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Renal Disease from Exposure to Solvents

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ABSTRACT

Exposure to a variety of solvents may result in renal disease. Tubular renal disease with anuria occurring fairly promptly after exposure is most commonly seen. There is evidence that some cases of glomerular disease, such as extra-capillary glomerulonephritis and membranous nephropathy, may be causally related to chronic solvent exposure. Their detection may be impeded by the prolonged latent period between exposure and onset of disease, the non-specificity of the glomerular lesions and the non-availability of a history of exposure.

Introduction

It is well known that exposure to certain volatile solvents may have a toxic effect on the kidney manifested by oliguria or anuria, associated with tubular lesions and often resulting in renal failure (table I). Recently, several volatile hydrocarbons have been incriminated in the occurrence of a different spectrum of kidney diseases ranging from proteinuria and nephrotic syndrome to chronic renal disease in which glomerular lesions were found.[3,8,27] The number of such cases reported is relatively small, but this may not represent their actual frequency. The long latent period usually seen between exposure and onset of chronic renal disease, the often obscure history of exposure and the non-specificity of the renal glomerular lesions contribute to the difficulty in identifying such cases and establishing an etiological relationship.

Exposure and Entry

Types of exposure to all volatile hydrocarbons may be occupational, environmental, accidental or voluntary. The widespread use of solvents in industry and by the general population is well known and need not be documented. Accidental exposure to solvents has often been reported, both in industry and in individuals. Deliberate exposure to solvents is a recurring social phenomenon, such as in the use of ethylene glycol as a substitute for alcohol or from glue-sniffing in recent years.

The route of entry may be by inhalation, skin contact or ingestion. Inhalation is the most important and most effective means of entry and is facilitated by the volatile nature of the substances under consideration. Their absorption and retention is related not only to the nature of the substance, but also to its concentra-

TABLE I

Solvents Associated with Renal Disease

Aromatic Hydrocarbons*†
Toluene[20,21]
Xylol
Halogenated Hydrocarbons*
Carbon tetrachlorids[11,15,22]
Chloroform[12]
Ethylene dibromide[24]
Trichlorethylene[12]
Glycols*
Ethylene glycol[9]
Diethylene glycol[10]
Dioxane[2,26]
Glycerol
Aliphatic-aromatic (Technical) Hydrocarbons†
Gasoline[3,17,27]
Turpentine[5]
Mineral spirits
Naptha
Variety of Solvents (Some Unidentified)*†§[3,8,27]
Glue (Sniffing)*
(Toluene, carbon tetrachloride, chloroform, etc.)
Dimethylnitrosamine†[4]

*Acute renal failure †Glomerulonephritis
§Membranous nephropathy

tion and rate of metabolization and elimination. Skin contact is a frequent route of entry because of the common use of solvents as cleaning and degreasing agents; however, the amount absorbed through the skin may be small. Ingestion is infrequent and may occur accidently or voluntarily. In the course of inhalation some of the inhaled material present in the upper respiratory tract is also swallowed.[14]

Identification of Etiologic Agents

These substances are absorbed principally from the lungs but also from the gastrointestinal tract or skin. Because of their solubility in lipids, they may be deposited unchanged in fat or in tissue with a high fat content. Some of the absorbed material is exhaled unchanged, and the metabolites are excreted in the urine. Thus the unchanged substances may be identified in blood, fat or exhaled air and the metabolites recovered in urine.

It is possible to recover and analyze the solvent vapors from the exhaled air and to estimate the degree of exposure. The recovery and identification is more likely to succeed during the period of exposure or, if the exposure has been discontinued, during the acute phase of the disease. Once the disease has become chronic and there is no further exposure, the substances will have been excreted or metabolized and detection can be sought only in fat, a method with obvious limitations.

Toxicological examination presents other difficulties inherent in the nature of the solvents used. These are rarely a single chemical and are more apt to be a mixture of several hydrocarbons depending upon the degree of purification, particularly in the industrial use of solvents. Not infrequently, a given solvent is contaminated with another class of solvents or another toxic substance. This renders detection and identification particularly difficult and in practice it is not frequently attempted unless the offending substance is known.

The diagnosis of these agents is usually made by a chronological lifetime history of occupational and environmental exposure, including an evaluation of the working conditions, analysis of the suspected compound and an estimation of its concentration or quantity. Identification of an agent may be confirmed by its known effect on more than one organ. For example, carbon tetrachloride frequently affects both kidney and liver. Further confirmation may be derived from the occurrence of similar organic changes in other individuals with comparable exposure. Finally, animal experimentation provides definitive confirmation and etiological proof, particularly when faced with a compound whose toxicity is not well established or with unfamiliar lesions.

Toxicological Aspects of Compounds

The important hydrocarbons or compounds known or suspected of nephrotoxicity will be considered and related to the pathological changes reported.

Toluene and Xylene

Toluene (toluol) and xylene (xylol) usually contain a substantial amount of benzene (up to 20 percent) and have only recently become available with a fractional percentage of benzene. (Benzene is known principally for its leukemogenic and hepatotoxic effects; renal disease has not been reported.) Toluene is present in glue and acute renal failure has been reported following glue sniffing, as well as being found in painters. Renal failure may be accompanied by myoglobinuria and is probably secondary to liver damage and not due to primary kidney toxicity.[20,21]

Carbon Tetrachloride

Carbon tetrachloride[11,15,22] is one of the most toxic of the solvents and has been considered to be the most common cause of toxic anuria. It is no longer widely used as a cleaning agent or in fire extinguishers; its principal application is now industrial. It affects the liver and kidneys, although renal disease may occur in the absence of hepatotoxicity. Alcoholism or the ingestion of alcohol has an aggravating effect on carbon tetrachloride poisoning. The nephrotoxicity of this compound has been attributed to its direct toxic effect on the proximal tubules or on the loop of Henle. Anuria occurs one to seven days after acute exposure by inhalation and is preceded by proteinuria. During the period of anuria, there is a greater degree of proteinuria and microhematuria than is usually present in acute tubular necrosis. Anuria may last up to 15 days; dialysis is a useful adjunct in therapy. The renal lesion is that of acute tubular necrosis.

Toxicological analysis has been attempted in carbon tetrachloride poisoning by measuring the level of chloride derivatives in the circulating blood. It was found that the test is more likely to be positive during the early period of anuria. Moreover, the method used was not specific for carbon tetrachloride since it detected other halogen compounds. This is a practical demonstration of the point that was made previously: clinical and occupational history may be more important than toxicological analysis.

Trichlorethylene

Trichlorethylene is much less toxic and is used instead of carbon tetrachloride. Its principal metabolite, trichloracetic acid, is excreted in the urine for several weeks following exposure and may be assayed. Its main toxic effect is non-specific hydrocarbon narcosis. Acute renal failure has been reported.[6,12]

Ethylene Glycol

Ethylene glycol[9] is the active ingredient of permanent antifreeze. Inhalation or skin exposure is not toxic. Serious and often fatal poisoning follows when it is ingested either as a substitute for alcoholic beverage or by mistake. The central nervous system and kidneys are principally affected. If the patient survives the initial coma, respiratory failure and pulmonary edema, then acute tubular necrosis ensues, characterized by oliguria, proteinuria and urinary calcium oxalate crystals. Ethylene glycol is oxidized to oxalic acid by alcohol dehydrogenase. Human alcohol dehydrogenase has an appreciably greater affinity for ethanol than for ethylene glycol. Ethanol administration in ethylene glycol poisoning results in reduction of oxalate production with increased excretion of glycol and has been used in treatment of this poisoning.

Diethylene Glycol

Diethylene glycol[10] is not an industrial hazard but may be very nephrotoxic when ingested. In 1937 there were numerous deaths owing to ingestion of an

elixir which contained 72 percent diethylene glycol and 10 percent sulfonamide. The renal lesions consisted of tubular necrosis with ballooning of the cytoplasm of the cells of the proximal convoluted tubules and extensive cortical necrosis. Tubular lesions, but not cortical necrosis, was produced experimentaly in animals by administration of diethylene glycol.

Diethylene Dioxide

Diethylene dioxide (Dioxane)[2] serves for dehydration in histology and as a solvent in industry. Exposure is by inhalation and symptoms may not appear for several hours. Hepatic and renal toxicity have been seen and confirmed by animal experiments. The renal disease is acute tubular necrosis, similar to that seen with ethylene glycol but without the crystals.[26]

Hydrocarbons

Aliphatic-aromatic (technical) hydrocarbons are mixtures of hydrocarbons derived from petroleum and used as fuels, lubricants and solvents. The liquids are fat solvents and include gasoline, turpentine, mineral spirits (Stoddard solvent, white spirits) and naptha. Chemical pneumonitis with hemorrhagic lung disease and central nervous system depression or coma are the most common clinical manifestations of excessive exposure. However, recently chronic glomerulonephritis and Goodpasture's syndrome have been reported following exposure to petroleum fuel.[3,27]

Pathology

Acute Tubular Necrosis

Acute tubular necrosis (toxic nephrosis, toxic nephropathy) is typically associated with most of the solvents under consideration and correlates with the clinical aspects of oliguria following a short latent period of a few days. Renal changes are confined to the tubules; the glomeruli are intact. The tubular epithelium undergoes changes ranging from swelling, ballooning and hydropic changes to necrosis. The tubular lumen may contain desquamated cells, pigmented casts or eosinophilic amorphous granular material which may be mistaken for erythrocytes. The lesions may progress to hemorrhagic cortical necrosis. The proximal and distal convoluted tubules as well as the collecting tubules may be affected. During the period of recovery, the tubules may be lined by hyperchromatic flattened cells signalling regeneration.

While the renal changes are generally non-specific, some solvents have been associated with certain characteristic features. In carbon tetrachloride poisoning, the tubular lining cells may contain fat

TABLE II

History of Patients with Membraneous Nephropathy

			Kidney Biopsy			
Case	*Age*	*Symptoms*	*Years of Exposure*	*Stage of Membranous Nephropathy*	*Treatment*	*Follow-up*
1	24	Proteinuria	3	Early I & II	Steroids	Renal failure 3 years
2	45	Proteinuria	18	Advanced III	Diuretics	Renal failure 9 years
3	47	Nephrotic syndrome	30	Full-blown II & III	Steroids	Persistent proteinuria
4	44	Nephrotic syndrome	11	Full-blown III	Steroids	Renal failure 1 year - died

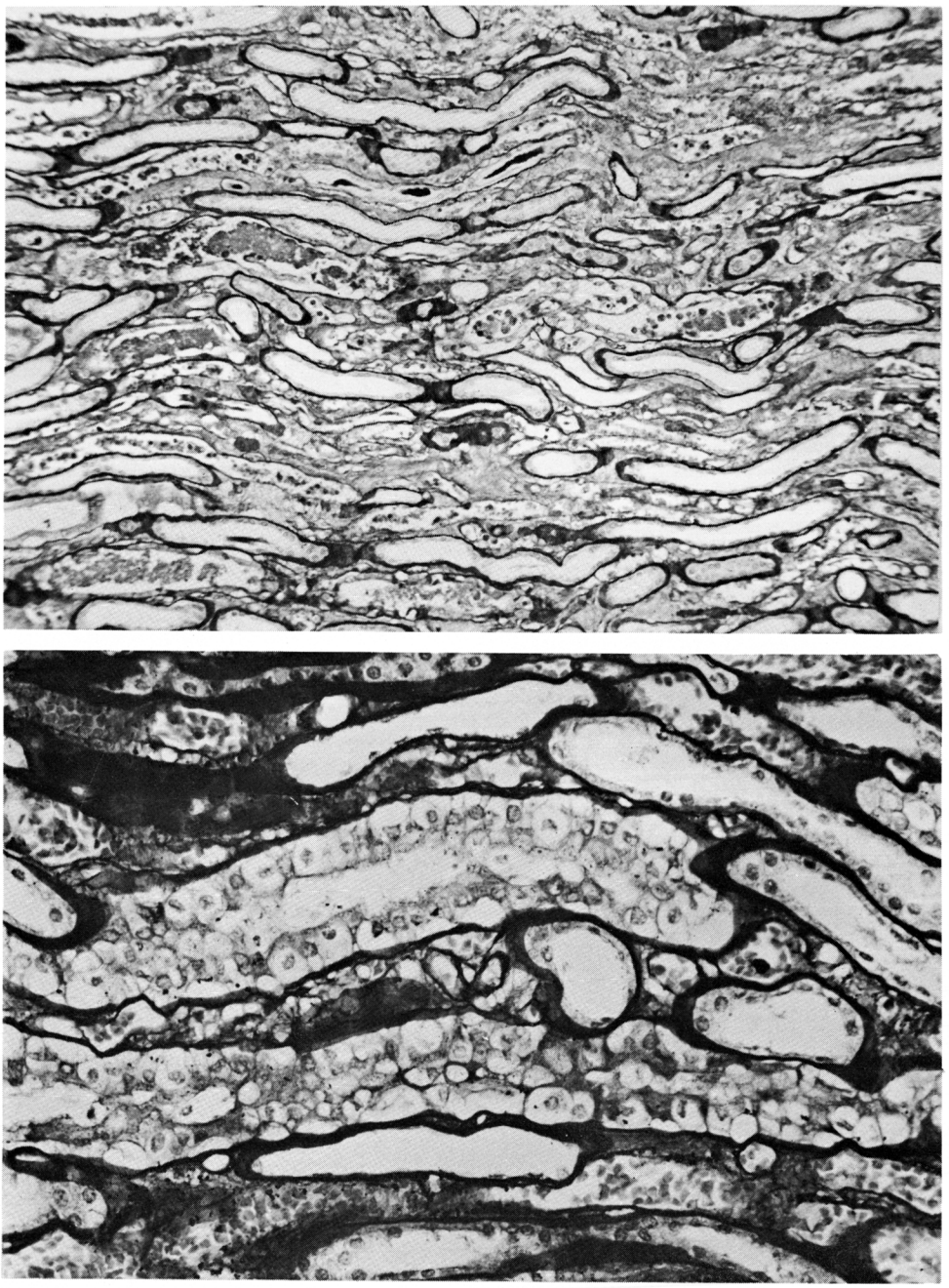


FIGURE 1 (top). Case of carbon tetrachloride poisoning. Granular casts and desquamated tubular cells in collecting tubules. PAS 120×.

FIGURE 2 (bottom). Vacuolization of tubular lining cells, carbon tetrachloride poisoning. PAS 300×.

vacuoles. Calcium oxalate crystals in the tubular lumen are typical of the glycols (ethylene and diethylene) but may also be seen in oxalic acid poisoning. The changes in the glycols and in dioxane are similar with marked ballooning of tubular cells and are apt to progress to focal hemorrhagic cortical necrosis.

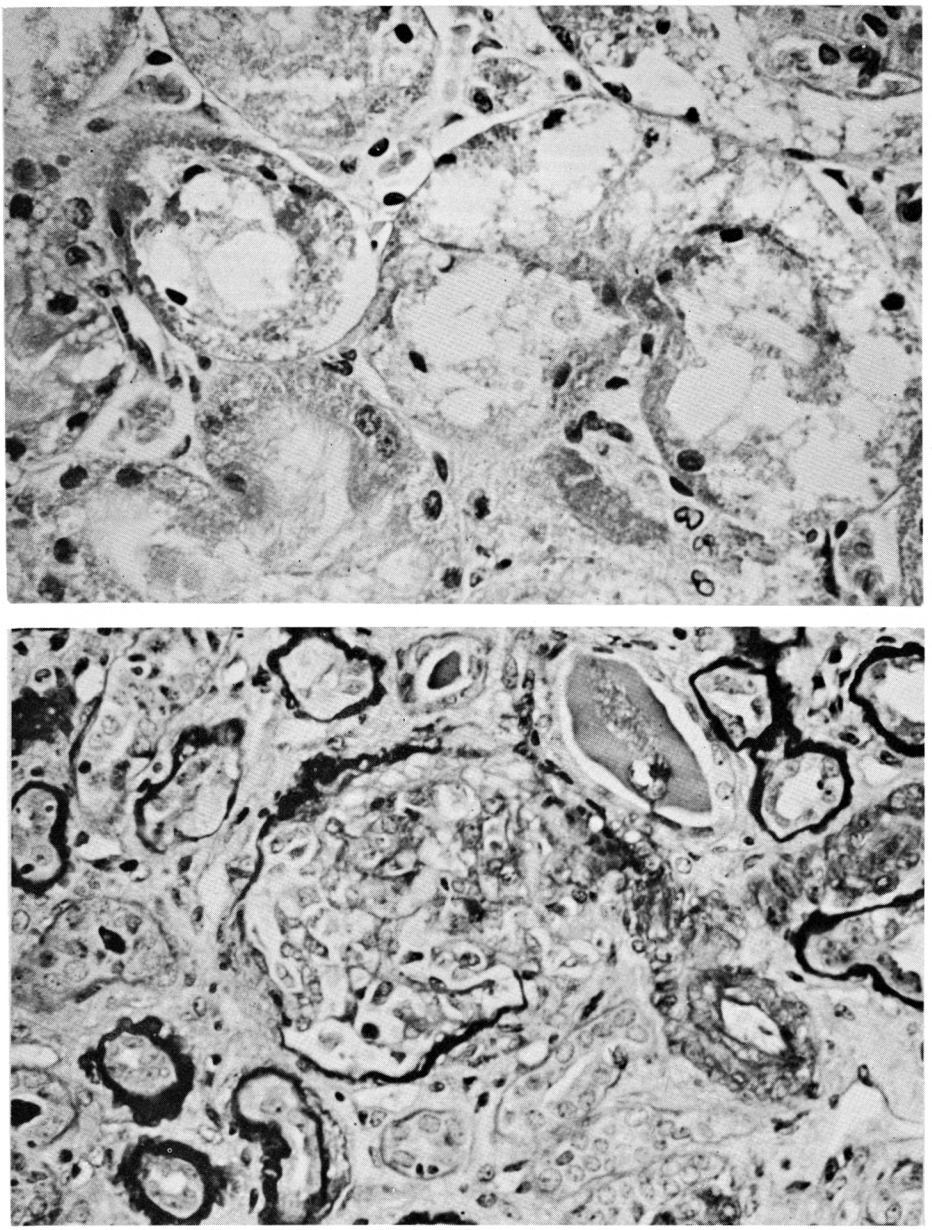
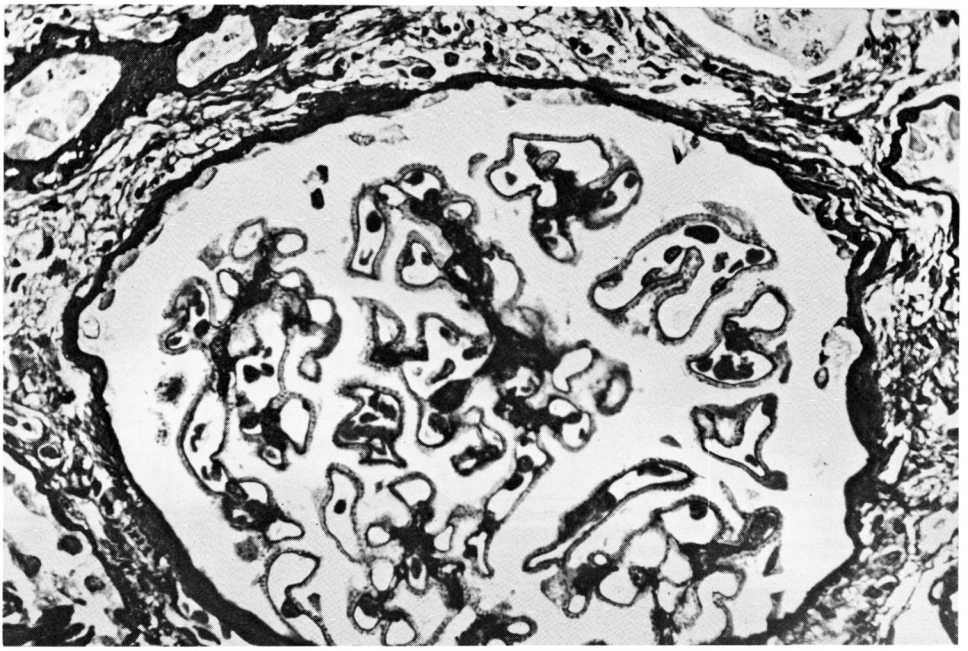


FIGURE 3 (top). Experimental dioxane nephropathy in rats. Large and small vacuoles and necrosis of proximal tubular cells. H & E 600×. (Photograph from Dr. Jacob Churg.)

FIGURE 4 (bottom). Extra-capillary glomerulonephritis with glomerular hypercellularity, crescent formation and necrosis. Anuria following inhalation of unknown solvents. PAS 380×. (Photograph—Dr. Jacob Churg.) (Case of Dr. Robert S. Rigoloso.)

GLOMERULONEPHRITIS

Glomerulonephritis has not been associated with exposure to solvents except for occasional sporatic reports.[17] Recently, Beirne[3,27] found that in a number of patients with proliferative glomeruloneph-



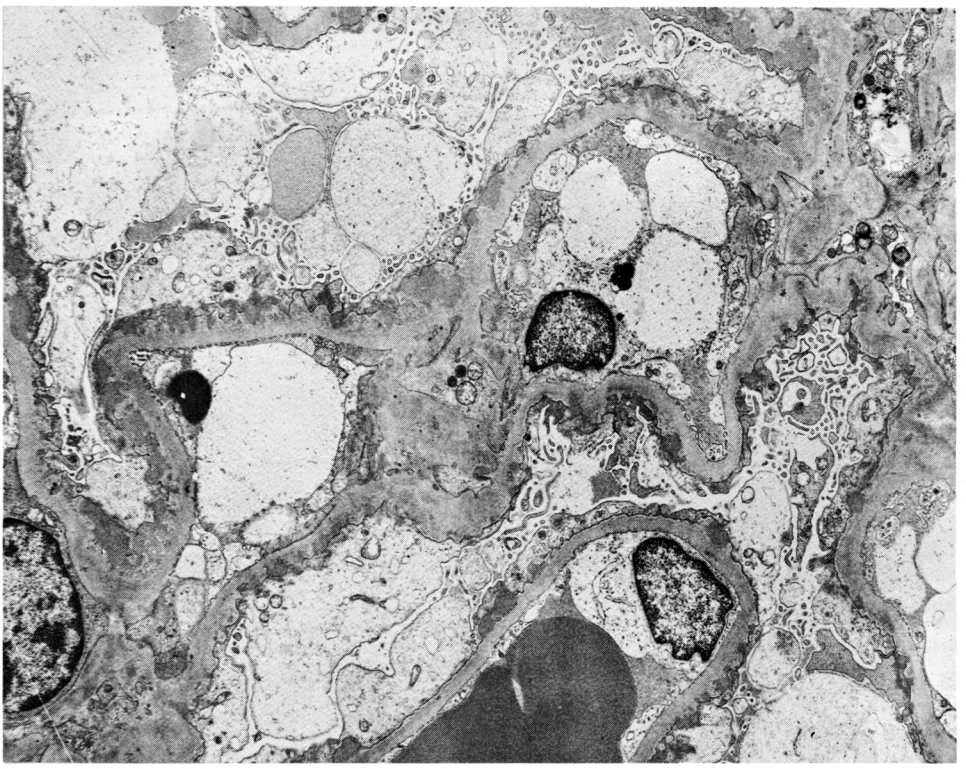


FIGURE 5 (top). Membranous nephropathy, glomeruli in full-blown Stage II. Spikes and deposits on outer aspect of basement membrane. Case 4. CSM 500×.

FIGURE 6 (bottom). Electron microscopy of the biopsy shown in figure 5. Glomerular capillary loops showing numerous electron dense deposits separated by irregular projections of the basement membrane (spikes). 5,250×.

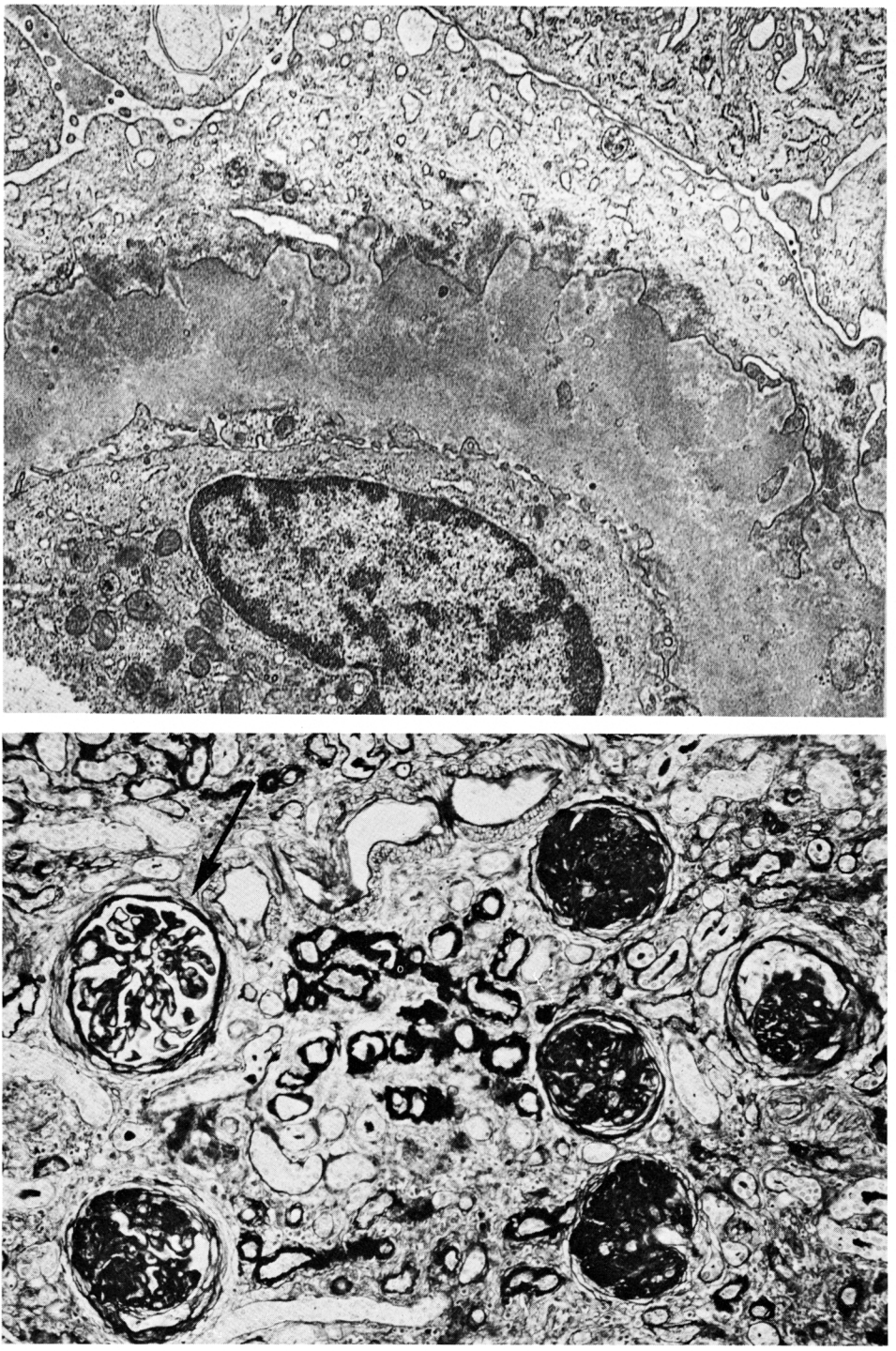


FIGURE 7 (top). Stage II and advanced Stage II, case 3. Large electron dense deposits are encircled by proliferating spikes and being incorporated into the basement membrane. 6,970×.

FIGURE 8 (bottom). End-stage kidney with marked glomerular sclerosis and tubular atrophy in case 1. In one glomerulus without sclerosis (arrow) typical lesions of membranous nephropathy are present. PAS 120×.

ritis there was a history of extensive, long-term exposure to solvents. This was a retrospective study and the hydrocarbon solvents were not specifically identified but included many petroleum products. The mean period of solvent exposure in one group of 28 patients with advanced proliferative glomerulonephritis was significantly greater than in a group of 35 patients with other forms of renal disease.

The morphology of the glomerular disease in these patients were reported as: (1) Goodpasture's syndrome predominated with nine cases in which kidney biopsies showed extra-capillary (crescentic) glomerulonephritis; (2) proliferative glomerulonephritis, four cases; (3) extra-capillary (crescentic) glomerulonephritis, four cases; and (4) membrano-proliferative disease, one case.

Extra-capillary glomerulonephritis occurring with or without hemorrhagic lung disease would appear to be the predominant glomerular lesion in this group of patients. It is also seen in rapidly progressing glomerulonephritis and is characterized by cellular crescents which may be associated with cellular proliferation of the glomerular tuft as seen in proliferative glomerulonephritis. The crescents are made up of epithelial cells derived principally from Bowman's capsule. The glomerular tuft is compressed and altered by the proliferating crescents resulting in breaks of the capillary wall. The crescents may resolve or undergo fibrosis. In Goodpasture's syndrome, there is linear deposition of IgG along the capillary wall.

In the case of Goodpasture's syndrome reported by Beirne, there was linear deposition of IgG. The presumed pathogenesis is direct toxic alteration of the pulmonary alveolar basement membrane with subsequent antibody formation and glomerular basement injury. In the other cases of glomerulonephritis, there may have been direct toxic effect upon the glomerulus or indirect effect mediated by direct tubular injury.

The development of glomerulonephritis in these cases occurs after a latent period which may be prolonged, unlike most cases of solvent exposure with tubular lesions in which anuria occurs promptly and may be related to the exposure with greater certainty.

Membranous Nephropathy

Membranous nephropathy, a glomerular disease, was found in four patients who had lengthy occupational exposure to a variety of aromatic and aliphatic hydrocarbon solvents.[8] The period of exposure before onset of symptoms ranged from two to 20 years. Two patients had the same quantity and quality of exposure. Membraneous nephropathy is a chronic, usually slowly progressive disease characterized by proteinuria and nephrotic syndrome.[7,23] The onset is slow and insidious. It may be present for many years without clinical manifestation. In most patients there is no known etiology or underlying disease. However, some cases have been related to specific tumors, infections, drugs or metals.

It is generally considered to be an immune complex disease. The renal lesions are confined to the glomerular capillary wall which appears to be thickened on light microscopy. This is due to diffuse deposition of electron-dense deposits on the epithelial aspect of the basement membrane. In the early stages of the disease, there are few deposits. As they increase in number, they are joined by thin projections ("spikes") of basement membrane-like material which tend to encircle the deposits. Eventually, the deposits become incorporated within a markedly thickened basement membrane and renal failure may be present at this stage.

Many of these features can be seen with the light microscope and silver stains. Electron microscopy is needed for the

finer details. The deposits contain IgG and complement and have a granular appearance with appropriate immunofluorescent staining. Three of the four patients with membranous nephropathy following solvent exposure progressed to renal failure, although in two the exposure was discontinued after the disease became known. Based on previous experience with other cases of membranous nephropathy secondary to drugs or chemicals, arrest of the disease after cessation of exposure could have been anticipated. However, the exposure in these four cases had been intense and prolonged, and the disease was too far advanced. The pathogenesis of membranous nephropathy in these cases is not known, although an indirect immunological mechanism has been considered.

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