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Contents

A. Morphology of Erythrocytes

In lead-induced anemia, red blood cells are microcytic and hypochromic, as in iron deficiency, and usually reticulocytosis and basophilic stippling are also observed. Iron deficiency may be a coincident factor, but microcytic hypochromic anemia is seen in children with lead poisoning even when serum iron is normal or elevated (Leikin and Eng, 1963).

Basophilic stippling of red blood cells has long been recognized as a feature of lead-induced anemia and has been employed as a method of monitoring workers in lead industry (McCord *et al.*, 1935), but this test has the disadvantages of being nonspecific and probably does not correlate well with levels of lead exposure (Griggs, 1964). Stippling is more common in erythroblastic cells in bone marrow than in cells in peripheral blood (Waldron, 1966).

The nature of the basophilic stippling has received considerable attention. Stipples are thought to represent clustered ribosomes (Jensen *et al.*, 1965). They may or may not stain for iron (Waldron, 1966).

Large concentrations of lead in blood *in vivo* (25–100 mg Pb^2 given intravenously) or added *in vitro* (20 μg per milliliter of blood) produce red cell shrinkage, distortion, and wrinkling of the membrane (Waldron, 1966).

B. Functional Effects on Erythrocytes

A number of reports following the early studies of Aub and his associates (1925) have shown that the osmotic fragility of red blood cells from lead-intoxicated people or of cells exposed to lead *in vitro* is decreased or altered. However, osmotic fragility may be increased after sterile incubation for 24 hours. These studies are reviewed by Waldron (1966). On the other hand, the mechanical fragility of leaded cells is increased. Whether this effect is related to lead-binding phosphate as suggested by Aub and associates (1925) or to other functional effects of lead on the red cell membrane is unclear. Prankerd (1961) has suggested that decrease in red cell membrane integrity follows impairment by lead of glycolytic enzyme activity. Incubation of red blood cells from workers exposed to lead results in excessive potassium loss (Hasan *et al.*, 1967a), and may be related to inhibition by lead of sodium- and potassium-dependent ATPase's (Hasan *et al.*, 1967b; Hernberg *et al.*, 1967).

C. Hemolytic Effect of Lead

The anemia that occurs in lead poisoning results from two basic defects, shortened erythrocyte life-span and impairment of heme synthesis.

Whether shortened erythrocyte survival is due to an effect on the developing red cells in bone marrow or on the membrane of the circulating cell is debated (Waldron, 1966). A recent study of heme and porphyrin metabolism in an adult with lead poisoning (Berk *et al.*, 1970) has shown that there is a direct hemolytic effect of lead on mature red blood cells which is independent of effects on heme biosynthesis. Previous workers who postulated decreased erythrocyte survival on the basis of shortened half-life of ^{51}Cr-labeled erythrocytes in lead poisoning, were misled by the fact that lead increases the rate of ^{51}Cr elution from tagged cells (Berk *et al.*, 1970). This conclusion was based on the demonstration of an early excretion of ^{14}C-labeled stercobilin and on erythrokinetic studies with multiple tracers.

D. Inhibition of Heme Synthesis

A schematic presentation of the effect of lead on heme synthesis is shown in Fig. 16. At least three steps in heme synthesis may be affected by lead. *d*-Aminolevulinic acid dehydratase (ALA-D) is probably the enzyme in the heme pathway that is most sensitive to lead. Inhibition of this enzyme results in a block in utilization of *d*-ALA and in subsequent decline in heme synthesis. Second, in the scheme of negative feedback

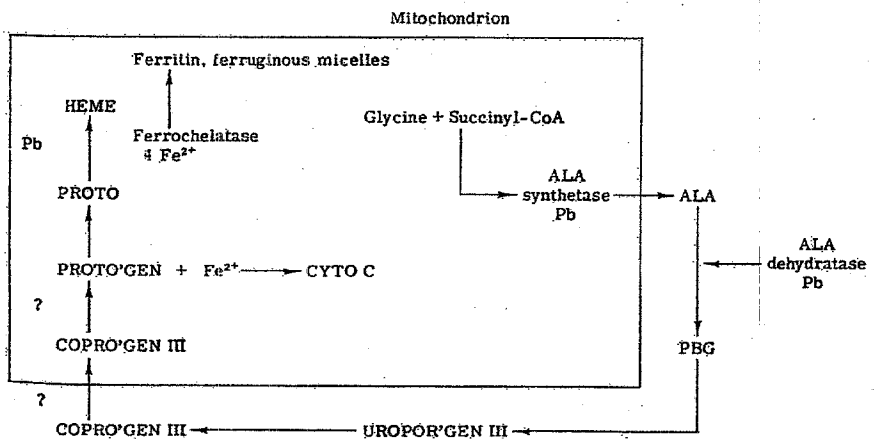

FIG. 16. Scheme of heme synthesis showing sites of lead effect. PBG, porphobilinogen; UROPOR III, uroporphyrinogen III; COPRO III, coproporphyrinogen III; PROTO, protoporphyrin; CoA, coenzyme A; ALA, aminolevulinic acid; CYTO C, cytochrome *c*.

control of heme synthesis proposed by Granick and Levere (1964), *d*-ALA synthetase activity is derepressed, which results in increased activity of the enzyme and increased synthesis of *d*-ALA. Since utilization of *d*-ALA is blocked, urinary excretion of *d*-ALA is greatly increased, serves as a sensitive biochemical index of lead toxicity and is widely used as such (Haeger-Aronsen, 1960).

A third abnormality of heme synthesis in lead intoxication is inhibition of the enzyme ferrochelatase (Ortzonsek, 1967), which is located on the inner membrane of mitochondria (Jones and Jones, 1968). This effect is particularly interesting because of associated ultrastructural changes in the mitochondria. Ferrochelatase catalyzes the incorporation of the ferrous ion into the prophyrin ring structure. Bessis and Jensen (1965) have shown that iron in the form of apoferritin and ferruginous micelles may accumulate in mitochondria of bone marrow reticulocytes from lead-poisoned rats.

Other steps in the biosynthetic pathway of heme may also be abnormal in lead toxicity, but the evidence for this is incomplete. Increase in urinary excretion of coproporphyrin, the degradative product of coproporphyrinogen III, is a sensitive reflection of lead toxicity. Metabolism of porphobilinogen to coproporphyrinogen proceeds unimpaired. However, since ALA-D is an extramitochondrial enzyme, and later steps in heme synthesis are intramitochondrial, coproporphyrinogen must reenter the mitochondrion to be metabolized further. It has been suggested that transport of metabolites like coproporphyrinogen into the mitochondrial matrix might be impaired in the presence of altered inner membrane permeability and reduction in oxidation and phosphorylation (Haeger-Aronsen *et al.*, 1968). Whether the increased urinary coporporphyrinogen occurring in lead poisoning is a reflection of a nonspecific alteration in mitochondrial membranes or reflects a more specific effect of lead on the intramitochondrial enzyme, coproporphyrinogenase, is not known.

VII. Renal Effects of Lead

A. Lead Nephropathy in Human Beings

1. *Acute or Early Effects on the Kidney*

Acute effects of lead on the kidney were distinguished from lead-induced chronic nephropathy more than 50 years ago by the English toxicologist Thomas Oliver (1914). Acute renal effects of lead are seen in persons

dying of acute lead poisoning or suffering from lead-induced anemia and/or encephalopathy, and are usually restricted to nonspecific degenerative changes in renal tubular lining cells, usually cloudy swelling and some degree of cellular necrosis. Cells of the proximal convoluted tubules are most severely affected. There is little evidence that the glomerulus is affected in acute lead poisoning, although a recent report suggests that ultrastructural changes in the glomerular basement membrane may occur (Macadam, 1969). These consist of complete fusion of epithelial cell foot processes and of increased cytoplasmic density of epithelial cells adjacent to a normal looking basement membrane. As long ago as 1928, Pejic emphasized that the degenerative changes in proximal tubules rather than the vascular changes often referred to in earlier studies, are primary evidence of injury to the kidney in lead poisoning. Many subsequent studies have shown at least three pathological alterations in the renal tubule, with onset during the "early" or the acute phase of lead intoxication in the kidney. These include the formation of inclusion bodies in nuclei of proximal tubular lining cells and the development of functional as well as ultrastructural changes in renal tubular mitochondria. These have been discussed in Section IV.

Dysfunction of proximal renal tubules (Fanconi's syndrome) is manifested by aminoaciduria, glycosuria, and hyperphosphaturia, and was first noted in acute lead poisoning by Wilson and co-workers in 1953. Plasma amino acids were normal, which suggested that the aminoaciduria and other functional abnormalities were of renal origin. Subsequently, aminoaciduria in children with acute lead poisoning was observed by Marsden and Wilson (1955) in England, and Chisolm (1962) found that 9 of 23 children with lead encephalopathy had aminoaciduria, glycosuria, and hypophosphatemia. The aminoaciduria was generalized in that the amino acids excreted in greatest amounts were those normally present in urine, and it was related to severity of clinical toxicity, most marked in children with encephalopathy. The aminoaciduria disappears after treatment with chelating agents and clinical remission of other symptoms of lead toxicity (Chisolm, 1962, 1968). This is an important observation relative to the long-term or chronic effects of lead on the kidney. Restoration of the functional integrity of renal tubular lining cells following treatment of acute lead poisoning implies restoration of normal morphology, but this has not been confirmed experimentally.

2. *Chronic Lead Nephropathy in Man*

The occurrence of a chronic form of renal disease in man is controversial. There are numerous reports in the medical literature of the past

century which describe a form of end-stage renal disease and renal failure in humans which is said to follow many years of excessive exposure to lead. The pathogenesis of chronic lead nephropathy expressed by Charcot and Gombault in 1881 (cited by Aub *et al.*, 1925) relates renal effects of lead on the tubular lining cells resulting in diffuse renal fibrosis characterized by "epithelial cirrhosis of the kidney." Later descriptions by Oliver (1914) and Aub *et al.* (1925) are consistent with this hypothesis, and emphasize tubular atrophy and dilatation with interstitial fibrosis, but with minimal inflammatory cell infiltration. There is progressive contraction of kidney size with subsequent sclerosis of glomeruli. These descriptions have no specific pathological feature, so that the role of lead in the pathogenesis of diffuse chronic nephropathy in a particular person has always been uncertain. The implication of lead as etiological agent of chronic nephropathy is largely the result of association of chronic renal disease with chronic exposure to lead and signs and symptoms of chronic lead poisoning, such as abdominal colic and peripheral neuropathy.

a. Lead Intoxication in Childhood and Chronic Lead Nephropathy in Adulthood. A series of reports from Queensland, Australia, points to a strong association between severe lead poisoning in childhood associated with central nervous system symptoms and chronic nephritis in early adulthood. Henderson (1954) followed up 401 children who had been diagnosed as having lead poisoning in Brisbane between 1915 and 1935. Of these 165 had died, 108 from nephritis or hypertension. This is greatly in excess of expectation. Information was obtained from 101 of the 187 living survivors, and of these 17 had hypertension and/or albuminuria. In a more recent study, Emmerson (1963) presented criteria for implicating lead as an etiological factor in such patients: the patients should have an excessive urinary excretion of lead following administration of calcium EDTA. In his study, 32 patients with chronic renal disease attributable to childhood lead poisoning showed increased excretion of lead. Only 4 of 19 patients with chronic renal disease not attributable to lead poisoning had similarly elevated excretion of lead. A photomicrograph of part of a kidney from a 26-year-old male with a childhood history of lead poisoning is shown in Fig. 17. The presence of intranuclear inclusion bodies is very helpful establishing a relationship between renal lesions and lead toxicity, but inclusion bodies are not always present in persons with chronic lead nephropathy.

Attempts to confirm the relationship between childhood lead intoxication and chronic nephropathy have not been successful in at least two studies in the United States. Tepper (1963) found no evidence of chronic renal disease in 42 persons with a well documented history of childhood plumbism 20–35 years previously at the Boston Children's Hospital. Likewise, Chisolm (1970) found no evidence of renal disease in 62 ado-

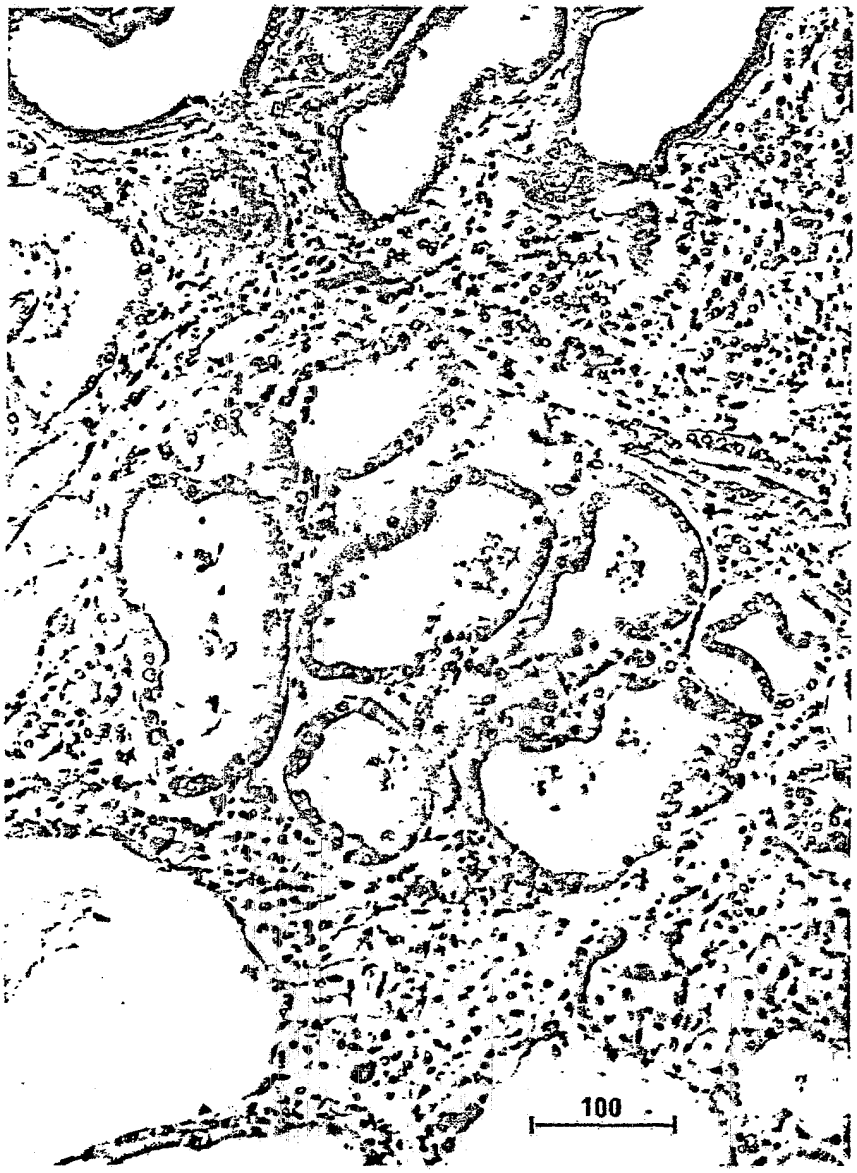

FIG. 17. Renal cortex from a 26-year-old male with history of childhood lead poisoning and chronic lead nephropathy. The patient was hypertensive and died in uremia. At autopsy the kidney was small and fibrosed. Bone lead was high. The histological picture is a mixture of interstitial fibrosis and dilated tubules. Some tubules are atrophic (lower left). Intranuclear inclusion bodies are not present. ×210. (Slide furnished by J. A. Inglis, M.D., Department of Pathology, University of Queensland, Australia.)

lescents known to have had intoxication 11–16 years earlier. An important distinction between the Australian group and American patients was that none of Chisolm's (1970) subjects showed evidence of increased residual body lead burden following the EDTA mobilization test. This difference has suggested to Chisolm (1970) that lead toxicity in the Australian children must have been of a different type, with a more protracted course than that experienced by the American children. Most American children suffer from lead toxicity early in childhood, between the ages of one and four, the source being oral ingestion of flecks of wall paint and plaster containing lead. Australian children, at least at the time of the Nye (1929) and Henderson (1955) studies, ingested lead from powder or chalky paint on veranda rails of their homes while playing. They tended to be older than the American children, and had a more chronic form of lead poisoning.

b. Occupational Exposure to Lead—Renal Hypertension and Chronic Lead Nephropathy. Several studies of workers in lead industries in the early part of this century showed an increased incidence of hypertension which appeared to correlate with exposure to lead (cited by Cantarow and Trumper, 1944). However, a relationship of hypertension to renal disease was not established. A retrospective study (Dingwall-Fordyce and Lane, 1963) reviews causes of death among men eligible for pension (65 years of age) who had worked in an accumulator factory in England between 1926 and 1960. The incidence of deaths from cerebral hemorrhage and from thrombosis or arteriosclerosis was higher than expected. All affected persons were employed for not less than 25 years. Again, a renal basis for the hypertension was not demonstrated.

Control of occupational exposure to lead has undergone continued improvement during the past 50 years, which may be responsible for the failure of other investigators (Belknap, 1936; R. E. Lane, 1949) to find an increase in frequency of hypertension and chronic renal disease. More recently, Cramér and Dahlberg (1966) did not find an excessive incidence of hypertension among workers in a Swedish accumulator factory in which 265 workers were employed for more than 10 years. On the other hand, in those parts of the world where occupational exposure to lead is not closely controlled, there continued to be a high incidence of chronic nephropathy and renal failure. In Yugoslavia, in a study of 53 patients with chronic exposure to lead (2 months to 35 years) and with clinically manifest lead poisoning, Radošević *et al.* (1961) concluded that lead may induce functional and anatomical lesions of the kidneys. Studies of renal function in 102 patients admitted to the Occupational Diseases Clinic in Bucharest, Rumania, during a 10-year period (1957–1967) were reported by Lilis and co-workers (1968). Renal failure was found in 17

patients who had had several episodes of abdominal colic and occupational exposure to lead for more than 10 years. Thirteen of these patients had arterial hypertension and evidence of renal disease preceding the rise in blood pressure by several years. The authors related the progressive development of renal failure to prolonged exposure to lead, with repeated episodes of lead-induced abdominal colic.

c. Illicit Whiskey and Renal Disease. Contamination with lead, intentional or accidental, is a long-recognized risk attending the consumption of "home brew" or illegally produced alcoholic beverages. The Romans are said to have added lead to wine to improve flavor (Gilfillan, 1965). Devonshire colic, an endemic disease in the County of Devonshire, England, in the middle of the 18th century, was found to be a symptom of lead intoxication caused by drinking cider contaminated with lead (Anonymous, 1968). Homemade wine may be contaminated by lead glaze in earthenware crocks (Whitehead and Prior, 1960; C. R. Lane and Lawrence, 1961).

Contamination of illicit whiskey by lead has been a problem of major proportions in the southeastern region of the United States. Lead is leached into the distilling alcohol from lead-soldered pipe joints. Hammack (Owen *et al.*, 1967) has recorded that over 250 patients were admitted to the Birmingham Alabama Veterans Administration Hospital for intoxication with lead in illicitly distilled whiskey This number of acutely ill patients suggests that many others must be affected with subclinical or chronic lead toxicity and continue to go unrecognized. Morgan and coworkers (1966) have described renal biopsies in 13 of such patients, aged 35–50, with early renal failure, anemia, and increased urinary excretion of lead with or without provocation by EDTA. Two of the patients had fixed hypertension. The biopsies from all cases showed interstitial fibrosis with few inflammatory cells. Some glomeruli were sclerosed; others showed a mild increase in basement membrane thickness. All cases were found to have intranuclear inclusion bodies.

At the Veterans Administration Hospital in Nashville, Tennessee, Sandstead *et al.* (1970) studied the renin–aldosterone response to salt deprivation in 9 men with subclinical or "occult" lead poisoning. All nine had elevated body burdens of lead demonstrated by increased urinary excretion of lead following administration of EDTA. Plasma renin activity and aldosterone secretory rate were measured after administration of the diuretic furosemide and ingestion of a low sodium diet for 5 days. Neither of the measured parameters increased to expected levels in most of the men. Lead toxicity is believed to be responsible for abnormal sodium-conserving functions of the renal tubule.

It cannot be proved unequivocally that lead in alcoholic beverages was

since these animals tolerate large doses of lead for long periods of time and since they both develop progressive structural and functional renal changes in response to lead. Dose-effect relationships can also be studied in animals.

The progressive morphological and functional changes induced by lead in rat kidneys may be divided into three stages—primarily, for the purpose of observing the development of lead effects and, secondarily, for making comparisons to observations in man.

1. *Stage I—Tubular Effects, Reversible*

The first stage of lead nephropathy in rats fed a diet containing 1% lead as lead acetate continues for about 20 weeks and is characterized by the development of intranuclear inclusion bodies after about 4 or 5 weeks. No other changes are apparent by light microscopy. An electron micrograph of a nucleus of a proximal tubular lining cell containing an inclusion body is shown in Fig. 3. Swelling of organelles and mitochondria is also seen by electron microscopy, as shown in Fig. 9B. Impairment of respiratory and phosphorylative abilities of mitochondria isolated from kidneys of rats fed a 1% lead acetate diet for 10 weeks are discussed in Section IV, B. The mitochondrial changes may be related to the triad of functional defects in proximal renal tubules, that is, to aminoaciduria, glycosuria, and hyperphosphaturia, as noted in children with acute lead poisoning.

Excessive aminoaciduria also occurs during stage I nephropathy in rats. After about 10 weeks on the experimental diet, nearly all amino acids are excreted in greater amounts than in control rats. The aminoaciduria is "generalized," with greatest increases occurring in amino acids normally present in urine in largest amounts. These are the small neutral monoamino, monocarboxylic acids, e.g., glycine, serine, and alanine. Renal clearances for most individual amino acids (Fig. 18) increase approximately 1–3 times. Exceptions include a decreased clearance of tyrosine, little change in the clearance of glycine and valine, and a very large increase in the clearance of histidine. Plasma levels of nearly all amino acids from lead-fed rats are either the same or less than plasma levels of control rats. Exceptions are increases in threonine, glycine, and lysine. Renal clearance of glycine is normally considerably larger than that of other amino acids, but it does not increase appreciably in the lead-fed rats. This suggests a prerenal factor in the excessive glycinuria. The large increase in histidine clearance and the disproportionate increases in uninary excretion of other amino acids may also reflect complexing of lead with amino acids (Goyer, 1971b; Goyer *et al.*, 1970a).

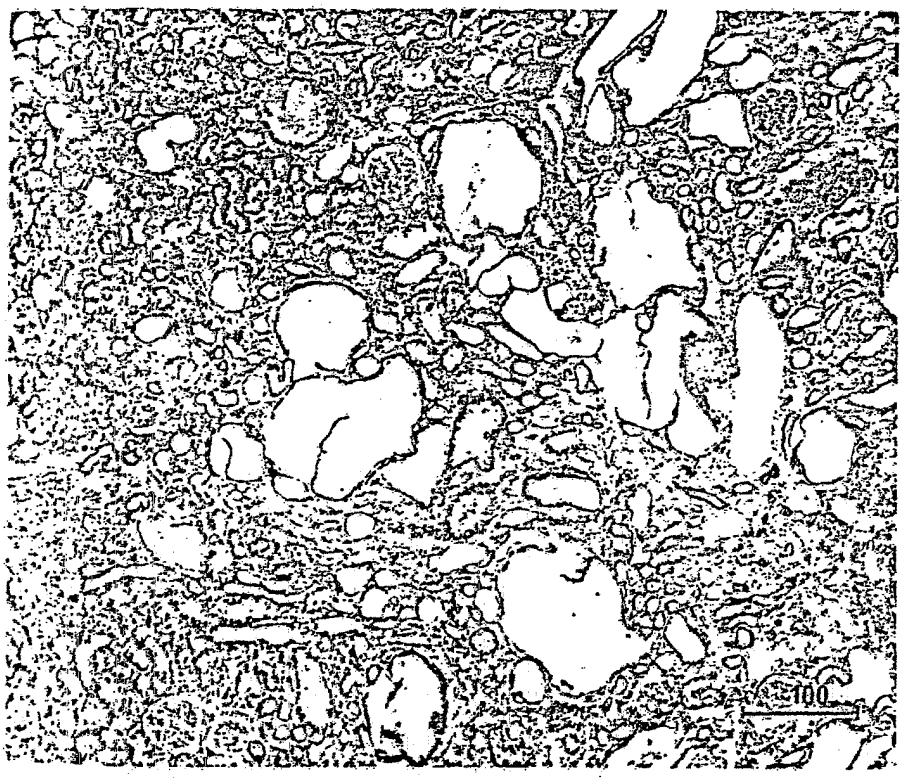

FIG. 19. Renal cortex of rat fed a diet containing 1% lead acetate for 9 weeks. Many tubules, particularly in the deep cortex, are dilated and lined with atrophic epithelium. Cells lining other tubules are hyperplastic and contain hyperchromatic nuclei. Interstitial fibrosis is present, but inflammatory cells are sparse. ×150. From Goyer (1971c), by permission of Springer-Verlag, Berlin and New York.

3. *Stage III—Renal Failure and Cancer*

Rats fed 1% lead as lead acetate in their diets for more than one year have progression of interstitial scarring and fibrosis, sclerotic glomeruli, and frequently develop renal failure and adenocarcinoma. Blood urea levels of six rats after 84 weeks of ingesting a lead-containing diet are shown in Fig. 21A. Elevation of blood uric acid also occurs (Fig. 21B) and may be related to the renal failure, although in these 6 rats there was no clear relationship between the hyperuricemia and uremia. On the other hand, the elevated blood uric acids levels may be analogous to the hyperuricemia seen in human lead nephropathy (Section VII, A, 2, d).

ange in renal clearance of individual amino acids from three rats fed lead for 10 weeks and three controls week prior to collection of samples. Bars indicate mean and range of percent change. From Goyer *et al.* rmission of Academic Press, New York.

Effects of lead on morphology and function of the distal tubules in rat kidneys are less dramatic than those on proximal tubules, and they have not been studied as intensively. Pardoe and Weatherall (1952) showed a number of years ago that tubular excretory activity, as measured by *p*-aminohippuric acid excretion, progressively increases during lead intoxication. Other experiments by these authors suggest that water diuresis is slightly increased, with reduced sensitivity to vasopressin. These functional changes are reversible on reduction of lead dosage. Such studies have not been repeated by others.

Absence of effects of lead on glomeruli is emphasized by Pardoe (1952), who showed normal creatinine clearances in rats fed lead for as long as 6 months, but a later study (Macadam, 1969) suggests that ultrastructural changes in glomerular basement membranes may occur.

Rabbits fed lead subacetate (0.5–1.0%) in their diets also develop intranuclear inclusion bodies (Hass *et al.*, 1964) and hyperaminoaciduria (von Studnitz and Haeger-Aronsen, 1962) in 8–12 weeks. These early lead-induced renal changes progress to stage II nephropathy which is characterized by the development of permanent scarring and tubular changes after about 20 weeks.

2. *Stage II—Chronic, Irreversible Nephropathy*

Continued feeding of lead results in atrophy of tubular lining cells in some tubules, with dilatation and eventual cystic change (Fig. 19) (Goyer, 1971c). The cellular lining of some tubules becomes hyperplastic. There is a progressive increase in interstitial fibrous tissue with few inflammatory cells. The number of intranuclear inclusion bodies becomes maximal between stage I and II and decreases as scarring and tubular atrophy progress. Hyperplastic tubular lining cells do not contain intranuclear inclusions, but many of these cells have hyperchromatic nuclei and are atypical in appearance, which suggests premalignancy. Similar progressive renal effects in rats fed lead for several months have been previously reported by others (Chiodi and Sammartino, 1947; Pardoe, 1952; Murphy *et al.*, 1964), and also occur in kidneys of lead-fed rabbits (Hass *et al.*, 1964).

Greater deposition of lead in renal tubular lining cells may be induced by giving 13 successive intraperitoneal injections with 1 ml of 1% lead acetate solution once in 2 weeks over a period of 26 weeks. In addition to the already described intranuclear inclusion bodies, dense concretions appear in the cytoplasm (Fig. 20). The concretions stain with hydrogen sulfide, suggesting that they contain lead (Murakami, 1971).

(Morgan *et al.*, 1966). In each case, lead nephropathy preceded the onset of gout.

From a review of all admissions for gout at the Birmingham Alabama Veterans Hospital, Ball and Sorensen (1969) were able to classify 33 of 43 patients with gout as secondary to prolonged consumption of "moonshine" contaminated with lead. Kinetic studies of uric acid on three of these patients confirmed the role of the kidneys in the pathogenesis of the hyperuricemia. There was no evidence of overproduction of uric acid. These findings suggest that lead impairs renal tubular secretion of uric acid. However, in another recent study of urate excretion in lead nephropathy, Emmerson (personal communication) measured renal tubular reabsorption and secretion of urate separately by observing the effect on renal deposition of urate of the drug pyrazinamide which blocks active tubular secretion of urate. Tubular reabsorption of urate was found to be greater than expected whereas active tubular secretion of urate was within the range predicted from the plasma urate concentration. These results suggest that lead-induced gout is mediated by excessive tubular reabsorption of urate.

Klinenberg (1969) has noted that few patients with chronic renal disease per se develop gouty arthritis, whereas patients with saturnine gout, despite prolonged exposure to lead, have only moderate impairment of glomerular infiltration rate and are not azotemic. Also, patients with lead gout have normal triglyceride and cholesterol levels; patients with primary gout have a high incidence of hypertriglyceridemia (Emmerson and Knowles, 1971).

B. Experimental Lead Nephropathy

Questions about effects of lead on the kidneys, based on observation of patients with lead poisoning, are difficult if not impossible to investigate in man. The sequence of pathological events leading to a chronic nephropathy induced by lead requires a major portion of the lifetime of an individual. Continuity of study for such a long period is difficult if not impossible. Also, in human studies there is no control of lead dosage or of other (intercurrent) renal disease. And finally, it is not possible to obtain renal tissue at the periodic intervals necessary to document such a chronic, progressive pathological process in man. It is important, therefore, to study progressive effects of lead on the kidney in experimental animals, and to correlate the findings with stages of lead nephropathy seen in man. The rat and the rabbit serve as good models for this purpose

responsible for the renal disease in either of these studies. Increased body burdens of lead were demonstrated in all the patients. Also, the finding of intranuclear inclusion bodies is further evidence of excessive renal lead.

It is also possible that lead and alcohol have a synergistic toxic effect on the kidney. Alcoholic beverages have long been thought to enhance lead toxicity (Oliver, 1914), and avoidance of alcohol is recommended for workmen in lead industries (Cramér, 1966). Lead and alcohol have some similar toxic effects at the cellular level. The basis for this presumption is discussed in Section X in terms of alcohol as a factor influencing susceptibility to lead toxicity. Even though the molecular mechanisms underlying the toxicity of alcohol and lead probably differ, the fact that they affect the same organelle, the mitochondrion, may result in a mutual enhancement of cellular injury. It is also possible that illicitly distilled whiskey contains other impurities that are toxic to kidneys, although none have been documented.

d. Gout and Lead Nephropathy. Because of the common association of chronic renal disease with gout among lead industry workers, industrial physicians and toxicologists in 19th Century believed strongly in a relationship between gout and chronic lead nephropathy. Several case reports of the 19th century linking lead with gout are summarized by Ludwig (1957). Even Sir Alfred Barring Garrod, who is credited with first recognizing elevated blood uric acid levels as an etiological factor in gout, emphasized the relationship of lead poisoning with gout (cited by Ludwig, 1957). A typical early study was Lorimer's (1886) of 107 cases of gout and lead poisoning. Lorimer distinguished saturnine gout as occurring earlier in life than ordinary gout. In addition, there was absence of familial predisposition, and the anemia of lead poisoning was always present. Arthritis was of early onset. But even in this report, the question was raised whether joint involvement could be due to coexistent "rheumatism." Fewer cases have been seen in recent years and the review by Aub *et al.* (1925) questions the lead–gout relationship.

The problem of gout and lead-induced nephropathy has recently been reopened. Among the 33 individuals in Emmerson's (1968) study of patients with lead nephropathy, 16 suffered from acute attacks of gout. Emmerson found that his patients differed from those with idiopathic gout in that more women were afflicted, and often before the menopause. There was often a history of lead poisoning in childhood. Also, the lower limbs were more commonly affected, and attacks of gouty arthritis were less frequent than in patients with idiopathic gout.

Many patients with chronic nephropathy associated with ingestion of illicit whiskey contaminated by lead also have hyperuricemia and gout

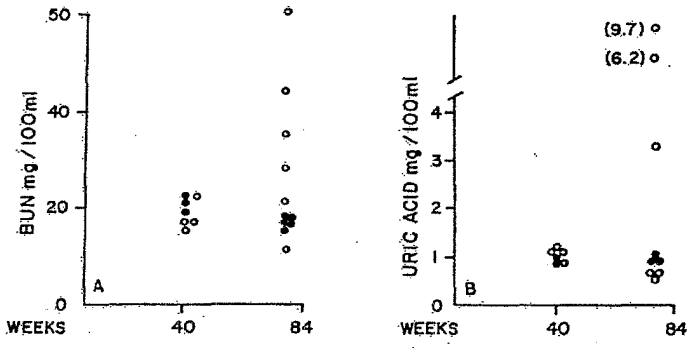

FIG. 21. Blood urea (A) and uric acid (B) from control (●) and lead-poisoned (○) rats sacrificed after ingestion of diet containing 1% lead for 10, 40, and 84 weeks. From Goyer (1971c), by permission of Springer-Verlag, Berlin and New York.

Since hypertension may occur in persons with chronic lead nephropathy, there have been several studies of blood pressure levels in experimental lead poisoning. The results are inconsistent. Several years ago, Fouts and Page (1942) tried unsuccessfully to produce hypertension in dogs by chronic lead poisoning. Griffith and Lindauer (1944) showed a progressive increase in systolic blood pressure of lead-poisoned rats over a 2-month period, but these results were not confirmed in similar studies by Pardoe (1952) and by Padilla *et al.* (1969).

Renal adenomas or carcinomas develop in 60–80% of rats fed for more than one year a diet containing lead. Incidence and size of the tumors are related to duration of lead feeding (Fig. 22). By light microscopy, the tumors are adenocarcinomas, presumably arising from focal areas of hyperplasia of renal tubular lining cells (Fig. 23A).

The ultrastructure of the tumors (Mao and Molnar, 1967) is characterized by cellular and nuclear hypertrophy, numerous lysosomes and microbodies, and absence of infolding of basal plasma membranes as normally seen in renal tubular lining cells. Tumor cells do not contain intranuclear inclusion bodies, and lead content of the tumors is less than that of adjacent renal cortex. In our investigations, about one-fourth of the rats with tumors had metastatic foci in the lungs, but not in other organs (Fig. 23B) (Goyer, 1971c). Renal tumors in lead poisoning were first observed in rats by Zollinger (1953) following long-term injections of lead phosphate, and later by Kilham *et al.* (1962) in wild rats believed to have been exposed to lead fumes in burning refuse in a city dump. Lead-induced renal epithelial tumors have since been studied by a number of investigators (Boyland *et al.*, 1962; Van Esch *et al.*, 1962; Hass

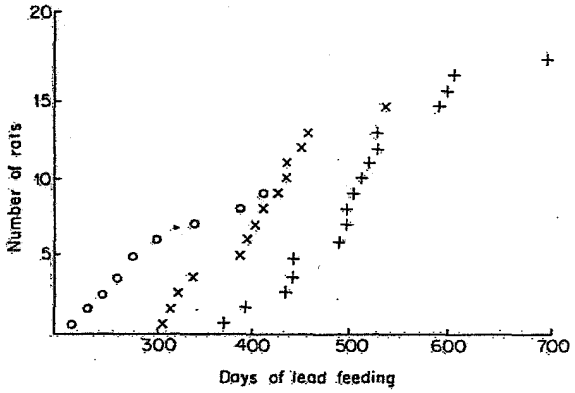

FIG. 22. Correlation of incidence of renal tumors with duration of lead feeding. Open circles indicate rats without tumors (9); ×, rats with microscopic tumors (14); +, rats with gross tumors (17). From Mao and Molnar (1967), by permission of *Amer. J. Pathol.*, Durham, North Carolina.

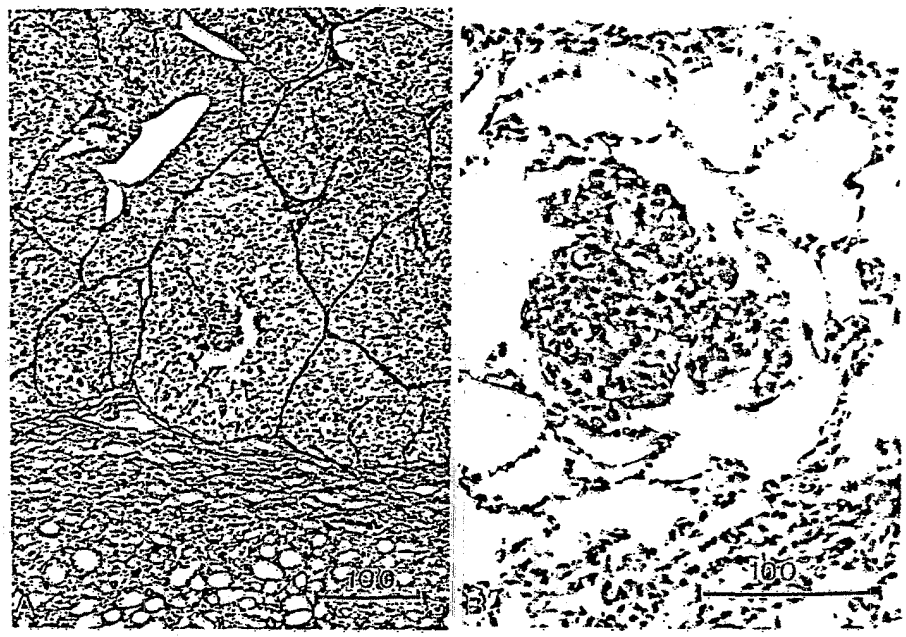

FIG. 23. (A) Renal adenocarcinoma in cortex of kidney of rat fed 1% lead acetate diet for 84 weeks. The tumor appears well demarcated from adjacent cortex, but the cells are poorly differentiated. From Goyer (1971c). ×150. (B) Pulmonary metastases occur as small nests of cells in the periphery of the lung parenchyma. ×250. From Goyer (1971c), by permission of Springer-Verlag, Berlin and New York.

et al., 1967). They have not been noted in lead-intoxicated experimental animals other than rats and mice, less frequently in the latter (Van Esch and Kroes, 1969). The tumors do not appear to have any obvious or immediate relevance to man, since renal tumors have not been noted in industrial workers with chronic exposure to lead. Moreover, the incidence of carcinoma of any type in such workers is not greater than expected in the general population (Dingwall-Fordyce and Lane, 1963).

4. *Comparison of Experimental and Human Lead Nephropathy*

Morphological and functional reactions of kidneys in experimental animals fed lead orally and in people, particularly children with acute lead toxicity, have features which are comparable. In both instances, proximal tubular lining cells are affected, intranuclear inclusion bodies are formed, and there is an associated aminoaciduria. Impairment of mitochondrial function has not been demonstrated in man, but may be inferred from morphological changes in human biopsy material (Section IV, A). Recovery from the lead-induced acute tubular lesion in man certainly occurs. Excessive aminoaciduria returns to normal a few weeks after chelation therapy, but intranuclear inclusion bodies may persist for several years after acute lead poisoning (Galle and Morel-Maroger, 1965). Continued formation of inclusion bodies probably reflects a certain body burden of lead.

In man, progression of acute effects of lead on renal tubular epithelial cells to chronic lead nephropathy has been less clearly documented. Morphological changes observed in kidneys of persons with histories of excessive exposure to lead are similar to the changes seen in kidneys of experimental animals. The problem is that in the absence of intranuclear inclusion bodies, the pathology of chronic lead nephropathy, like that of many other forms of chronic renal disease, lacks specificity. Hyperuricemia occurs in rats with lead poisoning and in persons with chronic lead nephropathy. A major difference between the renal reaction to lead in man and in the rat is that rats develop renal adenocarcinoma. There is no evidence that lead enhances malignancy of any type in man.

A problem in the understanding of the progression of acute renal effects in man to chronic renal disease is the paucity of renal biopsy material from persons with excessive exposure to lead.

It appears, however, from reports of studies on man and on experimental animals that chronic effects of lead on the kidney are dependent on a particular renal content of lead during a prolonged period of time, and that lead is certainly capable of inducing a chronic nephropathy. More information is needed about factors that influence susceptibility of the kidneys to effects of lead.

Concern for potential toxic effects of lead has arisen from growing areness of the relatively large amounts of lead in the environment. here is no question that excessive exposure to lead results in clinical xicity. There is uncertainty, however, regarding the potential harmful fects of low levels of lead that do not produce overt toxicity. Clarification this problem will only be achieved with greater knowledge of the etabolism and cellular pathology of lead.

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