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Endemic Balkan Nephropathy

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1. Introduction

Endemic Balkan nephropathy (EBN) is a unique form of chronic interstitial renal disease which is endemic to isolated rural populations of Bulgaria, Romania, and Yugoslavia. The area is confined within a 200-mile radius of Belgrade. The involved villages lie along river valleys in multiple areas of Romania and Yugoslavia where flooding periodically occurs (Wolstenholme and Knight, 1967). The disease is clinically characterized by the insidious onset of a normocytic, normochromic anemia, azotemia, and persistent proteinuria usually of <1 g/24 hr. There is no increase in the incidence of hypertension in the involved populations and the disease slowly progresses to end-stage renal failure over a period of 5–10 years following the onset of azotemia. While there is no uniform agreement concerning the early pathologic changes, it is generally accepted to be a chronic interstitial disease as it appears in the uremic patient. There is marked tubular atrophy with focal areas of tubular regeneration, interstitial fibrosis, and minimal round cell infiltration. The tissue loss is predominently cortical and most marked in the cortex opposite the hilum (Radonic *et al.,* 1966).

The diagnosis of EBN will be made by the clinician if the patient presents with the majority of the findings summarized in Tables I and II. The differential diagnosis of a patient presenting with these findings, without the geographic exposure, might be nonobstructive pyelonephritis, reflux nephropathy, or

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TABLE I. Typical Findings in Endemic Balkan Nephropathy

History
Lived in an endemic village >20 years, native or immigrant
As likely male as female
Farm workers almost exclusively
Negative history for hypertension, edema, or any form of urinary tract disease
Multiple family members may be involved
Complaints
Vague, symptomatic only, consisting of fatigue, backache, and headache
Physical findings
Yellow skin pigmentation in advanced disease
Negative for hypertension, edema, or organomegaly

analgesic abuse nephropathy. The laboratory and physical findings would be most unusual for chronic glomerulonephritis or vascular disease. The nature of the proteinuria and the absence of hypertensive changes would mediate against these diagnoses. If no reflux or anatomical abnormalities can be demonstrated, the diagnosis of pyelonephritis would be most unlikely. If analgesic abuse can be ruled out, one is left with the diagnosis of chronic interstitial disease, etiology unknown. This is the situation reported to exist in greater than 10% of the cases of chronic interstitial nephritis studied at the University of Pennsylvania Hospital (Murray and Goldberg, 1975).

2. Epidemiologic Investigations

Epidemiologic methods have been employed to define the geographic distribution, the natural history of the disease, the relationship to climate, altitude, season

TABLE II. Typical Findings in Endemic Balkan Nephropathy—Diagnostic Studies

Urinalysis: trace 1+ proteinuria, <1 g/24 hr; occasional granular casts; no RBC or WBC casts
Blood studies: mild normocytic normochromic anemia of chronic renal failure
Chemistries: typical for any form of chronic azotemic renal failure; increased anion gap acidosis; normal serum proteins, Na, K, Cl
Renal function studies
a. Increased α-amino nitrogen and amino acid excretion; minimal glycosuria
b. Tubular proteinuria with increased excretion of B_2M, retinol binding protein, lysozyme, ribonuclease, 3S gamma globulin, and IgG kappa light chains
c. Diminished ability to dilute and concentrate; pitressin resistant
Radiologic studies: symmetric, bilaterally small kidneys without evidence of calyceal distortion, scarring, or obstruction

of the year, occupation, etc. The disease is found in the highest prevalence in rural areas where the population density is the lowest. Such evidence points against an infectious agent. A geographic area is defined to be "endemic" if population surveys for proteinuria, using the sulfosalicyclic acid (SSA) test, show an incidence >7% and the public health records indicate a high death rate from kidney disease. In many of these villages, the incidence of proteinuria has been reported as high as 34% (Stojimirovic, 1974).

The SSA screening test is sensitive but not specific for EBN. The diffuse tubuloinsterstitial pathology described in EBN suggested to us that the nature of the protein spilled in the urine might be of differential diagnostic aid. The initial studies, utilizing electrophoretic analysis of urine protein concentrates, demonstrated the common occurrence of tubular proteinuria in village populations in Bosnia, Yugoslavia where EBN is highly endemic (Hall *et al.*, 1967). We repeatedly screened a small village population (403 individuals) 3–6 times/year for 10 years. Children of <10 years of age showed intermittent proteinuria. The percent of the population involved increased with age (Fig. 1). Twelve of the 403 people died of kidney disease over this period of observation (mortality rate 298/100,000/year). The deaths occurred in people 36–79 years of age (M. Vasiljevic, N. Popovic, J. Gaon, and P. W. Hall, unpublished observations). To further establish the extent of the involvement of the disease, we investigated a village population in the Vratza district of Bulgaria (Ts. Dimitrov, I. Dinev, T. Sattler, and P. W. Hall, unpublished observations). The incidence of tubular proteinuria, as detected by radioimmunoassay, increased from 5% of those individuals between 30–40 years of age to 60% of those >69 years of age (Fig. 2). An elevated serum creatinine concentration (SCr)

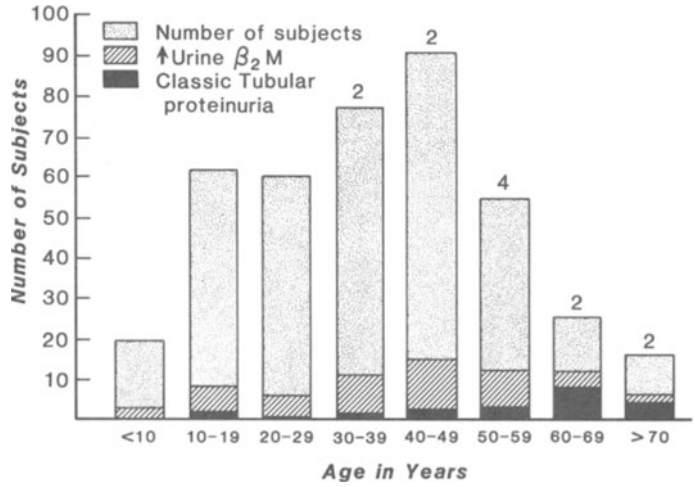

FIGURE 1. The relationship of age (abscissa) to the prevalence of B_2 microglobulinuria and classic tubular proteinuria (ordinate) in a population of 403 individuals living in an "endemic" village in Bosnia, Yugoslavia. The numbers at the top of the bars from the fourth decade on are deaths that occurred in these groups during the 7-year followup.

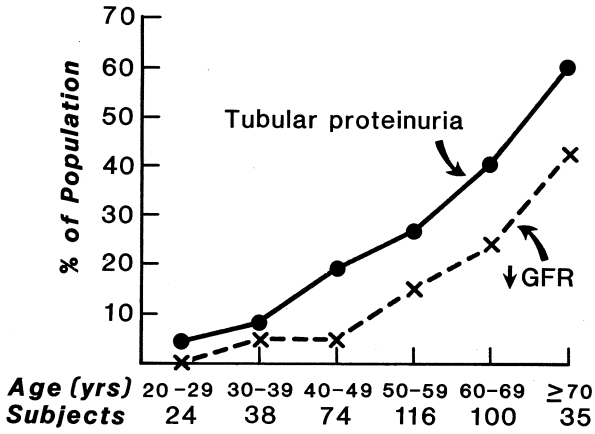

FIGURE 2. The relationship of age (abscissa) to the incidence of tubular proteinuria and decreased glomerular filtration rate (GFR) (ordinate) in a population of 387 adults living in the Vratza district of Bulgaria where EBN is prevalent.

occurred in 5% of the population between 40 and 50 years of age and increased to 40% of those over 69 years of age.

Epidemiologic studies, reviewed elsewhere (Hall and Dammin, 1978), have demonstrated that immigrants acquire this disease after a 20-year exposure to an endemic focus. Followup studies of identical twins, where one twin left the endemic area by age 18, demonstrated that continued exposure in the remaining twin resulted in the development of the disease, while the twin who emigrated to a "nonendemic" area remained free of the disease (Danilovic and Stojimirovic, 1967). Essentially all involved individuals, male and female, farmed the land. In one survey of an entire village population, we were able to find only 7 of 35 individuals over the age of 65 who did not have tubular proteinuria; all were men and all were nonfarmers; wives of these men actually farmed (A. Gaon, S. Schwab, J. Gaon, and P. W. Hall, unpublished observations). The study also revealed that the most involved families were the socioeconomically poorest families in the village. This most likely was due to the fact that their farm lands, in contrast to the farm lands of the less involved families, were periodically flooded, making soil fertilization useless and resulting in poor crop production. Attempts to correlate variations in the incidence of proteinuria, clinical appearance of the disease, or death rates with seasons of the year have not yielded significant patterns.

In order to determine what part genetics plays in the development of EBN, a collaborative study was done examining the relationship between HLA antigens and EBN (Minev *et al.*, 1978). These investigators studied 180 patients with the clinically established diagnosis of EBN whose residence was the Vratza district of Bulgaria. This group was compared to a healthy group of 1264 individuals from the same village. A significant increase in the frequency of the occurrence of HLA B_{18} was found in the patients as compared to healthy individuals. These data can be interpreted to suggest that a predisposition to develop EBN may exist in certain

families. Although the disease seems to be a progressive one once azotemia is established, we observed many individuals with tubular proteinuria who did not show progression of renal disease over a period of more than 10 years. It would be of interest to determine whether or not such individuals had HLA B_{18}.

3. Possible Etiologic Factors

The epidemiologic studies point to an environmental rather than an inherited etiology to EBN. The natural history of the disease, the pathology, and the epidemiology suggest a toxic agent. Using such reasoning, several substances have been considered. The list includes silica, cadmium, lead, uranium, aristolochic acid, ochratoxin, citrinin, and coronavirus. On the basis of the evidence collected, a case can be made for each of the above agents. When the available data are reviewed, however, none pass the critical test and many can be readily discarded.

Lead was the first element to be incriminated as an etiologic agent in EBN (Danilovic, 1958). Bread consumed by inhabitants of some villages was found to contain 5–10 times normal lead concentrations. The bread was made of wheat ground in mills where cracks in the millwheel were filled with a lead compound. Such milling is no longer the custom in most areas where the disease is still prevalent. Two different clinical presentations have been described in patients with lead poisoning when considered from the standpoint of kidney disease. That seen in children consists of a Fanconi-like syndrome with amino aciduria, glycosuria, and renal tubular acidosis. It presents as an acute illness in association with other systemic manifestations. The second type of renal disease is more chronic in nature and is characterized by a course similar to that of hypertensive nephrosclerosis and EBN. There is a gradual onset of uremia which is asymptomatic. The pathology described in such cases is primarily vascular and glomerular in location. The pattern of proteinuria seen in this disease is that of a glomerular one (Vacca *et al.*, 1980). Studies using chelating agents have failed to show any difference in lead excretion when comparing a normal to an "endemic" population (Gaon *et al.*, 1962). These data make it most unlikely that lead is the causative agent in EBN.

The epidemiology, clinical pattern, and laboratory findings in EBN suggest to some investigators that cadmium may be the causative agent. Cadmium nephropathy is characterized by subtle alterations in proximal tubular functions which can only be demonstrated by research techniques. These include altered handling of glucose, amino acids, and low-molecular-weight proteins by the proximal tubule. Long-term studies on populations exposed to chronic cadmium demonstrate that such a nephrotoxicity does not lead to the development of chronic end-stage renal disease in a significant percent of an exposed population (Kazantzis, 1979). Cadmium concentrations in hair samples, limited autopsy and biopsy material, and water supplies obtained from Yugoslavian populations at risk to develop EBN have been found to be within normal limits (Fajgelj *et al.*, 1975; M. Piscator, M. Vasiljevic, and P. W. Hall, unpublished data).

The chronic interstitial fibrosis and tubular atrophy characteristic of EBN can be induced by radioactivity. An evaluation of the concentrations of radioactive

elements in the water and soil samples from villages in Bulgaria where the disease is prevalent showed that the concentrations of radon, radium, thorium, and uranium were within the accepted range of normal by international standards (Karamikhailova *et al.,* 1960). These findings were confirmed in Yugoslavia (J. Peric, D. Stefanovic, Z. Radovanovic, and P. W. Hall, unpublished observations). There are too few data available to determine whether or not radioactivity plays a significant role in the development of EBN.

Silicic acid, released from silicate minerals, induces a proliferative inflammatory lesion in the interstitial tissue of the kidney with subsequent necrosis (Newberne and Wilson, 1970). The pathology seen in the experimental animal studies (Markovic and Lebedev, 1979) is that of lymphocytic and plasma cell infiltration around blood vessels, glomeruli, and tubules, with sclerosis of the interstitial tissue. This lesion was produced by feeding mice drinking water containing 50 mg of quartz plus 100 mg of quartzite/liter. Silicon has been described as inducing renal disease in humans. Neither the clinical course nor the histologic lesions described by light and electron microscopy are typical for those reported in EBN (Hauglustaine *et al.,* 1980). Silicate concentrations in renal tissue have been reported from only three cases reviewed by these authors. In each case it was found to be approximately ten times the normal level. No data are available on the silicate concentrations in the kidneys of patients with EBN. Analysis of water samples obtained from Bulgarian and Yugoslavian endemic foci, as reviewed elsewhere (Hall and Dammin, 1978), has not revealed concentrations of silicate approaching those used to induce the disease in experimental animals. This element has widespread distribution throughout the world. Not all forms of the element ingested or inhaled are toxic (Newberne and Wilson, 1970). Biopsy analysis of silicate concentrations, using emission spectroscopy, should yield valuable data to establish whether or not silica plays a role in endemic nephropathy. Although the silicon hypothesis is an intriguing one, there seems to be little evidence to support it as the causative agent.

The major pathology in EBN appears to be confined to the kidney. Preliminary data concerning involvement of the kidney in other species with lesions similar to human disease are very limited. A chronic interstitial nephropathy has not been observed in several species of domestic animals, including dog, sheep, cow, horse, pig, and chicken, nor in frogs (personal observations). That the disease is species- and organ-specific and that it requires several years to develop meet several of the criteria describing a slow virus diseae. This was first suspected to be the case in EBN when viral-like particles were seen by electron microscopy in the renal tubules of patients dying from EBN (Georgescu *et al.,* 1970). Subsequent attempts to isolate and cultivate a virus in culture were unsuccessful (Georgescu *et al.,* 1977). Numerous cytoplasmic vesicles in the proximal tubule containing particles which were characteristic of coronavirus were seen in seven cases of EBN using electron microscopic techniques (Apostolov *et al.,* 1975). The glomerular mesangial reaction and segmental thickening of the glomerular basement membrane with subendothelial membranous deposits observed by these investigators are quite different than the electron microscopic findings reported by others. Examination of renal biopsy material from 33 cases failed to reveal any

recognizable lesion in the glomerulus by light or electron microscopy (Hall and Dammin, 1978). The data supporting a viral etiology remain controversial and relate only to the electron microscopic findings. A significant part of the problem leading to the confusion rests in variations in the diagnosis and selection of cases for microscopic study.

Ochratoxin A is a nephrotoxic mycotoxin metabolite occurring in foodstuffs. This toxin has been isolated from certain strains of *Aspergillus ochraceus,* which are commonly found contaminating wheat and grain stores. It has been established to be the cause of porcine nephropathy, which is comparable, in many ways, to EBN (Krogh, 1974). The toxin itself has been isolated in increased amounts in foodstuffs collected from several villages in Yugoslavia and Bulgaria where the disease is endemic (Barnes *et al.,* 1977; Krogh *et al.,* 1977). In addition, ochratoxin has been isolated from the serum of patients with EBN (Hult *et al.,* 1979). The renal pathology is characterized by extensive interstitial fibrosis and proximal tubular degeneration (Krogh *et al.,* 1977). Animal experiments have demonstrated that liver glycogen stores are depleted and serum glucose concentrations increased within hours after the administration of ochratoxin A (Suzuki *et al.,* 1975). Renal glycogen is also diminished (Meisner and Selanik, 1979). Meisner's study demonstrated that ochratoxin A diminished renal phosphoenolypruvate carboxykinase activity (PEPCK). The addition of ochratoxin A to fresh renal cortical slices depressed the transport of both organic anions and cations (Berndt and Hayes, 1979). Several studies, reviewed elsewhere (Hall and Dammin, 1978), have demonstrated an increase in amino acid excretion in patients with endemic nephropathy. Polyuria, glycosuria, proteinuria, and decreased urine osmolality are common findings in the animal with ochratoxin A-induced nephropathy and also in EBN (Berndt *et al.,* 1980). These investigators point out that repeated small doses of ochratoxin A have an cumulative effect. As PEPCK and ochratoxin are both found in the proximal tubule of the experimental animal, these tubular functional abnormalities may be a representation of the toxic effect of ochratoxin A. Measurement of the PEPCK in renal biopsy material obtained from appropriately selected cases of EBN should yield valuable information concerning the relationship between ochratoxin A and EBN.

The progression of EBN that occurs in emigrants who have left the endemic foxus is suggestive of a self-perpetuating disease having an autoimmune component. There are multiple brief conflicting reports concerning the detection of IgA, IgG, and IgM in kidney tissue (Hall and Dammin, 1978). No immune deposits could be detected, using a fluorescent tagged antibody, in the 33 renal biopsy cases from an endemic focus in Yugoslavia (Hall and Dammin, 1978). Doichinov was unable to detect C_3 or C_4 component of complement, IgA, IgG, or IgM in the glomeruli or tubules of ten renal biopsies taken from EBN patients from Bulgaria (personal communication). In a preliminary report, attempts to identify the presence of tubular antigen in biopsy material from patients with EBN were unsuccessful (Radonic *et al.,* 1977). Low titer antibodies to smooth muscle antigen and cytoplasmic antibodies have been reported in the sera of patients from Romania with tubular proteinuria (Moraru *et al.,* 1977). These investigators postulated that these antigen–antibody complexes subsequently become trapped in

the glomerulus and lead to the development of the late glomerular alterations seen in EBN. Although there are some isolated reports to the contrary, available data do not support the concept of a major immunologic component in this disease.

There are similarities between EBN and analgesic abuse nephropathy. Both produce a chronic interstitial disease which takes a comparatively long time to develop. One very unusual and unique feature of both diseases is the associated increase in the prevalence of papillary transitional cell tumors of the renal pelvis and ureters but not the bladder. Histologic evaluation was made on tissue obtained from patients undergoing surgery for papillary transitional cell tumors. Carcinoma-*in-situ* was found in multiple sites in the transitional epithelium of the upper urinary tract. These patients were long-term residents of epidemic foci (Petkovic *et al.,* 1976). As early as 1960 it was suggested that the coincidental occurrence of the endemic nephropathy and the tumors was the result of a toxic and "blastogenic action at the same time, the latter being manifested after a prolonged period of time, more than 30 years" (Petrinska-Venkova, 1960). Data on the use of analgesics by the populations involved are not available. A combination analgesic containing phenacetin, aspirin, and caffeine has been found in many households of several village populations in endemic foci in Yugoslavia (personal observation). The availability (in 1976) of such analgesic compounds to the rural farm populations makes analgesic abuse a possibility. However, papillary necrosis, common in analgesic-induced disease, has not been seen in EBN patients. Further studies are needed to determine what role analgesics play in the development of EBN.

4. The Relationship of EBN to Papillary Transitional Cell Tumors

The coincident increased incidence of tumors in patients suffering from both analgesic abuse nephropathy and EBN suggests that some similar mechanism for induction of both diseases may exist. Phenacetin derivatives are most likely the carcinogenic agent in analgesic-associated cases (Bengtsson *et al.,* 1978). As these investigators pointed out, there is a close chemical relationship between *n*-hydroxylated metabolites of phenacetin and known carcinogenic amines which have been established to cause bladder cancer. Multiple metabolites of phenacetin are known to be carcinogenic. The increased prevalence of the carcinogenic changes in the renal pelvis and ureter in contrast to the bladder is similar in both analgesic abuse and EBN (Gonwa *et al.,* 1980; Petkovic, 1978). This finding suggests that the carcinogenic agent may only be active in the urine for a brief period as it flows through the pelvis and ureter and is inactivated by the time it reaches the bladder. An alternative explanation is that the metabolic activities of the renal pelvis and ureteral epithelial cells are different from those of the bladder cells, making them more susceptible to the mutagenic or carcinogenic agent. Embryologically the tissues are derived from different origins. The ureter and renal pelvis develop from the metanephric kidney tubules, while the bladder develops from an outpouching of the cloaca. No extensive search for mutagenic or carcinogenic compounds in the "endemic" environment has been conducted.

The relationship between cancer and renal tubular functional abnormalities is

well recognized. Renal tubular acidosis has been described as a complication in chronic myelogenous leukemia and multiple myeloma. There is experimental evidence to indicate that an overload of low-molecular-weight proteins, particularly Bence-Jones proteins, results in proximal tubular functional abnormalities (Clyne *et al.,* 1979). We demonstrated, in prospective studies, the sequential changes in protein excretion that occur in a population destined to develop EBN (Hall and Vasiljevic, 1973). The urine concentrations of several low-molecular-weight proteins, including retinol binding protein, lysozyme, ribonuclease, 3S gamma globulin, IgG kappa light chains, and beta$_2$ microglobulin (B_2M), were determined 3–6 times/year for more than 5 years. The first of those proteins to be increased in the urine was B_2M. This protein continued to be spilled in increased quantities for a long period of time in some instances without the additional changes in proteinuria or development of kidney disease. Prior to a change in the SCr, the next protein to be detected elevated was the IgG kappa light chain. This was followed by a generalized increase in all the other low-molecular-weight proteins measured.

Beta$_2$ microglobulin is a light-chain-like protein having a molecular weight of 11,800 daltons. It occupies a position in the HLA molecule similar to that of the light chains on the immunoglobulin molecules. Amino acid sequencing studies have demonstrated that there are homologous regions on the constant fractions of IgG light and heavy chains to those of the B_2M molecule (Peterson *et al.,* 1972). Loading experimental animals with B_2M is associated with a marked tubular proteinuria consisting of several low-molecular-weight proteins, suggesting that this protein may play a role in inducing tubular injury (Hall *et al.,* 1980).

The similarities between light-chain nephropathy and EBN led us to consider the possibility that B_2M itself, if presented in increased loads to the kidney, may cause proximal tubular damage. In order to determine whether the B_2 microglobulinuria of EBN was representative of injury to the proximal tubule or an increased load of B_2M presented to the tubule, it was necessary to measure serum B_2M concentrations (SB_2M) and compare those with SCr in an "endemic" population. Such a study (Sattler *et al.,* 1977) showed that 13.4% of a "healthy" population living in a village where EBN is endemic had elevated SB_2M and normal SCr. This finding suggested that B_2M production may be increased in such populations. Elevated SB_2M has been reported in the sera of cancer patients, as reviewed elsewhere (Hall and Dammin, 1978). The source of the increased B_2M production could be the papillary transitional cell tumors. We have examined renal and tumor tissue obtained from patients operated on for papillary transitional cell tumors for the presence of B_2M in the tissue. All patients came from an endemic area of Bulgaria. Beta$_2$ microglobulin was found in the proximal tubular cytoplasm as well as in the stroma of the tissue, using the fluorescent conjugated antibody technique (Doichinov and Hall, 1978). Renal function studies were carried out on a group of such patients. We compared SB_2M, SCr, and fractional excretion of B_2M (FeB_2M) in three groups: (1) a suitable control population; (2) a "healthy" group living in a highly "endemic" area; and (3) a group of tumor patients operated on for papillary transitional cell tumors, all of whom came from the same area as those of group 2. The SB_2M/SCr ratios of those healthy individuals living in an endemic

area were significantly higher than the control population ($p < 0.01$) and were as equally elevated in the tumor group. The FeB_2M was higher in the endemic healthy population than in the control and was highest in the tumor-operated patients (Hall *et al.,* 1981). These data can be interpreted to indicate that B_2M production was increased in both "healthy" individuals exposed to an endemic focus and in tumor patients. The findings of an increased fractional excretion in these groups suggested that tubular damage had occurred in addition to overloading.

It is interesting to speculate about the role of B_2M in the development of EBN. The protein itself can induce renal tubular functional abnormalities in experimental animals. The kidneys of a significant percent of the population at risk to develop EBN are presumably subjected to an increased load of this protein. Similar proximal tubular functional abnormalities have been attributed to an increased production of light chains in such diseases as multiple myeloma and myelomonocytic leukemia (Muggia *et al.,* 1969, Maldonado *et al.,* 1975). The fact that chronic interstitial nephropathy is not seen in patients with these diseases could be explained by the rapidity with which the patients succumb to their underlying malignancy. In contrast, papillary transitional cell tumors, which appear to contain large amounts of B_2M, are slow growing and much less malignant. As a consequence, people live for many years with carcinoma-*in-situ* lesions and papillomas without evidence of metastases. Several cases of bilateral tumors occurring sequentially have been reported (Petrinska-Venkova, 1960; Petkovic, 1978). The occurrence of B_2 microglobulinuria, elevated SB_2M concentrations, EBN, and papillary transitional cell papillomas in the same geographically isolated populations and often in the same patient seems more than a chance happening.

5. Prevention and Therapy

Without the etiology of EBN defined, preventative and therapeutic measures are limited. The available evidence indicates that the disease can be prevented if the individual has less than 15–20 years of exposure. A group of 110 individuals were relocated from a highly "endemic" area to a nonendemic area in Bulgaria and followed for 15 years (Dinev, 1974). Among the emigrants, 40% developed evidence of EBN over the followup period. There were 26 deaths during that time, 18 of which had EBN established at autopsy. Individuals relocated who had spent less than 10 years in the endemic focus prior to relocation showed no evidence of the disease during the followup period. Although this appears to be a satisfactory preventative measure, it obviously is not a practical one. Improvement in water supply, sanitary conditions, and other indicators of the standard of living has occurred over the past 15–20 years. Preliminary data (Fajgelj *et al.,* 1981) indicate that the prevalence of EBN is decreasing in certain endemic villages in Bosnia, Yugoslavia. These investigators imply that this is due to an improvement in the overall standard of living.

The therapy for EBN is supportive only. Multiple hemodialysis centers are now operating in the involved countries. Transplantation has proven to be effective in early reports. Several centers are now performing transplants in Yugoslavia. The

first transplant of a patient with endemic nephropathy was performed in Romania recently (Pasare *et al.,* in press). Suitable candidates for transplant in Bulgaria are being sent to Moscow. Followup studies are available on seven transplants performed on patients with EBN from Nis, Yugoslavia who received their cadaver transplants in Lyon, France (Touraine *et al.,* in press). Six patients underwent transplants and one had a second transplant. The followup period was 4–46 months. All results, including biopsies, indicate that the course followed by these patients is typical of that of the transplant population in general. The individuals are currently living in endemic areas of Yugoslavia.

6. Summary and Conclusions

In summary, EBN is a chronic interstitial renal disease, the pathology of which is principally tubular atrophy and interstitial fibrosis of a uniform nature with minimal cellular infiltrate. It does not appear to have an immune component. It does appear to be an acquired disease and not a genetically inherited one. The ochratoxin A-induced animal disease is the model most closely approximating the human disease. The epidemiology fits very well with a slow virus etiology, but supporting data are morphologic only and controversial. Radiation, analgesic abuse, and silica have been implicated, but definitive studies have not been conducted to determine that any of these are causative agents. The coincidental occurrence of B_2 microglobulinuria, an elevated SB_2M, EBN, and papillary transitional cell tumors in the same population leads to the interesting speculation that the renal disease may be a "light-chain nephropathy." The solution of the problem of what causes EBN may have a direct bearing on the etiology of 5–15% of the patients currently being treated for end-stage renal disease in the United States who carry the diagnosis of chronic interstitial disease.

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