies demonstrated the absence of laryngeal tumours. Two years after transplantation, the patient was admitted to the hospital for malaise, dyspnea and chest pain. Computed tomography revealed two round masses of 5 cm in diameter, with a badly defined contour, situated in the upper and lower lobules of the right lung. Abnormal laboratory parameters included: proteinuria, microhaematuria, and an increase in serum creatinine. The patient refused complete withdrawal of immunosuppression and other exploratory procedures and died 25 months after renal transplantation.

Autopsy revealed absence of residual tumours in the larynx. A tumour originating in the main bronchi was seen in the upper, middle and lower lobules of the right lung. Histopathology was consistent with a poorly differentiated, primary squamous cell carcinoma of the lung (Figure 1B). The native kidneys appeared atrophic with multiple small-sized cysts. One tumour of 8 cm in diameter and two smaller

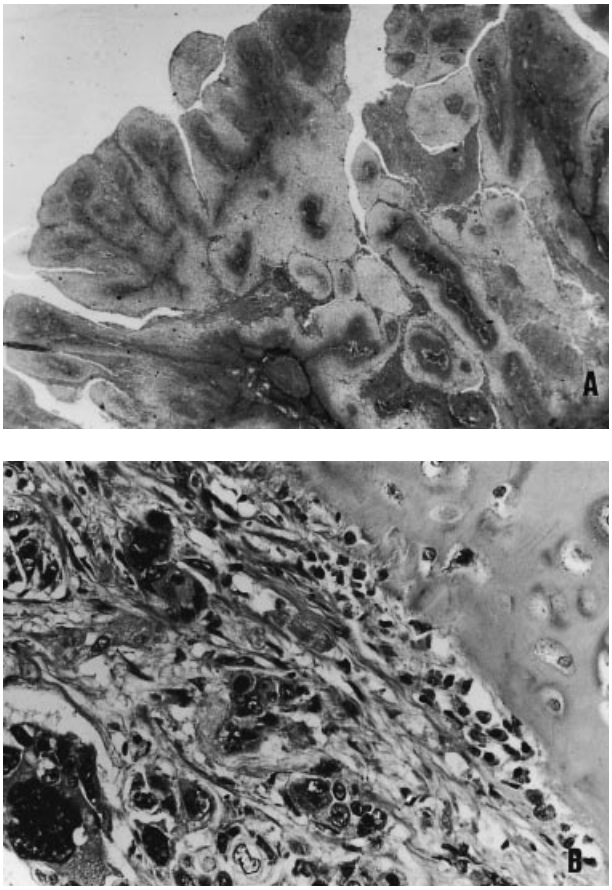

Fig. 1. (**A**) Verrucous carcinoma of the larynx (Haematoxylin-eosin stain, magnification ×20). (**B**) Primary bronchial squamous cell carcinoma of the right lung (Haematoxylin-eosin stain, magnification ×200).

tumours, histologically classified as well-differentiated renal cell carcinomas, were seen in the right kidney (Figure 2A). A papillary-appearing tumour with only minimal stromal invasion, corresponding to a transitional cell carcinoma of the renal pelvis, was also seen on the right kidney (Figure 2B).

The common characteristic of these four types of tumours is that they are all related to smoking [3]. Even though the exact mechanisms are not well known, multiple factors contribute to the increased incidence of malignancies in transplant recipients, such as the direct damage of immunosuppression on the DNA and/or the presence of oncogenic viruses [4]. Genetic, environmental, or toxic factors (such as tobacco) could also play a role in tumour development.

A few cases of multiple malignancies in organ transplant patients have been published. Belldegrun *et al.* [5] published one case of a patient with Kaposi's sarcoma and an adenocarcinoma of the thyroid. Studniberg *et al.* [6] described the association between lymphoangiosarcoma and Kaposi's sarcoma in a renal transplant. Barroso-Vicens *et al.* [7] reported concomitant skin cancer, lymphoma and malignant histocytoma. Although other associations have been described [8,9], to our knowledge no other cases have been published concerning a patient with four different solid malignancies.

From the time we first observed this case, and another with laryngeal cancer in a 42-year-old heavy smoker, the policy in our unit was been to carry out a complete laryngeal

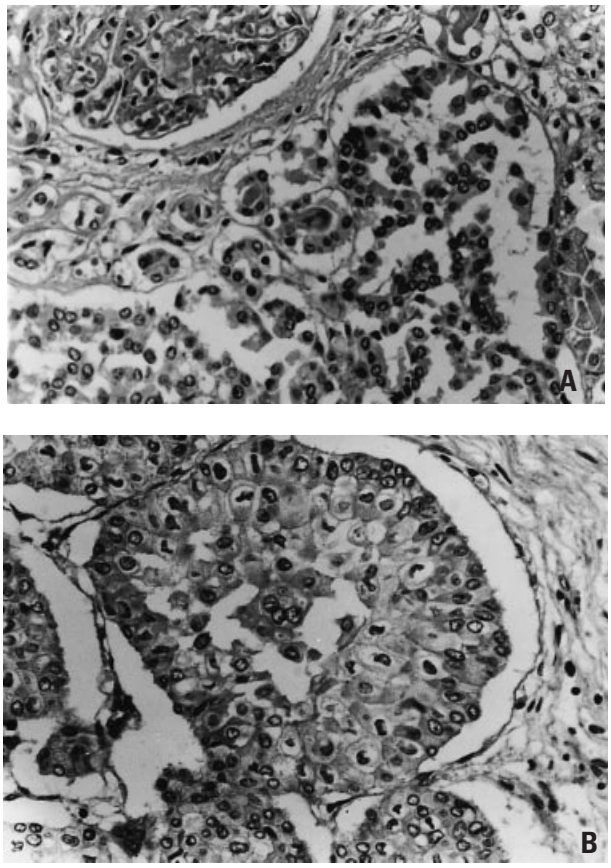

Fig. 2. (**A**) Well-differentiated renal cell carcinoma (Haematoxylin-eosin stain, magnification ×200). (**B**) Transitional cell carcinoma of the renal pelvis (Haematoxylin-eosin stain, magnification ×200).

examination in all patients who currently smoke or who have a history of smoking prior to their inclusion in the waiting list for a renal transplant. This simple practice could avoid some unnecessary deaths in transplant patients.

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