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The effects of hemodialysis on the cognitive and sensory -motor functioning of the adult chronic hemodialysis patient.

Dennis P. Ratner
University of Windsor

THE EFFECTS OF HEMODIALYSIS ON THE COGNITIVE AND SENSORY-MOTOR FUNCTIONING OF THE ADULT CHRONIC HEMODIALYSIS PATIENT

by

Dennis P. Ratner

B.A. Brooklyn College, 1971

M.S.W. University of Michigan, 1975

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ABSTRACT

End stage renal disease is a terminal illness which is pervasive in its ill effects. With the advent of hemodialysis the end stage renal patient is in the fortunate position of adding productive years to his/her life. Research identifying the intellectual sequalae of end stage renal disease (untreated by dialysis) has shown that these patients evidence cognitive dysfunction suggestive of cerebral impairment. After beginning hemodialysis a general improvement in cognitive functioning is observed.

The number of research investigations on the cognitive functioning of toxically uremic, undialyzed patients and those new to dialysis, exceeds research activity on the cognitive and sensory-motor functioning of the long term hemodialysis patient. The latter area was the province of the present study.

The purpose of this study was to answer three questions: 1) How does the cognitive and sensory-motor functioning of the long term adult hemodialysis patient compare with available norms for a normal sample? 2) What patterns of strengths and/or weaknesses may be found in the cognitive and sensory-motor functioning of the chronic hemodialysis patient? and 3) Do significant changes in cognitive and sensory-motor functioning occur when pre, post, and pre-dialysis performances are compared? If so, do specific serum measures seem to be correlated with changes in cognitive and sensory motor performance when test results across repeated test administrations are compared?

To answer these questions 14 male and 6 female adult chronic renal patients, stabilized on hemodialysis for at least 10 months, were administered a repeatable battery of cognitive and sensory-motor tests, just prior to their midweek dialysis (D_0), approximately twenty to twenty four hours

later (D_1) and again just prior to their end of the week dialysis (D_2). At each test session subjects were also administered a subjective rating scale. This scale was designed to measure self perceived changes in psychological and medical states across Do, D_1 and D_2, for purposes of identifying possible sources of unwanted variance which might have affected cognitive and sensory-motor functioning. Finally, blood samples were drawn at each test session to determine levels of BUN, creatinine, sodium, potassium, chloride, carbon dioxide, calcium, phosphate, dimethylamine (ph 7-8, ph > 10) and trimethylamine (ph 7-8, ph > 10).

With regard to levels of performance, dialysis patients scored within the normal range in a wide variety of areas: verbal comprehension, abstraction, short term rote memory (auditory), mental manipulation of symbols (when no switching of set was required), sustained attention, concentration, auditory discrimination, visual-motor planning (when no switching of set was required), visual-motor reaction time, visual recognition and interpretation of pictorially presented objects and social cues, grip strength (males), sustained motor speed (male dominant) and the maximum repetitive performance of an elementary language function (speeded color identification).

Significant improvements in performance, from the mildly impaired to the low end of the normal range, occurred on the Digit Symbol and Speech Sounds Perception tests. These improvements appear to have been due to practice effects.

Dialysis patients were clearly impaired on tests requiring speeded visual-motor coordination, motor speed (females), grip strength (females),

visual search skills, visual-motor planning (involving the ability to switch set) and visual memory. Impairments in the areas of speeded visual-motor coordination, motor speed and grip strength most probably were due to the effects of peripheral neuropathy. The most pronounced impairment was in the ability to execute a plan involving the switching of set. Performance in this area was severely impaired. While not definitively suggestive of cerebral impairment, this pronounced dysfunction has been associated with mild cerebral dysfunction of the anterior region.

With regard to question three, despite significant daily changes in serum levels of small molecule and middle molecule toxic renal metabolites, there was little or no evidence to suggest that dialysis patients undergo daily fluctuations in their cognitive and sensory-motor functioning. This finding was at odds with prior research investigations. Research suggestions, for purposes of resolving differences in findings and expanding our knowledge base were offerred.

DEDICATION

This dissertation project is dedicated to my parents Marian and Nathan Ratner whose never ending support and love has been so meaningful to me throughout the years.

ACKNOWLEDGEMENTS

The completion of this dissertation project is the culmination of a long process beginning with my enrollment in graduate school. My wife and best friend Roberta shared in this process with me and it is to her that I owe my greatest debt of gratitude for her continual support and patience.

I wish to thank Dr. Rourke my chairman, and Drs. Frisch and Daly for their guidance and support in helping me carry out this study. I would like to thank Drs. Adams and Levin for the important role they played in this dissertation project. They provided me with crucial intellectual and administrative support and were involved to a degree far and above that of the usual external examiner. To Dr. Simenhoff my thanks for both showing an interest in this study and for carrying out the special serum amine analyses.

This dissertation project would have been impossible to carry out were it not for the untiring cooperation of the Henry Ford Hospital Fairlane Hemodialysis and Laboratory staffs and the dialysis patients who volunteered as subjects in this study. To Judy Meister R.N. and Ronald Sawyer goes my never ending gratitude. They provided me with an unending source of intellectual and emotional support, so crucial to this project. I cannot thank both of them enough for their willingness to help and be there at all times.

Finally, I would like to thank Michael Joschko, fellow graduate student and friend, who sat down with me when I first thought of this research project and who provided me with the feedback and encouragement that was necessary for getting this project off the ground.

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CHAPTER I

INTRODUCTION

Neuropsychological assessments have served as an aid in neurological diagnosis, as a means for ascertaining neurobehavioral correlates of various systemic diseases and as a basis for remediation. The present research will utilize various neuropsychological tests to study cognitive and sensory-motor functioning in adults with end stage renal disease on long term maintenance hemodialysis.

Uremia and Hemodialysis

An investigation into the cognitive functioning of adults with end stage renal disease, on long term maintenance hemodialysis, presupposes at least a limited understanding of the terms "uremia" and "hemodialysis". As such these and allied terms will be considered here.[1] Uremia is defined as "The clinical condition resulting from a multitude of pathologic processes which lead to derangement and insufficiency of renal excretory and regulatory functions (uremia)." (Berkow, 1977, p. 705)[2] Chronic renal failure may be viewed function-

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[1]The reader will be referred to various appendices in this section of the paper, a consideration of which will aid in obtaining a more global understanding of the present research project.

[2]A brief presentation of renal structure and function appears in Appendix A.

ally in three stages: diminished renal reserve, renal insufficiency, and uremia. Patients with diminished renal reserve usually present as asymptomatic. Their renal dysfunction may only be detected through a careful diagnostic workup. In renal insufficiency there is a slight retention of toxic nitrogenous compounds (a condition referred to as azotemia). This is seen diagnostically in elevated plasma urea[3] and elevated creatinine[4]. With continued renal dysfunction fluid and electrolyte balance are further disturbed. There is an increase in azotemia and systemic manifestations will occur.[5]

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[3]Urea is a nitrogenous waste product formed by the metabolism of protein. Elevated plasma urea refers to blood urea nitrogen (BUN), a clinical determination of the amount of nitrogen derived from urea. Urea = BUN x 2.14. Normal BUN = 8.25 mg/100 ml. The variability in the renal handling of urea, along with the influence of diet and catabolism (the process by which complex substances are reduced to simpler ones), make BUN unsatisfactory as a sole measure of renal function. (Berkow, 1977.)

[4]A nitrogenous waste product of normal metabolism produced at a fairly constant rate in the body. (Normal Value = .7-1.5 mg/100 ml. (Berkow, 1977).)

[5]See Appendix B for a brief presentation of causes of chronic renal insufficiency and systemic manifestations of kidney disease. Neurologic systemic manifestations will be included in the main text of the Introduction.

Uremia is usually seen in patients with a glomerular filtration rate[6] of less than 10 ml/min. Characteristic laboratory findings of uremia include nitrogen retention, moderate acidosis[7] and anemia.[8]

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[6]"The glomerulus acts as an ultrafilter allowing passage of water, electrolytes, and small organic molecules such as glucose, but not red blood cells and large protein molecules. The ultrafiltrate produced by the glomeruli of both kidneys amounts to about 70 ml/min/sq m or 150 L/day/sq m; this rate is termed the glomerular filtration rate (GFR). (Berkow, 1977, p. 655.) See Appendix A for a further explanation of the GFR.

[7]There are two types of acidosis, metabolic and respiratory. The bicarbonate (HCO_3^-) buffer system is of great importance here. The Henderson-Hasselbalch equation pertains to acidosis:

$$pH = 6.1 + \log \frac{HCO_3^-}{\alpha (Pa_{Co_2})}$$

where α = .03 mM/L/mm Hg at 38 C.

Rises and falls in the numerator respectively are called metabolic alkalosis or acidosis. Rises and falls in the denominator refer respectively to respiratory acidosis or alkalosis. Impaired renal excretion of acid is seen in chronic renal failure where the major defect is insufficient ammonia production leading to decreased ion excretion. CO_2 content = 15-20 M/L. (Berkow, 1977.)

[8]Hematologic picture is of anemia of moderate severity. Hematocrit changes vary from 20-30%. (Berkow, 1977.)

Serum urea and serum creatinine are elevated. Plasma sodium concentrations may be normal or reduced. (Normal value = 135-143 mEq/L.) Hypocalcemia (normal value = 8.5-10.5 mg/100 ml) is found regularly. Serum potassium is normal or moderately elevated (less than 6.5 mEq/L.) (Bekow, 1977.)

Neurobehavioral signs of chronic uremia are numerous and vary in each individual patient. The earliest signs of uremic encephalopathy are changes in alertness (e.g., drowsiness), mental sluggishness, diminished attention span, difficulty concentrating, impaired memory, loss of interest in self, and the presence of thought preoccupations. These symptoms may be episodic and fluctuate in severity with clear periods of functioning observed. As the disease process progresses the patient's attention span further diminishes. There may be perceptual errors including misidentification of people and objects. Further dysfunction involving progressive impairment of recent memory and the presence of mild confusion may be evident. Illusions and misperceptions may be manifested in visual hallucinations where the patient is agitated in a state of delirium. Dysarthria attending uremic encephalopathy may be observed with speech being thick, slurred, and slow. (Earley, 1968; Kemph, 1966; Locke, Merrill & Tyler, 1961; Raskin & Fishman, 1976[9]; Schreiner, 1959; Schreiner & Maher, 1961; Tyler, 1965.) Ginn (1975) noted that emotional irri-

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[9]All citations to Raskin and Fishman (1976) refer to their extensive review of the literature.

tability with withdrawal, disorientation, confusion, catatonia, mumbling and muttering, and paranoid and compulsive personality changes may be seen in patients with untreated end stage renal disease.

Asterixis[10] is usually present once the onset of sensorial clouding appears in the uremic patient. Tremulousness often appears before aterixis is present and may be a more sensitive index of encephalopathy. Multifocal myoclonus, a gross twitching of muscles which is sudden, arrhythmical and asymmetrical commonly occurs and is a strong indicator of severe metabolic disturbance. (Berkow, 1977; Raskin & Fishman, 1976.) Tetany[11] is not uncommon in uremia and may be associated here (Tyler, 1968). Cranial nerve involvement in uremia has been reported and may be manifested as nystagmus, pupil asymmetry and facial weakness (often transient, varying from side to side) (Earley, 1968).

Muscle wasting and muscle tenderness occur relatively rapidly in advanced renal disease (Earley, 1968). Muscle tone is usually heightened and may be asymmetrical. Most patients are weak and have focal motor signs including stretch reflex asymmetry and hemiparesis. (Raskin & Fishman, 1976.) Transient monoplegia, hemi-

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[10]Arrhythmic hand flapping seen with the arms outstretched and the wrists dorsoflexed (Berkow, 1977).

[11]Sensory symptoms including paresthesias of the lips, tongue, fingers and feet, carpopedal spasm and spasm of the facial musculature (Berkow, 1977).

plegia, aphasia, apraxia, blindness (without a demonstrable lesion to the eye), deafness, and severe vertigo may be seen. Cerebellar signs of unsteadiness and change in gait may also be in evidence. Stupor may progress to semi-coma and coma. Slurred speech may progress to semi-coma and coma. (Schreiner, 1959.)

Convulsions are usually a late manifestation of chronic renal failure and may precede death (Tyler, 1968). Convulsions may be focal, show a Jacksonian progression, or be of the grand mal type (Schreiner, 1959). The electroencephalogram may evidence background activity with increased content of theta and delta waves (Jacob et al., 1965). As the uremic state progresses in severity there is a slowing in the electroencephalogram (Earley, 1968; Raskin & Fishman, 1976).

Earley (1968) noted that cerebral spinal fluid pressure may be elevated. Meningeal signs, cerebral spinal fluid pleocytosis[12], alteration of the blood cerebral spinal fluid barrier, nuchal[13] rigidity as well as Kernigs sign[14] may occur (Maddonick, Berke &

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[12]"The condition in which, as in some diseases of the nervous system, there is an increase in leucocytes in the cerebrospinal fluid." (Critchley, 1978, p. 1329).

[13]Referring to the nape of the neck (Critchley, 1978).

[14]"Attempts to flex the knee from the flexed thigh position are met with strong passive resistance (Kernigs Sign)." (Berkow, 1977, p. 1429.)

Schiffer, 1950). Fishman and Raskin (1967) noted that "It appears likely that uremic encephalopathy is in part due to the excessive accumulation of toxic organic acids which overwhelm the normal mechanisms for excluding such compounds from the nervous system " (p. 18).

Uremic neuropathy occurs in at least sixty-five percent of patients with chronic renal failure about to begin dialysis. It is perhaps the most common neurological manifestation of chronic uremia. Rates of progression and severity are variable. Males have a greater incidence than females. (Raskin & Fishman, 1976.) Neuropathy shows as a progressive, peripheral involvement of sensory and then motor fibers. Patients on long term dialysis also may have neuropathy as evidenced by slowed nerve conduction. (Tenckhoff et al., 1965.) Restless legs syndrome including creeping, crawling, prickling, itching sensations deep within the lower limbs are noted. Burning feet, muscle cramps of the distal limbs occur commonly. Impaired vibratory sense in the lower limbs and the loss of deep tendon reflexes and angle followed by knee jerk are noted as the usual first signs of uremic neuropathy. It is generally agreed that the presence of early symptoms of peripheral neuropathy is an indication for dialysis and/or renal transplantation, in order that further progression and disability may be prevented. Patients beginning dialysis with mild neuropathy often recover completely, while patients who begin dialysis with severe neuropathy rarely recover. (Raskin & Fishman, 1976.)

I will now turn to a consideration of "hemodialysis" and allied terms. Hemodialysis is a mechanical procedure utilizing an artificial membrane through which toxic renal metabolites and excess plasma water are cleared from the blood. More technically "Hemodialysis may be considered as a diffusion-based, membrane-modulated transfer of mass between plasma water and dialysis fluid." (Henderson, 1976, p. 1644.)[15] Mass solutes that are retained in the patient experiencing end stage renal failure range in molecular weight from one to greater than five thousand daltons (Henderson, 1976). Most of the membranes utilized in hemodialysis are impermeable to particles having a molecular weight of greater than 5000 daltons (Gutch & Stoner, 1975). Molecules in the range of 300 to 5000 daltons (the middle molecules) are suspected of being a cause of uremic neuropathy, a neurological complication (discussed previously) which in many cases may be controlled or arrested with adequate dialysis (Tenckhoff, Shilipetar & Boen, 1965; Tenckhoff, Boen & Spiegler, 1965; Jebsen, Tenckhoff & Hoult, 1967). Molecules of differing molecular weights are not subject to the same dialyzer clearance. Various factors operate

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[15]Many of the basic principles of hemodialysis are presented in Appendix C. A description of positive and negative effects associated with hemodialysis are presented in Appendix D. (Dialysis dementia and dialysis disequilibrium are discussed in the main text). A technical description of the hemodialyzers employed in this dissertation project is included in Appendix E.

to determine the dialyzer clearance for molecules of differing molecular weights.[16]

There is much controversy over which molecules are responsible for the uremic syndrome, particularly the presence of peripheral neuropathy. A brief summary of this controversy (portions of which are cited here) is presented in Friedman (1978). Tenckhoff, Shilipetar and Boen (1965) noted that long term peritoneal dialysis patients[17] were clinically well and free from peripheral motor

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[16]"For small molecular weight solutes (molecular weight less than 300 daltons) clearance by a hemodialyzer is greatly modified by relatively small changes in the rate of blood flow, or dialysate flow. Clearance of large molecules such as inulin (molecular weight 5200 daltons) is unaffected by alterations in blood or dialysate flow rates and depends mainly on membrane permeability and surface area. Intermediate weight solutes, so called middle molecules (molecular weight 300 - 5000 daltons) are dialyzed according to membrane surface area and duration of dialysis." (Friedman, 1978, p. 48.)

Nolph (1977) noted that some middle molecules are small enough to be affected by blood flow and dialysate flow rates. In addition to factors mentioned by Friedman (1978) above, Nolph noted that middle molecule clearances are also affected by membrane permeability, ultrafiltration, blood channel width, protein binding, and rate of equilibration between body and fluid spaces.

[17]A method of dialysis utilizing the patients own peritoneum as the exchange membrane through which toxic renal metabolites diffuse into a bath of instilled dialysate fluid which is then drained from the abdominal cavity.

neuropathy in spite of high blood levels of small molecular weight solutes including uric acid, urea and creatinine. Bab et al. (1973) noted that the peritoneal membrane was found to be more permeable to Vitamin B12 and inulin (5200 daltons). They suggested that patients being dialyzed peritoneally may be receiving an optimal type of molecule removal i.e., appropriate removal of middle molecules without excessive removal of smaller molecules. They concluded that during peritoneal dialysis lower molecular weight solutes are removed at much lower rates than in standard hemodialysis and higher molecular weight solutes are removed at significantly higher rates, relative to urea, than in hemodialysis. (Longer peritoneal dialysis times are utilized to reduce the concentrations of lower molecular weight solutes to acceptable levels, rather than those of higher molecular weights.) Despite the fact that small molecule peritoneal clearances are one quarter to one sixth of those in hemodialysis, peritoneal patients maintain their well being. The absence of neuropathy and other evidence of toxicity in peritoneal patients may be attributable to the greater removal of middle molecules.

Oreopoulous et al. (1975) reported progression of uremic neuropathy with peritoneal dialysis thereby questioning the contribution of middle molecules to the uremic syndrome. Other studies (Maiorca et al., 1974; Kjellstrand et al., 1973; Hurst et al., 1975) have failed to show that the impairment of the patients overall physical condition, acceleration of peripheral motor neuropathy or inhibition of lymphocyte function was due to a toxic buildup of middle molecules.

Freidman (1978), in attempting to place the question of middle molecules in perspective stated:

> No conclusions are warranted as to the extent to which accumulations of middle molecules are responsible for the uremic syndrome. While it is clear that solutes in the middle molecular weight range are detectable in the serum of uremic patients and not in normal controls the case for their clinical importance must be judged as unproved." (p. 49.)

While dialysis may improve or reverse early neurological manifestations, such reversal is often incomplete in end stage renal disease patients (Earley, 1968). In fact, hemodialysis itself may precipitate various neurological complications which will be briefly considered here. The dialysis disequilibrium syndrome is now widely viewed as a possible complication of hemodialysis. Symptoms may begin or persist during hemodialysis and may continue for twenty four hours or more. Clinical symptoms may include headache, confusion, lassisitude, drowsiness or coma. Increases in blood pressure, heart rate and respiration are noted (Earley, 1968). Other symptoms may include exopthalmos[18], increased intraocular pressure, papilledema[19], and generalized slowing of the EEG (decrease in alpha activity and increase in theta and delta waves) (Raskin & Fishman, 1976).

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[18]Protrusion of one or both eyeballs (Berkow, 1977).

[19]Swelling of the optic nerve head due to increased intracranial pressure (Berkow, 1977).

The symptoms of dialysis disequilibrium syndrome are attributed to the slow rate at which urea diffuses from the tissue of the central nervous system as compared to the more rapid removal of urea from the blood. The higher concentration of urea in the tissue of the nervous system sets up an osmotic gradient where an inward movement of H_2O occurs, leading to swelling and increased pressure in the brain. (Arieff et al., 1973; Earley, 1968; Kennedy et al., 1962; Tyler, 1965; Wakim, 1969.) This may be avoided by a slow reduction of blood urea through a slower dialysis or by adding urea to the dialysis bath (Arieff et al., 1973; Peterson & Swanson, 1964). As the content of urea in the central nervous system decreases so do the symptoms cited. A period of twenty four hours may be required for equilibration of urea in the blood plasma and cerebrospinal fluid. (Early, 1978.) A disturbance in the equilibration of uric acid, creatinine, inorganic phosphorus and bicarbonate, between the blood and cerebrospinal fluid, is also created by hemodialysis (Rosen, O'Connor & Sheldon, 1964). A mild increase of blood calcium may cause mental confusion in uremic patients treated with adequate dialysis. A parathyroidectomy may be required to control calcium levels. (Coburn et al., 1969.)

A condition much rarer than dialysis disequilibrium may occur in end stage renal patients maintained on chronic dialysis for periods of more than one year (Alfrey et al., 1972; Mahurkar et al., 1973). Mahurkar et al., noted dialysis dementia as a bizarre neurological syndrome characterized by progressive dementia (described by Alfrey et al., (1972) as impaired concentration, decreased

memory, personality changes, psychosis with depression, paranoia and hallucinations) disturbances in speech, dyspraxia, bizarre involuntary movements, facial grimacing, multifocal seizures, myoclonus, and characteristic electroencephalographic changes. Speech and language disturbances are included as among the earliest manifestations of this syndrome, including episodes of stuttering, inability to articulate words, inability to recognize objects or obey commands, and perseveration (Alfrey et al., 1972; Makurkar et al., 1973; Rosenbeck et al., 1975). Prosodic, phonatory, and articulatory disturbances as well as language deficits occur in most patients (Madison et al., 1977). Mutism frequently occurs in the final stages of dementia. A total inability to speak has been seen in the later stages of dialysis dementia (Mahurkar et al., 1973; Rosenbeck et al., 1975). Mutism in affected patients may be different from that seen in typical dementia in that mutism may be intermittent with periods of fluency noted in the terminal stages of the disease (Madison et al., 1977).

The cause of dialysis dementia has remained unknown. It is suggested that neither uremia or disequilibrium are implicated since affected patients have been regarded as receiving adequate treatment by dialysis. No abnormal changes have been found at necropsy despite profound dementia. Psychological testing on two cases revealed varying signs of organicity including poor visual-perceptual skills, perceptual-motor deterioration, perseveration, concreteness, and gross dysfunction on verbal and performance measures. (Madison et al., 1977.)

Schreiner and Ziesat (1976) noted that on psychological test performance, in a case of cerebral dyspraxia associated with hemodialysis, the Bender Gestalt was replete with organic signs and the Rotter Incomplete Sentences Blank showed poor line control in formation of letters, disorganized grammatical structure and perseveration, suggestive of brain pathology.

Madison et al., (1977), concluded on the basis of their investigation of two patients diagnosed as having dialysis dementia, that the neurological syndrome found in dialyzed patients is, in fact, a dementia. The global nature of cognitive and communicative dysfunctions suggested an etiology of diffuse and multifocal brain damage as opposed to a focal lesion. Raskin and Fishman (1976) noted that the EEG in this condition is abnormal with diffuse multifocal slow delta waves interrupted by bilaterally synchronous high voltage complex consisting of slow, sharp triphasic and spike waves. Cerebrospinal fluid is noted as unremarkable. Renal transplantation has been performed with no benefit.

Finally, Glick, Goldfield and Kovat (1973) noted a psychosis associated with a metabolic abnormality secondary to hemodialysis. Although no metabolic abnormality was evident the presence of confusion, disorientation, memory loss, and an abnormal EEG was suggestive of cerebral pathology.

Cognitive and Sensory-Motor Functioning Associated With Uremia and Hemodialysis

Sharp and Murphy (1964) were able to produce a uremic state in

seven monkeys through bilateral nephrectomy,[20] uretral ligation, or by urine reinfusion. The primates were previously trained to avoid shock by pressing a lever or signal. After surgery primates behavioral responding was compared to blood levels of urea, nitrogen, sodium and potassium,all of which rose linearly as long as the animals survived. Behaviour post-surgically was compared to stable pre-surgical performance. It was found that reliable decrements in performance occurred after 80 hours post-surgery. No animal survived more than 121 hours. Teschan, Murphy and Sharp (1964) produced similar results utilizing the method of continuous urine reinfusion. Behavioral decrements occurred when BUN levels reached 95 mg/100 ml and were completely reversed when the procedure of continuous urine reinfusion was discontinued. On a note of commentary behavioral decrements would naturally be expected to occur post-surgically from the trauma of the surgical procedure. This must be considered when post-surgical performance is compared to stable pre-surgical performance.

Fishman and Raskin (1967), in an animal experimental procedure, injected isotopically traceable inulin ^{14}C, sucrose ^{14}C, sodium sulfate ^{35}S, sodium chloride ^{24}Na and potassium ^{42}K in rats bilaterally nephrectomized for 46 hours. Histological and chemical changes in brain and other tissue were studied. The most significant finding was that there was a disruption in sodium potassium transfer in the brains

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[20]Surgical removal of both kidneys.

of these uremic animals. The entry of K+ into uremic brain greatly increased while Na+ rate of entry slowed. Altered behavioral states including tremors, weakness, stupor, occasional seizures and uremic encephalopathy were suggested as arising from altered membrane functioning producing disturbances in sodium potassium exchange. As Fishman and Raskin (1967) stated:

> "Uremic encephalopathy is characterized by a non-specific increase in brain permeability, a manifestation of disordered membrane function. It is suggested that this would enable greater accumulation in brain of the dialyzable toxic compounds that accumulate in uremia, thus establishing a vicious circle which could further derange brain metabolism. The changes in sodium and potassium concentration and flux in brain and muscle suggest altered function of the sodium potassium ion pump associated with cell membranes." (p. 20.)

McDaniel (1971), in commenting on the above study, noted the loss of intracellular K+ from most body tissue in uremia, which increases the plasma concentration. Potassium concentration in brain tissue is twenty times that of plasma. In uremic states the entry of K+ into brain tissue is greatly increased. Thus a relatively small increase of plasma K+ concentration would result in a great increase in the entry of K+ into brain tissue, possibly affecting CNS functioning.

To test the above hypothesis McDaniel (1971) administered a visual discrimination learning task[21] to seventeen patients (being

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[21]"...S's were instructed in the task, a match to sample problem in which they must match a .5 sec. stimulus from a multiple choice array of like stimuli on the basis of color, form, or number of designs." (p. 706.)

maintained on intermittent hemodialysis) the afternoon immediately following a morning dialysis. (This is a questionable time period during which to administer psychological testing since patients may have been somewhat disequilibrated so soon after dialysis, thereby possibly negatively affecting test performance.) Patients were then retested preceding dialysis within one week of initial testing. Patients were compared to a control group of physically healthy volunteers. Mean errors during initial problem solving stages were greater at every point for the group maintained on dialysis. In the second half of the initial testing, a repeat of the first half, error rates for the dialysis group and control group tended to decrease and become similar. As regards solution times for each problem the renal group was significantly inferior to controls only during the early stages and was somewhat quicker than controls during the later stages. This result and the fact that dialysis patients had much faster responding times in executing ten consecutive correct choices at each stage of the match to sample problem, prompted McDaniel to suggest "...that the cognitive dysfunction accompanying renal failure is primarily an interference with information processing capacities rather than visual-motor integration." (p. 707).

Retesting of patients preceding dialysis (within one week after their initial dialysis) resulted in error rates still being higher than controls. Solution search times and solution execute times were near normal or below. Identical testing procedures carried out on a group of ten renal transplant patients tested within sixty days post-

surgery resulted in no cases where patient performance was significantly inferior to controls. This is not surprising as one would expect the biochemistry of transplant patients to more nearly approximate that of the controls than would be the case with dialysis patients.

Routine blood chemistries were undertaken for dialysis patients from the morning prior to initial testing and from the morning following their subsequent retesting. (It is difficult to understand why blood samples were not taken closer to the times of actual testing in order that the blood values would more accurately reflect the condition of the patient at the time of testing.) "Correlation coefficients (Kendalls W) were calculated for two behavioral indexes - total number of incorrect choices and mean solution search times - with plasma concentrations of BUN, Creatinine, sodium, potassium, chloride, and carbon dioxide." (p. 709.) Creatinine and plasma K+ concentrations were significant ($p < .01$) at both initial and retesting as regards their correlation with performance data. Pre and post-test power spectral density analyses were computed from resting electroencephalograms of dialysis patients. There was a highly consistent shift toward lower frequencies. McDaniel noted that his findings indicate an underlying relationship between elevated plasma K+, a relative shift to lower electroencephalogram activity, and difficulty in information processing on learning tasks in renal subjects. Their findings lend support to those of Fishman and Raskin (1967) (previously cited) in which they reported a great increase of K+ in uremic brain and slowed rate of

entry of sodium in bilaterally nephrectomized rats in which altered behavioral states were noted. Fishman and Raskin (1967) and McDaniel (1971) suggested that disordered membrane functioning may play a part in cognitive and behavioral dysfunction.

Several authors (Blatt & Tsushima, 1966; Sand, Livingston & Wright, 1966; Abrams, 1969; Treishman & Sand, 1971; and Greenberg, Davis & Massey, 1973) assessed end stage renal disease patients, apparently untreated by dialysis, for cognitive functioning. In all the above studies the Wechsler Adult Intelligence Scale (WAIS) was utilized as the primary psychometric instrument. The Bender-Gestalt and Graham-Kendall (tests requiring the reproduction of geometric designs) were also employed in several of these studies. With the exception of Sand, Livingston and Wright (1966) all the above studies found a pattern of deficits suggestive of cortical dysfunction. Typical deficits included those of visual-motor coordination, ability to learn new material, abstracting ability, and attention and concentration skills. Blatt and Tsushima found that the correlation between BUN levels and intellectual functioning was not significant (Spearman correlations of BUN with full scale IQ = .21 with performance I.Q. = .19 and with verbal IQ = .04). Treishman and Sand found the average score of renal patients on the WAIS to be below the norm for all performance subtests and for arithmetic and digit span. Differences between performance and verbal I.Q. was significant ($p < .05$). Multiple regression analysis revealed that WAIS scores of women were more likely to be influenced by advanced renal disease

than men. Regression coefficients for creatinine were significant ($p < .05$) for women on arithmetic, similarities, digit span and full scale I.Q.. Thus creatinine levels were significantly associated with a lower WAIS score.

The study of Sand, Livingston and Wright (1966) yielded results which were significantly discrepant from the studies cited above. The patient population of Sand, Livingston and Wright had a range in full scale I.Q. of 94 - 143 with a mean I.Q. of 115, well above the norm for intelligence. No cognitive deficits were found in the patients tested. Greenberg, Davis and Massey (1973) noted that the large I.Q. difference between their sample and that of Sand, Livingston and Wright should caution against generalizing results from one study to another (as different centers may not be equivalent on many dimensions). The sample of Sand, Livingston and Wright may have been a non-representative sample of uremic patients at large. All other studies cited thus far, in addition to those studies yet to be cited, have findings which are contrary to those of Sand, Livingston and Wright. (A criticism to be offered of many of the above studies is their failure to clearly state whether or not their patients were untreated by dialysis. Statements like "being evaluated for a dialysis program" are unclear. Few studies offer demographic data which more clearly define their sample. In addition, no statements of patients' pre-renal disease intellectual functioning are provided, information which would be invaluable in judging the effects of uremic syndrome on intellectual functioning. Such infor-

mation would of course be difficult to obtain.)

Hagberg (1974) administered psychological tests to twenty-three patients with end stage renal disease before the onset of dialysis, twenty-one of the twenty-three patients six months after commencement of dialysis and sixteen of the original twenty-three patients twelve months after the start of dialysis. The tests administered included: (A) a timed test of verbal ability including items of similarities, opposites and synonyms[22], (B) paired associate task used to measure immediate recall of material[23], (C) Block Design[24], (D) Memory for Designs Test[25], (E) Visual Retention Test[26], (F) Mirror Test[27], and (G) Visual Reaction time measure.[28] Tests A (similarities), C, D, E (part C) F, G, were administered in the first examination.

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[22]Test items were of the multiple choice type.

[23]This test has been used to measure memory reduction in cases with cerebral damage (Riklan & Levita, 1964).

[24]Based upon block design of the Wechsler Bellevue Intelligence Scale.

[25]Assesses subject's spatial perceptual abilities as well as immediate memory for simple geometric designs (Graham & Kendall, 1960).

[26]Benton, A. L. The Revised Visual Retention Test, Iowa City, 1963.

[27]This test requires the patient to draw the diagonals in twenty squares by viewing the squares in a mirror. The time needed to complete the task is scored. The test is assumed to measure the patient's ability to shift and is used clinically as a measure of rigidity mainly in connection with cerebral disorders.

[28]Utilizes a conventional reaction time apparatus.

Tests A (opposites) B, C, E (part d), G were administered at six months follow-up and tests A (synonyms), E (part e) and G were administered at twelve months post-commencement of dialysis. At initial examination on verbal test A the general intellectual level of the patient group as a whole did not deviate from the normal level. Results on paired associates, block design, spatial memory tests, mirror test and reaction time were lower than expected from the general intellectual level as estimated from the test of verbal ability. On paired associates and Block Design the differences were significant. Results on the Visual Retention Test were outside the normal range. Hagberg expressed the conclusion that this patient group showed a cognitive reduction similar to that found in patients with a cerebral disorder, although the dysfunction was classified as minor.

Changes in cognitive functioning after six and twelve months of dialysis revealed a consistent trend on all tests toward better performance as treatment progressed. Improvement was especially apparent on tests measuring functions vulnerable to organic decline (paired associates, spatial tests and spatial memory tests) with a significant increase in performance in paired associates and Block Design. Normal level of performance on all performance tests was first approached at the six month follow-up level. No signs of organic dysfunction were found twelve months after beginning dialysis. No statement as to when testing was carried out during the six and twelve month follow-up periods was provided. As will be noted shortly

fluctuations in certain aspects of sensory motor and cognitive performance have been reported when long term maintainence dialysis patients are tested serially (pre, post, and pre-dialysis) over a three day period. Hagberg's investigation would have been more conclusive had he administered serial testing at the follow-up periods, thereby providing a clearer assessment of cognitive functioning with which to compare pre-dialysis cognitive performance. In addition, the number of tests utilized during the follow-up periods were less than the number utilized at the initial testing, further compromising the results. For example, at the twelve month follow-up period three measures were utilized compared to six measures at initial testing.

Denour, Shaltiel and Czaczkes (1968) studied nine patients on chronic hemodialysis over a one year period. Psychological tests included the Raven Progressive Matrices and the Kohs (a sub-test from the Wechsler Bellevue Intelligence Scale). Signs of brain dysfunction were suggested as being present in the majority of patients and suspected on the rest. The authors noted that while no gross signs of brain dysfunction were evident, some manifestations of cortical dysfunction might have been explained by patient rigidity and inability to readapt to changing situations. Claims concerning brain dysfunction were particularly unclear in this study considering that on the Raven only four patients scored below the normal range and on the Kohs only two patients scored outside the normal range. Additionally, patients were tested while actually on the dialysis machine, a time during which

various reactions to dialysis (e.g., change in blood pressure, muscle cramping, disequilibration, and headache) may occur, introducing a potentially significant source of unwanted variance(affecting test performance.)

Murawski (1970) administered the Continuous Performance Test[29] to nineteen patients beginning hemodialysis. Continuous Performance Test, BUN and Creatinine values, before and after hemodialysis are presented in Table 1 below. First dialysis is three hours, subsequent dialyses are six hours in duration.

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[29]"The patient has to monitor a rapidly changing sequence of letters which are exposed for 0.2 seconds. The sequence is randomized by having a random noise generator scramble the sequence after each stimulus. Each time an "X" appears the patient must press a hand switch. Twelve letters were on the film strip which are lit by separate bulbs; for this study 10 stimuli (A, C, E, H, K, L, N, S, U, X) were exposed and as each letter has equal probability of occurrence, the critical stimuli "X" was lit with a frequency of approximately 10%. For his response to be scored correct, this must be within, for example, 0.7 seconds of the appearance of the "X". Late correct responses are also recorded. The rate of stimulus presentation can be varied as can be the stimulus and response variables." (Murawski, 1979, p. 54-55). The Continuous Performance Test was first utilized by Roswald et al., (1956).

Table 1

Continuous Performance Test, BUN and Creatinine

	Pre Dialysis	Post 1st Dialysis	Post 2nd Dialysis	Post 3rd Dialysis
	N = 19	N = 8	N = 8	N = 7
C.P.T. (Average % correct)	66	80	70	87
BUN (Average)	121	61	52	43
Creatinine (Average)	13.7	12.0	11.0	9.1

Murawski noted that there appeared to be a significant increase in performance post first dialysis, however, the mean value of eighty percent, he suggested, was undoubtedly biased by including only those patients who were willing and able to undergo the test procedures (a drop from nineteen to eight patients). C.P.T. results after the second dialysis were still below normal levels. Murawski noted that after dialysis improvement was not immediate and individual variations in the effects of uremia were noted, with recovery patterns varying. Individual profiles were presented. It was suggested that the dialysis disequilibrium syndrome was reflected in the C.P.T. results. No statistical results of significance, as regards post second and third dialyses, were reported.

Murawski, Spector and Follette (1973) noted that errors generally increased and a slower response rate was observed on the C.P.T. in clinically uremic patients. Improvements in performance were noted

with dialysis therapy. Murawski, Spector and Follette compared blood flow and time on dialysis for their effects in returning vigilance attention to normal levels. Within the constraints of the data, it is apparent from the results cited in Table 2 below, that blood flow is the critical factor. (Percentages refer to mean Continuous Performance Test Scores. Higher percent equals higher score.)

Table 2

Effects of Blood Flow and Time On Dialysis On Vigilance Attention

		Blood Flow	
		High (220 ml/min)	Low (220 ml/min)
Hours dialysis/week	18	56.0%	72.8%
	15	55.7%	72.6%

Different results might have been found had the range for the time variable been expanded, particularly at the lower end. The time factor may then have become more critical.

Spehr et al. (1977) administered electroencephalograms and psychological tests to long term maintenance dialysis patients before and after hemodialysis.[30] After hemodialysis there was a significant improvement in maximal tapping speed (repetitive

[30]A full presentation of psychological test results is reported by Spehr et al., to be in Wiedemann (1976). No complete citation is provided however, and a computer search of the world literature revealed no such citation.

pressing of a button) and visual discrimination and memory (assessed by tachistoscopic presentation of numbers with variable presentation time.) Spontaneous tapping speed is noted as not changing significantly. Some linkage was found between electroencephalograph and test performance. "Visual discrimination and memory improved after hemodialysis, parallel to the decrease of BUN, creatinine and potassium. They were correlated negatively with low voltage, fast and complex electroencephalograph recordings." (p. 796.) The increase in maximal tapping speed post-hemodialysis seemed to indicate a decrease in impairment caused by toxic metabolites. Spontaneous tapping speed, while showing no significant hemodialysis effects, did show a tendency toward a positive correlation with the removal of agents liable to alter CNS dysfunction.

Teschan et al. (1974), Ginn (1975) and Ginn et al. (1975) (The Vanderbilt Group) utilized various performance tests of cognitive functioning to measure, in quantitative terms, the cognitively based neurobehavioral impairments associated with uremia. To measure sustained attention span and alertness the Trailmaking Test (T.M.T.)[31] from the Reitan Neuropsychological Battery (Reitan, 1969), the Choice

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[31] "As rapidly as possible the subject connects with a pencil line a sequence of labelled randomly located circles (labelled 1, A, 2, B, etc.) on a sheet of paper. The time required is measured by stopwatch and recorded in seconds." (Ginn, 1975, p. S-218.)

Reaction Time Test[32] (Color choice) and the Continuous Performance Test (described previously) were utilized. To measure short term recognition memory the Auditory Short Term Memory Task[33] was employed.

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[32]Choice Reaction Time Task - "The subject is presented with a series of five tasks which measure reaction time and vigilance, according to the description in examples one and two below. The set size is varied, using two, three, and four colors, and either the proportion of target (Red) stimuli is equal to the proportion of other colors (when there are two colors, half of them are red; when there are four colors, one fourth of them are red) or else half of all items presented are red, regardless of the set size.

Example 1: Instructions: Push the button as soon as the light goes on.

Example 2: Push the button as quickly as you can when you see the red light, but only for the red light. Ignore all others. (Ginn, 1975, p. S-219.)"

[33]Auditory Short Term Memory: "Each form of the test begins with five practice lists of nine words each. The word pool consists of words which are highly familiar, occurring at least 15 times per million, are five to eight letters in length and consist of two syllables with the stress on the first syllable. The 15 test items are presented by tape recorder through earphones. Each list consists of three beeps, nine different words, a single beep and a test word. The subject's task is to decide whether or not the test word occurred

To assess mental manipulation of symbols an answer recognition task[34] was administered. Psychological tests were administered variously to azotemic patients not on dialysis and uremic patients on maintenance hemodialysis.

Ginn (1975) and Teschan et al. (1974) found a direct relationship between serum creatinine concentration and Trail Making Test performance for azotemic subjects (correlation coefficient, $r = 0.818$, significance = .01; reported by Ginn et al. (1975) as $r = .890$, $p < .001$, on a similar sample). Eleven out of fourteen subjects dialyzed only twice a week had performances below normal limits. Subjects being dialyzed three times a week were within normal limits with but one exception. Similar results were noted by Ginn (1973).

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[33](Cont'd) in the list of nine that he has just heard and to push the appropriate button to indicate a "yes" or "no" response. The dependent variables are speed and accuracy of response." (Ginn, 1975, p. S-219). Because of the multiple test series this instrument is repeatable.

[34]By means of a Carousel projector, the subject is presented with a basic addition problem, made up of some combination of numbers from zero to nine, and an answer that is either correct or the correct answer plus or minus one. His task is to respond by pushing a button labelled "correct" or a button labelled "incorrect". Half the answers are correct and half incorrect. The dependent variable is speed of response." (Ginn, 1975, p. S-220). (Five lists have been developed.)

As regards short term recognition memory Ginn (1973), Teschan et al. (1974) and Ginn (1975) reported that regardless of the absolute value of the pre-dialysis (Do) level of performance on the Auditory Short Term Memory Task, subjects showed a temporary improvement in level of performance on the morning following dialysis (D_1) and a regression to a lower level of performance just prior to the next dialysis (D_2). This effect was significant at the $p < .01$ level. Results reported in Ginn et al. (1975) showed a significant improvement post-dialysis (D_1) and a significant regression on the second day post dialysis (D_2) ($p < .001$). Mean response times were prolonged in azotemic patients worsening with degree of renal failure ($r = .687$, $p < .001$).

In the assessment of mental manipulation of symbols utilizing the answer recognition task, Teschan et al. (1974) and Ginn (1975) reported that for varying degrees of azotemia there is a direct correlation between answer recognition times and serum creatinine concentration (correlation $r = .757$, $p < .05$; reported by Ginn et al., (1975) on a similar sample as $r = .768$, $p < .001$). Serum creatinine is used here as a measure of decreasing kidney function. Four of four patients had improvements in their answer recognition times within two weeks of commencement of dialysis treatment. Performances were still below normal limits, however.

Results for the Continuous Performance Test and Choice Reaction Time Test were being assessed by Ginn (1975) at the time of writing and were not reported.

Ginn et al. (1975) reported that several neurophysiological measures, i.e., the spontaneous electroencephalogram, and visual evoked response latency[35] were highly correlated with the severity of renal failure. In patients not on dialysis, as renal failure increases, increasing amounts of EEG power are associated with slower wave frequencies ($r = .695$, $p < .001$). Slow wave associated EEG power returns to, or nearly to normal when uremic patients not dialyzed are then treated over time (days - weeks) on maintenance dialysis. EEG power spectrum analyses of patients on twice weekly dialysis improved when they were dialyzed thrice weekly.

When visual evoked response results are analyzed electronically according to peak latencies and amplitudes in non-dialyzed kidney patients there is a significant correlation between the latency of the major negative deflection and the degree of renal failure ($r = .496$, $p < .01$). The latency of this peak is shortened in patients on maintenance dialysis.

Teschan et al. (1975) compared dialysis patients' EEGs (3-7 Hz EEG power) and cognitive performance (Choice Reaction Time and Answer Recognition) when dialyzed for 2-4 months on a standard hemodialyzer (D4 Kiil, period A_1), subsequently when dialyzed for seven months on two Gambro dialyzers with 174 membranes (period B) designed to increase the clearance of middle molecules, and then

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[35]"...strobe light flashes before a subject's eyes will produce a visual evoked response (VER) in the occipital EEG..." (Ginn et al., 1975, p. 5-358.)

again when patients were returned to a D4 Kiil dialyzer for three months (period A_2). When the data in B was compared to A_1, all measures became more normal. The 50% decline in EEG value was statistically significant at the 1.0% level, the change in performance for Answer Recognition was significant at the 5.0% level, while improvement in performance on the Choice Reaction Time did not reach significance. When subjects were returned to D4 Kiil dialysis in A_2, there was an 11% decline in the clearance of B12 and an 18% rise in urea clearance. Average slow wave EEG power increased by thirty-eight percent of the value in period B (an abnormal trend) significant at the $p < .01$ level. However, the cognition dependent measures, despite the increase in average slow wave EEG power, continued to improve, although at a level not reaching significance. It is suggested that EEG slowing may be improved by increasing the clearance of molecules approximately the size of B12 and not the clearance of smaller molecules. The dissociated connection between EEG behaviour and cognitive performance (when average slow wave power increased significantly cognitive performance continued to improve) was surprising and was suggested by the authors as arising from the dialysis format, or as yet unidentified variables.

Summary & Conclusions

The literature on the sensory-motor and cognitive functioning of uremic adults not undergoing hemodialysis reveals a pattern of deficits suggestive of cortical dysfunction. When untreated uremic patients are

treated with hemodialysis there is an improvement in their cognitive functioning. A significant correlation between plasma levels of creatinine and potassium, and cognitive functioning is further supported by the literature.

Prior studies (e.g., Denour, Shaltiel & Czaczkes, 1968; Murawski, Spector & Follette, 1973; Hagberg, 1974; Teschen et al., 1974; Ginn, 1973, 1975; Spehr et al., 1977) have investigated the cognitive and/or sensory-motor functioning of the chronic hemodialysis patient. These studies suggest that 1) chronic dialysis patients on the machine for 12 months show no evidence of cerebral impairment, 2) fluctuations in performance, pre and post-dialysis, may be seen on measures of maximal tapping speed, visual discrimination and memory and auditory short term memory, and 3) fluctuations in performance, pre and post-dialysis, parallel a decrease in levels of BUN, potassium and creatinine.

No study, however, has investigated the cognitive and sensory-motor functioning of the chronic long term hemodialysis patient in a manner which includes all of the following key components: 1) the use of a test battery measuring a wide range of cognitive and sensory-motor abilities, 2) serial testing pre, post and pre-dialysis, 3) the use of a test instrument to monitor changes in the patient's perception of his/her psychological and medical condition at each test administration, in order that variance in test performance, due to perceived changes in psychological and/or medical condition, may be identified, and 4) the monitoring of serum chemistry pre, post and pre-dialyses (coinciding with cognitive and sensory-motor test administration on Do, Dl, and D2),

for purposes of analyzing whether or not changes in serum chemistry are significantly correlated with possible changes in cognitive and sensory-motor test performance over D_o, D_1 and D_2. The present study included 1-4 above for purposes of answering the following key questions: 1.How do chronic dialysis patients' performances on cognitive and sensory-motor tests compare to available norms for a normal population? 2.What patterns of strengths and/or weaknesses may be found in the cognitive and sensory-motor functioning of the chronic hemodialysis patient? and 3. Do significant changes in cognitive and sensory-motor functioning occur when pre, post and pre-dialysis performances are compared? If so, do specific serum measures seem to be correlated with changes in cognitive and sensory-motor performance when test results across D_0, D_1 and D_2 are compared.

Through the inclusion of methodological criteria 1-4 (above) questions 1-3 (above) will hopefully be more clearly understood. In this manner a clearer integration of many unanswered and controversial questions may be achieved.

CHAPTER II

METHOD

Subjects

Twenty adult (ages 25 - 68 yrs., $\bar{x}$ = 46.5, S.D. = 11.330) end stage renal disease patients on maintenance hemodialysis for 10 - 86 mos. ($\bar{x}$ = 39.7, S.D. = 21.582), currently being dialyzed in the Henry Ford Hospital network, were selected for this study. Fourteen male and six female subjects were included, the exact proportion of which depended upon subject availability. All subjects were on a three times/week dialysis regimen. To insure that all subjects had been adequately dialyzed prior to the commencement of this study all subjects chosen had a pre-dialysis BUN of 50-100 mg/100 ml as determined by each of their last three bi-weekly pre-dialysis BUN values. No patient judged by medical staff to be acutely ill, to be diabetic or to have a history of known cerebrovascular disease was included in this study. The exclusion of subjects with diabetes was designed to prevent any variations in cognitive performance from being due to biochemical changes associated with diabetes. The exclusion of subjects with known cerebrovascular disease was designed to insure the possibility of performance variation on psychological testing, i.e., there was no a priori reason to believe that hemodialysis had no possibility of affecting cognitive performance (as might be the case in subjects

with prior organic dysfunction).

Subjects were paid a sum of thirty dollars for their participation in this study.

Equipment

All subjects were dialyzed on a Century I or II Dialysis Control Unit manufactured by Cobe Laboratories. The type of hemodialyzer used for each subject's dialysis was determined by which size Cordis Dow Hollow Fiber dialyzer he/she was typically dialyzed on. Available dialyzers and their clearance properties are included in Appendix E. Subjects were dialyzed according to normal procedures, i.e., no change in a subject's typical dialysis regimen was required for this study.

Rationale for Psychological Test Selection

All subjects received the following battery of psychological tests.[36] 1) Trailmaking Test, 2) Digit Symbol, 3) Digit Span, 4) Finger Tapping, 5) Speech Sounds Perception, 6) Seashore Rhythm, 7) Grooved Pegboard, 8) Grip Strength, 9) Color Naming, 10) Word Fluency, 11) Proverbs Test, 12) Quick Test, 13) Choice Reaction Time, 14) Benton Visual Retention, 15) Subjective Rating Scale.

Test selection was dictated by the need for a relatively brief, repeatable battery of psychological tests which accurately and re-

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[36]A description of all tests administered in this study appears in the section entitled "Description of Psychological Tests". The schedule of administration appears in the section entitled "Test Administration".

liably measures a wide variety of cognitive and sensory-motor abilities. Several tests (5, 6 above) were selected directly from the Halstead-Reitan Neuropsychological Test Battery, a valid, reliable set of instruments utilized for its sensitivity to a wide variety of neurological dysfunctions (Reitan & Davison, 1974) and for its rigid standardization (Reitan, 1969). Other tests (1-4, 7-10 above) were chosen from among the subtests of the Rennick Repeatable Cognitive-Perceptual-Motor Testing and General Neuropsychological Assessment Battery (Rennick, 1974), a set of repeatable neuropsychological test instruments many of which (1-4, 7, 8 above) were adapted from the Halstead-Reitan Battery and developed into a repeatable format by Rennick and his co-workers at Lafayette Clinic. A repeatable battery similar to that utilized in the present study was employed by Adams et al. (1975) in their study of the neuropsychological sequalae of multiple drug abuse. In order to include areas of cognitive and sensory-motor performance not adequately measured by tests from the batteries of Halstead-Reitan and Rennick (above), other test instruments (11-14 above) were included.

The complete cognitive, sensory-motor battery (1-14 above) measures a wide variety of simple to complex cognitive and sensory-motor abilities, including skills in attention-concentration, auditory short term memory, auditory discrimination, auditory (verbal) comprehension, visual-motor coordination, visual-motor planning and organization, visual memory, visual analysis of pictorially presented stimuli, verbal association, verbal abstraction, verbal reasoning, motor speed, motor

strength, symbol processing, and learning of novel tasks. Each test has a floor and ceiling which permits assessment of a wide range of cognitive and sensory-motor abilities.

Description of Psychological Tests

Proverbs Test: The Proverbs Test (Gorham, 1956) consists of three parallel sets of twelve proverbs measuring verbal comprehension and abstract thinking. The three parallel forms have equality of means, variances and co-variances. Each item is matched for difficulty with its corresponding item in the other two scales. One form was administered at each testing session. Subjects were instructed to write their interpretation of the meaning of each proverb according to a specified set of directions. The scoring system developed by Gorham was utilized.

Word Fluency: This test is a measure of a subject's ability at verbal association, requiring the subject to write as many words beginning with a specified letter as possible in two minutes time. Three alternate forms (the letters H, B, C) were administered, one at each session. This test forms part of the repeatable battery developed by Rennick (1974).

Color Naming: "Color Naming is a time measurement of the maximum repetitive performance speed of an elementary language function. Subjects were presented with 48 successive patterns of sets of four colored circles (red, green, or blue) in a horizontal line, and were asked to name the four colors as quickly as possible. Total time and

various naming errors are scored." (Adams et al., 1975). A two page practice trial was utilized to eliminate any confusion as regards the requirements of the task and to facillitate the attainment of a stable threshold of responding. This test forms part of the Rennick (1974) repeatable battery and was administered once at each test session.

Quick Test: (Ammons & Ammons, 1962.) This is a standardized individual intelligence test in three equivalent forms primarily tapping verbal comprehension and visual search skills. One form was administered at each test session. Three plates, each with four line drawings on it, were used, one plate for each of the three fifty item forms. The tester had the testee indicate which of the four drawings on a plate best illustrated the meaning of a given word. Answers were usually given by pointing. Correlations between the Quick Test (all forms) and the Full Scale WAIS**, Verbal WAIS**, Performance WAIS* and vocabulary subtest* were all significant (* = $p < .05$, ** = $p < .01$). (Ogilvie, 1965.)

Strength of Grip: The Smedley Hand Dynamometer was used to measure motor strength of the upper extremities. The subject was required to squeeze the dynomometer two times with his/her dominant hand and two times with his/her non-dominant hand, alternating between hands on each trial. The mean pressure which was exerted on the two trials was recorded in pounds for each hand. If the difference between trials was greater than 22 pounds for the same hand, further trials were administered until the difference was 8.8 pounds or less. Complete

directions appear in Reitan (1969). The test forms part of the Rennick (1974) repeatable battery and was administered at each test session.

Finger Tapping: This test is a speeded motor task requiring planning and motor coordination as the subject continuously taps on an apparatus similar to a telegraph key: For finger tapping the subject used alternately the index finger of the dominant and non-dominant hand. The subject was given 5 trials of 10 seconds each for each hand. The score was the mean for 4 consecutive valid trials (i.e., trials which did not deviate by more than 5 taps). Subjects were given a practice period in which to become familiar with the task and reach stable thresholds, thereby minimizing possible practice effects. The subject was asked to tap 30 times with each hand during this practice period. The test was administered in its entirety, once at each test session. To minimize fatigue effects a rest period of 30 seconds was given after each trial. This test is described by Reitan (1969) and forms part of the Rennick (1974) repeatable battery.

Grooved Pegboard: This is a speeded measure of visual-motor coordination and spatial orientation. Subjects were required to fit 25 keyhold shaped pegs into similarly shaped holes on a 4 inch by 4 inch board beginning at the left side with the right hand and at the right side with the left hand. Subjects were urged to fit in all pegs as rapidly as possible. Subjects performed one trial with the dominant hand followed by one trial with the non-dominant hand. The scores obtained were the length of time required to complete the task

with each hand, and the total number of times the pegs were dropped with each hand. A time limit of four minutes per hand was imposed. The time required for each subject to remove the pegs was also recorded. A practice trial, during which time subjects both familiarize themselves with the task and reach a stable threshold was carried out. This consisted of filling in the first three rows of the pegboard. This test is described in Klove (1963) and forms part of the Rennick (1974) repeatable battery. Grooved Pegboard was administered once at each test session.

Digit Symbol: This is a subtest of the Wechsler Adult Intelligence Scale (Wechsler, 1955). It is a complex visual-motor performance task which has components of motor speed, visual-motor coordination, visual memory, planning and symbol processing. Three forms of the Digit Symbol subtest were utilized to minimize practice effects. The Digit Symbol test is part of the Rennick (1974) repeatable test battery.

Digit Span: This is a subtest of the Wechsler Adult Intelligence Scale (Wechsler, 1955) adapted by Rennick (1974) as part of his repeatable battery. It is a measure of short-term rote memory, mental manipulation of symbols, attention and concentration skills. Each subject was read one series of numbers at a time, commencing with a short series of three numbers, gradually progressing to a longer series of up to nine numbers. After each series was read, the subject's task was to repeat the series in the order presented by the examiner. On the second part of the test the subject was read other series of numbers (starting with a series of 2 numbers and progressing to a series of eight numbers).

Here the subject's task was to repeat the numbers in each series in reverse order, immediately after each series was presented by the examiner. Alternate forms of the test were used to prevent practice effects. Subjects were given a practice trial at each administration to familiarize themselves with the task.

Benton Visual Retention Test (Revised): "The Revised Visual Retention Test is a clinical and research instrument designed to assess visual perception, visual memory and visuoconstructive abilities. Three drawing forms of the Test (Forms C, D, E) consist of 10 designs each, upon which one or more figures have been drawn. Retest reliability for Administration A (10 seconds exposure with immediate reproduction), as estimated by the correlation coefficients between equivalent forms, has been found to be approximately .95." (Benton, 1963, p. 1) One form was administered at each test session. Administration B (5 seconds exposure with immediate reproduction) was utilized.

Speech Sounds Perception Test: On this task the subject matched a spoken nonsense word with the identical word presented among a group of four written nonsense words. The double vowel, ee, was in the middle part of every word spoken. Thus, the subject had to key to the consonant or combination of consonants at the beginning and end of each word and relate the auditory perception visually by identifying the correct printed nonsense word. The test was played from a tape recorder with the intensity of sound adjusted to the subject's preference. (Reitan, 1969.)

To make this into a repeatable test I looked at the files of

twenty-nine patients administered series A-F of the Speech Sounds Perception Test and broke down their performance into their scores on series A+B, C+D, E+F. A t-test was then performed to determine if there was a significant difference between the mean performances on series AB and CD, AB and EF and CD and EF. No significant differences were found. Thus, at each administration, different series consisting of twenty test items (AB, CD, or EF) were administered.

Trailmaking Test (Parts A & B): The Trailmaking Test assesses visual scanning, visual sequencing, visual-motor coordination and most importantly (in Trails B) the ability to switch set. In Trails A the subject was required to connect twenty-five circles (numbered 1-25) in numerical order by tracing a line. The circles were 1/2 inch in diameter and were scattered somewhat randomly on a blank 8 1/2 x 11 sheet of white paper arranged so that no line crossing needed to occur as the subject connected the circles. Errors were scored if the subject attempted to draw his line to a circle out of sequence. Time recorded was the total time to complete the task correctly with the examiner having pointed out errors as the subject worked on the task. In part B (given after part A) the subject was required to connect thirteen numbered circles (1-13) and twelve lettered circles (A-L) in the following manner: 1-A, 2-B, 3-C, 4-D, etc. Errors and time recorded were the same as in Part A. The same form for Trails A was used on all three days. Trails B had three alternate forms. Trails A and B form part of the Rennick Repeatable Neuropsychological Test Battery (Rennick, 1974). Standard practice trials were administered to familiarize the

subject with the task.

Seashore Rhythm: This is a subtest of the Seashore Tests of Musical Talent. The subject must differentiate between 30 pairs of rhythmic beats which are sometimes the same and sometimes different. This test taps alertness, sustained auditory attention, and the ability to perceive and compare different rhythmic sequences. No alternate forms of this test were available. In order to familiarize subjects with the task, a practice trial was included at each administration. Complete instructions are in Reitan (1969).

Choice Reaction Time Test: This is a speeded test of visual discrimination, visual-motor planning and visual-motor coordination. Subjects were required to differentiate between the colors red and not red (as they are flashed on a screen), by pushing a red button if the color was red and a white button if the color was other than red. The subject was given 8 practice trials at each administration to facillitate both familiarity with the task and the reaching of stable threshold, thereby minimizing possible practice effects. Three programs were administered, one at each test session. Complete instructions for administration are included in the National Cooperative Dialysis Study Procedures Manual, Section VI, p. 3.1.

Subjective Rating Scale: This is a subjective rating scale developed specifically for this study. At Do, D_1 and D_2 subjects filled out the same twenty-one item rating scale investigating such factors as clarity of thinking, mood state, physical state, etc. The actual rating form appears in Appendix F. An index of subjective

discomfort, an additive sum of the ratings for each element of the Subjective Rating Scale, was calculated for each separate administration.

Test Administration

Each subject received the above test battery three times according to a specified schedule. Subjects utilized in this study were on a three times/week regimen of hemodialysis. All subjects were dialyzed on Monday, Wednesday and Friday or Tuesday, Thursday and Saturday. Subjects dialyzed on Monday, Wednesday and Friday received the battery on Wednesday, Thursday and Friday. These subjects were asked to come to the dialysis center for psychological testing two hours prior to their regularly scheduled dialyses (Wednesday and Friday). On the day in between their dialyses (Thursday), subjects came in for psychological testing approximately twenty hours after the end of their Wednesday dialysis. (A period of twenty hours was chosen to allow time for disequilibrium effects to wear off and to provide subjects with a time of relative convenience for psychological testing.) Subjects dialyzed on Tuesday, Thursday and Saturday received the above battery on Thursday, Friday and Saturday. Subjects were asked to come to the dialysis center for psychological testing two hours prior to their regularly scheduled dialyses (Thursday and Saturday). On the day in between their dialyses (Friday) subjects came in for psychological testing approximately twenty hours after the end of their Thursday dialysis (for the same reasons outlined above). Monday, Wednesday, Friday subjects

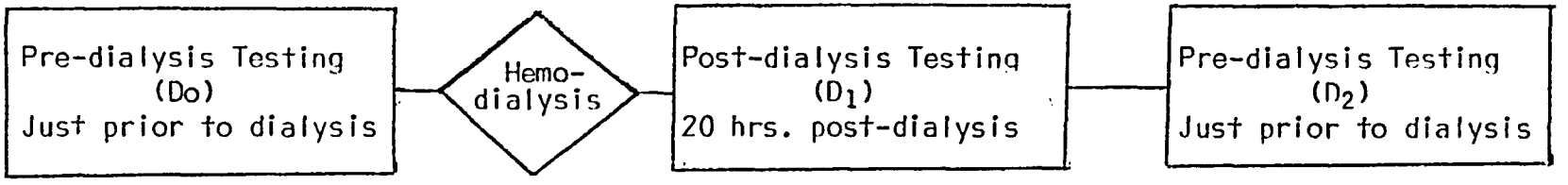
and Tuesday, Thursday, Saturday subjects were tested on Wednesday, Thursday, and Friday, and Thursday, Friday, Saturday, respectively to insure that the number of hours elapsed since their last dialysis was held constant for each pre-dialysis testing. In other words, at each pre-dialysis testing the time elapsed since the last hemodialysis treatment was the same.

Each subject was tested at approximately the same time each day to control for variations in performance due to possible diurnal effects. A schematic summary of the schedule for psychological testing follows in Figure I.

The order of administration of psychological tests was incompletely counterbalanced to prevent order effects. Complete counterbalancing was not possible due to the number of tests and subjects. In order to keep practice effects at a minimum, parallel forms of tests were utilized for the majority of test instruments. (See "Description of Psychological Tests".) The order of parallel form administration was randomized to prevent order effects. Practice trials were administered as outlined in the "Description of Psychological Tests" to insure that the first pre-dialysis testing did not reflect both the subject's lack of familiarity with the task and a less than stable threshold.

Blood Sampling and Analyses

Blood samples were drawn at each testing session. To insure that serum values most nearly approximated existing values at the time of psychological testing, blood samples were taken according to the follow-



M,W,F Subjects:	Wednesday	Wednesday	Thursday	Friday
T,Th,S Subjects:	Thursday	Thursday	Friday	Saturday

Figure 1: Schedule For Psychological Testing

ing schedule: On dialysis days subjects had blood samples drawn while being set up on the machine (immediately after testing) in order that subjects did not have to be punctured specially for this study. On the day in between dialyses blood samples were drawn at the culmination of psychological testing. Serum measures included: 1) Urea Nitrogen, 2) Creatinine, 3) Sodium, 4) Potassium, 5) Chloride, 6) Carbon dioxide, 7) Calcium, and 8) Serum amines (dimethylamine, trimethylamine). Serum amine analyses were performed by Dr. M. Simenhoff, a nephrologist at Jefferson Medical College. Blood samples were flown to him for analysis. All other serum analyses were performed at Henry Ford Hospital laboratory facilities.

Hypotheses

Prior studies (Teschan et al., 1974; Spehr et al., 1977) utilized an experimental design similar to that employed in the present study. A significant improvement in maximal tapping speed (Spehr et al.) and auditory short term memory (Teschan et al.) was found when subject's post-dialysis test scores (D_1) were compared to their pre-dialysis test scores (D0). Teschan et al. found a significant regression on a task measuring auditory short term memory when subjects' second pre-dialysis test results (D_2) were compared to their post-dialysis (D_1) test results. Additionally, Spehr et al. found that visual discrimination and memory improved after dialysis parallel to the decrease in BUN, creatinine and potassium. All subjects were on long term maintenance hemodialysis at the time of testing.

With the exception of Finger Tapping Test, the test instruments

employed in the present study were sufficiently unlike the instruments employed in Spehr et al., and Teschan et al., that predictions based upon the similarity of instruments would be questionable. For example Choice Reaction Time, although measuring visual discrimination and visual memory, also has a visual-motor component which makes it significantly different than the tachistoscopic instrument utilized by Spehr et al., above. Similar arguments may be formulated for the relationship between the Auditory Short Term Memory Task (Teschan et al.) and the Speech Sounds Perception Test. Thus, the one prediction which may be solidly made based upon prior research is that when pre-dialysis (Do) test scores on Finger Tapping are compared to post-dialysis (D_1) and pre-dialysis (D_2) performance, a significant improvement, followed by a significant regression respectively will be expected. No significant difference between mean scores at Do and D_2 is likely to be observed.

This study takes on an exploratory nature when the other measures employed in this study are considered. Whether sub-normative performance will be observed on initial pre-dialysis testing is open to question. If cognitive and sensory-motor dysfunction is observed, whether the improvements in biochemistry due to hemodialysis will be sufficient to cause a significant improvement in cognitive and sensory-motor functioning is difficult to determine in other than a speculative manner.

As regards predictions of possible significant correlations between specific plasma values and test performance at Do, D_1, D_2, the literature supports a significant correlation between levels of serum creatinine

and performance on a visual discrimination learning task (pre and post-dialysis (McDaniel, 1971), on the Trailmaking Test (in azotemic patients) and on the answer recognition test (in azotemic patients beginning dialysis) (Teschan et al., 1974; Ginn, 1975), all described previously. Additionally, a significant correlation between performance on a visual discrimination learning task (pre and post-dialysis) and plasma concentrations of potassium was noted by McDaniel (1971). Thus, based on prior research findings, the blood variables having the greatest probability of a statistically significant correlation with test performance (pre, post, or pre-dialysis) are creatinine and potassium.

Statistics

The mean, standard deviation and range were calculated for each cognitive, sensory-motor and serum measure. The dialysis groups' mean performance for each test measure was compared with available norms for a normal sample. The mean, standard deviation and range were also calculated for each independent variable (age, education, time on dialysis). A one factor analysis of variance with repeated measures (20 subjects each tested repeatedly on a series of cognitive, sensory-motor, serum and subjective rating scale measures over 3 days, Do, D_1 and D_2) was performed to determine if significant differences in cognitive and sensory-motor test performance, subject rating scale measures, and levels of serum chemistry occurred across the following three day pair comparisons: $Do-D_1$, D_1-D_2, $Do-D_2$. The format for the analyses of variance follows below:

Classification Variables	Levels	Values
Day	3	0, 1, 2
Subjects	20	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20

Test = Day, Error = Day*Subjects

Source	DF
Day	2
Subjects	19
Day*Subjects	38

For each measure in which there was a significant difference between means on at least one day pair ($Do-D_1$, D_1-D_2, $Do-D_2$), the Duncan Multiple Range Test was employed to identify on which day pair(s) the significant difference between means occurred.

The following correlation matrices utilizing the Pearson Product Moment Coefficient (r) were calculated: 1) Each cognitive, sensory-motor measure with each serum measure, separately for Do, D_1 and D_2. 2) Difference scores for each cognitive and sensory-motor measure with difference scores for each serum measure. (Difference scores were calculated according to the following format: $Do_{xo}-D1_{x1}$, $D1_{x1}-D2_{x2}$, $Do_{xo}-D2_{x2}$. Do, D_1 and D_2 have been defined previously. Xo, X1, and X2 stand for the values of a given measure, the subscripts o, 1, 2 noting whether the measure occurred on Do, D_1, or D_2). 3) Age, education, time on dialysis with each cognitive and sensory-motor

measure separately for Do, D_1, and D_2. 4) Each serum measure with every other serum measure, separately on Do, D_1 and D_2. 5) Each independent measure with every other independent measure. 6) Each cognitive, sensory-motor measure with every other cognitive, sensory-motor measure, separately on Do, D_1 and D_2.

Finally, the following correlation matrices utilizing the Spearman Correlation Coefficient were calculated: 1) Discomfort index with each cognitive, sensory-motor measure, separately on Do, D_1 and D_2. 2) Discomfort index with each element of the Subjective Rating Scale, separately on Do, D_1 and D_2.

The results of the above analyses follow in the next chapter.

CHAPTER III

RESULTS

It is important that the reader bear in mind that the results and conclusions cited in the following two chapters are based on a sample of long term ($\bar{x}$ = 39.7 months) stable hemodialysis patients with serum chemistry levels on Do, D_1 and D_2 as listed in Table 4 below. Results might have been different had a sample of medically unstable dialysis patients, or those with serum chemistry levels significantly in excess of the values cited in Table 4 been subjects in this study. With this caution in mind a presentation of results follows below.

Table 3 lists the mean, standard deviation and range for independent variables: age, education and time on dialysis. A broad range of ages and time on dialysis was represented.

Table 4 contains the mean, standard deviation and normal values for each serum measure. Mean values for BUN, creatinine, potassium, chloride, carbon dioxide, phosphorus, dimethylamine (ph7-8, ph > 10) and trimethylamine (ph7-8, ph > 10) were all outside normal limits on Do, D_1, and D_2.

Table 5 contains the mean, standard deviation, range and normal performance range (where available) for each cognitive and sensory-motor measure on Do, D_1, and D_2. Alphabetic notation under

Table 3

Mean, Standard Deviation, Range For Age, Education and Time On Dialysis

N = 20

Independent Variable	Mean	S.D.	Range
Age (yrs.)	46.5	11.330	25 - 68
Education (yrs.)	13.150	2.007	11 - 16
Time On Dialysis (Mo.)	39.7	21.582	10 - 86

Table 4

Mean, Standard Deviation, Range and Normal Values

For Serum Measures

(N = 20)

Serum Measure	Day	Mean	S.D.	Range	Normal Values
BUN mg/100ml	0	75.450	13.570	56-110	8.25
	1	56.450	10.092	42-80	8.25
	2	71.250	12.703	55-101	8.25
Creatinine mg/100 ml	0	16.445	3.689	10.2-24.3	.7-1.5
	1	13.710	3.114	8.3-22.0	.7-1.5
	2	16.010	3.574	10.2-24.6	.7-1.5
Sodium mEq/L	0	138.60	2.683	131-143	135-145
	1	139.30	3.420	132-145	135-145
	2	138.35	3.265	131-144	135-145
Potassium mEq/L	0	5.305	.596	4.3-6.5	3.5-5.0
	1	5.210	.564	4.4-6.4	3.5-5.0
	2	5.130	.609	3.9-6.1	3.5-5.0
Chloride mEq/L	0	99.050	3.316	93-104	100-106
	1	96.350	3.392	90-103	100-106
	2	98.30	4.318	89-107	100-106
Carbon Dioxide mEq/L	0	18.650	3.856	13-27	24-30
	1	24.350	2.498	20-29	24-30
	2	19.200	2.648	15-24	24-30
Phosphorus (Inorganic) mg/100 ml	0	5.180	1.614	2.3-8.6	3.0-4.5
	1	5.325	1.368	3.0-8.1	3.0-4.5
	2	5.540	1.599	2.9-9.00	3.0-4.5

Table 4 Continued

Serum Measure	Day	Mean	S.D.	Range	Normal Values
Calcium	0	9.165	.752	7.6-11.0	8.5-10.5
mg/100ml	1	9.595	.701	8,3-11.2	8.5-10.5
	2	9.245	.655	8.1-11.2	8.5-10.5
Dimethylamine	0	336.80	89.357	193-540	30*
ph7-8	1	261.75	73.743	165-448	30*
micrograms %	2	311.50	82.084	198-486	30*
Dimethylamine	0	603.25	174.9	334-927	30*
ph > 10	1	456.00	154.790	304-885	30*
micrograms %	2	549.25	151.590	351-801	30*
Trimethylamine	0	362.7	221.065	166-956	30*
ph7-8	1	233.7	77.514	94-455	30*
micrograms %	2	342.1	189.795	134-825	30*
Trimethylamine	0	568.65	200.833	308-904	30*
ph > 10	1	449.85	199.532	125-1060	30*
micrograms %	2	527.35	159.353	241-815	30*

* = Mean normal value.

Table 5

Mean, Standard Deviation, Range and Normal Performance

(Where Available) For Cognitive and Sensory-Motor Measures

(N = 20)

Test	Day	Mean	S.D.	Range	Normal Level
Proverbs	0	18.25-A	6.257	3-24	13.97
	1	17.70-A	5.750	2-24	13.97
	2	17.45-A	6.083	4-24	13.97
Digit Span Forward	0	6.650*	1.461	5-9	
	1	6.450*	.887	5-8	
	2	7.10*	1.165	5-9	
Digit Span Backwards	0	4.25*	1.482	2-8	
	1	4.30*	1.490	3-8	
	2	4.50*	1.638	2-8	
Digit Span Forward & Backward	0	9.75**-B	3.39	6-19	8-11
	1	9.60**-B	2.60	6-15	8-11
	2	10.75**-B	3.40	6-19	8-11
Color Naming Time (Sec.)	0	129.70-C	23.846	92-178	110-133
	1	121.95-B	19.525	92-155	110-133
	2	120.70-B	24.377	90-173	110-133
Color Naming Errors	0	1.150	1.387	0-5	
	1	.750	1.446	0-5	
	2	.350	.988	0-4	
Quick Test	0	39.6-B	4.684	30-48	36-44
	1	40.8-B	4.675	29-49	36-44
	2	41.450-B	4.989	29-49	36-44

Table 5 Continued

Test	Day	Mean	S.D.	Range	Normal Level
Seashore Rhythm (Number Correct)	0	25.00-B	3.784	15-30	25-28
	1	25.25-B	3.583	15-30	25-28
	2	25.25-B	4.253	14-30	25-28
Choice Reaction Time (Sec.)	0	.507-B	.072	.395-.699	$\leq$ .6
	1	.499-B	.082	.375-.681	$\leq$ .6
	2	.482-B	.088	.336-.684	$\leq$ .6
Choice Reaction Errors	0	.650	.763	0-2	
	1	.425	.613	0-2.5	
	2	.725	.924	0.35	
Grooved Pegboard Dominant Time Out (Sec.)	0	26.250	8.831	18-60	
	1	20.950	3.170	15-27	
	2	22.100	4.204	15-31	
Grooved Pegboard Non-Dominant Time Out (Sec.)	0	25.800	7.438	19-53	
	1	24.600	7.301	16-52	
	2	24.250	4.644	15-35	
Grip Strength Male, Dominant (Lbs.)	0	91.21-B	22.97	44-131	77-121
	1	93.25-B	23.26	40-145.5	77-121
	2	97.21-B	22.05	32.5-145	77-121
Grip Strength Male, Non-Dominant (Lbs.)	0	80.84-B	19.04	50-111	66-99
	1	80.43-B	20.61	45-111	66-99
	2	82.49-B	20.74	45-111	66-99
Grip Strength Male & Female Dominant (Lbs.)	0	77.725	29.229	30.5-131	
	1	78.755	30.887	30-145.5	
	2	81.675	31.250	31-145	

Table 5 Continued

Test	Day	Mean	S.D.	Range	Normal Level
Grip Strength	0	63.385	27.390	20-111	
Male & Female	1	67.275	29.180	15-111	
Non-Dominant (Lbs.)	2	68.795	29.139	15.5-111	
Finger Tapping	0	50.34-C	7.07	39.8-62.7	50-54
Male, Dominant	1	50.91-C	6.75	39.3-65.5	50-54
	2	51.81-B	7.45	37.0-67.6	50-54
Finger Tapping	0	43.46-C/D	7.41	27.6-61.0	44-48
Male, Non-Dominant	1	45.11-B	7.56	31.8-60.1	44-48
	2	45.69-B	6.34	34.6-59.4	44-48
Digit Symbol	0	7.4**-C/D	1.86	6-12	8-12
	1	7.95**-C	2.26	5-12	8-12
	2	8.35**-C	2.08	5-12	8-12
Finger Tapping	0	44.13-D	2.77	40.8-48	46-50
Female, Dominant	1	45.65-C	4.44	39.5-50	46-50
	2	45.90-C	7.09	36-55	46-50
Finger Tapping	0	48.475	6.691	39.8-62.7	
Male & Female	1	49.330	6.519	39.3-65.5	
Dominant	2	50.035	7.674	36.0-67.6	
Finger Tapping	0	41.325	7.522	27.6-61.0	
Male & Female	1	43.030	7.477	31.8-60.1	
Non-Dominant	2	43.635	7.294	30.0-59.4	
Speech Sounds	0	16.00-D	2.714	11-20	17.66-18.66
Perception Test	1	17.650-B	1.663	14-20	17.66-18.66
(# Correct, 20 Items)	2	17.350-C	2.134	12-20	17.66-18.66

Table 5 Continued

Test	Day	Mean	S.D.	Range	Normal Level
Word Fluency	0	14.850-D	3.951	9-25	16-20
	1	16.850-C	4.356	10-23	16-20
	2	16.850-C	3.977	10-24	16-20
Trailmaking A Time (Sec.)	0	53.350-E	18.511	29-92	24-30
	1	43.950-D	11.646	28-63	24-30
	2	39.550-D	12.219	24-70	24-30
Trailmaking A Errors	0	.05	.224	0-1	
	1	.1	.308	0-1	
	2	.2	.410	0-1	
Benton Visual Retention Test (Admin. B)	0	4.650-D	2.207	0-9	6-7
	1	4.550-D	1.701	1-8	6-7
	2	4.400-D	2.210	0-8	6-7
Grooved Pegboard Dominant Time In (Sec.)	0	85.550-E	20.631	59-122	61-66
	1	74.700-D	16.874	48-106	61-66
	2	74.000-D	14.640	51-102	61-66
Grooved Pegboard Dominant Error In	0	1.1	1.071	0-3	
	1	.65	.671	0-2	
	2	.80	1.105	0-4	
Grip Strength Female, Dominant (Lbs.)	0	46.25-D	13.83	30.5-70	55-88
	1	44.90-D	16.04	30-75.5	55-88
	2	45.42-D	13.89	31-65	55-88
Grip Strength Female, Non-Dominant (Lbs.)	0	39.17-D	15.40	20-65	48.4-77
	1	36.58-D	22.72	15-80	48.4-77
	2	36.83-D	18.88	15.5-67	4814-77

Table 5 Continued

Test	Day	Mean	S.D.	Range	Normal Level
Finger Tapping	0	36.35-D	5.44	31.2-46.7	41-44
Female, Non-	1	38.17-D	4.84	31.8-44.8	41-44
Dominant	2	38.83-D	7.62	30-52.5	41-44
Grooved Pegboard	0	90.150-E	21.463	61-145	66-73
Non-Dominant	1	82.000-E	15.475	55-115	66-73
Time In (Sec.)	2	84.100-E	19.358	54-123	66-73
Grooved Pegboard	0	1.000	1.076	0-4	
Non-Dominant	1	.600	1.188	0-5	
Error In	2	1.000	1.257	0-5	
Trailmaking B	0	132.10-F	77.677	52-377	46-64
Time (Sec.)	1	126.45-F	94.046	49-480	46-64
	2	117.15-F	55.467	51-251	46-64
Trailmaking B	0	1.250	1.650	0-6	
Errors	1	1.350	2.207	0-9	
	2	1.250	1.333	0-4	

*raw score

**scaled score

Performance Levels:

A - High normal
B - Normal
C - Low normal
D - Mildly impaired
E - Moderately impaired
F - Severely impaired

the "Mean" column classifies each measure according to the level of performance (high normal to severely impaired) as compared to a normal population. (See key at end of Table 5.) Cognitive and sensory-motor measures are listed in order of decreasing levels of performance. A review of Table 5, including the levels attained and abilities involved in each test measure, follows below.

On the Proverbs Test, a measure of verbal comprehension and abstract thinking, the mean for the dialysis sample was in the high normal range on Do, D_1 and D_2. Dialysis patients achieved performances in the normal range on Do, D_1, and D_2 on the following tests: Quick Test (measuring verbal comprehension, visual search and recognition skills, interpretation of pictorially presented social cues), Digit Span (a test of short term rote memory, mental manipulation of symbols, sustained attention and concentration skills), Color Naming (a test requiring the repetitive use of an elementary language function as the subject identifies a series of different color squares as rapidly as possible across a series of pages), Seashore Rhythm (a test tapping alertness, sustained auditory attention and the ability to perceive and compare different rhythmic sequences), Choice Reaction Time (a speeded test of visual discrimination, visual-motor planning and visual-motor coordination), Grip Strength (male dominant and non-dominant), and Finger Tapping (male dominant) (a speeded motor task requiring sustained motor coordination).

In the next group of tests to be reviewed, mean performances on Do, D_1 and D_2 were sometimes within and sometimes outside of the normal

range. On Digit Symbol (a complex, speed dependent, visual-motor performance task having components of planning, symbol association and memory, and visual-motor coordination) the dialysis groups mean performance was slightly outside the low end of the normal range on Do and within the low end of the normal range on D_1 and D_2. On Finger Tapping (male, non-dominant) performance was in the borderline low normal range on Do and mid-normal range on D_1 and D_2. Finger Tapping performance (female dominant) was mildly impaired on Do and barely within the low end of the normal range on D_1 and D_2. On the Speech Sounds Perception Test (requiring auditory attention and discrimination, and visual recognition of auditory input) the dialysis group's mean performance was mildly impaired on Do and within the normal range on Do and D_2. Performance on Word Fluency (a speeded task of verbal association) was mildly impaired on Do and within the low end of the normal range on D_1 and D_2.

In this final group of tests mean performances were consistently outside of the normal range. On Trailmaking A (assessing visual scanning, visual sequencing, visual-motor coordination) overall mean performance was moderately impaired on Do and mildly impaired on D_1 and D_2. On Trailmaking B (requiring the additional ability to switch set) severe impairment was evident on Do, D_1 and D_2. On the Benton Visual Retention Test (assessing visual perception, visual memory and visuoconstructive abilities) mean group performance was moderately impaired on Do, D_1 and D_2. Mean performance on Grooved Pegboard dominant time in (a speeded test of visual-motor coordination and

spatial orientation) was mildly impaired on Do, D_1 and D_2, while mean performance on Grooved Pegboard non-dominant time in was moderately impaired on Dl, D_1 and D_2. Mean performance on Grip Strength (female dominant and non-dominant) was mildly impaired on Do, D_1 and D_2, as was performance on Finger Tapping (female non-dominant). The significance of these results will be discussed in the next chapter.

Table 6 lists the results of the analysis of variance for cognitive and sensory-motor measures. Eleven out of twenty-seven measures showed a significant difference on at least one day pair when comparisons were made between Do and D_1, D_1 and D_2 and Do and D_2.

Table 7 lists the results of the Duncan Multiple Range Test for the eleven cognitive and sensory-motor measures in Table 6 significant at $p \leq .05$ on at least one of the three day pair comparisons: ($Do-D_1$), (D_1-D_2), ($Do-D_2$). Table 7 identifies which of the day pair comparisons were significant and notes the significance level ($p = .05$ or .01). Mean performances for each measure on each day (Do, D_1 and D_2) are also listed.

Table 8 includes the Analysis of Variance Results for each serum measure. Only three serum measures (sodium, potassium and phosphate) did not change significantly on any of the three day pair comparisons: ($Do-D_1$), (D_1-D_2), ($Do-D_2$).

Table 9 lists the results of the Duncan Multiple Range Test for the nine serum measures from Table 8 significant at $p = .05$ on at least one of the three comparison pairs: ($Do-D_1$), (D_1-D_2), ($Do-D_2$). Table 9 identifies which of the day pair comparisons are significant and notes

Table 6

Analysis of Variance: Cognitive & Sensory-Motor Tests

Dependent Measure	Source	DF	ANOVA S.S.	F-Value
Digit Span Backward	Day	2	.7000000	.55
Trail - A - Error	Day	2	.23333333	1.43
Trail - B - Time	Day	2	2279.433333	.82
Trail - B - Error	Day	2	.13333333	.04
Word Fluency	Day	2	53.33333	3.03
Proverbs Test	Day	2	6.700000	.44
Benton Vis. Ret.	Day	2	.633333	.17
Seashore Rhythm	Day	2	.833333	.09
Grooved Pegboard Dominant Error In	Day	2	2.100000	1.05
Grooved Pegboard Non-Dominant Error In	Day	2	2.133333	1.03
Grooved Pegboard Non-Dominant Time Out	Day	2	26.43333	.85
Choice Reaction (Time)	Day	2	.00646333	1.04
Choice Reaction (Errors)	Day	2	.9750000	1.07
Grip Strength-Dominant	Day	2	167.932000	1.12
Grip Strength - Non-Dominant	Day	2	311.404000	.89
Finger Tapping - Dominant	Day	2	24.411000	1.49
Digit Span Forward	Day	2	4.433333	3.38*
Digit Symbol	Day	2	251.633333	8.56**
Color Naming Time	Day	2	950.83333	8.00**
Color Naming Error	Day	2	6.400000	4.63*

Table 6 Continued

Dependent Measure	Source	DF	ANOVA S.S.	F-Value
Trail - A - Time	Day	2	1987.73333	8.88**
Speech Sounds Perception	Day	2	30.900000	4.67*
Quick Test	Day	2	35.233333	3.41*
Grooved Pegboard Dominant Time In	Day	2	1677.43333	21.70**
Grooved Pegboard Non-Dominant Time In	Day	2	716.23333	5.62**
Grooved Pegboard Dominant Time Out	Day	2	310.90000	6.12**
Finger Tapping Non-Dominant	Day	2	57.394333	3.76*

* = $.01 < p \leq .05$.
** = $p < .01$.

Table 7

Duncan's Multiple Range Test For Cognitive and Sensory-Motor Measures From Table Six With $p \leq .05$

Dependent Measure	DF	MS[1]	Day - Mean	Significance by Day Pairs		
				Day	To	Day
Digit Span Forward	38	.655	2 - 7.10	0	→	1
			0 - 6.65	1	→	2*
			1 - 6.45	0	→	2
Digit Symbol	38	14.69	2 - 44.45	0	→	1*
			1 - 42.30	1	→	2
			0 - 39.45	0	→	2**
Color Naming Time	38	59.4	0 -129.7	0	→	1**
			1 -121.95	1	→	2
			2 -120.7	0	→	2**
Color Naming Error	38	.69	0 - 1.15	0	→	1
			1 - .75	1	→	2
			2 - .35	0	→	2**
Trail - A - Time	38	111.94	0 - 53.35	0	→	1**
			1 - 43.95	1	→	2
			2 - 39.55	0	→	2**
Speech Sounds Perception # Correct	38	3.31	1 - 17.65	0	→	1**
			2 - 17.35	1	→	2
			0 - 16.00	0	→	2*

Table 7 Continued

Dependent Measure	DF	MS[1]	Day - Mean	Significance by Day Pairs		
				Day	To	Day
Quick Test	38	5.16	2 - 41.45	0	→	1
			1 - 40.80	1	→	2
			0 - 39.60	0	→	2*
Grooved Pegboard Dominant Time In	38	38.65	0 - 85.55	0	→	1**
			1 - 74.70	1	→	2
			2 - 74.00	0	→	2**
Grooved Pegboard Non-Dominant Time In	38	63.76	0 - 90.15	0	→	1**
			2 - 84.10	1	→	2
			1 - 82.00	0	→	2*
Grooved Pegboard Dominant Time Out	38	25.42	0 - 26.25	0	→	1**
			2 - 22.10	1	→	2
			1 - 20.95	0	→	2*
Finger Tapping Non-Dominant	38	7.63	2 - 43.635	0	→	1
			1 - 43.03	1	→	2
			0 - 41.325	0	→	2*

* = .05.

** = .01.

[1]Ms = $\frac{\text{Error SS (Day * Subjects)}}{\text{DF (Day * Subjects)}}$

Table 8

Analysis Of Variance Results: Serum Measures

(N = 20)

Serum Measure	Source	DF	ANOVA S.S.	F-Value
BUN	Day	2	3984.5333	104.16**
Creatinine	Day	2	86.396333	119.85**
Sodium	Day	2	9.700000	1.11
Potassium	Day	2	.3070000	1.92
Chloride	Day	2	77.7000	4.83*
Carbon Dioxide	Day	2	395.4333	43.37**
Phosphate	Day	2	1.3123333	1.33
Calcium	Day	2	2.092000	11.90**
Dimethylamine ph7-8	Day	2	58317.7	19.06**
Dimethylamine ph> 10	Day	2	221960.833	12.35**
Trimethylamine ph7-8	Day	2	192106.1333	8.99**
Trimethylamine ph> 10	Day	2	145502.533	7.84**

* = $.01 < p \leq .05$.

** = $p < .01$.

Table 9

Duncan's Multiple Range Test For Serum Measures From Table Eight With $p \leq .05$

(N = 20)

Blood Measure	DF	MS[1]	Day - Mean	Significance By Day Pairs
BUN	38	19.13	0 - 75.450 2 - 71.250 1 - 56.45	0 → 1** 1 → 2** 0 → 2**
Creatinine	38	.36	0 - 16.445 2 - 16.010 1 - 13.710	0 → 1** 1 → 2** 0 → 2*
Chloride	38	8.04	0 - 99.05 2 - 98.30 1 - 96.35	0 → 1** 1 → 2* 0 → 2
Carbon Dioxide	38	4.56	1 - 24.35 2 - 19.20 0 - 18.65	0 → 1** 1 → 2* 0 → 2
Calcium	38	.088	1 - 9.59 2 - 9.24 0 - 9.165	0 → 1** 1 → 2** 0 → 2
Dimethylamine ph7-8	38	1529.99	0 -336.8 2 -311.5 1 -261.75	0 → 1** 1 → 2** 0 → 2*

Table 9 Continued

Blood Measure	DF	MS[1]	Day - Mean	Significance To Day Pairs
Dimethylamine ph> 10	38	8983.33	0 -603.25	0 → 1**
			2 -549.25	1 → 2**
			1 -456.00	0 → 2
Trimethylamine ph7-8	38	10687.4	0 -362.7	0 → 1**
			2 -342.1	1 → 2**
			1 -233.7	0 → 2
Trimethylamine ph> 10	38	9283.46	0 -568.15	0 → 1**
			2 -527.35	1 → 2*
			1 -449.85	0 → 1

* = .05
** = .01
[1]Ms = $\frac{\text{Error SS (Day*Subjects)}}{\text{DF (Day*Subjects)}}$

the significance level (p = .05 or .01). Mean serum values for each serum measure on each day (Do, D_1, D_2) are also listed.

The discomfort index was significant at the .05 level (F = 4.00, DF = 2) when comparisons across Do, D_1, D_2 were made. Table 10 lists the results of the Duncan Multiple Range Test for the Discomfort Index. Mean values for the discomfort index are listed for Do, D_1, D_2.

Table 11 lists the Pearson Product Moment correlation coefficient (r) with the corresponding significance level for the correlation of each cognitive and sensory-motor measure with each serum measure. Only those variable pairs with Pearson correlations of $p \leq .01$ are listed. (The total number of correlations with $p \leq .01$ is less than would be expected by chance.)

Table 12 includes the Pearson correlation coefficient and corresponding significance level for the correlation of serum measure difference scores with cognitive and sensory-motor difference scores. Only those variable pairs with (r) significant at $p \leq .01$ are listed. (The total number of correlations with $p \leq .01$ is less than would be expected by chance.)

Pearson correlation coefficients resulted in but two significant correlations when age and time on dialysis were correlated with each cognitive and sensory-motor measure on Do, D_1 and D_2: age with choice reaction time, day 1, r = .5731, p = .008; time on dialyses with grip strength dominant, day 0, r = -.5424, p = .013. Spearman correlation of the discomfort index with each cognitive and sensory-motor measure on Do, D_1 and D_2 resulted in two significant correlations: discomfort

Table 10

Duncan's Multiple Range Test For Discomfort Index

(N = 20)

Measure	DF	MS[1]	Day - Mean	Significance By Day Pairs
Discomfort Index	38	33.18	0 - 49.35	0 → 1*
			2 - 45.25	1 → 2
			1 - 44.60	0 → 2*

* = .05.

[1]MS = $\frac{\text{Error SS (Day*Subjects)}}{\text{DF (Day*Subjects)}}$

Table 11

Pearson Correlation Of Cognitive & Sensory-Motor Measures With Serum Measures*

(N = 20)

Pair	Day	Pearson Corr. Coeff.	Sig. Level
Chloride & Digit Span Forward	0	-.5394	.014
Creatinine & Grooved Pegboard Non-Dominant Time In	0	.5751	.008
Sodium & Quick Test	0	.6286	.003
Phosphate & Proverbs Test	0	.5748	.008
Creatinine & Finger Tapping Dominant	0	.5611	.010
Dimethylamine ph7-8 & Digit Span Forward	0	.5365	.015
Dimethylamine ph> 10 & Grooved Pegboard Dominant Time In	1	.6138	.004
Trimethylamine ph > 10 & Benton	1	.5298	.016
Sodium & Benton	1	.5493	.012
Potassium & Quick Test	1	.6479	.002
Carbon Dioxide & Grooved Pegboard Dominant Error In	1	-.5827	.007
Creatinine & Finger Tapping Dominant	1	.6639	.001
Calcium & Seashore Rhythm	1	.5682	.009
Creatinine & Word Fluency	2	-.5867	.007
Potassium & Grooved Pegboard Non-Dominant Time Out	2	-.5836	.007
BUN & Choice Reaction Time	2	.5478	.012
Creatinine & Grip Strength Dominant	2	.6115	.004
Dimethylamine ph7-8 & Digit Span Backwards	2	.5440	.013

Table 12

Pearson Correlation Of Difference Scores (Day (0-1), Day (1-2), Day (0-2)) For Serum Values And Sensory-Motor & Cognitive Measures

(N = 20)

Serum Measure With Sensory-Motor and Cognitive Measure	Pearson Correlation Coefficient	Significance Level
Phosphate (0-1) with Trails B Time (0-1)	-.5756	p = .008
Dimethylamine ph > 10 (0-1) With Color Naming Time (0-1)	-.5679	p = .009
BUN (1-2) with Word Fluency (1-2)	.5536	p = .011
Sodium (1-2) with Word Fluency (1-2)	-.6537	p = .002
Carbon Dioxide (1-2) with Quick Test (1-2)	-.5537	p = .011
BUN (1-2) with Grip Strength Dominant (1-2)	.5905	p = .006
Chloride (1-2) with Choice Reaction Time Error (1-2)	-.5411	p = .014
Trimethylamine ph7-8 (1-2) with Digit Span Forward (1-2)	.5526	p = .012
Trimethylamine ph > 10 (0-2) with Trailmaking B Time (0-2)	-.5331	p = .016
Trimethylamine ph > 10 (0-2) with Proverbs (0-2)	.5377	p = .015
Dimethylamine ph > 10 (0-2) with Grooved Pegboard Non-Dominant Time In	.5241	p = .018

index with digit span forward, day 0, Spearman coefficient = .6442, p = .002; discomfort index with Benton Visual Retention, day 2, Spearman coefficient = .5412, p = .014.

Pearson intercorrelation of age, time on dialysis and education yielded one significant correlation: education with time on dialysis, r = -.6185, p = .002. Pearson intercorrelation of serum measure pairs on Do, D_1 and D_2 with $p \leq .01$ are listed in Table 13.

Finally, Spearman correlations of the Discomfort Index and individual elements of the Subjective Rating Scale were generally highly significant and are listed in Appendix G. Pearson intercorrelations of Sensory-motor and cognitive measures for Do, D_1 and D_2 with $p \leq .01$ are included in appendices Ho, Hl, H2 respectively.

A discussion of all results cited above follows in the next chapter.

Table 13

Pearson Intercorrelation of Serum Variables ($p \leq .01$)

(N = 20)

Blood Measure Pair	Day	Pearson r	Significance Level
Sodium with Chloride	0	.6293	$p = .003$
Dimethylamine ph7-8 with Dimethylamine ph > 10	0	.9108	$p \leq .0009$
Trimethylamine ph7-8 with Trimethylamine ph > 10	0	.8722	$p \leq .0009$
Sodium with Chloride	1	.5985	$p = .005$
Dimethylamine ph7-8 with Dimethylamine ph > 10	1	.5577	$p = .011$
Trimethylamine ph > 10 with Dimethylamine ph7-8	1	.5471	$p = .013$
Trimethylamine ph > 10 with Dimethylamine ph > 10	1	.7823	$p \leq .0009$
Trimethylamine ph7-8 with Trimethylamine ph > 10	1	.6522	$p = .002$
Dimethylamine ph7-8 with Dimethylamine ph > 10	2	.8166	$p \leq .0009$
Trimethylamine ph7-8 with Dimethylamine ph7-8	2	.5815	$p = .007$
Trimethylamine ph7-8 with Trimethylamine ph > 10	2	.7532	$p \leq .0009$

CHAPTER IV

DISCUSSION

Effects of Hemodialysis On Serum Chemistry

Prior to discussing the possible effects of changes in serum chemistry (across Do, D_1 and D_2) on repeated cognitive and sensory-motor test performance, it is first necessary to specify what changes in serum chemistry actually occurred.[37] A consideration of Tables 4, 8 and 9 (Mean, Standard Deviation, Range and Normal Values for Serum Measures; Analysis of Variance Results for Serum Measures; and Duncan Multiple Range Test for Serum Measures) reveals that hemodialysis and those physiological processes occurring thereafter (rebound effects, continued buildup of toxic metabolites), significantly affected serum chemistry. Levels of BUN, creatinine, chloride, carbon dioxide, calcium, dimethylamine (ph 7-8, ph > 10) and trimethylamine (ph 7-8, ph > 10) all changed significantly in the expected direction when pre and post-hemodialyses comparisons ($Do-D_1$), and post and pre-hemodialyses comparisons (D_1-D_2) were made. Additionally, when the means for each

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[37]Serum chemistry changes due to hemodialysis obviously include other serum measures not monitored in this study. Only BUN, creatinine, chloride, carbon dioxide, calcium, sodium, potassium, phosphorus, dimethylamine (ph7-8, ph > 10) and trimethylamine (ph7-8, ph > 10) were included.

serum variable at Do and D_2 were compared, significant differences were found for BUN, creatinine and dimethylamine (ph7-8). At D_2 these serum measures were, as expected, significantly below their Do levels.

No significant differences for the Do-D_2 comparison were found for chloride, carbon dioxide, calcium, dimethylamine (ph > 10) and trimethylamine (ph7-8, ph > 10). No significant differences occurred for sodium, potassium and phosphate on any of the following comparisons: Do-D_1, D_1-D_2, Do-D_2. These findings are in keeping with expected results.[38]

Most importantly, individual levels of BUN and creatinine (small molecules) and dimethylamine and trimethylamine (middle molecules) were changed significantly by hemodialysis and allied physiological processes, across Do, D_1 and D_2. These particular serum measures served as crucial signposts for assessing "adequacy" of dialysis in this study. The fact that these serum measures were significantly changed across Do, D_1 and D_2 legitimizes an inquiry into the possible effects of such changes on repeated cognitive and sensory-motor test performance (on Do, D_1 and D_2).

Levels of Performance: Areas of Strength and Weakness

Despite a daily buildup of toxic renal metabolites, dialysis

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[38]The fact that the comparison across Do, D_1 and D_2 was not significant for potassium is not surprising considering that the D_1 serum test was done approximately 20 hours post-dialysis. Had the D_1 serum test immediately followed dialysis, significant differences between Do-D_1 and D_1-D_2 levels would have been observed.

patients scored within the normal range on Do, D_1 and D_2 in a wide variety of areas when their performance was compared with available norms for a normal population.[39] These areas included: verbal comprehension, abstraction,[40] short term rote memory (auditory), mental manipulation of symbols (where no switching of set was required),

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[39]See Table 5 for a presentation of available normal ranges for many of the cognitive and sensory-motor tests utilized in this study. See Appendix I for a listing of ranges of impairment in performance (from severely impaired to high normal).

[40]On the Proverbs Test, a measure of verbal comprehension and abstract thinking, the mean for dialysis patients was in the upper end of the high normal range on Do, D_1 and D_2. This finding must be tempered by the fact that the scoring of responses on the Proverbs Test is based not on accuracy of content, but simply on whether or not the subject is able to "abstract" each concrete element of the proverb into a more generalizable phrase, in explaining its meaning. In other words, although a subject's interpretation of a proverb may be poor, as long as it represents an abstract generalization, full credit is given. Dialysis patients, as a whole, demonstrated a well developed ability as regards satisfying the scoring requirements (noted above), however, an informal review of the quality of proverb interpretations suggests that the quality achieved did not always match up to the ability to abstract each concrete element of the proverb. This seems true despite the admittedly subjective nature of judging the quality of content. The quality of interpretations seems to have been compromised by the admittedly difficult nature of many of the proverbs.

sustained attention, concentration, auditory discrimination, visual discrimination, visual-motor planning (when no switching of set was required), visual-motor reaction time, visual recognition and interpretations of pictorially presented objects and social cues, grip strength (males), sustained motor speed (male dominant) and the maximum repetitive performance of an elementary language function (speeded color identification).

On each of several tests (Digit Symbol, Finger Tapping (male non-dominant, female dominant), Speech Sounds Perception and Word Fluency) mean performances fluctuated between the normal and mildly impaired range, across Do, D_1 and D_2. (See Table 5.) Explanations for these fluctuations will be briefly considered below. A more detailed discussion will follow at a later point in this chapter.

Performance on Digit Symbol improved from mildly impaired on Do to barely within the lowest end of the normal range on D_1 and D_2. (Differences between Do and D_1, and Do and D_2 were significant, $p = .05$, $p = .01$ respectively.) Apparent on this test was the subjects' slowness in switching set from number to symbol (despite the presence of a reference model) and non-reliance on memory (symbol association). There is little or no evidence to suggest that the changes in performance, noted above, were due to changes in serum chemistry and/or discomfort levels. My speculation is that changes in performance were due to a practice effect in which a stable threshold of response was not achieved until after the D_1 test administration (the "practice effect" hypoth-

esis).[41] If the Digit Symbol Test had not been repeated and a post-dialysis testing was used to assess level of performance, my speculation is that performance would fall in the mildly impaired range (as there would have been no practice effect to increase the score and thus place it within the normal range).

Both mild impairment (female dominant, Do) and borderline impairment (male non-dominant, Do) on Finger Tapping may have been due to the effects of peripheral neuropathy and /or other peripheral damage at the access site.[42] A trend towards better performance, from mildly impaired on Do, to borderline impairment on D_1 and D_2, was recorded for females. A trend towards better performance, from borderline impairment on Do, to normal functioning on D_1 and D_2, was recorded for males (non-dominant). A test of the significance of these trends was not analyzed by sex due to the very disproportionate ratio of males to females (6/14).

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[41] Evidence against serum chemistry changes, and in favor of practice effects, will be offerred as an explanation for changes in cognitive and sensory-motor test performance at a later point in the discussion section (under "Effects of Time of Test Administration On Cognitive and Sensory-Motor Test Performance").

[42] Performance with the dominant hand was superior to performance with the non-dominant hand. While such results would be readily expected in a normal population, the possible effects of peripheral neuropathy, the location of the access site(s) and other possible peripheral damage, make such a prediction more tenuous in a dialysis population.

When the males and females were grouped together, neither a significant improvement from Do-D_1, nor a significant regression from D_1- D_2 was seen on statistical analysis.

Performance on the Speech Sounds Perception and Word Fluency tests improved from mildly impaired on Do to within normal limits on D_1. Improvements in performance on Word Fluency were not significant, however. If the mean performances for Word Fluency on Do, D_1 and D_2 are averaged (since it is unlikely that there was a significant practice effect), the mean score would fall within the low end of the normal range. Fluctuations in performance on Speech Sounds Perception were significant, however, the difference between mean scores on both Do and D_1, and Do to D_2 amounted to but one test item (out of 20). (The difference between the mean D_1 and D_2 scores was not significant.) These minor fluctuations do not appear to be clinically significant. While they cannot be accounted for by changes in serum chemistry levels, it is possible that a slight practice effect was responsible for the improvement from Do to D_1. After D_1, subjects seemed to have reached a stable level of responding. This will be further discussed under the "practice effect" hypothesis later in this section.

Dialysis patients were clearly impaired on Do, D_1 and D_2 in the following areas: speeded visual-motor coordination (Grooved Pegboard) and strength of grip (female dominant and non-dominant). Deficits in speeded visual-motor coordination (mildly to moderately impaired on Grooved Pegboard dominant time in, moderately impaired on Grooved Pegboard non-dominant time in) appear to be due to the effects of

peripheral neuropathy. Subjects typically complained of numbness in their fingers, with consequent difficulty feeling the pegs. Mild impairment in strength of grip (female dominant and non-dominant) may also have been due to the effects of neuropathy and other peripheral problems. A possible explanation for the males' success on grip strength was their greater muscle mass, which may have enabled them to overcome the effects of peripheral problems as noted above.

Dialysis patients' mean performance was also clearly impaired on each of Do, D_1 and D_2 in the following areas: visual search skills, visual motor-planning (involving the ability to switch set) and visual memory.[43] For example, on Trailmaking A and B subjects had difficulty finding the appropriate circles (even when they knew which number or letter was required). In the case of Trails B subjects had great difficulty shifting set from number to letter to number, etc.[44] Ad-

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[43]Performance on Trails A was moderately impaired on Do and mildly impaired on D_1 and D_2. Impairments on D_1 and D_2 are especially surprising considering the fact that the same form of Trails A was used on Do, D_1 and D_2. Performance on Trails B was severely impaired on each of Do, D_1 and D_2. Performance on the Benton was mildly impaired on each of Do, D_1 and D_2.

[44]The reader is reminded of the dialysis group's difficulty on the Digit Symbol Test. Even in the presence of a reference model, mean performance was outside of normal limits on Do and barely within the low end of the normal range on D_1 and D_2. The correlation between

ditionally, subjects found the directions for Trails B difficult to comprehend, despite repeated explanations on my part. Many subjects said they found Trails B to be the most difficult of all tests in the cognitive and sensory-motor battery. On the Benton Visual Retention Test, a testing of limits suggested that the difficulty was not in the visuoconstructive area, but rather was in the area of visual memory. When a reference drawing was provided, with no visual memory component required, subjects demonstrated little difficulty on the task.

The pronounced difficulty successfully implementing a plan requiring the switching of set, although not definitively suggestive of cerebral impairment, has been associated with persons having mild cerebral dysfunction of the anterior region. Sub-normal and borderline impairment on motor tasks, specifically those involving speeded fine motor coordination, appear to be due to the presence of neuropathy variously manifested as numbness, tingling sensations and mild discomfort of the wrist, forearm and fingers.

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[44]Cont'd..Digit Symbol and Trails A and Trails B was $p = .005$ and $p = .003$ respectively (Do). Impairment on Trails B and Digit Symbol, where the switching of set is a strong component of success, provides strong evidence that dialysis patients generally will have difficulty on tasks requiring these skills.

The results suggestive of cerebral impairment (cited above), appear at first glance, to contradict the findings of Hagberg (1974). In testing dialysis patients just prior to beginning dialysis and again six and twelve months later, Hagberg concluded that no signs of cerebral dysfunction were evident at the twelve month follow-up testing. Hagberg's battery at the twelve month follow-up[45] was sufficiently scant (compared to the test battery used in the present study), that the discrepancy in results is not surprising. Of singular exception, however, is the direct contradiction in findings on the Benton Visual Retention Test. Hagberg's sample scored within normal limits, while the present sample scored in the mildly impaired range. Hagberg's sample size decreased from 23 to 16 subjects at the 12 month follow-up testing, however, it is unlikely that the majority of subjects who dropped out were significantly impaired on the Benton. An important sample difference between the present study and that of Hagberg was the mean length of time on dialysis. At the 12 month follow-up testing all of Hagberg's subjects were on hemodialysis for 12 months, while the mean time on dialysis in the present study was 39.7 months (range: 10-86 months). While it is theoretically possible that the difference in mean time on dialysis may have been responsible for the discrepancy in results on the Benton, statistical analyses do not support such a hypothesis. (Pearson correlation of time on dialysis with each cog-

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[45]See page 21 for a discussion of Hagberg (1974).

nitive and sensory-motor test resulted in but one significant correlation.)

Discrepancy on the Benton aside, while conclusions in the present study regarding possible cerebral impairment are by no means definitive, Hagberg's follow-up testing at 12 months lacks the comprehensiveness necessary to reach a conclusion regarding the presence or absence of cerebral impairment. Longitudinal research,[46] employing a comprehensive test battery, would be helpful in clarifying 1) the progression of cognitive and sensory-motor performance as time on dialysis increases and 2) conclusions regarding the presence and/or absence of cerebral impairment.

It is important that amidst the controversy over questions of cerebral impairment the reader not lose sight of the fact that dialysis patients who are stable and "adequately" dialyzed perform within the normal range on a wide variety of cognitive and sensory-motor tests. Considering the well known findings that undialyzed uremic patients experience cognitive and sensory-motor impairment,[47] this study further demonstrates the beneficial effects of hemodialysis on cognitive and sensory-motor functioning.

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[46]A cross sectional type of design would facillitate the comparison of several groups of patients, differring only in the length of time on dialysis. This will be discussed further under "Suggestions For Further Research."

[47]The reader is referred to p. 19 for a review of this area of the literature.

Effects of Time of Test Administration on Cognitive and Sensory-Motor Test Performance

A review of Table 6 (Analysis of Variance: Cognitive and Sensory Motor Tests) reveals that there was a significant difference in performance, on at least one of the three possible day pair comparisons ($Do-D_1$, D_1-D_2, $Do-D_2$), for 11 of 27 test measures. Table 7 (Duncan's Multiple Range Test) identifies which day pair(s) were significant for each of the 11 test measures. Each pair will be considered in detail below.

The day pair comparison which most nearly serves as an indication of the possible effects of changes in serum chemistry on cogntive and sensory-motor test performance is Do-Dl (pre vs. post-dialysis comparison). It is this comparison which reflects the greatest quantitative difference in individual levels of the various serum measures. The $Do-D_1$ comparison will thus be examined first.

Of the 11 cognitive and sensory-motor test measures significant on at least one day pair comparison, seven measures showed a significant difference on the $Do-D_1$ day pair (all improvements in performance): 1) Trailmaking A, 2) Digit Symbol, 3) Speech Sounds Perception, 4) Color Naming Time, 5) Grooved Pegboard dominant time in, 6) Grooved Pegboard non-dominant time in, and 7) Grooved Pegboard dominant time out. (These tests will be referred to by the numbers just assigned throughout this chapter.) Trailmaking A is not considered to be a legitimate test measure for day pair comparisons. The same form was utilized on all three days making it clearly susceptible to practice

effects. Thus, six variables significant on the Do-D_1 comparison remain for consideration. Of these six test variables (2-7 above), none showed a significant regression on the D_1-D_2 comparison. (Such a regression would theoretically be due to an increase in the level of toxic renal metabolites on D_2, resulting in a significant reduction in the level of the D_2 performance when compared to D_1). Each test measure showed a significant difference on the Do-D_2 day pair comparison, however.[48] The results of the significant day pair comparisons will now be discussed. Tests 2, 3, 5, 6, and 7 will be considered first, followed by a discussion of test 4.

The significant difference in performance between Do and D_1 and Do and D_2 for Digit Symbol, Speech Sounds Perception, Grooved Pegboard dominant time in, Grooved Pegboard non-dominant time in and Grooved Pegboard dominant time out do not appear to be due to a significant change in serum levels.[49] A consideration of Tables 11 and 12 con-

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[48]The "nullification" and "practice effect" hypotheses will be presented shortly, to account for the D_1-D_2 and Do-D_2 day pair comparison results.

[49]The evidence for changes in cognitive and sensory-motor test performance being due to changes in the discomfort index over Do, D_1 and D_2 is also minimal. Spearman correlation of the discomfort index with each cognitive and sensory-motor measure on Do, D_1 and D_2 resulted in but two out of a possible 81 significant correlations ($p \leq .01$).

firms this. Both the number and consistency of significant correlations between serum levels and tests 2, 5, 6, 7 in Table 11 is small. In Table 12 no significant difference score correlations are seen on the critical Do-D_1 comparison. The change in serum levels and test scores was generally sufficiently large that, if significant correlations were present, they would have been observed on statistical analysis.

The significant difference in performance between Do and D_1 on Digit Symbol, and Grooved Pegboard (dominant time in, non-dominant time in, dominant time out) will now be considered. A careful consideration of the mean test scores in Table 7 for the above tests, shows that subjects continued to improve on each test administration (Do, D_1 and D_2). The improvement on test scores for Grooved Pegboard was most probably due to the dialysis patients ability to implement a strategy which successfully overcame the effects of peripheral neuropathy, especially numbness. As one subject stated, "It took me a long time to learn how to do this test". This suggests that an even longer practice trial, than was provided, was necessary for subjects to reach a stable level of responding. Despite significant improvements from Do-D_1 and Do-D_2 for Grooved Pegboard (dominant time in and non-dominant time in) performances on D_1 and D_2 were still in the impaired range.

Significant differences between Do-D_1, and Do-D_2, for Digit Symbol also appear to be due to a practice effect. As noted previously, subjects had difficulty both switching set and utilizing memory for purposes of symbol association. By D_1, subjects seemed to have reached a stable threshold of responding. While they continued to improve on D_2, differences between D_1 and D_2 were not significant. Even with

significant improvements from Do - D_1 and Do - D_2, performances on D_1 and D_2 were still barely within the normal range on the Digit Symbol Test. Significant differences on Speech Sounds Perception will be considered below.

The question of why no significant regression occurred on the D_1-D_2 day pair comparison, when significant differences occurred between Do-D_1, and Do-D_2, on tests 2, 3, 5, 6, and 7, must be considered. Two hypotheses will be offerred. The first is termed the "nullification" hypothesis and the second the "practice effect" hypothesis. The nullification hypothesis will be considered first.

It conceivably could be argued that there would have been a regression in performance from D_1 to D_2 (due to the increasing buildup of toxic renal metabolites) had there been no practice effects. Such an argument would conclude that the theoretical regression on D_2, due to the increasing buildup of toxins, was nullified by a practice effect, and therefore was not statistically obvious. This argument deserves serious consideration.

In order for the nullification hypothesis to be credible, it must be demonstrated that a decrease in the levels of toxic renal metabolites was significantly correlated with an improvement in performance levels on psychological testing. In other words, if performance levels should decrease due to a buildup of toxic renal metabolites (from D_1 to D_2), then performance levels should improve due to a reduction in the levels of toxic renal metabolites (from Do to D_1). Evidence that a reduction in the levels of toxic renal metabolites was significantly correlated

with an improvement in test performance is lacking (as previously demonstrated). Since the significant decrease in the levels of toxic renal metabolites was not significantly correlated, on a consistent basis, with a significant improvement in performance, then it cannot be credibly argued that a significant increase in toxic renal metabolites caused a decline in performance. Thus, the nullification hypothesis fails to be supported.

A consideration of the "practice effect" hypothesis follows next. This hypothesis presumes that effects on performance, due to changes in serum levels, were minimal or non-existent, a presumption which was supported above. The practice effect hypothesis argues that the reason there was no significant difference between D_1 and D_2 (despite significant differences between Do and D_1 and Do and D_2), was that after completing the D_1 testing (tests 2, 3, 5, 6, and 7), subjects had achieved a relatively stable level of performance. Although they continued to improve on D_2, it was not a significant improvement. In other words, the assumption that the practice period on Do would be sufficient to eliminate practice effects was mistaken. It was not until after the D_1 performance that stable levels of performance were finally achieved. Thus, when the D_1-D_2 day pair comparison was calculated, no significant differences were found. When, however, Do was compared to D_2, a significant difference was naturally observed since if the Do-D_1 comparison was significant, the Do-D_2 comparison must also have been (since D_2 was greater than D_1).

The practice effect hypothesis appears to be the most reasonable

explanation for the absence of a significant regression between D_1 and D_2 for test 2, 3, 5, 6, 7. The nature of Digit Symbol and Grooved Pegboard (dominant time in, non-dominant time in and dominant time out), along with the specific difficulties that dialysis patients encountered on these tasks (discussed previously), support this conclusion. As noted previously, the statistically significant differences between mean scores D_0-D_1 and D_0-D_2 on the Speech Sounds Perception Test does not appear to be clinically significant. (the differences between scores on D_0-D_1 and D_0-D_2 amounted to but one test item.) It is quite possible that given the novel nature of this task, a slight practice effect occurred on the second test administration (D_1), causing the significant improvement from D_0 to D_1. (Although the score on D_2 was not significantly different from D_1 the fact that the score on D_2 was larger than the score on D_1 accounts for the significant difference between the mean scores on D_0 and D_2.)

Based upon the nature of the Color Naming Test it is unlikely that the significant difference between D_0 and D_1 was due to a practice effect. (The practice trials on this test would appear to be sufficient to allow subjects to achieve a stable level of responding.) It is also unlikely, however, that the difference was due to changes in serum levels.[49] This conclusion is supported by the data in Tables 11 and 12. The significant difference score correlation in Table 12 (dimethylamine ph>10 (D_0-D_1) with Color Naming Time (D_0-D_1) most probably was due to chance factors as this correlation did not also occur on the D_1-D_2 comparison . Additionally the related amine, trimethylamine , was not significantly correlated with Color Namimg Time. No explanation for significant improvements on the D_0-D_1 and D_1-D_2 comparisons and the

absence of a significant regression on the D_1-D_2 comparison is immediately obvious. If the assumption that a practice effect was not responsible for significant improvements in test performance (from Do-D_1 and Do-D_2) is incorrect, then the practice effect hypothesis (explained above) would readily account for both the significant improvements and the absence of a significant regression (D_1-D_2). The presence of a practice effect appears unlikely, however.

In summary, changes in those serum chemistry variables monitored across Do, D_1, and D_2 do not appear to be responsible for significant changes in performance on Digit Symbol, Color Naming Time, Speech Sounds Perception, Grooved Pegboard dominant time in, Grooved Pegboard non-dominant time in and Grooved Pegboard dominant time out. Changes in serum chemistry did not significantly affect performance of tests 1-16 of Table 6: no significant differences across Do, D_1 and D_2 were found. The remaining five measures (Digit Span Forward, Color Namimg Error, Quick Test, Finger Tapping non-dominant and Trails A) were also unaffected by changes in serum chemistry, since with the exception of Trails A,[50] no significant difference in performance on the Do-D_1 and D_1-D_2 comparisons was observed.

Thus, when all twenty-seven test measures are taken into account, changes in those serum chemistry levels monitored over Do, D_1 and D_2

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[50] Trailmaking A was not a legitimate measure for day pair comparisons, since the same form was used on Do, D_1 and D_2. Of note here, however, is the fact that despite repeated use of the same form of Trails A, performance on the third trial (D_2) was within the mildly impaired range.

appear to have had a minimal effect on test performance.[51] The same may be said of the discomfort index. Spearman correlation of the discomfort index with each cognitive and sensory-motor measure on Do, D_1 and D_2, resulted in but two significant correlations (below that which would be expected by chance.) Finally, the practice effect hypothesis appears to explain fluctuations in performance for Digit Symbol, Grooved Pegboard and Speech Sounds Perception, while fluctuations in performance for Color Naming Time remain unexplained. The prediction that performance on Finger Tapping would significantly improve after hemodialysis and then evidence a significant regression prior to the next dialysis, was unsupported.

A comparison of the results of the present study with those of prior research, points to several discrepancies. Spehr et al. (1977), in administering cognitive and sensory-motor tests to long term maintenance hemodialysis patients, found that after hemodialysis there was a significant improvement in maximal tapping speed (repetivive pressing of a button) and visual discrimination and memory (assessed by tachistoscopic presentation of numbers with variable presentation time). Visual discrimination and memory improved after hemodialysis, parallel to the decrease of BUN, potassium and creatinine. Ginn (1973), Teschan et al. (1974) and Ginn (1975) reported that regardless of the absolute value

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[51]Had subjects been tested immediately post-dialysis, changes in serum chemistry may have caused significant changes in test performance. The author, however, chose to wait a period of 20 hours to allow for possible disequilibrium, fatigue factors, etc. to wear off.

of the pre-dialysis (Do) level of performance on the Auditory Short Term Memory Test, subjects showed a temporary improvement in level of performance ($p < .01$) on the morning following dialysis (D_1), and a regression to a lower level of performance just prior to the next dialysis ($p < .01$).

For purposes of comparison, maximal repetitive pressing of a button will be equated with Finger Tapping. Within the battery employed in the present study no clear equivalents exist for the Visual Discrimination and Memory Task. For purposes of comparison with the Auditory Short Term Memory Test, Speech Sounds Perception and Seashore Rhythm will be used as very rough equivalents, since both have an auditory memory component. (Seashore Rhythm requires more of a memory component than does Speach Sounds Perception.) The present research does not support a significant improvement in maximal tapping speed when pre and post-dialysis performances are compared. When Speech Sounds Perception and Seashore Rhythm are compared to the results of the Auditory Short Term Memory Test, only partial support is present. While there were no significant differences across Do, D_1 and D_2 for Seashore Rhythm, significant differences pre and post-dialysis did occur on the Speech Sounds Perception Test.[52] No regression on D_1-D_2 was seen,

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[52]This finding is of much less significance than would be the case if Seashore Rhythm had shown a significant difference between Do and D_2 (since Seashore Rhythm is a much closer equivalent to the Auditory Short Term Memory Test than is Speech Sounds Perception.) Additionally, while

however. The authors (Ginn, Teschan et al.) concluded that changes in levels of performance for the Auditory Short Term Memory Test, across Do, D_1 and D_2, were due to changes in serum chemistry. No evidence, in support of this conclusion, was found for any of the auditory tests utilized in the present study.

Thus, the aspect of the present research concerning the effects of hemodialysis on cognitive and sensory-motor functioning, lends little or no support to prior research findings. Cross study comparisons remain quite unexacting, however, since one cannot be certain that the discrepant results among studies do not derive from differring, but unknown methodological factors. It is for this reason that a very detailed specification of sample characteristics, methodological procedures, etc., so often neglected in research publications, is absolutely essential in helping the researcher determine the origin of the variance in discrepant results. Individual exacting replication studies would be helpful in determining the validity of prior research investigations. Although such studies would not account for cross study differences, clearly defined findings, which withstand the test of replication, would become part of an expanding knowledge base.

Suggestions For Further Research

Many questions pertaining to the cognitive and sensory-motor

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[52]Cont'd..the difference between ($Do-D_1$) and ($Do-D_2$) was statistically significant, its clinical significance is questionable.

functioning of the chronic hemodialysis patient remain unanswered. The following research proposals are offerred to help attain more clarity in areas in which there are discrepant results and to make inroads into those areas which are as yet unexplored.

Research methodologies utilizing longitudinal designs have strong potential in helping to resolve questions concerning the effects of hemodialysis on cognitive and sensory-motor functioning. The most important single factor in such longitudinal research is the use of a comprehensive test battery, sensitive to cerebral impairment. The use of such neuropsychological tests is compromised in studies utilizing a classical longitudinal design, since only test instruments amenable to repeated administrations with minimal practice effects, or those with several alternate forms, may be employed. The classical longitudinal design does, however, have certain advantages over the cross sectional design. The former does not require that different treatment groups be formed. This eliminates a source of possible unwanted variance, which may derive from between-group differences which are not well controlled for.

In utilizing the classical longitudinal design to assess cognitive and sensory-motor functioning, prior to commencing dialysis and again at various points thereafter[53] (e.g., 0, 6, 12 months), it is imper-

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[53]This method was employed by Hagberg (1974). (See p. 21.) His results were compromised, however, through the use of a psychological test battery lacking in the comprehensiveness necessary to properly assess cerebral impairment.

ative that 1) the same battery be utilized at each test administration and 2) that the time of both post-dialysis test sessions (6 and 12 months) be the same. (Subjects might be tested midweek, 20 hours post-dialysis at both the 6 and 12 month test administrations. This latter requirement increases the likelihood of obtaining similar serum chemistry profiles, thereby decreasing a potential source of unwanted variance.) Performances at 0, 6, and 12 months would be compared both for significant differences and for levels of impairment. Practice effects would be minimized through the use of alternate test forms and by the 6 month time span between test sessions. A subjective rating scale (similar to that employed in the present study) would be utilized to identify changes in self perception of psychological and medical states, across test administrations. Analyses, similar to those performed in the present study, would be employed to determine if possible changes in perceived psychological and medical states were a significant source of variance. Parallel to each psychological test session (0, 6, 12 months) an electroencephalograph recording, nerve conduction evaluation and serum chemistry profile would be administered and correlated with the results of cognitive and sensory-motor test performance.

An alternative to testing patients serially at 0, 6 and 12 months post-dialysis lies in the use of a cross sectional tvpe design. In this design, several treatment groups, each differing in the number of months on dialysis (e.g., 0, 3, 6, 12, 18 months post-dialysis), would be administered a battery assessing cognitive and sensory-motor

functioning. Comparisons across groups would provide data relating the effects of time on dialysis and cognitive and sensory-motor functioning. Limitations in the number of treatment groups would derive from subject availability. Such a design facilitates the rapid collection of a large amount of data. The chief difficulty with the cross sectional design is assuring that treatment groups differ only in the time on dialysis factor. This may be achieved through several methods: 1) random sampling, 2) subject by subject matching across groups, and/or 3) covariance analysis. Control of serum levels across groups could be achieved through the use of kinetic modelling.[54] One of the more attractive aspects of the cross sectional design is the freedom of test selection, so restricted in the present study. Instruments such as the Category Test (Reitan & Davison, 1974) could be freely employed without concern for possible practice effects.

The comparative effectiveness of small (e.g., BUN, creatinine) vs. middle (as measured by e.g., inulin) molecular clearances on improving the cognitive and sensory-motor functioning of undialyzed toxically uremic adults, about to begin dialysis, is an important area for research investigation.[55] The following protocol is suggested.

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[54]Kinetic modelling is a computer assisted method for keeping a patient's serum levels within a specified range through the manipulation of various parameters associated with dialysis.

[55]The reader is referred to p. 9 for a review of the middle molecule controversy.

New dialysis patients would be randomly assigned to one of two dialyzer groups: 1) a dialyzer with a high clearance of small molecules and a low clearance of middle molecules, and 2) a dialyzer with a similiarly high clearance of small molecules and a high clearance of middle molecules. (The exact specifications of the dialyzers chosen would depend upon product availability.) Each group would be administered a repeatable neuropsychological test battery at 0, 3, and 6 months post-dialysis. The effectiveness of each dialyzer in improving cognitive and sensory-motor functioning would be assessed. The effect of different clearance properties on electroencephalograph and nerve conduction evaluations would be assessed through the serial administration of these tests at the same time of the 0, 3, and 6 month neuropsychological evaluation sessions.

As noted previously, it is possible that the results of the present research project (regarding fluctuations in performance across D_0, D_1 and D_2) were an artifact of the time selected for the D_1 test administration (20 hours post-dialysis). Perhaps if another D_1 time was chosen, results might have been different. To investigate possible significant differences in results due solely to the time of the D_1 test administration, 3-5 experimental groups might be formed. Each group would have a different D_1 test administration time (e.g. 5, 10, 15, 20 hours post-dialysis). This research proposal is essentially a replication of this dissertation research project, with more than one treatment group employed. All treatment groups would be equated on all but the D_1 test administration time, utilizing available statistical procedures (discussed previously). The equating of groups is done to insure that the dif-

ferences among groups derive from the different D_1 times, as opposed to other sources of unwanted variance. Comparisons across Do, D_1 and D_2, within each group, would provide information regarding significant differences in performance (Do-D_1, D_1-D_2, Do-D_2). After each treatment group is analyzed separately, treatment groups would then be compared for purposes of ascertaining which D_1 time (if any) produced the greatest number of significant changes in cognitive and sensory-motor functioning across Do, D_1 and D_2.

The majority of research studies which correlate various serum chemistry measures with cognitive and sensory-motor test performance, utilize the same serum measures (e.g. an electrolyte profile). Correlating other serum variables (e.g. osmolality, oxygen uptake) with cognitive and sensory-motor test performance, might produce results which broaden our understanding of the interface between serum chemistry and cognitive and sensory-motor functioning, while also prompting new ideas for further research.

Finally, as a follow-up to the present research project, a further investigation of the pronounced impairment in switching set, seen in the dialysis patients tested, is suggested. This could be accomplished through the utilization of a series of tests, each of which requires slightly different skills in switching set as a prerequisite for successful test performance. This battery might include the following test instruments: Category Test (Reitan and Davison, 1974), Color Form Sorting Test, Object Sorting Test (Goldstein & Sheerer, 1941), Wisconsin Card Sorting Test (Berg, 1948), Kasanin-Hanfmann Concept Formation Test (Hanfman, 1953),

and the Mirror Test (Hagberg, 1974). These instruments might also be included as part of the test battery utilized in any of the research protocols suggested above not requiring repeatable test instruments. The results of this study would further broaden our understanding of the difficulties dialysis patients encounter on tasks requiring proficiency in the ability to switch set.

CHAPTER V

SUMMARY AND CONCLUSIONS

The purpose of this study was to answer three questions: 1) How does the cognitive and sensory-motor functioning of the long term adult hemodialysis patient compare with available norms for a normal sample? 2) What patterns of strengths and/or weaknesses may be found in the cognitive and sensory-motor functioning of the long term adult dialysis patient? and 3) Do significant changes in cognitive and sensory-motor functioning occur when pre, post and pre-dialysis performances are compared? If so, do specific serum measures seem to be correlated with changes in cognitive and sensory-motor performance when test results across repeated test administrations are compared?

To answer these questions 14 male and 6 female adult chronic renal patients, stabilized on hemodialysis for at least 10 months, were administered a repeatable battery of cognitive and sensory-motor tests just prior to their midweek dialysis (D_0), approximately 20 hours later (D_1) and again just prior to their end of the week dialysis (D_2). At each test session subjects were also administered a subjective rating scale. This scale was designed to measure changes in self perceived psychological and medical states across D_0, D_1 and D_2, for purposes of identifying possible sources of unwanted variance which might have affected cognitive and sensory-motor functioning. Finally, serum samples were drawn at each test session to determine levels of BUN, creatinine, sodium, potassium, chloride, carbon dioxide, calcium, phosphate, dimethylamine (ph 7-8, ph$>$ 10) and trimethylamine (ph 7-8, ph$>$ 10).

With regard to levels of performance, dialysis patients scored within the normal range (as compared to a normal sample) on tasks assessing verbal comprehension, abstraction, short term rote memory (auditory), mental manipulation of symbols (when no switching of set was required), sustained attention, concentration, auditory discrimination, visual-motor planning (when no switching of set was required), visual-motor reaction time, visual recognition and interpretation of pictorially presented objects and social cues, grip strength (males), sustained motor speed (male dominant) and the maximum repetitive performance of an elementary language function (speeded color identification). Significant improvements in performance, from the mildly impaired to the low end of the normal range, occurred on the Digit Symbol and Speech Sounds Perception Tests. These improvements appear to have been due to practice effects. Finally, performances were clearly impaired in the following areas: speeded visual-motor coordination (Grooved Pegboard), grip strength (females), visual search skills, visual-motor planning (involving the ability to switch set) and visual memory.

Impairments in speeded visual-motor coordination and strength of grip most probably were due to the effects of peripheral neuropathy. The most pronounced impairment noted, however, was in the ability to successfully execute a plan involving the switching of set. The level of impairment in this area was severe. While not definitively suggestive of cerebral impairment, this pronounced dysfunction has been associated with mild cerebral impairment of the anterior region.

Although dialysis patients were impaired in the areas noted above, they performed well in a wide variety of other areas (noted previously). Considering the well known finding that undialyzed toxically uremic adults evidence oftentimes severe impairment in their cognitive and sensory-motor functioning, the beneficial effects of dialysis clearly underscored when dialysis patients' overall level of performance in the present study are considered.

With regard to question three, out of 27 cognitive and sensory-motor measures, significant fluctuations, pre and post-dialysis (D_0-D_1) were evidenced on but six. Fluctuations on five of these measures were accounted for by practice effects, while fluctuations on the remaining measure (Color Namimg) were unaccounted for. Significant daily changes in serum levels of small and middle molecule toxic renal metabolites occurred over D_0, D_1 and D_2. The number of significant correlations between each serum measure and every cognitive and sensory-motor test was below chance, as was the number of significant correlations between the discomfort index and each cognitive and sensory-motor test measure. Thus, despite significant daily changes in the levels of toxic metabolites, the cognitive and sensory-motor functioning of those subjects remained remarkably stable. This finding is at odds with prior research investigations, where fluctuations in certain cognitive and sensory-motor areas, hypothesized as being due to fluctuations in serum chemistry levels , were identified. It remains quite difficult to acertain the origin of these discrepancies. Research suggestions, for purposes of resolving these differences and expanding our knowledge base were offerred.

In the past psychologists have played a major role in helping

dialysis patients cope with the emotional sequalae of chronic renal failure. Through the use of their unique skills psychologists are now in the special position of contributing to advances in hemodialysis technology, through assessing how new dialysis equipment and procedures affect the patient's cognitive and sensory-motor functioning. Considering the complexities of dialysis technology, this significant source of input must be considered as a welcome addition to the field.

APPENDICES

APPENDIX A

RENAL STRUCTURE AND FUNCTION

Appendix A: Renal Structure and Function. Berkow, R. (Ed.), The Merck Manual of Diagnosis and Therapy. Thirteenth Edition, Merck, Sharp and Dohme Research Laboratory, Rahway, N.J., 1977, Pgs. 654-664.

1. RENAL STRUCTURE AND FUNCTION

The kidneys control the volume, composition, and pressure of body fluids by regulating the excretion of water and solutes. They also influence red cell production and blood pressure by hormonal mechanisms. Urine is formed in the kidneys as an aqueous solution containing metabolic waste products, foreign substances, and water-soluble constituents of the body in quantities depending upon homeostatic needs.

Anatomy

The kidneys are bilateral, retroperitoneal structures, each consisting of an outer cortex and an inner medulla. The medulla is arranged into several cone-shaped or pyramidal projections separated from each other by sections of cortex called renal columns. The bases of the pyramids face the cortex of the kidney while the apices (papillae) point toward the hilus and project into the renal pelvis (FIG. 6-1). The cortex contains glomeruli and tubules; the medulla, tubules only.

The kidneys possess numerous blood vessels and because of their low vascular resistance receive approximately 1200 ml of blood or 25% of the cardiac output each minute.

The major resistance to blood flow occurs in the glomerular capillary bed and is produced by a relatively high resistance in the efferent arterioles. However, changes in renal arterial pressure produce proportional variations in the afferent arteriolar resistance, which tends to preserve a constant renal blood flow (RBF) and glomerular capillary pressure; i.e., autoregulation. In addition to autoregulation, the renal circulation is controlled by extrinsic factors such as neurogenic (sympathetic) and hormonal (epinephrine, norepinephrine, and angiotensin) regulators.

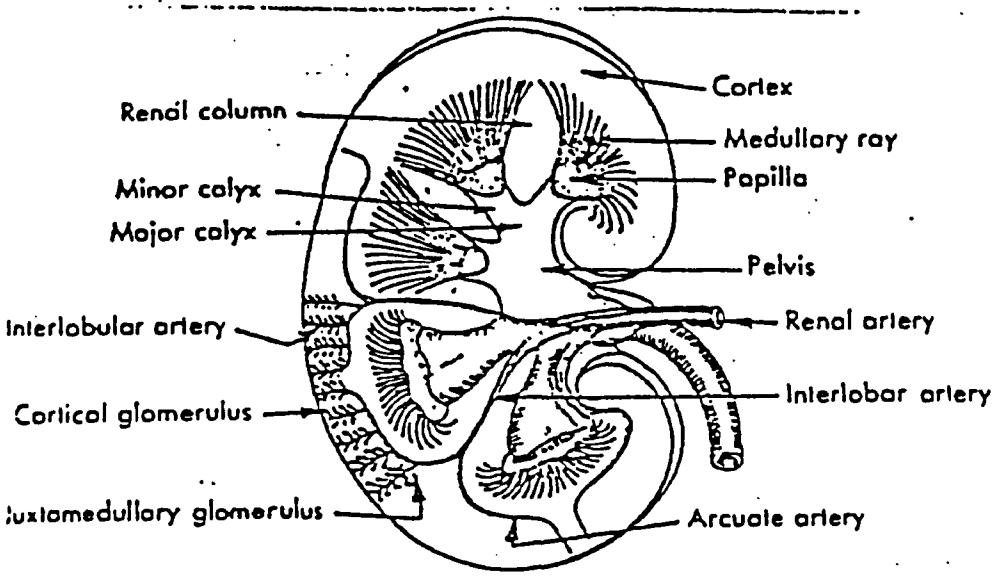


FIG. 6-1. Sagittal section of the kidney. The upper half depicts the overall gross anatomic arrangement. The lower half demonstrates the arterial supply. (From S. Papper, Clinical Nephrology. Copyright 1971 by Little, Brown and Company. Used with permission of Little, Brown and Company and the author.)

The Nephron

The basic functional unit of the kidney is the nephron, a long tubular structure made up of successive segments of diverse structure and transport functions. It includes (1) a renal corpuscle (Bowman's capsule and the glomerulus, a tuft of capillaries), (2) a proximal tubule (convoluted and straight portion), (3) a hairpin loop (Henle's loop), (4) a distal tubule (straight portion, macula densa, and convoluted portion), and (5) a collecting duct system. There are approximately one million nephrons in each human kidney; 85% are cortical nephrons with short loops of Henle, and 15% are juxtamedullary nephrons with glomeruli near the cortical medullary junction and with long, thin, looping segments (FIG. 6-2).

Glomerular Filtration

The glomerulus acts as an ultrafilter, allowing passage of water, electrolytes, and small organic molecules such as glucose, but not blood cells and large protein molecules. The ultrafiltrate produced by the glomeruli of both kidneys amounts to about 70 ml/min/sq m or 150 L/day/sq m; this rate is termed the glomerular filtration rate (GFR). About 99% of the glomerular filtrate is resorbed during passage through the renal tubules, with most of the resorption taking place in the proximal tubules.

The Concept of "Clearance" and the Measurement of GFR

A principal function of the kidney is to remove or "clear" various solutes from the blood which are not essential to the body, and to conserve those that the body requires. A solute is never totally removed from the blood in any one passage through the kidneys; rather, a portion is removed during each sweep of the blood through the renal system. Clearance may be defined as *the volume of plasma which is completely cleared of a solute in a unit of time* and is usually expressed in ml/min.

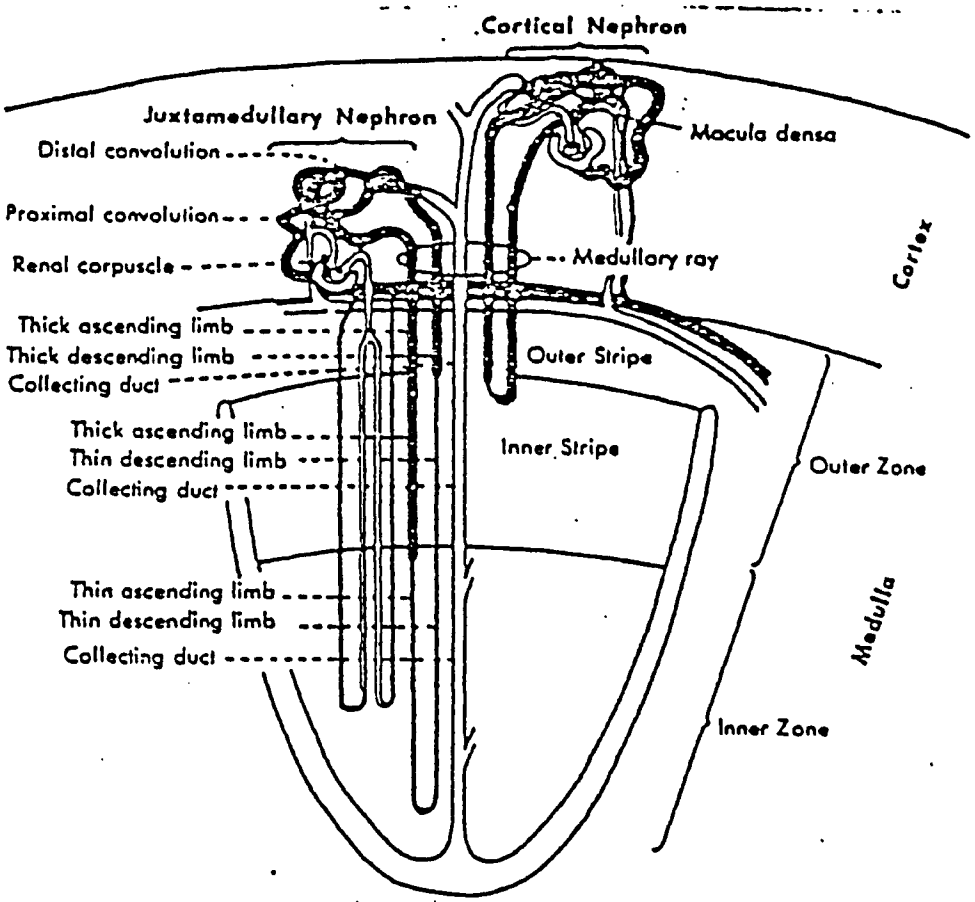


FIG. 6-2. Position of cortico- and juxtamedullary nephrons in the kidney. (From Histology, ed. 3, by R. O. Greep and L. Weiss. Copyright 1973 by McGraw-Hill, Inc. Used with permission of McGraw-Hill Book Company.)

Stated another way, *the renal clearance of a substance represents the volume of blood that would have to pass through the nephrons within a given time period to provide the amount of that substance in the urine.* Substances which are rapidly eliminated have a high clearance; those eliminated slowly, a low clearance.

The following equations illustrate the relationships involved in clearance calculations. "X" is considered as a substance which is cleared completely in one passage and can be used to measure renal plasma clearance. The symbolic relationships are:

U_x = concentration of "x" in urine.
P_x = concentration of "x" in plasma.
V = volume of urine excreted/min.
C_x = renal plasma clearance of "x."
U_xV = rate of excretion of "x."
C_xP_x = quantity of "x" removed or "cleared" by kidneys.

When the concentration of substance "x" in the body fluids is in a steady state, the amount leaving the kidneys equals that cleared from the blood. Symbolically, this may be stated as:

$$U_x V = C_x P_x$$

or

$$C_x = \frac{U_x V}{P_x}$$

Thus, from the urinary excretion rate and the plasma concentration of "x," one can compute its renal clearance. For example, if 550 mg/min of "x" are being excreted, the same amount has entered the nephrons. If the plasma concentration during these steady-state conditions is 1 mg/ml, then 550 ml/min of plasma were virtually cleared of this substance by the kidney:

$$C_x = \frac{U_x V}{P_x} = \frac{550 \text{ mg/min}}{1 \text{ mg/ml}} = 550 \text{ ml/min}$$

If a substance does not undergo tubular transport after passing through the glomerulus—i.e., if it is neither reabsorbed nor secreted within the renal tubule—then its clearance will be a measure of GFR. Because the measurement of GFR is useful in understanding normal function and in treatment of patients with renal disease, it is desirable to have a convenient and quantitative method of its estimation. A substance which is ideally suited for such measurements is inulin. It is a fructose polymer with an average size of about 5000 daltons. When given IV it is freely filtered by the glomeruli and passes through the renal tubules undisturbed. The normal GFR for average adults is about 125 ml/min.

A comparison of the renal clearance of any solute with that of inulin will give information concerning transport of that solute by the renal tubules. For example, a substance which (like inulin) is not protein-bound and is freely filtrable, but which has a lower clearance than inulin, has undergone net tubular resorption; a substance with a clearance greater than inulin, in addition to being filtered by the glomerulus, has had portions secreted by tubular cells. Certain organic substances like sodium p-aminohippurate (PAH) are rapidly secreted by tubular cells and are almost entirely removed from the blood perfusing the kidneys in a single circulation. Thus, these substances are useful in determinations of effective renal plasma flow (ERPF).

The clearance of endogenous creatinine is often used clinically as an estimate of GFR. Unfortunately, since some creatinine is secreted by the tubules, it does not give a true measure of GFR. Despite this, the creatinine clearance is convenient and adequate for most clinical purposes. If the urinary excretion of creatinine is constant, then the creatinine clearance and its plasma concentration are inversely proportional.

$$C_{creat}\, P_{creat} = U_{creat} V$$

creatinine removed from plasma = creatinine excreted in urine

or

$$C_{creat} = \frac{U_{creat} V}{P_{creat}}$$

One can thus determine changes in renal function (GFR estimates) through single measurements of plasma creatinine. For example, a patient with an initial creatinine clearance of 100 ml/min and a creatinine plasma concentration of

1 mg/100 ml (0.01 mg/ml) has a urinary excretion rate of creatinine of 1 mg/min or 1.4 Gm/day. If the serum creatinine concentration rises to 5 mg/100 ml (0.05 mg/ml) and the total urinary excretion of creatinine remains constant, then the creatinine clearance is 1/5 the previous value or 20 ml/min.

In the first instance:

$$C_{crea} = \frac{U_{crea}V}{P_{crea}} = \frac{1 \text{ mg/min}}{1 \text{ mg/dl}} = 100 \text{ ml/min}$$

In the second instance:

$$C_{crea} = \frac{U_{crea}V}{P_{crea}} = \frac{1 \text{ mg/min}}{5 \text{ mg/dl}} = 20 \text{ ml/min}$$

Thus, one could assume that the number of functioning nephrons in the kidneys has significantly decreased. Similar relationships would exist with the blood concentration of urea.

Tubular Function

Transport or movement of solutes and water across tubular cells is one of the principal activities of the renal tubules. Transport is termed resorption when it proceeds from the tubular lumen to the interstitial fluid and secretion when it proceeds in the reverse direction. Many solutes are transported in both directions simultaneously, but one direction usually dominates and the resultant is termed net transport.

Transport is energy-dependent. Tubular transport is classified according to the energy source used in the transfer process: active transport is the movement of a substance against a gradient of electrical potential or chemical concentration; passive transport or diffusion is the migration of a substance across an electrochemical gradient.

The activity of the tubules may be appreciated by comparing the rates at which substances are filtered into the nephrons with the rates at which they are excreted in the urine (TABLE 6-1). The tubules are largely occupied with conservation of water and essential solutes and the elimination of certain waste products.

Fine adjustments of water and solute excretion take place in the distal convolutions and adjoining collecting ducts. Transport in the distal tubule differs from that in the proximal tubule in its capacity to resorb and secrete against large gradients. Furthermore, it is the only segment of the nephron which responds to both antidiuretic hormone (ADH) and aldosterone. ADH enhances water resorp-

TABLE 6-1. SUBSTANCES FILTERED THROUGH THE NEPHRONS AND THEIR RESORPTION

Substance	*Amount Filtered Daily**	*Amount in Urine Daily**	*Net Tubular Resorption**
Water	180 L	1.5 L	99%
Sodium	26,000 mEq	150 mEq	99%
Potassium	810 mEq	100 mEq	88%
Glucose	1000 mM	nil	100%
Amino acids	65 Gm	2 Gm	98%
Urea	1280 mM	500 mM	60%

* These values are approximate.

tion, while aldosterone enhances the transport capacity for sodium resorption with reciprocal potassium and hydrogen ion secretion.

Tubular Resorption

Glucose resorption illustrates an active transport-limited system wherein, at normal plasma glucose levels and GFR, the glucose is completely resorbed and its clearance or excretion is nil. The mechanisms involved permit transporting a fixed amount of glucose in a unit of time (Transport maximum or T_m) across the tubular cells. If the filtered glucose load (plasma glucose x GFR) exceeds the T_m, glucose begins to appear in the urine. The higher the plasma glucose concentration, the greater the amount of glucose filtered, compared to that resorbed. The glucose clearance approaches the GFR as the plasma concentrations increase.

Although glucose is the best prototype for illustration, amino acids and other inorganic and organic compounds undergo transport-limited resorption. Phosphate is unique among transport-limited substances in having its resorption capacity modulated by parathyroid hormone.

Urea resorption: Urea, like water, is resorbed passively throughout the nephron. Because of passive resorption, the excretion of urea is variable and depends upon urine concentration and flow. About one third of filtered urea is resorbed in man when the urine is copious and dilute, while 80% may be resorbed during dehydration when urine flow is low and the urine concentrated. The variability in the renal handling of urea plus the influence of diet and catabolism make the blood urea nitrogen (BUN) *unsuitable* as a single measure of renal function.

Sodium (Na) resorption: After passage through the proximal tubules, resorption of Na and water causes a 20 to 40% reduction in the volume of glomerular filtrate. Since osmotic gradients between peritubular capillaries and proximal tubular fluid are not observed, both remain isosmotic with arterial plasma throughout proximal tubular resorption. Na and its associated anions (chloride and bicarbonate) account for most of the osmotic activity of water within the proximal tubules. It follows that Na and water are simultaneously resorbed and that their ratio is set by plasma osmolality. Present evidence indicates that water resorption is passive and coupled to active Na resorption.

Unlike threshold-limited transport, proximal tubular resorption of Na is not saturable but does appear to exhibit gradient-limited characteristics. This is evident when large quantities of nonresorbed solutes (e.g., glucose or mannitol) are present in the proximal tubular lumen. The presence of nonresorbable solutes, such as mannitol, within the lumen of the renal tubules decreases the resorption of Na and water therein, producing a large volume of urine. This obligate retention of Na and water in the presence of large amounts of unresorbed solutes is the basic mechanism of osmotic diuresis.

Na transport in the distal tubule and collecting duct differs from that in the proximal tubule in the former's capacity to resorb Na against large gradients and the influence of aldosterone in enhancing the transport capacity. The distal nephron serves as the final arbiter of Na elimination.

The interrelationship between the filtration and resorption of Na is a central factor in the renal regulation of Na. Under a variety of circumstances, the fraction of filtered Na resorbed in the proximal segment is relatively constant despite acute changes in GFR, a concept termed glomerulotubular balance. This balance is neither perfect nor constant. If the GFR is chronically reduced, the resorption of Na will decrease proportionately more than the decrease in filtration so that Na excretion equals dietary intake. Thus, renal control of Na balance resides not in regulation of filtration but in tubular resorption of Na. Nonetheless, the contribution of acute changes in GFR cannot be ignored, as small changes can produce

relatively large variations in the absolute rate of Na excretion before adjustment in tubular resorption occurs.

The physiologic factors which bring about changes in the rate of tubular resorption of sodium are not well understood, but are influenced by certain extrarenal and intrarenal factors (FIG. 6-3). For a discussion of regulation of water and sodium homeostasis see §11, Ch. 6.

Tubular Secretion

Although tubular transport is mainly concerned with returning the bulk of the glomerular filtrate to the plasma, some plasma solutes are actively secreted into the tubular lumen and excreted. A renal clearance greater than GFR is evidence of tubular secretion. Exogenous organic bases such as thiamine or quinidine and organic acids such as PAH and penicillin are rapidly excreted once they enter the circulation. They are both filtered and actively secreted into the urine. Most organic acids compete with each other for secretion as do most organic bases (competition between acids and bases is rare). This explains why probenecid, an organic acid, interferes with the secretion of penicillin.

Secretory processes also exhibit transport maximums. Therefore, at high plasma concentrations, filtration may become the dominant mode of excretion. PAH is so avidly secreted that at plasma levels far below saturation it is almost completely cleared from the plasma in a single circulation through the kidney and has, therefore, been found useful in estimating renal blood flow.

Potassium (K) excretion: The usual adult daily diet contains 50 to 100 mEq of K. Small quantities of K are lost in the feces and perspiration, but the kidney is the dominant organ of K excretion and regulation. Studies of renal clearance have demonstrated that K excretion is not closely linked to the filtered load of K. For example, with severe renal insufficiency, the K excretory rate may exceed the quantity filtered by the glomeruli.

Since approximately 90% of the filtered K and 60 to 80% of tubular fluid is resorbed in the proximal tubule, K concentration in this fluid is lower than the plasma concentration. However, in the distal tubule the K concentration is considerably greater than in plasma, even on a low K intake. Thus, K undergoes net secretion, and renal conservation of K is relatively poor compared to Na reabsorption where distal tubular fluid to plasma Na concentration ratios can be below 0.01. Whereas urinary Na concentration may be nil with a marked stimulus for Na conservation, the urinary K concentration rarely is < 5 to 10 mEq/L even with severe and prolonged K deprivation. The factors affecting potassium secretion are listed in TABLE 6-2.

Hydrogen ion (proton) excretion: The net quantity of protons excreted by the kidney is small (50 to 100 mEq/day) compared to that excreted by the lungs via carbonic acid (15,000 mEq/day). Therefore, *disturbances in pulmonary function can result in acidosis within minutes, while several days are required to produce the same degree of change following cessation of renal function.* The renal regulation of acid-base balance is discussed under DISTURBANCES IN ACID-BASE METABOLISM in §11, Ch. 6.

Concentration and dilution of urine: Urine concentration is accomplished in the renal medulla via three anatomic structures which work in concert: (1) the loops of Henle acting as countercurrent multipliers, (2) the looping capillaries as countercurrent exchangers, and (3) the collecting ducts which traverse the kidney. Only the *juxtamedullary nephrons* are involved in the countercurrent operations that concentrate the urine. The other nephrons produce a dilute urine due to the unique characteristics of their tubular cells in the thick segment of the ascending limb where transport of sodium chloride (NaCl) occurs *without* passive diffusion of water, thus creating a hypotonic tubular fluid.

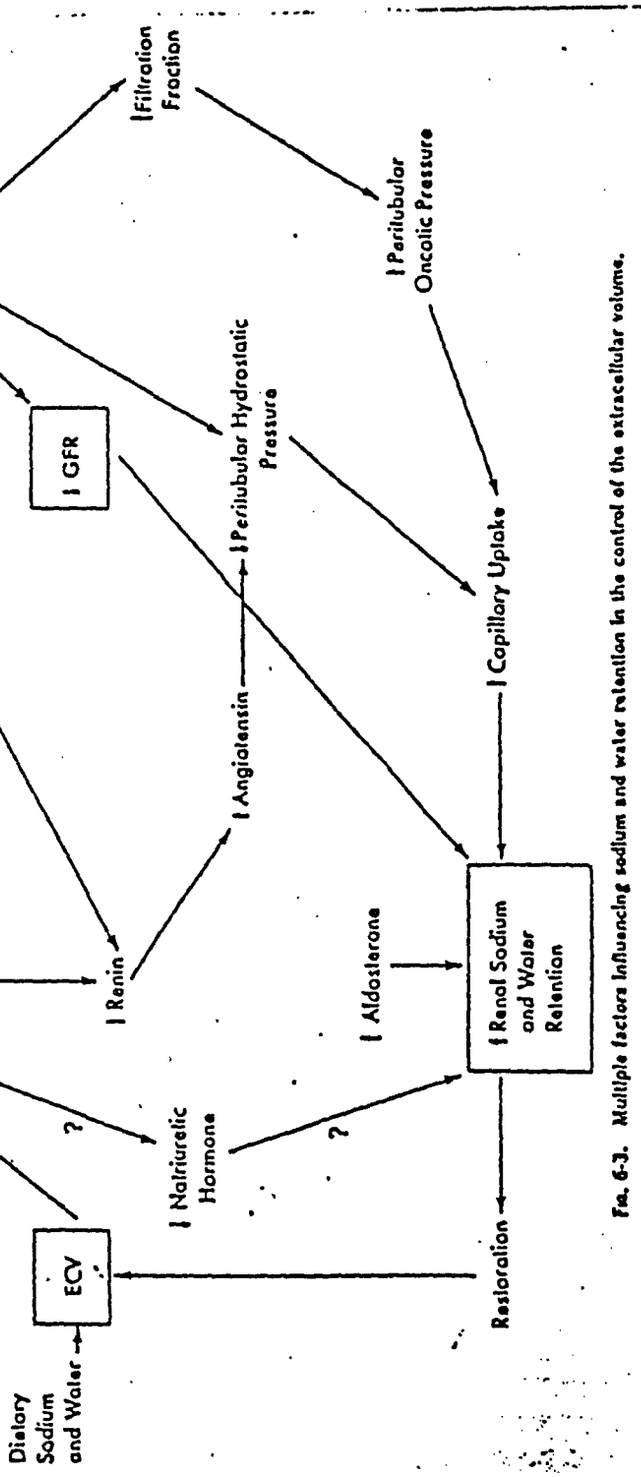


Fig. 6-3. Multiple factors influencing sodium and water retention in the control of the extracellular volume.

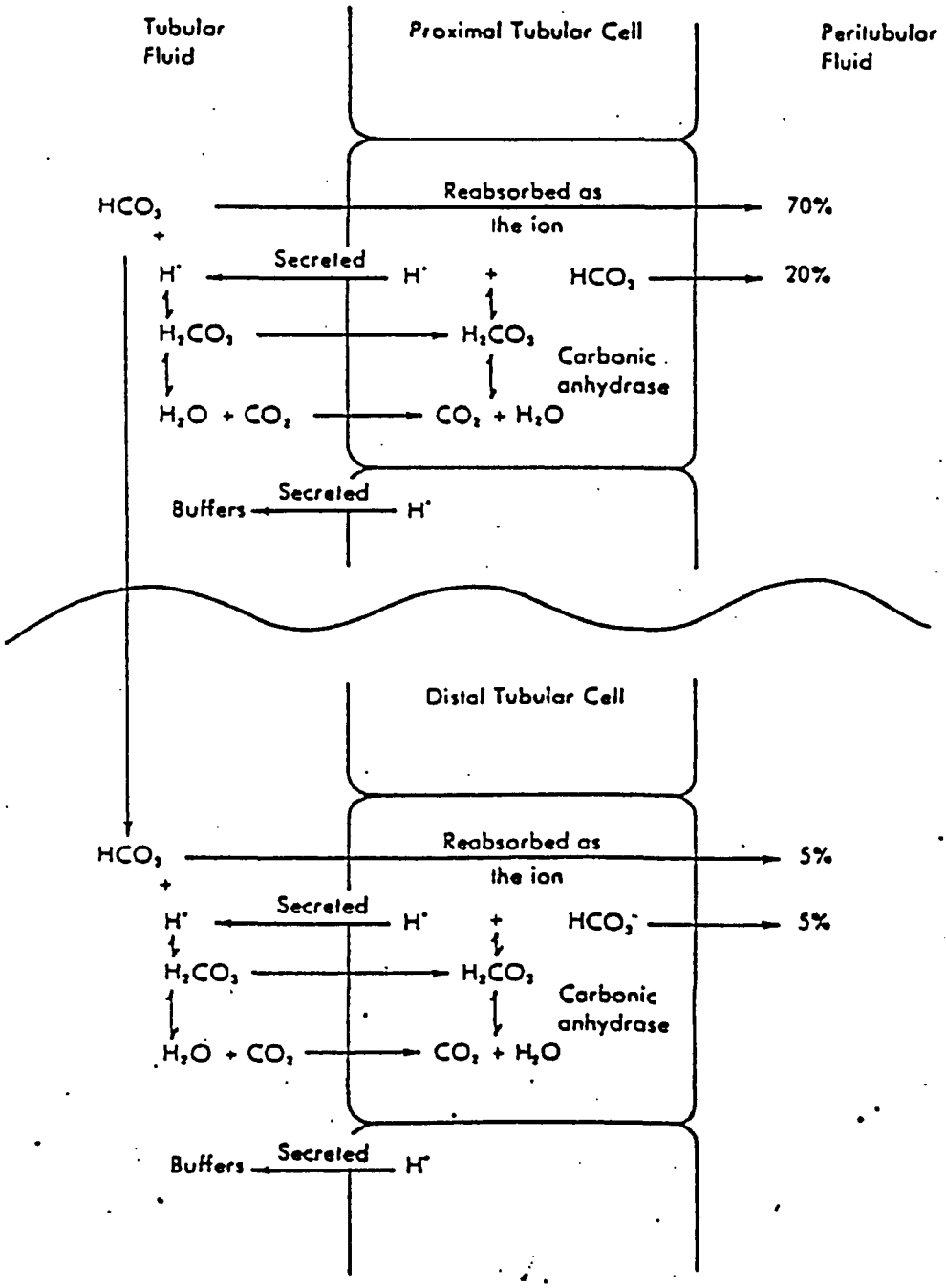


Fig. 6-5. Bicarbonate transport model.

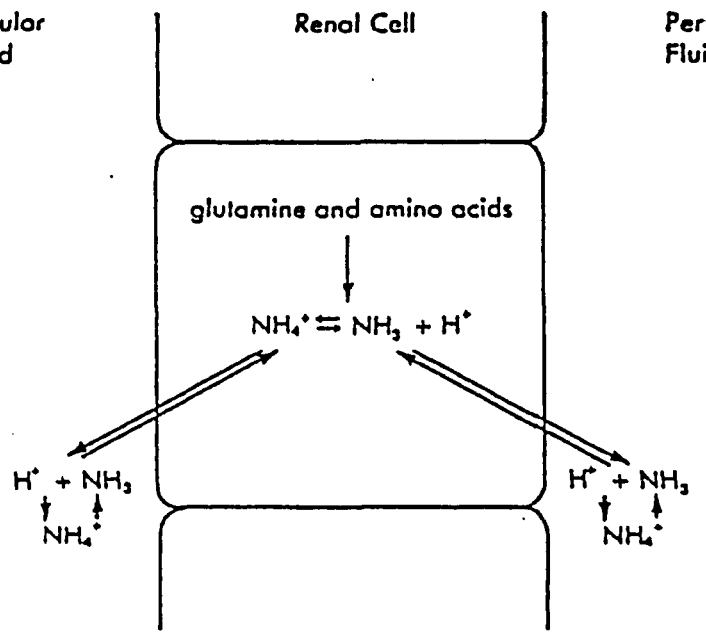


Fig. 6-6. Model of ammonium excretion. (From W. H. Chapman et al, The Urinary System. Copyright 1973 by W. B. Saunders Company. Used with permission of W. B. Saunders Company and the author.)

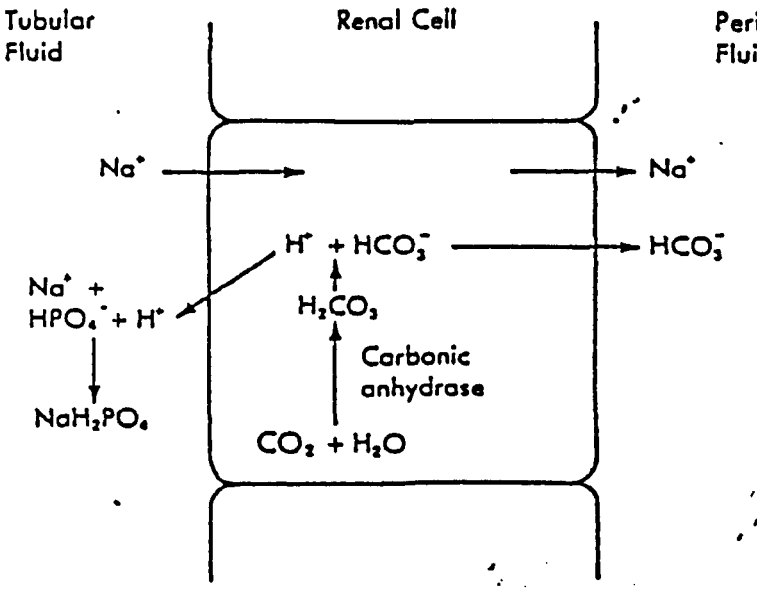


Fig. 6-7. Model of titratable acid excretion. (From W. H. Chapman et al, The Urinary System. Copyright 1973 by W. B. Saunders Company. Used with permission of W. B. Saunders Company and the author.)

Bicarbonate (HCO_3^-) resorption: Ordinarily, the rate of HCO_3^- resorption is adjusted to maintain a constant plasma HCO_3^- concentration of about 25 mEq/L. HCO_3^- resorption resembles a threshold-limited mechanism in which increases in filtered load above the threshold level lead to excretion of the excess HCO_3^- in the urine. However, no true threshold for HCO_3^- is demonstrable, and the rate of resorption can be altered by several important factors (see DISTURBANCES IN ACID-BASE METABOLISM in §11, Ch. 6).

A model of a widely held concept of HCO_3^- transport is shown in FIG. 6-5. Most of the filtered bicarbonate is resorbed directly as the ion and the remainder indirectly as carbonic acid and carbon dioxide (CO_2). Carbonic anhydrase within the tubules catalyzes the hydration of CO_2 to carbonic acid, which dissociates into hydrogen ion and HCO_3^-. The HCO_3^- generated by this reaction moves passively out of the cell and into the extracellular fluid. The remaining hydrogen ion is secreted into the tubular fluid and reacts with filtered HCO_3^- in the tubular lumen, reforming carbonic acid and then CO_2 and water. Both the H_2CO_3 and the CO_2 formed in the tubular lumen diffuse back into the cell, thus completing the cycle. Carbonic anhydrase inhibitors interfere with this sequence by impairing the hydration reaction and thus the generation of protons (hydrogen ions) from CO_2 and water in the cell. This limits the number of protons available for secretion into the tubule.

Ammonium excretion: Ammonia (NH_3) is formed in the tubular cells from amino acid precursors, principally glutamine. It carries no electrical charge, is lipid-soluble, penetrates cell membranes readily, and diffuses easily throughout the kidney. It reacts with hydrogen ions, forming ammonium ions (NH_4^+) which are highly soluble in water and do not readily penetrate cell membranes. The difference in membrane penetrability between NH_3 and ammonium ions is referred to as *nonionic diffusion* and best explains why ammonium excretion varies with urine pH. Differences in pH between collecting duct fluid and renal venous blood determine the distribution of ammonium ions between these compartments and thus regulate the proportion leaving the kidney. The lower the urine pH, the more ammonium appears in the urine (FIG. 6-6).

Ammonium excretion is also influenced by the production rate of NH_3. Changes in systemic acid-base balance regulate the rate of NH_3 formation from glutamine, with metabolic acidosis stimulating NH_3 production and alkalosis inhibiting it. This alteration in NH_3 formation and, hence, in ammonium excretion in response to acid-base disturbances represents one of the most important mechanisms by which the kidney can adjust hydrogen ion excretion in response to changing rates of hydrogen ion production.

Titratable acid: Hydrogen ions secreted into the tubular fluid are buffered by anions of weak acids in addition to NH_3. At the normal pH of urine, phosphate is the major buffer which contributes to the formation of titratable acid. When urine pH is between 4.5 and 5, creatinine and urate also buffer hydrogen ions in significant amounts and contribute to the titratable acid (FIG. 6-7).

APPENDIX B

SOME CAUSES OF CHRONIC RENAL INSUFFICIENCY AND SYSTEMIC MANIFESTATIONS OF THE UREMIC SYNDROME

Appendix B: Some Causes of Chronic Renal Insufficiency and Systemic Manifestations of the Uremic Syndrome.

[1]Some Causes of Chronic Renal Insufficiency:

- **What are some causes of chronic renal insufficiency?**

The following are some causes of chronic renal insufficiency:

1. Acute or rapidly progressive *glomerulonephritis* may progress relentlessly to loss of functioning renal mass. Often, however, the victim may be unaware of the underlying condition for many years. Symptoms may not develop until there is a rise in the serum urea and creatinine levels, by which time the amount of functioning renal tissue is down to 25% to 50% of normal. Insidious renal insufficiency of this sort may follow an unrecognized glomerulonephritis of many years' duration.
2. *Pyelonephritis* is another major cause of chronic renal failure. It is thought to be the result of direct invasion of kidney parenchyma by bacteria. Like glomerulonephritis, it may be indolent and unrecognized until kidney failure supervenes.
3. *Polycystic kidney disease* is a hereditary disease that may affect several members of the same family. As a result of a developmental defect, fluid-filled cysts develop and compress functional renal tissue. It may remain undetected until the person is 40 or 50 years of age, when increasing size of the kidneys may be noted, or until kidney failure begins to manifest itself.
4. *Diabetic glomerulosclerosis* may develop as a complication of long-standing diabetes mellitus, particularly that form of diabetes having its onset in childhood or adolescence. The course is often rapid.
5. Severe high blood pressure (hypertension) may lead to *arteriolar nephrosclerosis*, in which damage to kidney arterioles causes loss of function from inadequate blood supply.
6. Persons with *gout* may develop kidney damage of progressive nature from urate deposits in renal parenchyma caused by the high uric acid concentration. These deposits cause scarring and parenchymal damage.
7. *Obstruction* of the lower urinary tract (such as prostatic enlargement) or other anatomic defects may lead to damming back of urine. The obstruction causes distension of the kidney pelvis and calyces, called *hydronephrosis*. Decreased function results from the increased pressure on kidney tissue.
8. There are many other less common disorders that may cause insidious kidney damage to the point of chronic renal failure. It is important to remember that the body can adjust to severe biochemical disturbances if they have been gradual in developing. People can sometimes maintain an active life with as little as 10% of normal renal function.

1.Gutch and Stoner, 1975, pgs.28-31.

■ **Is retention of urea the cause of uremic syndrome?**

The severity of uremic symptoms usually *parallels* the increase of urea in the blood. However, most investigators believe metabolic wastes other than urea are involved. More than 200 nitrogenous compounds have been demonstrated to be present in excess in serum of uremic patients. No one or no group has been identified as *the* causative factor in uremia. However, patients dialyzed against a bath with elevated urea concentration display anorexia, malaise, nausea, and insomnia, even when other measurable parameters are normal. Urea retention, although not *the* toxic factor, has a role in the uremic syndrome.

■ **What are the metabolic effects of the uremic state?**

1. *Carbohydrate metabolism* is disturbed. There is often moderate elevation of blood sugar, which is probably caused by a completely different mechanism from that in diabetes mellitus. There is apparently a cellular insensitivity to the normal action of insulin. There may be a circulating insulin antagonist in uremic serum, but this does not seem to be the primary factor. Endogenous insulin production has been reported normal in amount in uremic persons. Also, there is evidence that exogenously administered insulin remains in the circulation longer in uremic persons than in normal persons.

Individuals who have been diabetic and then become uremic typically require *less* insulin than before the onset of azotemia. This decrease may be the result of the longer life of insulin in the circulation.

2. *Protein metabolism* is important in the production of nitrogenous wastes. Because of this production, protein has almost always been restricted as a form of treatment. Such is not always best for the patient, particularly after regular dialysis is begun. The uremic person has a number of amino acid abnormalities. Some may be elevated to two or three times the usual serum levels. Others, particularly certain essential amino acids, are decreased. Without adequate levels of these amino acids, the patient's ability to rebuild his own tissues may be seriously impaired.

3. *Fat metabolism* has not been extensively investigated. Most patients on hemodialysis have elevated levels of triglycerides and free fatty acids. Cholesterol and phospholipids are usually normal. What relation these findings may have to vascular changes in uremic patients while on dialysis is just beginning to be unraveled; there may be a very significant relationship.

■ **What changes are seen in the urine?**

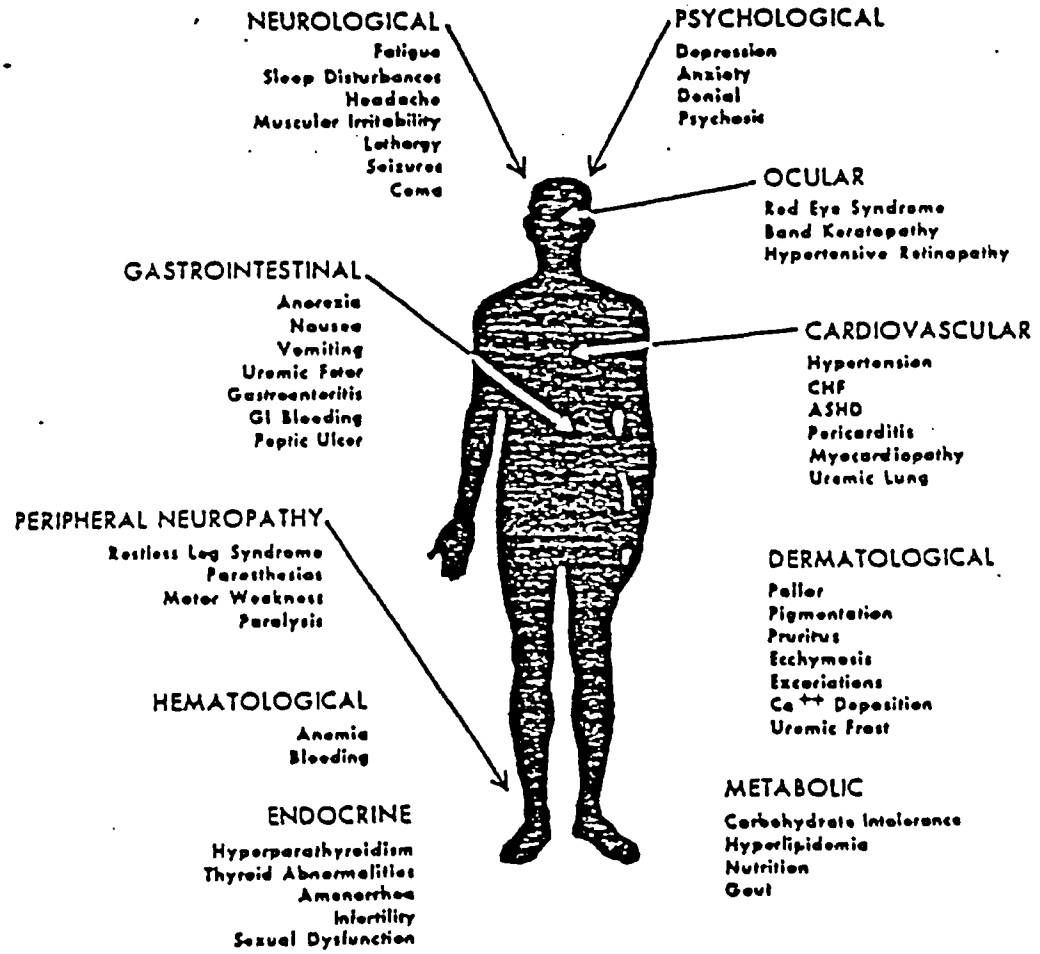
In acute renal failure, urine output is under 400 ml/24 hours (occasionally it may be higher). Usually there is little or no protein present. The specific gravity is 1.010 to 1.015. Sodium content most often is greater than 50 mEq/L. Urea concentration, which in normal urine is twelve to fifteen times that of serum, is usually only two or three times the serum value.

In chronic renal failure, with only moderate changes in serum chemistry, there may be high (2 to 3 L) urine output. There is often considerable protein, depending on the basic disease. Specific gravity is low; sodium concentration may vary from 40 to 90 mEq/L; and the urea concentration will be less than ten times that of serum. As kidney failure progresses toward the last stage, urine volume falls and the protein content decreases.

Systemic Manifestations of the Uremic Syndrome:

The following illustration is a convenient summary of systemic manifestations of the uremic syndrome. Definitions of many of the terms are cited below on the following page.

PATHOPHYSIOLOGY OF RENAL FAILURE [2]



THE UREMIC SYNDROME

2. Schoenfeld and Humphreys, 1976, p.1432. See also appendix D.

Systemic Manifestations of the Uremic Syndrome: Definition of Terms

Uremic Fetor: "Patients with advanced uremia often complain of an unpleasant, metallic taste in their mouths, and there may be an ammoniacal odor to the breath- uremic fetor." (Schoenfield and Humphreys, 1976, p.1434.)

Red Eye Syndrome: Red eyes due to conjunctival deposition of hydroxyapatite.(Schoenfeld and Humphreys, 1976.)

Band Keratopathy: Retinal hemorrhages, exudates, edema, ischemia, or infarction due to chronic essential or malignant hypertension (Berkow, 1977).

Myocardiopathy: Variety of noninflammatory pathologic lesions of the myocardium (Berkow, 1977).

Uremic Lung: Radiographic demonstration of perihilar vascular congestion with relatively clear peripheral lung fields (butterfly wings) which fails to respond to fluid extradition during hemodialysis (Friedman, 1978). Symptoms include shortness of breath, cough and orthopnea (respiratory condition in which there is discomfort in breathing in anything but an erect or standing position (Schoenfeld and Humphreys, 1976).

Ecchymosis: Extravasation of blood into tissue spaces showing itself in the form of a patch of purple color that is expected to resorb (Lieder and Rosenblum, 1968).

Excoriations: A linear or hollowed out crusted area caused by scratching, rubbing, or picking (Berkow, 1977).

Uremic Frost: White particles of uremic frost forming on the skin (Friedman, 1978).

APPENDIX C

HEMODIALYSIS: A BRIEF SUMMARY OF PRINCIPLES AND PROCEDURES

Appendix C: Hemodialysis: A Brief Summary of Principles and Procedures. Gutch, C.F. and Stoner, M.H., Review of Hemodialysis For Nurses and Dialysis Personnel. Second edition. C.V. Mosby Co., St. Louis, 1975. Pgs. 35-37,41-51.

HEMODIALYSIS

GENERAL

- **Define artificial kidney.**

An artificial kidney is an apparatus for removing metabolic wastes or other poisons from the body when the natural kidneys are not functioning adequately. Technically it is called an "extracorporeal (outside the body) hemodialysis apparatus."

- **What does hemodialysis mean?**

Hemo- indicates "blood." *Dialysis* is of Greek origin and means a "loosening from something else" (separation or filtration). In clinical usage, the waste materials in blood are filtered through a semipermeable membrane and eliminated.

- **What is a semipermeable membrane?**

A semipermeable membrane is a thin sheet or layer of material that may be regarded as having submicroscopic openings or holes. Particles smaller than these openings, called "pores," pass through, while larger ones are retained.

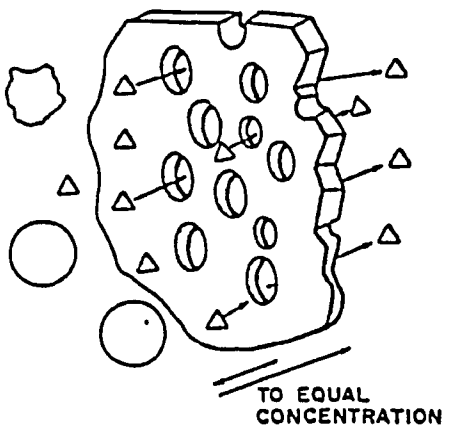


Fig. 3-1. Semipermeable membrane. (Adapted from Nosé, Y.: Manual on artificial organs, Vol. I: The artificial kidney, St. Louis, 1969, The C. V. Mosby Co.)

- **How does the semipermeable membrane function in hemodialysis?**

The patient's blood is passed through a compartment formed by semipermeable membrane on each side. Surrounding this compartment is dialyzing fluid. Red and white blood cells and most plasma proteins are too large to pass through the pores of the membrane (about 50 Å). Water and small particles pass freely across the membrane by diffusion. (See Fig. 3-1.)

- What is diffusion?

Since particles in solution are in constant motion, they tend to spread uniformly throughout the solution. The rate of spread depends on concentration, size, and electric charge of the particles (see Chapter 2).

- Why are not all the solutes and water from the blood removed by the dialyzer?

The dialyzing fluid, or dialysis bath, is made up of an electrolyte solution approximating the concentration of "normal" plasma. Water molecules pass freely across the membrane in both directions. Ions also pass, their speed depending on particle size and electric charge. If there is an excess of a given kind of particle on the blood side of the membrane, some of the excess will pass into the bath in an effort to reach equilibrium. The reverse is also true. Osmolality of the bath may be adjusted with dextrose or invert sugar to approximate that of the patient's blood and to prevent water from being attracted into the blood compartment by osmosis.

- What is osmosis?

Water molecules are very small and pass the pores of a semipermeable membrane quite easily. If we have a solution (some substance dissolved in water), we may think of the number of particles of the substance (solute) as indicating its concentration. Although we do not usually think about it, there is also a "water concentration" in the solution, represented by the number of water molecules present. If the number of *solute* particles is increased (solute concentration raised), the water concentration per volume of solution is decreased. If two solutions of the same substance (for example glucose) but of different concentrations are separated by a dialysis membrane, there will be two concentration gradients working. First, glucose molecules will tend to diffuse from the area of high glucose concentration to that of lower glucose concentration until equilibrium is reached. Second, water molecules will pass from the area of higher *water*

concentration to that which is lower. This will be *opposite* to the direction of passage of the glucose molecules. Since water particles pass through the membrane more quickly than do those of glucose, there will be an increase in volume on the high glucose side initially. Eventually equal concentrations of both water and glucose will be reached on each side of the membrane, and the volumes will be the same.

▪ **What waste products are removed by hemodialysis?**

More than 200 nitrogenous compounds have been shown to accumulate in the uremic person. These include urea, creatinine, indoles, phenols, guanidines, and many others. Such solutes will pass through the pores of the membrane, depending upon molecular size and concentration in serum.

Dialysis may be used in certain exogenous poisonings—particularly ethylene glycol, methyl alcohol, some barbiturates and other sedatives, salicylates, and others for which rapid removal from the blood is advantageous.

▪ **What is meant by selective permeability?**

There are many different particles, molecules, and ions in blood. They vary widely in size and molecular weight. The electrolytes are the smallest particles, with sodium having a molecular weight of approximately 23 and calcium 40. Urea has a molecular weight of 60, creatinine 113, and uric acid 168. Dextrose is 180, albumin 68,000, and globulin 150,000. Red and white blood cells, bacteria, and virus are all much heavier and larger. Membranes used for clinical dialysis currently are essentially impermeable to particles of molecular weight greater than 5,000. Much interest presently centers around "middle molecules"—those in the range of 300 to 2,000 molecular weight—which diffuse poorly across conventional membranes. Molecules in this range are suspected of being a cause of uremic neuropathy.

Even for particles that are sufficiently small to pass through the pores of the membrane easily, there are differences in their *rate* of passage. This rate is inversely proportional to the size of the particles involved and is reflected in their diffusibility. Thus chloride diffuses more readily than urea, which diffuses more quickly than creatinine or glucose.

Dialysis is an effective modality whereby desirable elements can be retained on the blood side of a membrane, unwanted particles can be passed through to the bath, and dangerous agents such as bacteria or viruses are prevented from entering the blood.

DIALYZER EFFICIENCY

Patient, physician, chemist, engineer, and equipment manufacturer all consider effectiveness of a hemodialyzer from different points of view. Factors involved in these differing perspectives are comfort, time, safety, cost, and so on. The ultimate measure of effectiveness for any dialyzer is that it produces a good, safe clinical result for the patient. *Technical* aspects of dialyzer efficiency have to do with solute clearance (mass transfer), ultrafiltration, blood volume, and internal resistance to blood flow.

▪ What does clearance mean?

The clearance concept is important to the nephrologist in judging the ability of the natural kidneys to remove metabolic wastes. The same clearance concept has been applied to artificial kidneys. The idea of "clearance" was developed in the 1920s by Austin, Stillman, and Van Slyke to compare the ability of diseased kidneys to excrete urea with that of normal kidneys. Clearance is an empirical measure indicating a calculated volume of blood completely cleared of a substance x in 1 minute. It is a theoretical volume, not a real volume.

The basic clearance equation is:

$$C_x = \frac{U_x \cdot V}{P_x}$$

where C_x = clearance of x (ml/min of blood)
U_x = concentration of x in urine (mg/100 ml)
V = volume of urine (ml/min)
P_x = concentration of x in plasma (mg/100 ml)

▪ How is this equation used to evaluate performance of a hemodialyzer?

The formula above is modified to:

$$C_x = \left(\frac{A_x - V_x}{A_x}\right) Q_b$$

where C_x = clearance of x (ml/min of blood)
A_x = arterial (inlet) concentration of x (mg/100 ml)
V_x = venous (outlet) concentration of x (mg/100 ml)
Q_b = blood flow rate (ml/min)

When the clearance of a solute is given as an indicator of the performance of a particular dialyzer, it is important that the blood flow rate be given. Within the usual working range, clearance increases directly as blood flow increases. Also, clearance results are affected by solute concentration; at a particular blood flow rate, the clearance of x is greater at higher arterial concentration than at a lower concentration for the same dialyzer. The diffusion gradient is less at lower concentrations. This should be remembered in interpreting dialyzer clearance data.

■ What is meant by mass transfer?

Mass transfer is a term borrowed from chemical engineering that indicates movement of chemical species across a phase boundary. As applied to dialysis, it refers to transfer of solute(s) from one compartment to another across the dialysis membrane. The rate of movement—*mass transfer rate*—is also termed the *solute flux.*

■ How is mass transfer rate determined?

The quantity of a given solute x entering the blood compartment of a dialyzer per unit time is equal to the concentration of x multiplied by the blood flow rate. Likewise the quantity of x leaving the dialyzer is the product of the outflow concentration times flow rate. The difference between quantity in and quantity out represents the solute flux, or mass transfer rate.

■ What factors affect mass transfer rate?

Flux, at a constant temperature, is governed by the solute concentration gradient and the physical characteristics of the dialyzer. The latter include effective membrane surface area, membrane permeability, and membrane sieving coefficient.

Solute flux, in flowing fluids, is the result of (1) diffusion *(conductive mass transfer)* and (2) ultrafiltration *(convective mass transfer).* Most flux in clinical dialysis results from conductive transfer, or diffusion.

■ What is the nature of convective mass tranfer?

The sieving coefficient is the ratio of solute concentration in blood to its concentration in ultrafiltrate and is expressed as $s = C_f/C_b$. That portion of solute flux resulting from ultrafiltration may be expressed:

$$N_f = s \cdot Q_f \cdot \bar{C}_b$$

where N_f = mass transfer rate from ultrafiltration
s = sieving coefficient
Q_f = rate of ultrafiltration
$\bar{C}_b$ = mean solute concentration in blood

Convective mass transfer is relatively unimportant in overall solute flux for particles the size of urea, creatinine, uric acid, and phosphate and accounts for about 3% of their transfer in conventional dialysis. However, as molecular size increases, convective transfer assumes a more important role and becomes a significant factor in the flux of molecules in the 1,000 to 5,000 molecular weight range.

■ What is the mass transfer coefficient?

From the laws of fluid mechanics, the differential equation for the rate of solute transfer, blood to dialysate, at a specific differential point is $dN = K_o (C_b - C_d)\, dA$. This is integrated to:

$$N = K_o A (\overline{\Delta C})$$

where N = mass transfer rate (moles/min)
K_o = overall mass transfer coefficient (cm/min)
A = membrane area (cm^2)
$\overline{\Delta C}$ = logarithmic mean concentration difference, blood to fluid (moles/cm^3)

It is important to note that the overall mass transfer coefficient (K_o) encompasses *diffusive* movement of solute in blood, across the membrane, and in dialysate and also the component resulting from *convective* transfer. K_o is an average coefficient based on varying concentration gradients progressively along the length of the dialyzer.

$\overline{\Delta C}$ is affected by flow rates of blood and fluid and by flow geometry.

■ Discuss flow geometry.

Flow geometry involves the relative directions of flow of blood and of dialysis fluid and the characteristics of these flows. Clinical hemodialysis is based upon four flow geometries: (1) cocurrent, (2) countercurrent, (3) well mixed, and (4) cross-flow.

Most parallel-flow dialyzers using single-pass utilize countercurrent flow (blood one direction, fluid opposite direction). Cocurrent flow (blood and fluid in the same direction) is less efficient and is rarely used. Cross-flow is employed in coil dialyzers. Completely mixed systems are represented by a totally recirculating fluid system or its modification, the recirculating single-pass, in which a small recirculating volume is constantly replenished by fresh fluid.

The geometry of the flows involved will affect the concentration gradients at the inlet and outlet ports and is an important factor in the calculation of $\overline{\Delta C}$ for dialyzer evaluation.

■ What is mass transfer resistance?

Mathematically, the average mass transfer resistance is the reciprocal of the average mass transfer coefficient, that is, $R_o = 1/K_o$. In clinical dialysis, it represents the total of all the resistance to solute passage through the blood, across the mem-

brane, and into the effluent fluid. Thus:

$$R_o = R_b + R_m + R_d$$

where R_b = resistance to diffusion in blood
R_m = resistance to passage across the membrane
R_d = resistance to diffusion in dialysate

- **How are the mass transfer resistances determined?**

Membrane resistance (R_m) can be measured with considerable precision by means of laboratory permeability test cells for a great variety of solutes. Dialysate resistance (R_d) is estimated, using a membrane of known permeability, by varying the fluid flow rate over a wide range (up to several thousand milliliters per minute). When overall transfer resistance becomes constant, it is assumed that dialysate resistance is near zero. Blood resistance (R_b) is extrapolated for a given dialyzer after R_o, R_m, and R_d have been determined.

- **Of what practical value is mass transfer resistance?**

An appreciation of the various resistance factors is important to understanding the design of new dialyzers and in the application of in vitro test data to clinical dialysis. In conventional hemodialysis, 50% or more of total resistance for such molecules as urea, creatinine, and uric acid is contributed by the blood film (R_b). A more permeable membrane may, therefore, not contribute a great deal to the performance of a dialyzer in removing these solutes.

However, for molecules in the range of molecular weights 1,000 to 5,000, the blood resistance decreases, relative to small particles, and *membrane* permeability becomes a dominant factor in overall transfer resistance.

- **What is dialysance?**

Dialysance is a term developed by Wolf during the early 1950s as an attempt to express the kinetics of hemodialysis. It was defined as "the net rate of exchange of a substance between blood and bath, per minute, per unit blood-bath gradient."

Renkin subsequently (1956) defined dialysance in terms of dialyzer parameters:

$$D = Q_b \cdot [1 - e\ (-PA/Q_b)]$$

where P = membrane permeability
A = membrane surface area
Q_b = blood flow rate (inlet)
e = base of natural logarithms

In the clinical setting, the usual equation for calculating dialysance is:

$$D = Q_b \cdot \frac{C_{bi} - C_{bo}}{C_{bi} - C_{di}}$$

where C = concentration of solute
bi = blood inflow
bo = blood outflow
di = dialysis fluid inflow

- How does dialysance relate to mass transfer?

Dialysance is useful in comparing the clinical effectiveness of various dialyzers in terms of specific solute removal at specific blood and fluid flow rates. The engineer considers this a "black box" approach that does not relate to the specifics of mass transfer. In terms of what has been stated, the Renkin equation may be represented: $D = Q_b \cdot [1 - e (K_o A/Q_b)]$. This substitutes for the permeability factor, the average overall mass transfer coefficient. Thus dialysance, as a clinical parameter, may be predicted from the design specifications of a dialyzer.

- Are there limitations on blood flow?

In clinical dialysis one is limited by the rate at which blood can be delivered by the patient's vessel, either arterial cannula or fistula. In passive flow systems (without a pump), the size of the cannula and the patient's blood pressure limit available blood to 150 to 200 ml/min. Even with a pump, the size of the cannula or fistula needle usually limits the flow to under 300 ml/min. Excessive pump speed creates negative pressure and may collapse the vessel. The most commonly used flow rate is approximately 200 ml/min.

- What limits membrane surface area?

Two factors prevent use of a very large membrane area: (1) The volume of blood contained within the dialyzer directly increases as dialyzing surface is increased. A practical upper limit is 500 ml of blood in the extracorporeal circuit, and less is desirable. (2) Geometric factors must be considered: a long dialyzer is less efficient than a short one; increasing width or number of channels leads to difficulty in getting even blood distribution; and coiling or folding the channels increases the resistance to flow.

- What membrane surface areas are currently used?

Many hemodialyzers employ a surface area about 1 m^2; some are smaller and some larger. Not all this area is effective dialyzing surface. Contact with membrane support structures produces dead space, which may account for 10% to 30% of total area, depending on the nature of the supports. Development of the middle molecule concept and the square meter–hour hypothesis has created new interest in very large surface area dialyzers—1.5 to 2.5 m^2. Whether long-term clinical results will confirm the theoretical assumptions is not yet determined.

- May other factors in dialyzer efficiency be modified to improve results?

1. Solute diffusibility is essentially a constant and is not subject to variation.
2. Temperature increase does raise diffusibility, but in clinical hemodialysis temperature higher than 42° C (107° F) causes hemolysis of red blood cells and is a practical limitation.
3. Blood-to-bath concentration gradient for low molecular weight solutes may be increased by increasing dialysis-fluid flow rate. By increasing fluid flow, one may keep the concentration of such metabolites in fluid very low. Practically, there is little significant increment in efficiency when dialysis-fluid delivery rate is increased beyond 500 ml/min. Utilization of countercurrent flow (blood flow in one direction, bath flow in the opposite direction) makes the best use of the concentration gradient.
4. Membrane permeability is a variable that is subject to improvement without violating practical limits of blood flow, extracorporeal volume, temperature, and the like.

- What determines permeability of a membrane?

It is convenient to visualize a semipermeable membrane as a very thin sheet with numerous tiny holes, or pores. These pores must be large enough to permit passage of water and solutes but small enough to hold back protein and the formed elements of blood.

Electron microscopy shows that the fibers of cellophane and other cellulose membranes swell upon being wet to form a tortuous maze. The "pores" are not simple holes but are twisting, irregular tunnnels that may require a solute molecule to travel a distance several times the thickness of the wet membrane itself in order to get through. Permeability can be improved by making the membrane thinner, by increasing the number of submicroscopic spaces between the fibrous strands, or by making them larger in diameter.

There is an alternative theory to the pore concept of permeability. This views the membrane as a homogenous phase, or solvent, into which solute diffuses from solution at one interface and from which this solute diffuses at the opposite interface. At each interface there is a concentration gradient. This concept is much more difficult to visualize than that of pores, yet it provides a better explanation of why some substances of similar molecular size have widely different permeability through a given membrane.

- What is the nature of cellulosic membranes?

Cellulose is derived from the matrix material of plant cell walls. It is processed commercially by a complex treatment with heat and chemicals that reduce the fibers to a slurry. The liquid material can be coagulated and formed into sheets or tubes. This "regenerated cellulose" is cellophane or Cuprophan or others, depending upon chemical treatment.

Chemically cellulose is a complex carbohydrate $(C_6H_{10}O_5)y$ that behaves like an alcohol and forms esters with acids. Most sheet or tubing of cellulosic material is on the order of 12 to 30μ in thickness when dry. When wet, the thickness is approximately doubled. Such membranes have a theoretical pore diameter of approximately 5 nm. Special ultrathin membranes have been prepared that have a dry thickness of less than 1.5μ.

- Are membranes other than cellophane used for dialysis?

In addition to the ultrathin membranes mentioned above, several other approaches have been developed. Most current hollow-fiber kidneys employ cellulose acetate fibers having a wall thickness of about 25μ. Other synthetic materials used include polymethyl-D-glutamate, polyacrylonitrite, and certain polycarbonates and polysulfones. The last two have the advantage of withstanding sterilization by the steam autoclave. All have permeabilities several times that of Cuprophan 150 for solutes in the middle molecule range.

- Why is ultrafiltration an important consideration in dialyzer efficiency?

Without normal kidney function, it is inevitable that a person will retain and accumulate water. This in itself will cause death. Controlled fluid removal is essential for the maintenance dialysis patient.

Ultrafiltration is the result of a pressure gradient from blood to dialyzer across the membrane, causing water to move from the

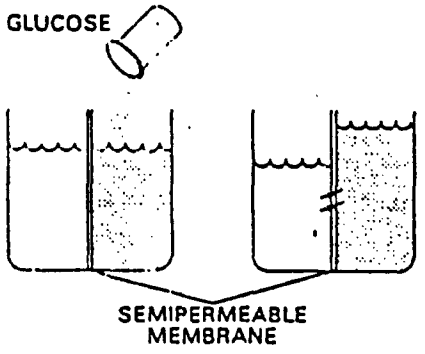


Fig. 3-4. Removal of water by osmosis. (Adapted from Nosé, Y.: Manual on artificial organs, Vol. I: The artificial kidney, St. Louis, 1969, The C. V. Mosby Co.)

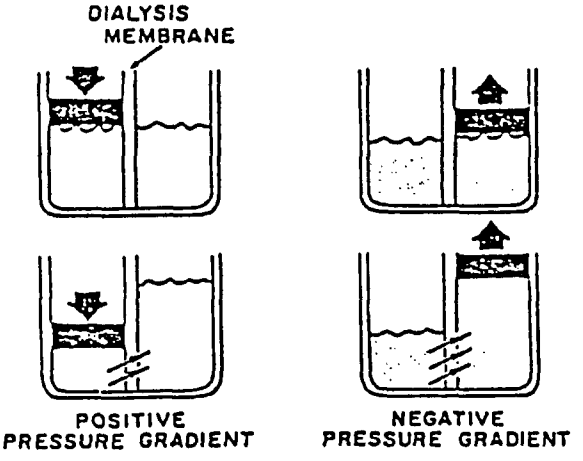


Fig. 3-5. Ultrafiltration. (Adapted from Nosé, Y.: Manual on artificial organs, Vol. I: The artificial kidney, St. Louis, 1969, The C. V. Mosby Co.)

blood compartment. There are two pressure components that may be used: osmotic pressure gradient and hydrostatic pressure gradient.

- **Describe fluid removal by an osmotic pressure gradient.**

A high concentration of a nonharmful solute such as dextrose or invert sugar may be added to the dialysis fluid (Fig. 3-4). Concentrations up to 2,000 mg/100 ml have been used. Higher levels are dangerous. Each 100 mg/100 ml increment of glucose increases osmolality of the bath by 5.5 mOsm/kg. This approach is not often used currently.

■ How does the hydrostatic gradient operate?

The difference in hydrostatic pressure, blood to fluid, represents the *transmembrane pressure* (Fig. 3-5). The rate of ultrafiltration is a function of the mean transmembrane pressure ($\Delta\bar{P}_m$), a constant peculiar to the particular membrane, membrane area, and the flow channel geometry of the dialyzer.

$\Delta\bar{P}_m$ may be calculated:

$$\Delta\bar{P}_m = \frac{P_{bi} + P_{bo}}{2} - \bar{P}_d$$

where P_{bi} = pressure at the blood inlet
P_{bo} = pressure at the blood outlet
$\bar{P}_d$ = mean dialysis fluid pressure

■ How may the ultrafiltration rate be calculated?

Graphs or nomograms are provided by most manufacturers, from which ultrafiltration may be estimated. Coil dialyzers operate with a positive *fluid* pressure, which is difficult to measure. However, because of their high frictional resistance to blood flow, a relatively high P_{bi} is always necessary. Additional transmembrane pressure may be obtained by increasing P_{bo} with a constriction at the outlet.

Parallel flow units have much less frictional resistance to blood flow and only modest blood compartment positive pressure. Transmembrane pressure may be increased by effecting negative pressure (suction) on the *fluid* compartment. From the equation $\Delta P_m = (P_{bi} + P_{bo})/2 - \bar{P}_d$ it becomes apparent that subtracting this negative force *adds* to the total $\Delta\bar{P}_m$.

It is well to remember that although $\Delta\bar{P}_m$ may be estimated from graphs according to blood outflow pressure or dialysate negative pressure, there is considerable variation in ultrafiltration because of compliance and flow path variation in different units of the same model dialyzer.

■ What aspects of dialyzer design affect internal resistance?

The important factors are:

1. The cross section of the blood flow path—primarily rectangular or circular
2. Length of blood passage(s)
3. Number of flow paths or passages

■ Of what importance is the internal resistance to flow?

From Poiseuille's law of the physics of flow, there is a direct

relation between the rate of flow and the pressure of the flowing liquid. The pressure drop from inlet to outlet of the blood compartment at a particular flow rate is $\Delta P_b = P_{bi} - P_{bo}$. This decrease in pressure, according to Poiseuille's law, is a function of flow rate, shape, and cross-sectional area of the passages, length of passages, number of passages, and viscosity of the blood.

As indicated on p. 50, transmembrane pressure is a function of P_{bi} and P_{bo}; thus a very high-resistance dialyzer has an intrinsic high ultrafiltration rate.

Internal resistance also affects the compliance of the dialyzer.

- What is meant by dialyzer compliance?

This is the change in internal volume of the blood compartment relative to change in transmembrane pressure. It results from distensibility of the membrane from increased pressure in the blood compartment. Parallel plate and coil designs in general are more compliant and have a larger dynamic volume than do hollow-fiber dialyzers. Not only is volume increased, but change in cross-sectional area may affect flow paths on both blood and fluid sides, altering the mass transfer characteristics of the dialyzer.

APPENDIX D

MEDICAL ABNORMALITIES THAT IMPROVE WITH DIALYSIS

Appendix D: Medical Abnormalities That Improve With Dialysis

"Some uremic problems improve as the biochemical aspects do. The BUN, serum creatinine level, and serum potassium level are decreased by dialysis. Serum pH rises. Improvement is temporary and is therefore reversed by the time the next dialysis treatment arrives. Improvement is sustained by repeated dialyses. Fluid removal by dialysis often improves congestive heart failure, hypertension and peripheral edema. The carbohydrate intolerance of uremia is corrected. Gastrointestinal problems and platelet abnormality improve and the patient's mental functioning improves markedly. He is oriented, able to concentrate, able to learn." (Brundage, 1976, p.104.)(Statements about mental functioning are more thoroughly reviewed in the introduction.)

"Apparently short repeated dialyses and adequate protein intake are important in arresting the bony lesions of renal osteodystrophy. Bone disease present before the initiation of hemodialysis usually improves. (Brundage, 1976, p. 105.) Anemia fequently improves slightly with chronic hemodialysis as do hemorrhagic symptoms of uremic patients (Schoenfield and Humphreys, 1976).

Appendix D: (Continued) Medical Problems Associated With Maintenance Hemodialysis (Gutch and Stoner, 1975, pgs. 154-155, 155-163, 165-166, 168-170).

MAINTENANCE HEMODIALYSIS

- **What does maintenance hemodialysis mean?**

Maintenance hemodialysis means the repetitive dialysis procedures necessary to keep a person with irreversible kidney failure alive and as healthy as possible.

- **How often is hemodialysis required for a chronic patient?**

Ideally, it would be continuous. Continuous treatment would require a small, portable, or wearable artificial kidney. Such a device is not clinically available. Practically, most patients are treated three times a week. Some have dialysis four or five times weekly, a few only twice.

- **Why is frequent dialysis desirable?**

Changes in the fluid and biochemical state of the body affect total body function by the *extent* of such changes and by the *rate* of change. A large accumulation of wastes or fluid makes the patient ill. Rapid reduction of the accumulation is also stressful because of the shifts between intracellular and extracellular compartments; again the patient is made ill. Frequent hemodialysis reduces the interval for accumulation of metabolic wastes and fluid. Total accumulation is less, and rate of reduction during dialysis is less.

- **Why not dialyze every day?**

Equipment and supplies are expensive. The dialysis procedure takes time, which the patient would prefer to spend elsewhere. The duration and frequency of most dialysis prescriptions are a compromise between what is best for the patient's health and the practical limitations of money and time.

ADVERSE REACTIONS

- **What adverse reactions are associated with maintenance hemodialysis?**

Many abnormalities are part of the uremic syndrome. Since the maintenance hemodialysis patient is a controlled uremic patient, it is important to recognize these abnormalities. Some may

be avoided, others may be treated or minimized by appropriate management.

Other abnormalities are directly related to the dialysis process. Dialysis as a procedure is subject to modification. The goal of every dialysis should be to provide a safe, smooth, and comfortable treatment, while accomplishing those chemical and fluid changes required for the best long-term care of the patient.

- What causes hypotension as a dialysis is begun?

Hypotension while beginning dialysis may occur in some patients with a relatively small blood volume (children, small women). It is the result of a blood volume shift as the dialyzer is filled with the patient's blood. It is much less frequent with small-volume dialyzers than with large units. This type of reaction is rarely serious and usually does not last long. It will respond to infusion of small amounts of saline or of blood. Careful technic in starting the dialysis will minimize occurrence of these episodes. One should start with a blood-pump speed of 50 to 75 ml/min and take 5 to 10 minutes to work up to full pumping speed.

- What about hypotension occurring later during dialysis?

Later hypotension is usually attributable to ultrafiltration. The hypotension may be symptomless until there has been a fall of 40 or 50 mm Hg in systolic pressure. It responds to fluid replacement, although the volume required may be greater than for the first type of hypotension. Skillful dialysis personnel can, by assessing the blood flow rate and with a knowledge of the ultrafiltration capacity of the particular dialyzer unit, make a fairly accurate prediction of the amount of fluid that will be removed per hour. It is possible to plan a program of fluid replacement throughout the dialysis that will avoid hypotension and bring the patient to the end of the run reasonably close to the desired weight.

- Some patients with gross edema become hypotensive early during a dialysis. Why does this occur?

Patients with gross fluid overload, unless they are in primary heart failure, are usually hypoproteinemic or have a low serum albumin. The dialysis removes fluid from their *vascular* compartment, but the low serum protein does not exert sufficient oncotic pressure to attract fluid in from the extracellular space. The patient becomes hypotensive from reduced blood volume, even though a massive load of fluid remains outside of the circulation, in tissue.

The physician may prescribe an infusion of albumin or colloid material in an effort to mobilize the extravascular fluid. This procedure is expensive, and the benefit is often transient. Such patients generally have a rather poor prognosis.

- What about a fall in blood pressure not related to any of the above?

Occasionally patients have a fall in blood pressure after dialysis is well started but before significant volume loss has been achieved. This fall may be from antihypertensive medication, or sedatives, or other medication. It is wise to check on the patient's medications. In a few instances there is an unstable vasomotor system. Careful use of mild vasopressor agents will usually help.

- Does hypertension occur during dialysis?

A minority (possibly 10%) of patients develop a rise in blood pressure during dialysis. Some have a gradual rise throughout the run. Others experience a prompt jump soon after starting, or it may develop any time. Often these persons show a repeat pattern of response in subsequent dialyses. The cause is ill defined. Occasionally the rise in pressure is the result of increased cardiac

output as fluid overload is relieved. In other instances there may be an increase in peripheral vascular resistance on a reflex or hormonal basis. Central nervous system response may be a factor. Often this sort of pressure response is best left alone. If the patient develops symptoms or the increase is sufficient to be alarming, small doses of hydralazine (Apresoline) or reserpine may be given intravenously. Response usually occurs in 5 to 10 minutes, and further dosage can be adjusted as needed. Rarely is a potent agent such as diazoxide indicated.

- **Is congestive heart failure seen in maintenance hemodialysis patients?**

Yes, most often this is directly the result of fluid overload, and ultrafiltration will relieve it. Often such patients are protein and calorie deficient as well as fluid overloaded from poor diet and fluid management. The dietician may be able to help in such instances.

A few of these patients develop a peculiar cardiomyopathy with a greatly dilated, flabby heart. Such patients are prone to arrhythmias, tolerate ultrafiltration poorly, and are very difficult to manage during dialysis.

- **Are arrhythmias common during dialysis?**

As older patients and persons with other complicating disease are taken into dialysis programs, arrhythmias have become not infrequent. When present, they are most often caused by underlying heart disease. The physician should make known to the dialysis personnel the presence of such problems and their significance. Evaluation of a new, or different, rhythm developing *during* dialysis requires an electrocardiogram. The patient should be queried as to medications and a review of recent serum potassium, calcium, and magnesium values made. Patients with myocardial damage may develop arrhythmias of various types in response to circulatory volume change or shift in electrolytes, particularly potassium. Patients receiving digitalis pose particular problems. Before dialysis, when potassium may be relatively high, digitalis effect may be minimal. During dialysis, as potassium is lowered, arrhythmias may occur as part of a relative digitalis excess. Such patients are often dialyzed with at least a 3 mEq/L potassium bath to minimize the magnitude of potassium change.

- **What if a patient develops chest pain during dialysis?**

Some patients have pain resembling angina pectoris that comes on at the beginning of dialysis. Often these persons have a history

of underlying heart disease, and the pain must be presumed to be angina. It may go away if blood flow is slowed. Often a tablet of nitroglycerin or other medication for angina taken just before hookup will prevent the symptoms. Some patients irregularly have a vague chest distress or sometimes low back pain. The mechanism is obscure but often seems related to blood volume change. Again, slowing the blood flow rate usually helps.

Other adverse reactions

- What causes muscle cramping during dialysis?

Muscle cramping has been related to a calcium or potassium shift. The most common cause is probably fluid shift from ultrafiltration. pH changes may play a part. Rapid infusion of 100 to 200 ml of saline solution usually brings relief. Heat and massage are temporary measures. In patients in whom there may be preexisting small-vessel disease (usually older men), prophylactic use of a quinine preparation before dialysis may reduce or prevent cramping. For some persons a small dose of diazepam (Valium) works well.

Use of a relatively high sodium bath (140 to 145 mEq/L) has been recommended, but we have had little success with this. Pickle-eating and intravenous administration of hypertonic saline are "fad" therapy, with little or no real support for their efficacy.

- Discuss febrile reactions during dialysis.

Chills and fever during dialysis occur much less frequently than they did a few years ago. But they do occur, often in clusters. In event of a definite chill followed by a temperature elevation, bacteremia should be suspected. Blood cultures should be taken, with a notation to the laboratory to "check for unusual organisms." A frequent site for bacterial contamination is the shunt connection or fistula puncture site.

Most febrile reactions are unexplained. They are likely pyrogen reactions. Any reused item that comes in contact with blood is suspect. Such pyrogen material is usually protein in nature, from breakdown products of blood in reused items or breakdown of killed bacteria. Formalin used as a sterilizing agent for reused items is highly effective in killing bacteria. It does not destroy them, however, but preserves the dead organisms. Formalin denatures and fixes any residual proteinaceous material in residual blood. It may thus contribute to the pyrogen problem.

Endotoxin-pyrogenic material produced by bacteria has been demonstrated to be present in the bath of many dialyzers. The Minneapolis group was able to show both in vitro and in vivo that

such endotoxin was able to cross the apparently intact dialysis membrane. Endotoxin was demonstrated in the bloodstream of more than 40% of patients with febrile reactions. A relatively simple test for the quantitative presence of endotoxin—the Limulus test—is now available. Samples of blood and dialysis fluid should be checked by this technic in event of a reaction to attempt to locate the source.

Finally, chemical agents such as formalin itself may cause febrile reactions when inadvertently introduced into the blood. On a few occasions, 2-chloroethanol, formed by ethylene oxide and water, has been implicated.

OTHER COMMON DIALYSIS-RELATED PROBLEMS

Itching

Many patients, by the time they come to maintenance dialysis, are troubled by itching. The mechanism is not clear. The skin is usually dry and lacks lubrication. Most such patients are improved by dialysis, but an occasional patient develops itching associated with the dialysis procedure. Usually these persons have a high serum phosphorus and are not taking adequate aluminum hydroxide. Rarely the pruritus may be related to magnesium taken as a laxative or as a magnesium and aluminum preparation. A few such patients have parathyroid disturbance related to osteodystrophy (see p. 33).

Soothing skin creams or lotions may give temporary relief of pruritus. Oral agents such as cyproheptadine (Periactin) or antihistamines may occasionally help. The basic cause should be sought.

Headache, restlessness, and mood changes

Such complaints are rather common. As indicated earlier, they are likely related to rate and/or extent of water and electrolyte changes between body compartments during dialysis. It is important to determine whether this is the result of dietary and fluid indiscretion between dialyses or whether it is the procedure that is at fault. If it is the latter, it is often possible to change blood flow and dialysis time or to utilize a different type dialyzer advantageously.

MEDICAL PROBLEMS ASSOCIATED WITH MAINTENANCE HEMODIALYSIS

Hematologic problems

The hematocrit for normal men is 46% to 52% and for women 40% to 45%. People with uremia or on maintenance hemodialysis are anemic and have considerably lower hematocrits.

■ What causes anemia?

Causes include (1) failure of production, or inhibition of action, of erythropoietin, a hormone produced by the kidney that stimulates bone marrow to produce red cells, (2) a shortened life span of the red blood cells, (3) impaired absorption of iron from the gastrointestinal tract, and (4) blood loss, including a tendency to bleed from the nose or gums, gastrointestinal tract, uterus, skin, and so on.

■ Does dialysis influence the anemia?

Dialyzer leaks, incomplete blood recovery after dialysis, and excessive blood sampling contribute to anemia. However, the patient who is receiving adequate dialysis, is in good nutritional state, and has adequate iron stores and intake will usually stabilize with a hematocrit between 20% and 30% without transfusions. It is unusual for the hematocrit to go much higher, except for persons with polycystic disease, in whom there may be greater than normal production of erythropoietin.

■ Does the anemia produce symptoms?

In chronic renal failure, the anemia has usually been present for many weeks or months, and the patient has become adjusted to it. As the hematocrit improves on dialysis, the person begins to feel better. Such people still have considerably fewer red cells than normal, and so they are apt to become dyspneic and tire easily.

■ When should transfusions be given?

The routine giving of blood at a certain hematocrit value is futile. If the patient suffers a large blood loss from a rupture of the dialyzer or from hemorrhage, the blood should be replaced. If a patient with a gradually falling hematocrit becomes short of breath or excessively fatigued or has angina, a transfusion may relieve the symptoms.

■ What are complications of transfusions?

1. *Incompatibility reactions* are caused by major or minor blood-group incompatibility. Manifestations, such as chest or back pain, chills, and fever, occur soon after blood is started. The transfusion should be stopped. A blood specimen should be drawn from the patient for hemolysis and for recheck of type and cross matching. Chills or fever should be treated symptomatically. Intravenous steroid may be used if symptoms are severe.

2. *Allergic reactions* to leukocytes, platelets, or protein of the

donor blood occur. Manifestations are chilling, fever, and/or skin eruption. They come on 30 to 60 minutes after start of transfusion. They should be treated by slowing the rate of infusion. An antihistamine diphenhydramine ([Benadryl], 20 to 50 mg) or steroid should be given intravenously if symptoms are severe.

3. *Hepatitis*, either the serum type or infectious type, may be transmitted by blood. The onset is from 1 to 4 months after the transfusion (see p. 164).

4. *Preformed antibodies* may result from minor incompatibility or allergic reactions. They are particularly important to the patient who hopes for transplantation. Preformed antibodies to leukocytes, platelets, or protein products may result in acute or hyperacute rejection of an otherwise excellent transplanted kidney.

- What can be done to minimize the anemia?

A good dietary intake of protein, including adequate amounts of the essential amino acids, is important. Adequate iron intake is essential if the patient's iron stores are depleted. Oral iron supplements, such as ferrous sulfate or ferrous gluconate, are often adequate. However, many chronic dialysis patients have an apparent absorptive defect of iron from the gastrointestinal tract (possibly related to their serum-protein status). These people are also prone to gastrointestinal upset, nausea, gas, vomiting, or anorexia, and these symptoms are sometimes aggravated by oral iron. Intravenous iron, as the saccharated iron dextran (Imferon), can be given in 100-mg doses, usually for a total course of 1 gm, depending on the adequacy of iron stores as indicated by marrow examination or by a significant degree of unsaturation of serum iron-binding capacity. Folic acid and vitamin B_{12}, both of which are important in red cell formation, are water soluble and are theoretically depleted by dialysis. Although there is little evidence that these vitamins are seriously deficient, it is usual to give a multivitamin supplement, either orally or parenterally, to all dialysis patients.

Abnormal calcium and phosphorus metabolism

Disturbances of calcium and phosphorus metabolism are frequent in persons who develop their renal insufficiency gradually, and they may be apparent before dialysis is required. Dialysis does not correct the disordered calcium-phosphorus metabolism, and progressive osteodystrophy (the term for the bony manifestations) is a serious problem for many chronic hemodialysis patients.

■ What are factors in the development of osteodystrophy?

During the development and gradual onset of kidney failure there is loss of ability to excrete phosphate. As phosphate ions accumulate in the blood, there is a reciprocal depression of serum calcium. The parathyroid glands, located in the neck behind the thyroid, are primarily concerned with maintaining a normal concentration of calcium in body fluid. They respond to the reduced serum calcium by increased production of parathyroid hormone and may hypertrophy or enlarge. Parathyroid hormone exerts an influence on bone, causing calcium to be resorbed from it. The result is loss of bone density and strength.

■ Are there other factors in the bone disorder?

The absorption of dietary calcium from the intestinal tract is decreased in chronic renal failure. This defect persists in persons on regular dialysis.

There is resistance to the action of vitamin D, which normally enhances the absorption of calcium from the gastrointestinal tract. It may also have an effect on the incorporation of calcium into the bone.

■ Describe some of the bony changes seen in osteodystrophy.

There is decreased calcium content of bone or loss of both calcium and supporting matrix (conditions known as osteomalacia and osteoporosis). These changes may result in multiple fractures of ribs or other bones and compression of vertebral bodies. Occasionally patchy areas of *increased* bone density are seen by x-ray. This condition is called "osteosclerosis." Its significance is not understood.

Another finding thought to indicate uncontrolled or "wild" parathyroid overactivity is osteitis fibrosa cystica. Cystic areas of reabsorption are seen near the ends of long bones on x-ray examination. There is also subperiosteal reabsorption of bone seen in the distal ends of clavicles and in small bones of the hands and feet.

■ Does osteodystrophy cause symptoms?

Some patients complain of sore, painful feet. Fractures, when they occur, are painful. Such fractures heal poorly.

■ Are there other problems from osteodystrophy?

Metastatic calcification (deposits of calcium in soft tissue) occurs. Because of the disturbance of the calcium-phosphorus ratio in serum, usually with a high phosphorus level, calcium pre-

cipitates in tissue around joints or is deposited at the periphery of the cornea of the eye. Medium-sized arteries may have calcium deposits to such an extent that they become visible on x-ray films. Less apparent, but more dangerous, are diffuse deposits of calcium in the heart muscle and in the lung. Itching may be intensified in presence of a high calcium-phosphorus ratio. Skin ulcerations and gangrene of the tips of toes and fingers have occurred. Aggravation of high blood pressure is frequent.

■ Can osteodystrophy be treated?

Knowledge of the mechanisms involved in this disorder is incomplete. Certain measures are generally accepted including the following:

1. Aluminum hydroxide preparations, (used as antacids in the treatment of peptic ulcer) are given in large doses. The aluminum hydroxide binds phosphorus in the gut and prevents its absorption. This lowers the serum phosphorus, allowing serum calcium to rise (hence, hopefully, reducing the response of the parathyroid glands), and reduces the likelihood of soft tissue calcification.

2. Oral intake of dairy products is restricted, since they are high in phosphorus content.

3. An oral calcium supplement (calcium carbonate, lactate, or gluconate) is given by some centers to overcome the absorptive defect of calcium. This should not be done until the serum phosphorus is under good control with aluminum hydroxide gel. Absorption is not predictable, and very large doses may be necessary.

4. The dialysis bath concentration of calcium should be kept at 3 mEq/L (6 mg/100 ml). A few units prefer a bath concentration of 4 mEq/L calcium. At lower levels there is a net loss of calcium from blood to bath, which aggravates the bone depletion. Higher bath calcium levels have been tried, but they often cause agitation, nausea, and vomiting during dialysis.

5. Vitamin D has been given when the serum calcium is low. Dosage is difficult to adjust—2 to 3 weeks are necessary to detect its effect—and should the serum calcium rise *higher* than normal, the effect of the vitamin requires many weeks to wear off.

Recent work has shown the kidneys are the normal site of conversion of vitamin D to the metabolically active form, 1,25-dihydroxycholecalciferol. This agent has been synthesized and is under investigation as a potent agent to alter calcium-phosphorus metabolism in uremia.

6. In instances in which it is clear that parathyroid gland overactivity is a major factor, subtotal parathyroidectomy is surgically performed (removal of seven eighths of the glands).

■ **What are the symptoms and findings of acute hepatitis?** 165

Jaundice (icterus) is the classic finding of hepatitis. However, cases of active hepatitis *without* jaundice (anicteric) greatly outnumber those with jaundice among dialysis patients.

Other symptoms are malaise, poor appetite, nausea, and in cigarette smokers the complaint that cigarettes do not taste right. There may be tenderness over the liver.

Serum bilirubin may be minimally elevated in anicteric patients. SGOT often is raised several orders of magnitude. Alkaline phosphatase may be elevated briefly.

■ **What is the risk of hepatitis in dialysis units?**

In the general United States population the reported incidence of all types of hepatitis is 0.02% to 0.03%.

In the period 1968 to 1970, there was a 10% incidence of diagnosed hepatitis in dialysis patients and a 4% incidence among personnel. A 1973 study of fifteen centers (slightly less than 1% of the total United States dialysis population) reported presence of HB Ag or HB Ab in 50% of patients and 30% of staff.

A 1972 review of European centers indicated nearly 20% of patients had either clinical B virus hepatitis or were HB Ag positive. Among European staff members who developed hepatitis in 1972, the fatality rate was 2.4%.

■ **Why is hepatitis such a problem in dialysis units?**

1. The uremic individual, because of diminished immune response, may have hepatitis without symptoms and with minimal laboratory findings other than HB Ag. Only 30% of patients develop jaundice. Patients who become HB Ag positive may remain so without developing HB Ab for prolonged periods and must be considered chronic carriers.

2. The dialysis environment is unique in potential for virus spread. Limited space, frequent blood spillage, and innumerable uses of needles contribute to ideal conditions for spread of the virus once introduced.

3. Emergency dialysis may bring unscreened patients—who may be carriers—into the unit. A report of a positive HB Ag after such a patient has already been dialyzed several times is too late.

■ **Is neuropathy relieved by dialysis?**

If dialysis is begun early, when burning feet or restless legs are the only symptoms or only prolongation of conduction time is demonstrable, frequent dialysis may prevent worsening. More severe nerve damage responds very slowly to dialysis, if at all. If the amount and frequency of dialysis are not adequate, neuropathy may develop or, if already present, will worsen.

Joint disorders

Uric acid is frequently elevated in chronic dialysis patients. This hyperuricemia may be associated with a goutlike involvement of one or more joints. Occasionally there is a true gouty attack, but most episodes are of pseudogout.

■ What is pseudogout?

Pseudogout is an acute inflammation, usually involving a single area at or near a joint. The back of the hand or wrist, finger joints, and shoulders are common locations. Pain comes on abruptly, followed rapidly by tenderness, swelling, and limitation of motion. This lasts 3 to 5 days or longer unless treated.

■ How may it be treated?

Usually the physician will prescribe colchicine or phenylbutazone (Butazolidin) or indomethacin (Indocin). They most often relieve the distress in 24 to 36 hours.

■ Are there residual effects of pseudogout?

Soft tissue swelling may persist for several weeks. One can often see areas of calcification at these sites by x-ray.

■ Is there any preventative treatment?

Frequent dialysis should keep the uric acid below serious levels. If the uric acid level persists at 10 ml/100 ml or higher, use of allopurinol to lower it should be considered. The patient needs to faithfully take his aluminum hydroxide, since phosphate has an important role in the deposition of calcium in soft tissue.

Gastrointestinal problems

■ Is peptic ulcer disease common in dialysis patients?

Medical opinion varies; some reports cite an increased incidence of peptic ulcer, others do not. There are reports of higher than normal gastric acidity related to high blood levels of gastrin, which may be in turn related to parathyroid overactivity. Other works indicate lower gastric acidity, presumably related to increased urea and hence ammonia. Our own experience, supported by others, suggests the incidence of ulcer disease in dialysis patients is some 10% to 12%, which is the same as for the nonuremic general population.

It has been an impression that peptic ulcer disease may be relatively nonsymptomatic in dialysis patients, with a greater propensity for sudden massive bleeding without warning.

■ Why is prevention of constipation important?

Because of diet, limited fluid intake, and regular ingestion of aluminum hydroxide, it is easy for the dialysis patient to become quite constipated or to develop fecal impactions. As more older patients are taken into dialysis programs, there is more functional constipation. More important, however, these people have a much higher instance of colon diverticuli. Diverticulitis or perforation is not rare. Hematomas of the bowel and even perforation after injudicious enemas have occurred.

■ How should constipation be treated?

Cathartics and laxatives should be avoided. Stool softeners, such as dioctyl sodium sulfosuccinate (Colace) or dioctyl cal-

cium sulfosuccinate (Surfak), seem to work well, although they are expensive and often require larger than usual doses. Usually a patient can arrive at a satisfactory individual dose.

Ascites

Ascites is a relatively infrequent problem that may be very troublesome. Most cases are related to repeated fluid overload and to poor nutrition. Abnormal cell membrane permeability may be a factor. Although some patients survive and overcome their ascites, the more common course is deterioration and death.

Reproductive tract problems

Menstrual dysfunction. Women commonly have cessation of menstruation as a part of the uremic syndrome. Some resume normal periods after dialysis is begun and with improvement in general health. Often, however, periods are irregular or flow excessive and/or prolonged. This may be aggravated by heparinization.

Since excess blood loss should be avoided, menstrual abnormalities should be brought to the physician's attention. Most excessive menstrual loss can be controlled without surgical intervention or by curettement only.

Infertility. Infertility, both male and female, is the rule. Biopsy studies indicate poor sperm formation in most men. The exact mechanism is less clear in women but is presumed to be endocrine in nature. Fewer than ten known term pregnancies have been reported around the world in female maintenance dialysis patients.

Sexual problems. Sexual dysfunction is a real problem for the majority of maintenance dialysis patients. Reduction of libido and impotence in men are common as uremia develops. The few studies that have been done suggest that this is not improved with return to general well-being after regular dialysis is begun and may indeed worsen.

The reasons for failure of sexual function to improve are unclear. It is usual to ascribe it to an emotional basis, and there is little doubt that there are many psychologic implications. However, there is a distinct possibility that nervous system abnormalities or subtle hormonal dysfunctions are involved. Little or no investigation has been reported in this area.

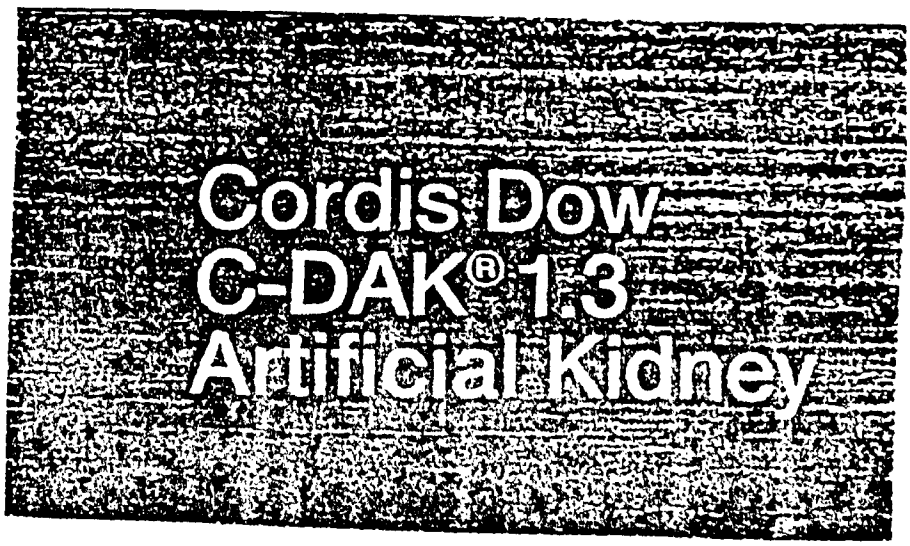
Insomnia

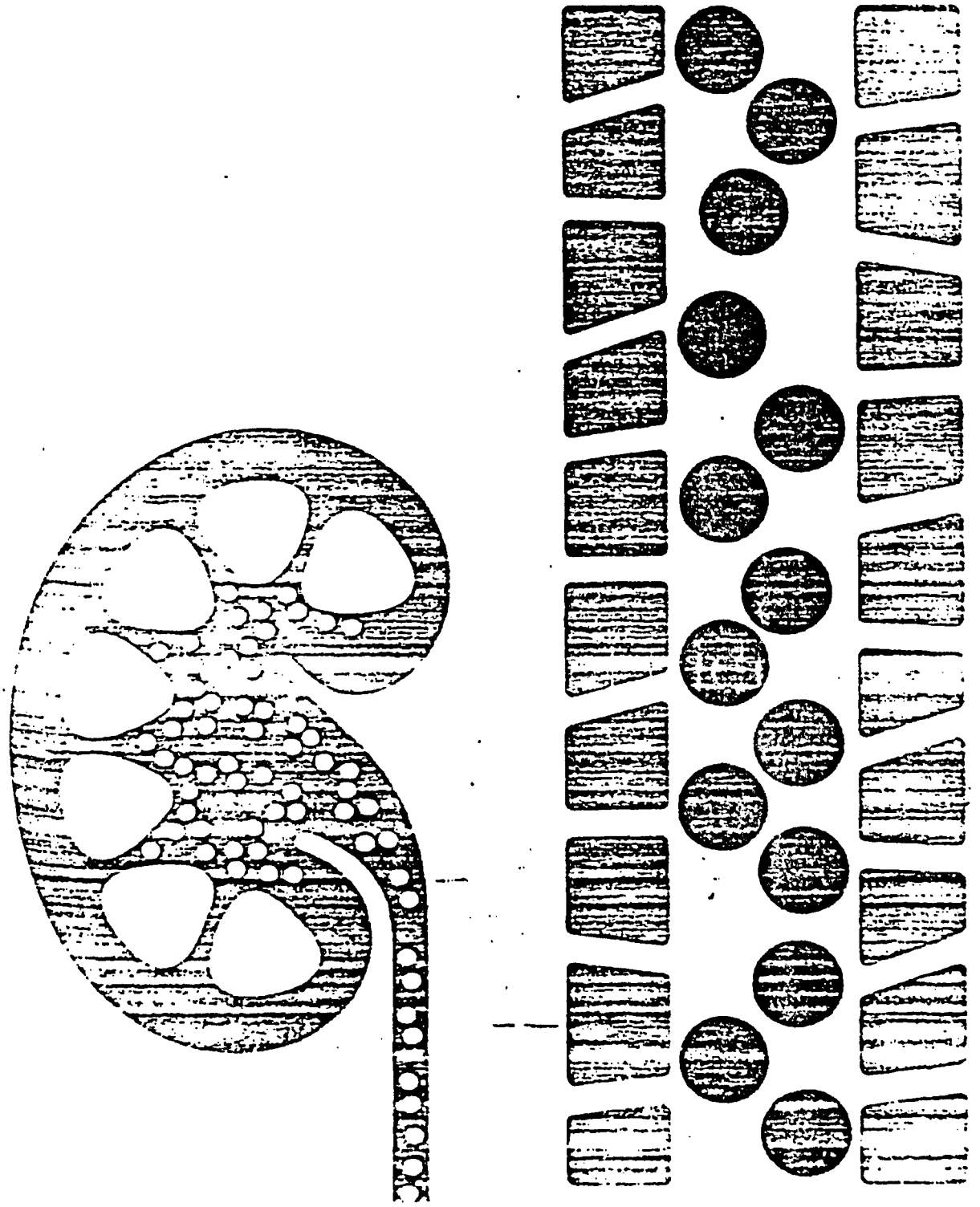
Inability to sleep, or fitful sleeping during the usual hours of rest, is a common complaint. The cause is obscure. Often the patients sleeps throughout the dialysis procedure, and it may be that the need for sleep is reduced. Other patients seem to have a pathologic inability to rest soundly.

Response to sedatives and tranquilizers is usually poor and the risk of dependency considerable. Often the best answer is for the patient simply to get up and perform some boring task until sleep comes. We have seen no adverse effects from the lack of sleep and suspect the problem is most often one of fitful or interrupted sleep—which is interpreted as "no sleep."

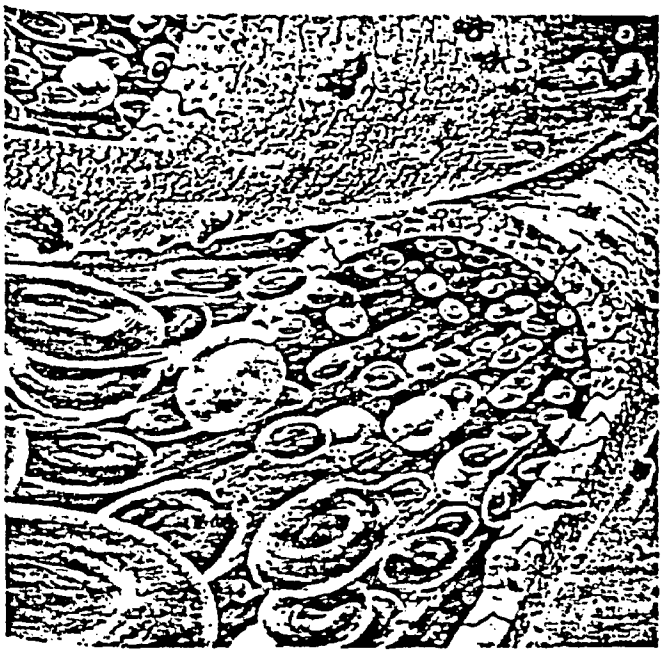
APPENDIX E

CORDIS DOW HOLLOW FIBER HEMODIALYZERS AND THEIR CLEARANCE PROPERTIES

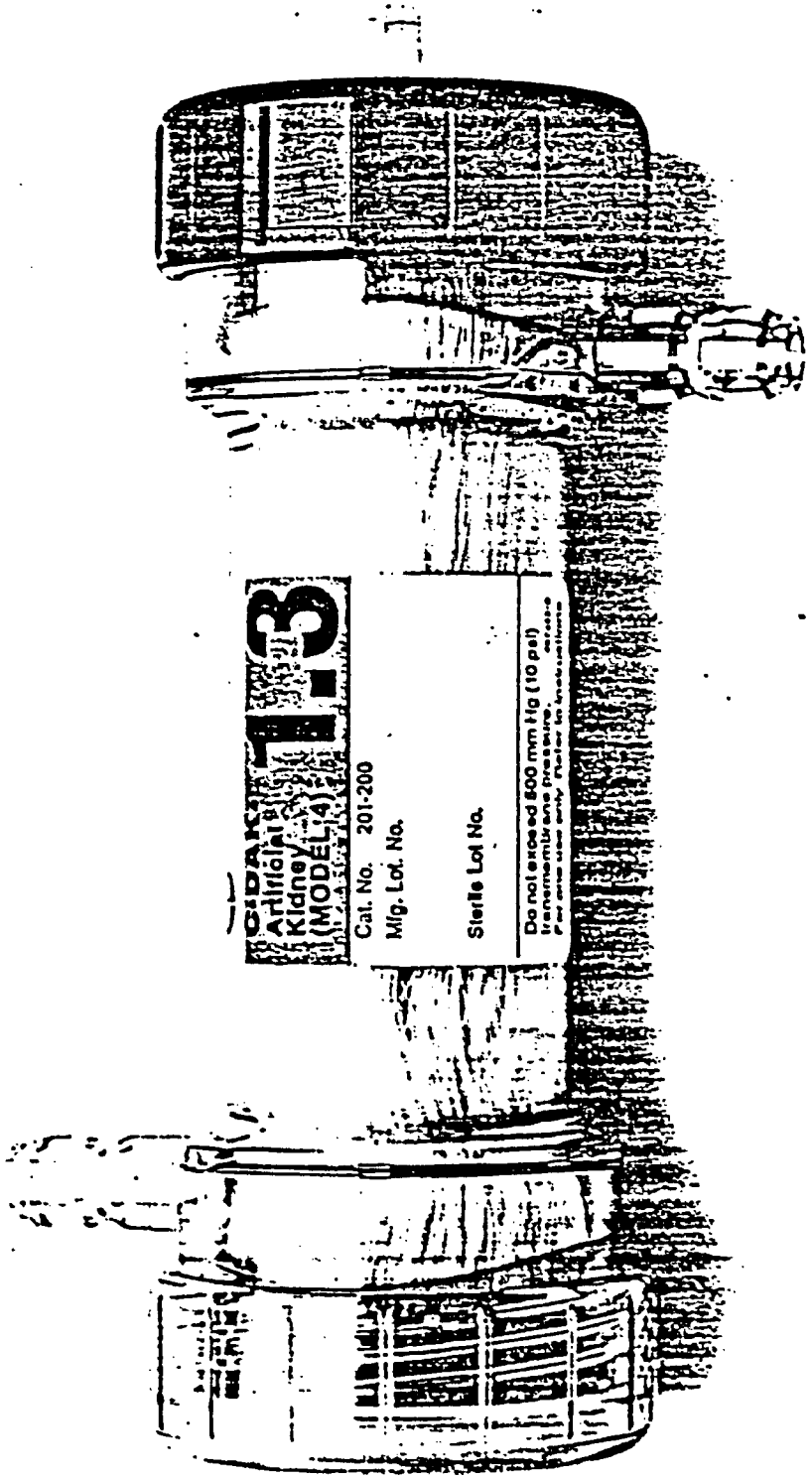




The C-DAK® 1.3 Artificial Kidney



Artist's representation of blood flow and solute removal through the hollow fibers of the C-DAK® Artificial Kidney.



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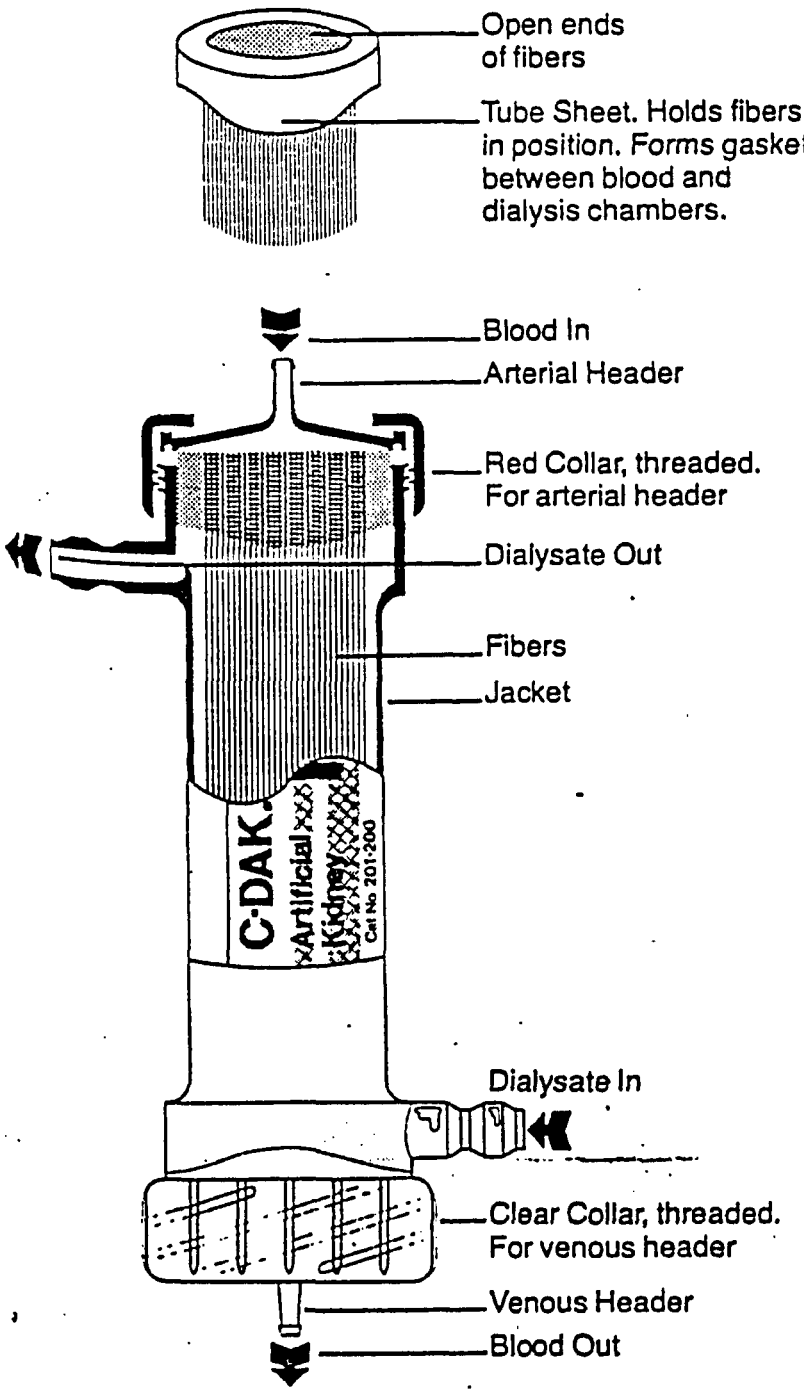
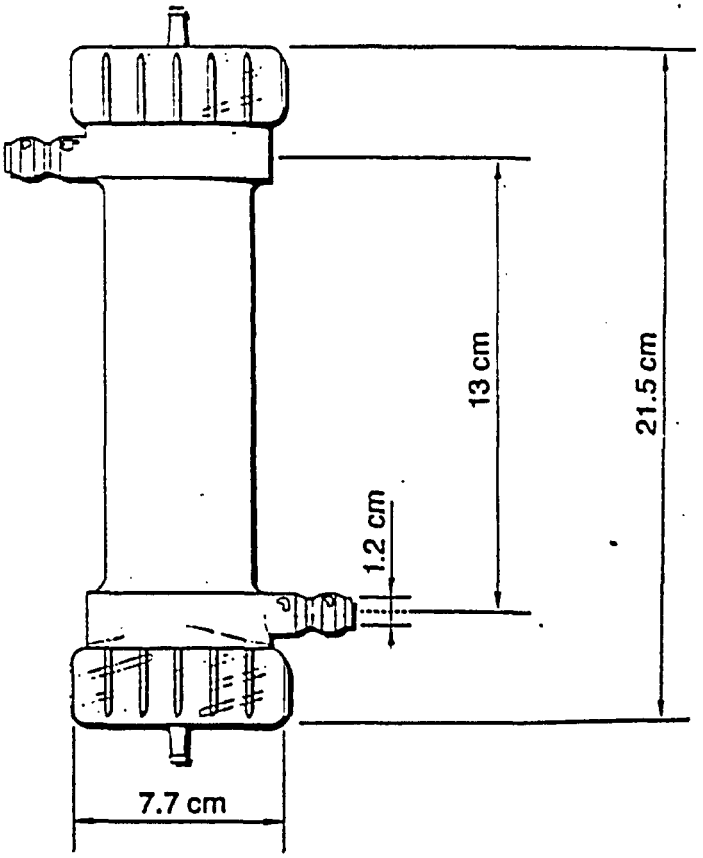


Specifications



Dimensions:	21.5 cm (8½ in.) long x 7.7 cm ($3^{1}/_{16}$ in.) diameter
Weight (filled):	650 gm (1½ lb) (approx.)
Blood volume:	100 ml average
Dialysate volume:	100 ml average
Fibers	
Material:	Regenerated cellulose
Quantity:	13,500
Effective length:	16 cm
Inside diameter:	200 μ
Wall thickness:	30μ
Effective surface area:	1.3 m^2 (approx.)

Catalog No. 201-200

Features and Characteristics

The Quality of Life is important to everyone, including those persons whose renal function is insufficient to support life without chronic dialysis. People undergoing dialysis want to *live*. For them, survival has never been the only point, and today more than ever there is a widespread desire for true rehabilitation and the attainment of an acceptable quality of life through technical and other important advances in the dialysis field. Thus the need to shorten time on dialysis and somehow improve treatment has stimulated the costly and often frustrating search for better dialyzers . . . dialyzers that can significantly improve the quality of life for those who must use them.

The development of the Cordis Dow Artificial Kidney with its unique hollow fiber design, small size, low priming volume, high efficiency, and controlled ultrafiltration capability has been a significant step toward improving the lives of dialysis patients. The features and performance of the C-DAK help minimize the time and effort patients must devote to their dialysis regimens. The superior design and resulting efficiency of the C-DAK have established it as the standard for comparison within the hemodialysis community. The C-DAK has met the demands for overall reliabilty, suitability for use within various treatment philosophies, and adaptability to available equipment and to individual patient needs. In addition, the geometry of the C-DAK hollow fiber blood compartment makes it possible to take maximum advantage of progress in membrane technology. In this respect, present C-DAK models are leading the way to a still more effective family of dialyzers in the future.

The C-DAK offers several important benefits to the patient and the medical staff with regard to the basic parameters that define dialyzer performance—i.e., solute removal, fluid removal, and blood priming volume. These performance benefits are discussed in the following sections.

Solute Removal

The C-DAK 1.3 is a small but efficient dialyzer. Its 1.3 m^2 surface is effective for mass solute transfer because the hollow fibers do not require a support mesh. Other designs cannot match the C-DAK in terms of the ratio of surface area (1.3 m^2) to blood volume (100 ml).

The physical dimensions of the blood channels in the C-DAK are optimal in terms of blood film thickness, resistance to blood flow, number of blood channels, channel width, and membrane thickness.

Another important advantage of the C-DAK over other designs is its predictable membrane permeability. The porosity of the membrane is controlled throughout manufacturing. As a result, variations in porosity fall within a predictable range, and this predictability offers reproducible solute removal and ultrafiltration. Control of permeability also facilitates the continued search for more efficient membranes.

Fluid Removal

Accurate control of fluid removal is provided without intermittent infusion of saline. As one physician has observed: "This offers a great advantage: by knowing dialysis time and weight gain, we are able to predetermine weight loss and therefore the necessary negative pressure." (1)

Blood Priming Volume

Traditionally, the priming volume of dialyzers has been expressed as static priming volume. However, as blood flow rate and pressure are increased to their operating ranges, the blood compartment in most dialyzers expands, leading to a shift of as much as 300 ml of blood from the patient to the dialyzer.

The C-DAK is the only dialyzer available that has a truly nonexpandable blood compartment. According to Gotch et al., "The small blood volume in the dialyzer . . ., which is fixed and does not increase more than one or 2 ml with high negative pressure, was found very helpful in virtually eliminating the hypotensive complications of dialysis which these patients frequently experience with other dialyzers." (2)

Summary

The C-DAK represents an important advance toward a better quality of life for hemodialysis patients. C-DAK advantages include: (a) significantly greater mass transfer of solutes, resulting in efficient urea and creatinine removal; (b) controllable ultrafiltration; (c) nonexpandable blood compartment; and (d) a low ratio of priming volume to surface area.

The following conclusion should interest both dialysis centers and home patients: "I have seen no dialyzer so easy to handle with any kind of equipment, neither bedside proportioning systems nor central delivery systems, as the hollow fiber kidney." (3) The author adds: "The ease of handling, storing and shipping make it a favorite of our seven home dialysis patients who use this device. The simplicity of setup and operation save valuable technician time in the hospital." (4)

High Efficiency of Solute Removal — permits shorter dialysis time than other passive/flow dialyzers. Advantageous Ratio of Large Membrane Surface Area to Small Volume — permits compactness with high efficiency. Small Blood Compartment (Priming) Volume — minimizes hypotensive tendency. Small, Fixed Blood Channel Height — maintains constant blood and dialysate volumes regardless of pressure changes. Operational Flexibility — adaptable to most dialysate systems; low resistance permits passive or pumped blood flow. Lightweight and Compact — ease of handling, storing and shipping. Simplicity of Setup and Operation — convenient for use in home or clinic. Disposability — reliable, timesaving, reduces risk of infection. Variable Ultrafiltration — selecting negative pressure allows control of ultrafiltration

Performance Characteristics

1. Typical flow resistance in blood compartment at blood flow rate of 200 ml/min whole blood: 20 mm Hg.
2. Typical flow resistance in dialysate compartment at dialysate flow rate of 500 ml/min: 10 mm Hg.
3. Typical clearances at 200 ml/min blood flow and 500 ml/min dialysate flow (see Fig. A):

Urea	160 ml/min	Uric acid	110 ml/min
Creatinine	133 ml/min	Phosphate	90 ml/min

4. Typical clearance of Vitamin B_{12}, as measured in vitro is 23 ml/min.
5. Typical *in vitro* ultrafiltation rate: 1.8 to 2.0 ml/hour per mm Hg transmembrane pressure. For example, at 300 mm Hg and 37°C, ultrafiltration will be 540 to 600 ml/hour. See Fig. B.

Note: Operation of the dialyzer under clinical conditions may produce slightly different ultrafiltration from that illustrated because of the variables involved in the clinical dialysis procedure.

Figure A ▲ Urea ■ Creatinine ○ Uric acid ● Phosphate

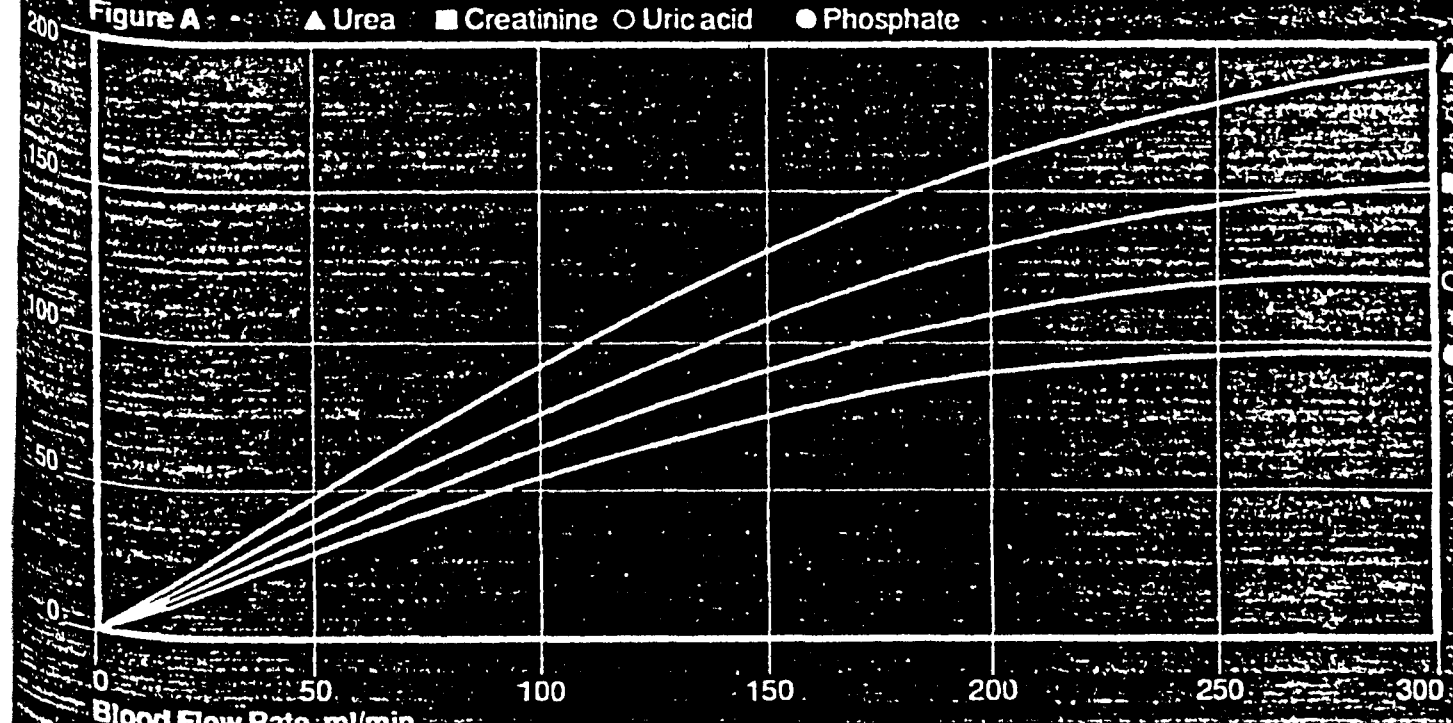
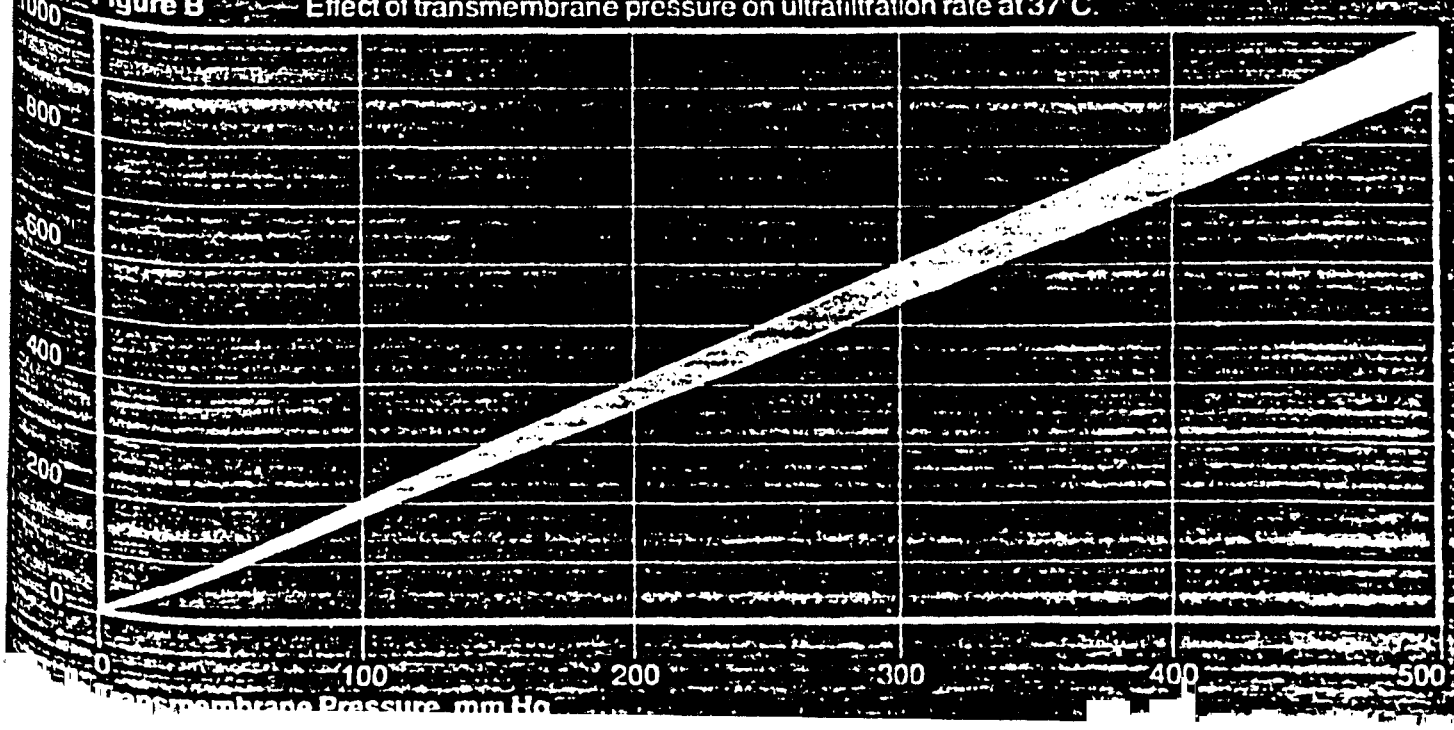


Figure B Effect of transmembrane pressure on ultrafiltration rate at 37°C.



Indications: Hemodialysis is indicated for patients with acute or chronic renal failure, when conservative therapy is judged to be inadequate.

Contraindications: There are no absolute contraindications to hemodialysis therapy recognized by the medical community.

Warnings and Precautions:

This dialyzer is intended for one use only. DO NOT REUSE.

Side effects such as hypertension, hypotension, headache and nausea which may be associated with dialysis can usually be avoided by careful management of the patient's fluid and electrolytic balance, blood flow rate and transmembrane pressure. Other complications such as blood loss, hemolysis, excessive ultrafiltration and electrolyte imbalance have been associated with equipment malfunction or procedural error associated with hemodialysis.

The blood pathway of this dialyzer is sterile and non-pyrogenic in an unopened, undamaged bag. Do not use if the bag is received open or the blood port caps are missing. An aseptic technique is required to avoid contamination of the blood path when connecting the blood lines and pateint to the dialyzer.

This dialyzer is sterilized with an aqueous solution containing formaldehyde. Care must be taken to insure that the formaldehyde solution is flushed from the dialyzer prior to use. Possible adverse reactions can occur to patients infused with formaldehyde. Refer to instruction manual for detailed setup and rinse procedure.

Do not exceed a transmembrane pressure of 500 mm Hg with this dialyzer.

All connections must be checked carefully prior to and during the first minutes of operation. At several times during dialysis there should be visual inspection of the connections to detect leaks and avoid blood loss.

7. Warning: Air entering the extracorporeal blood circuit if undetected, may cause fatal air embolism. The use of an air/foam detector is recommended at all times. Air return of blood to the patient at the termination of dialysis is not recommended due to the increased chance of air embolism to the patient.
8. Cordis Dow Artificial Kidneys can be damaged by high or low temperature. Suggested ambient temperature range is 32°F (0°C) to 100°F (38°C).
9. If tap water is used to rinse the C-DAK, be sure that the fluid in the dialysate and blood compartments is within proper dialyzing limits before initiating dialysis.
10. Although this dialyzer has been tested for mechanical integrity, there is a possibility that a leak may occur during dialysis leading to blood loss. Therefore constant monitoring by means of a blood leak detector in the dialyzing fluid line of the dialysis machine is recommended.

Frequency and duration of treatment is to be determined by the prescribing physician.

Refer to instructions manual for more complete information prior to use.

Caution: Federal (U.S.A.) law restricts this device to sale by or on order of a physician.

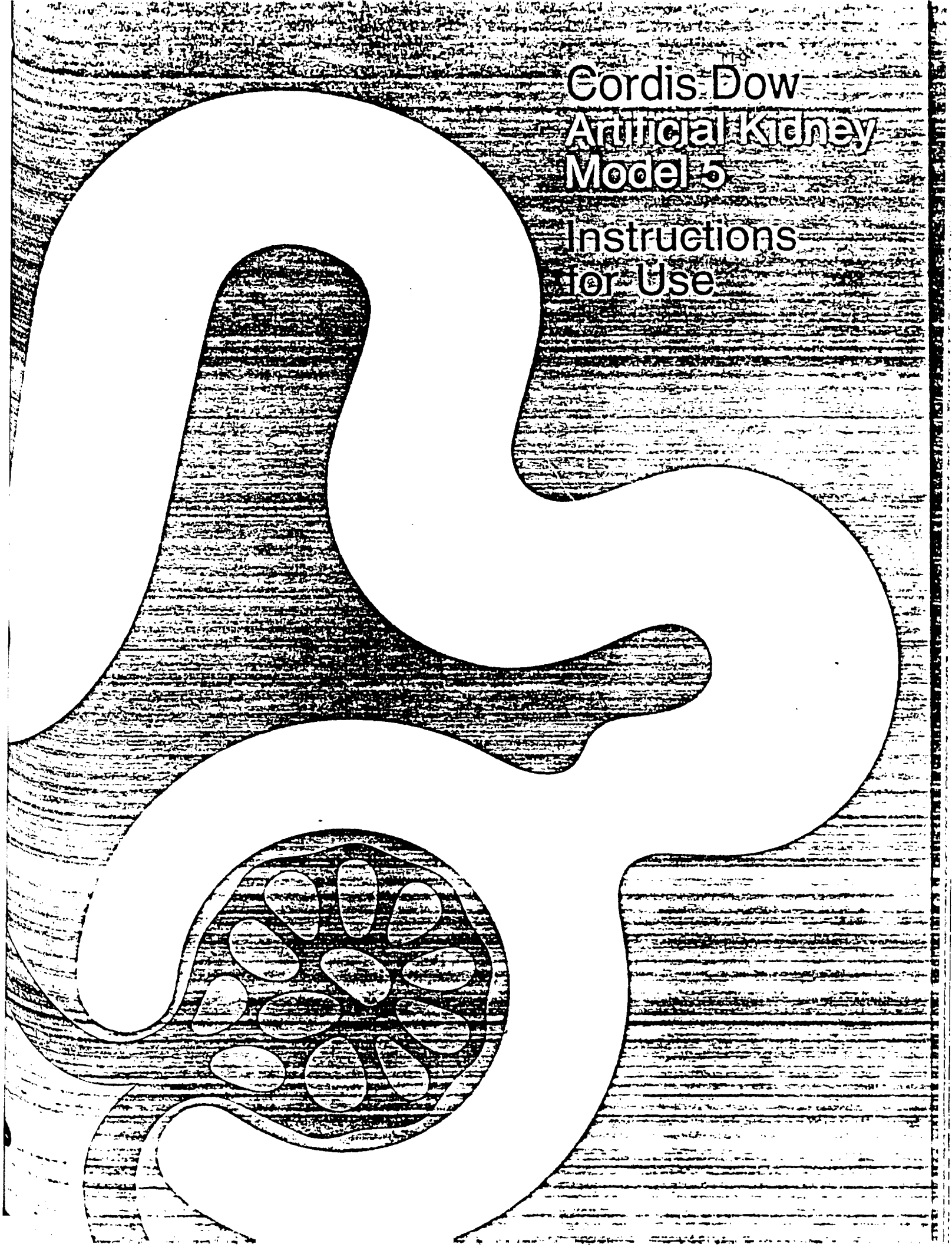
References

1. Pinggera W: The fiber dialyzer. *J. Extra-Corporeal Tech.* 4:6, 8, 15, 16, 1871.
2. Gotch F, Lipps BJ, Weaver Jr J, Brandes J, Rosen J, Sargent J, Oja PD: Chronic hemodialysis with the hollow fiber artificial kidney (HFAK). *Trans Amer Soc Artif Intern Organs* 15:95, 1969.
3. Pinggera W, op. cit., p. 6.
4. Ibid, p. 16.

Cordis Dow Corp.
Post Office Box 450990
Miami, Florida 33145, U.S.A.

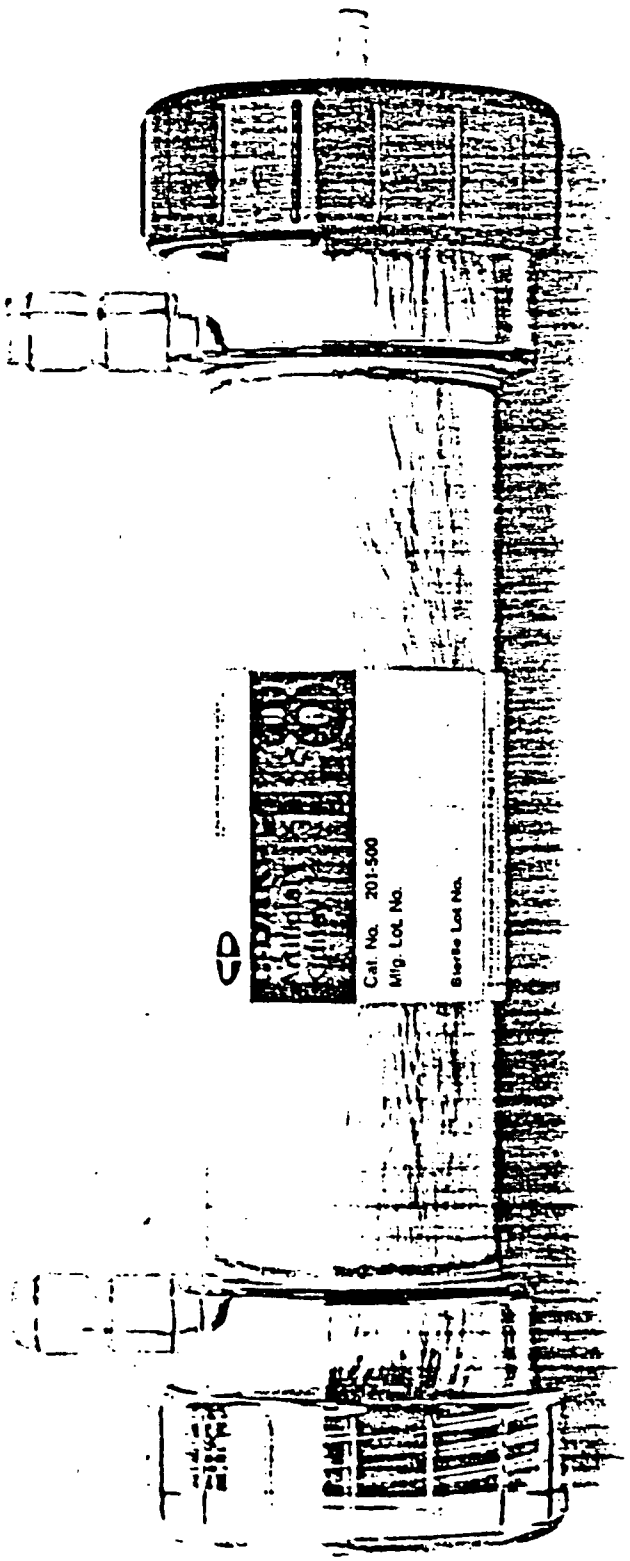
Cordis Dow Artificial Kidney Model 5

Instructions for Use



The C-DAK® 1.8 Artificial Kidney

Artist's representation of blood flow and solute removal through the hollow fibers of the C-DAK® Artificial Kidney.



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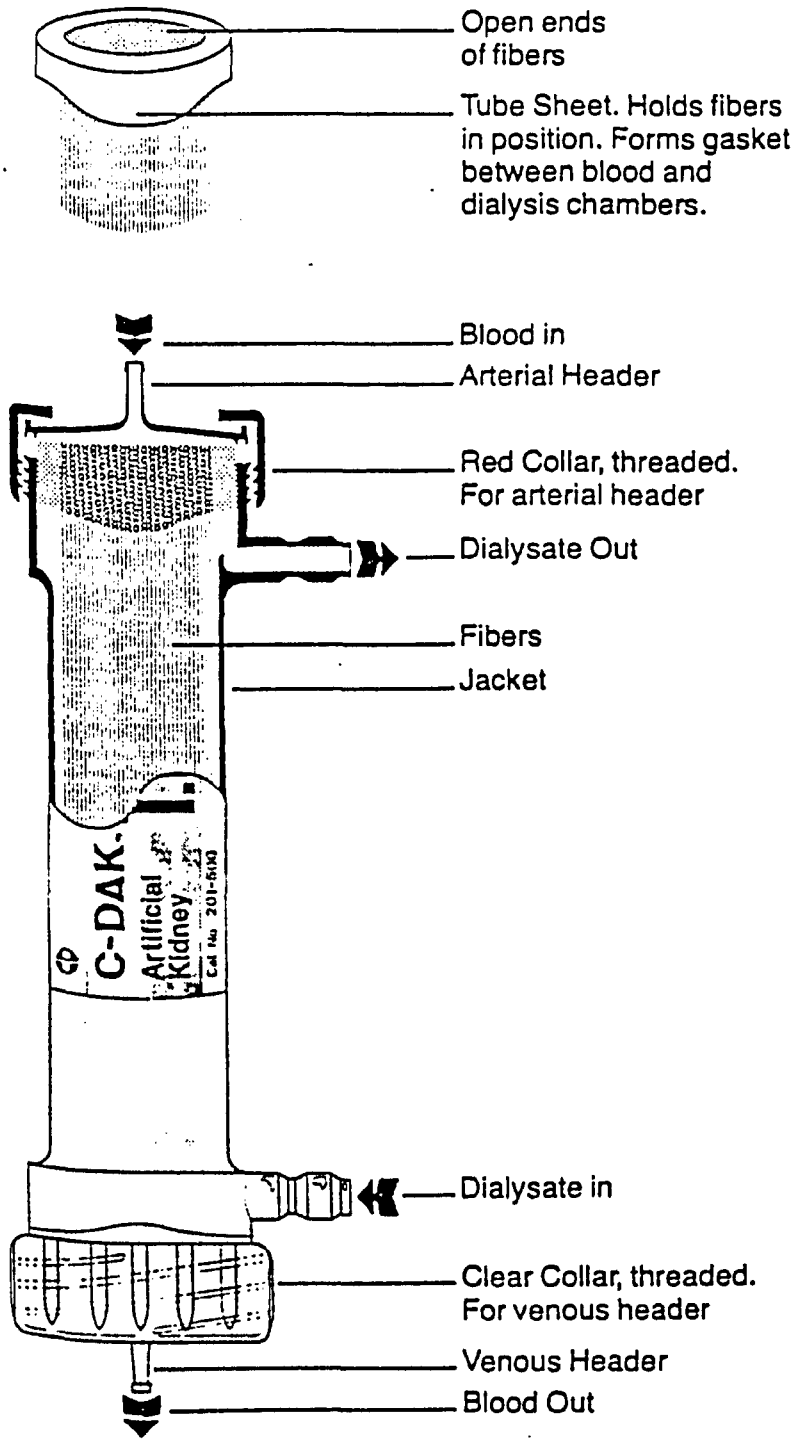

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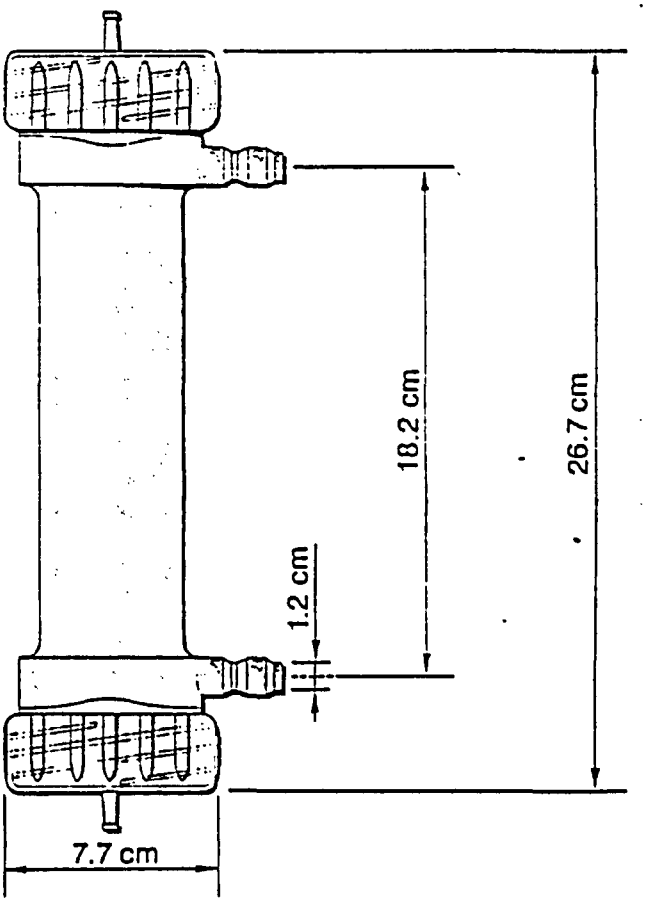

Dimensions:	26.7 cm long x 7.7 cm diameter
Weight (filled):	760 gm (1⅔ lb., approx.)
Blood volume:	135 ml average
Dialysate volume:	150 ml average

Fibers

Material:	Regenerated cellulose
Quantity:	13,500
Effective length:	21 cm
Inside diameter:	200 μ
Wall thickness:	30 μ
Effective surface area:	1.8 m² (approx.)

Catalog No. 201-500

Features and Characteristics

The development of the C-DAK® Artificial Kidney, with its unique hollow fiber design, small size, low priming volume, high efficiency, and controlled ultrafiltration capability, is recognized throughout the world as a significant step toward improving the quality of life for hemodialysis patients.

The need to advance hemodialysis treatment continues to be the stimulus for Cordis Dow's search for better hollow fiber dialyzer designs.

The addition of the 1.8m² hollow fiber dialyzer (the C-DAK 1.8 Artificial Kidney) to the Cordis Dow family of dialyzers offers added design features for meeting specific patient requirements.

C-DAK 1.8 Design Features

The C-DAK 1.8 Artificial Kidney combines features of the C-DAK 1.3 and the C-DAK 2.5 by using the same jacket diameter, number of fibers, header, and screw bands as the C-DAK 1.3, and adding the length of the C-DAK 2.5. These features have made it possible to increase the volume of the blood compartment to only 35 ml more than that of the C-DAK 1.3 Artificial Kidney.

Improved Clearances and Ultrafiltration

The C-DAK 1.8 Artificial Kidney provides performance characteristics that fall between those of the C-DAK 1.3 and the C-DAK 2.5. By improving the ultrafiltration by approximately 30% over the C-DAK 1.3, and also increasing clearances somewhat, a greater flexibility in ultrafiltration combinations can be offered to meet specific patient requirements.

C-DAK Features and Characteristics

High Efficiency and Solute Removal may permit shorter dialysis time than other passive-flow dialyzers. Advantageous Ratio of Large Membrane Surface Area to Small Volume — permits compactness with high efficiency. Small Blood Compartment (Priming) Volume — minimizes hypotensive tendency. Small, Fixed Blood Channel Heights — maintain constant blood and dialysate volumes regardless of pressure changes. Operational Flexibility — adaptable to most dialysate systems; low resistance permits passive or pumped blood flow. Lightweight and Compact — ease of handling, storing, and shipping. Simplicity of Setup and Operation — convenient to use in home or clinic. Disposability — reliable, timesaving, reduces risk of infection. Variable Ultrafiltration — selecting negative pressure allows control of ultrafiltration rate independent of solute clearances.

Indications: Hemodialysis is indicated for patients with acute, or chronic renal failure; when conservative therapy is judged to be inadequate.

Contraindications: There are no absolute contraindications to hemodialysis therapy recognized by the medical community.

Warnings and Precautions:

This dialyzer is intended for one use only. DO NOT REUSE

Side effects such as hypertension, hypotension, headache and nausea which may be associated with dialysis can usually be avoided by careful management of the patient's fluid and electrolytic balance, blood flow rate and transmembrane pressure. Other complications such as blood loss, hemolysis, excessive ultrafiltration and electrolyte imbalance have been associated with equipment malfunction or procedural error associated with hemodialysis.

The blood pathway of this dialyzer is sterile and non-pyrogenic in an unopened, undamaged bag. Do not use if the bag is received open or the blood port caps are missing. An aseptic technique is required to avoid contamination of the blood path when connecting the blood lines and patient to the dialyzer.

This dialyzer is sterilized with an aqueous solution containing formaldehyde. Care must be taken to insure that the formaldehyde solution is flushed from the dialyzer prior to use. Possible adverse reactions can occur to patients infused with formaldehyde. Refer to instruction manual for detailed setup and rinse procedure.

Do not exceed a transmembrane pressure of 500 mm Hg with this dialyzer.

All connections must be checked carefully prior to and during the first minutes of operation. At several times during dialysis there should be visual inspection of the connections to detect leaks and avoid blood loss.

7. Warning: Air entering the extracorporeal blood circuit, if undetected, may cause fatal air embolism. The use of an air/foam detector is recommended at all times. Air return of blood to the patient at the termination of dialysis is not recommended due to the increased chance of air embolism to the patient.
8. Cordis Dow Artificial Kidneys can be damaged by high or low temperature. Suggested ambient temperature range is 32°F (0°C) to 100°F (38°C).
9. If tap water is used to rinse the C-DAK, be sure that the fluid in the dialysate and blood compartments is within proper dialyzing limits before initiating dialysis.
10. Although this dialyzer has been tested for mechanical integrity, there is a possibility that a leak may occur during dialysis leading to blood loss. Therefore constant monitoring by means of a blood leak detector in the dialyzing fluid line of the dialysis machine is recommended.

Frequency and duration of treatment is to be determined by the prescribing physician.

Refer to instructions manual for more complete information prior to use.

Caution: Federal (U.S.A.) law restricts this device to sale by or on order of a physician.

Cordis Dow Corp.
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Miami, Florida 33145, U.S.A.

Performance Characteristics

1. Typical flow resistance in blood compartment at blood flow rate of 200 ml/min whole blood of hematocrit 20: 30 mm Hg.
2. Typical flow resistance in dialysate compartment at dialysate flow rate of 500 ml/min: 13 mm Hg.
3. Typical clearances at 200 ml/min blood flow and 500 ml/min dialysate flow rates: (see Fig. A):

Urea	172 ml/min	Uric Acid	137 ml/min
Creatinine	150 ml/min	Phosphate	124 ml/min

4. Typical clearance of Vitamin B^{12}, as measured in vitro is 28 ml/min with an ultrafiltration rate of 10 ml/min.
5. Typical in vitro ultrafiltration: 2.2 to 2.5 ml/hour per mm Hg transmembrane pressure. For example, at 300 mm Hg ultrafiltration will be 660 to 750 ml/hour. See Fig. B.

Note: Operation of the dialyzer under clinical conditions may produce slightly different ultrafiltration from that illustrated because of the variables involved in the clinical dialysis procedure.

Figure A

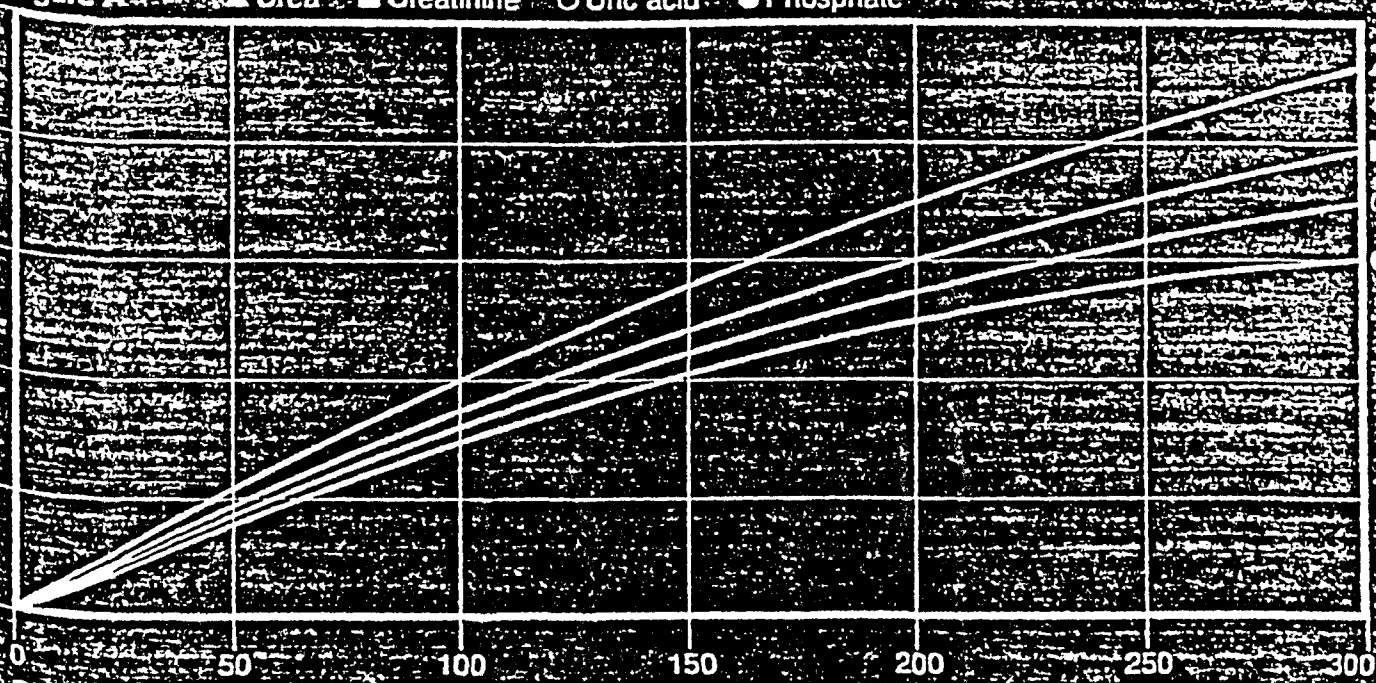
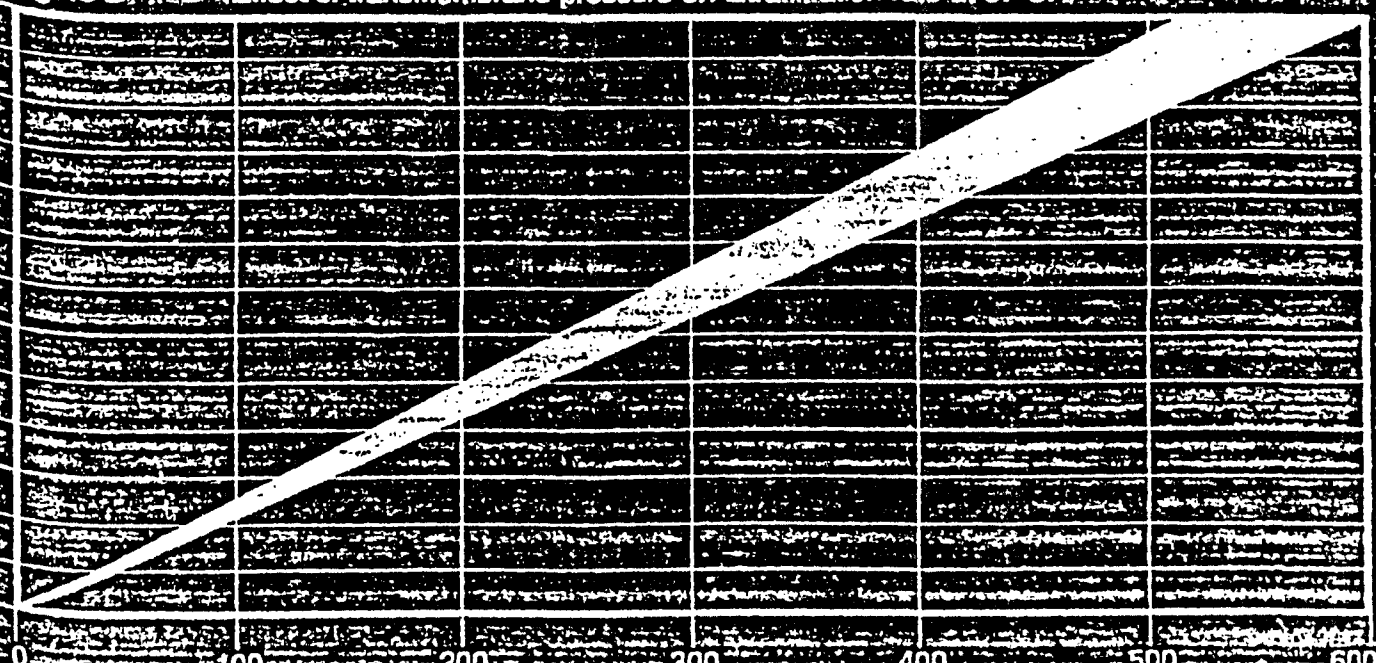
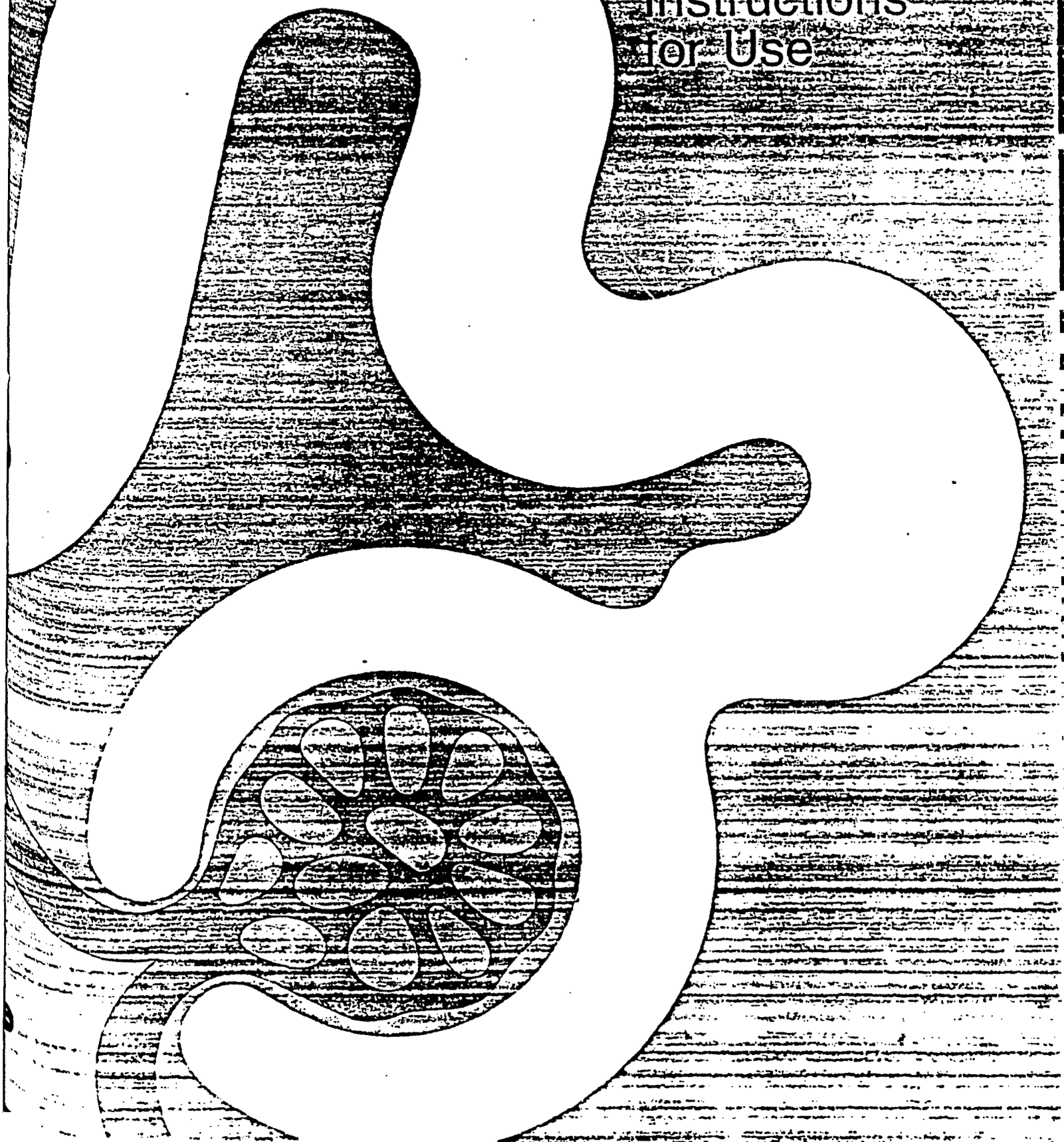


Figure B. Effect of transmembrane pressure on ultrafiltration rate at 37°C.



Cordis Dow Artificial Kidney Model 5

Instructions for Use



Description and Function

The Cordis Dow Artificial Kidney (C-DAK©) is a disposable hemodialyzer designed to be used at clinical centers or in the home. Dialysis takes place through small-diameter hollow fibers produced from a polymeric material specifically designed for hemodialysis. The C-DAK offers high dialysis efficiency along with other important advantages.

The C-DAK is manufactured by the Cordis Dow Corporation, which is owned jointly by Cordis Corporation and The Dow Chemical Company.

The construction, clinically obtained performance characteristics, and a diagram of the Model 5 are described on the following pages. Please refer to this material before using the Model 5 C-DAK.

Caution

Because of its large surface area (2.5 square meters), the Model 5 C-DAK is a highly efficient dialyzer. It is therefore recommended for use only with patients who can tolerate the rapid removal of solutes and water.

Cordis Dow Artificial Kidneys and related equipment should be discarded after one use because their integrity or function may be impaired through use or cleaning. In addition, blood components are extremely difficult to remove completely from these items, and therefore adverse patient reactions may result from reuse.

The Cordis Dow Artificial Kidney can be damaged by high or low temperatures. Suggested ambient temperature range: 32°F (0°C) to 98°F (37°C).

Federal (U.S.A.) law restricts this device to sale by or on the order of a physician.

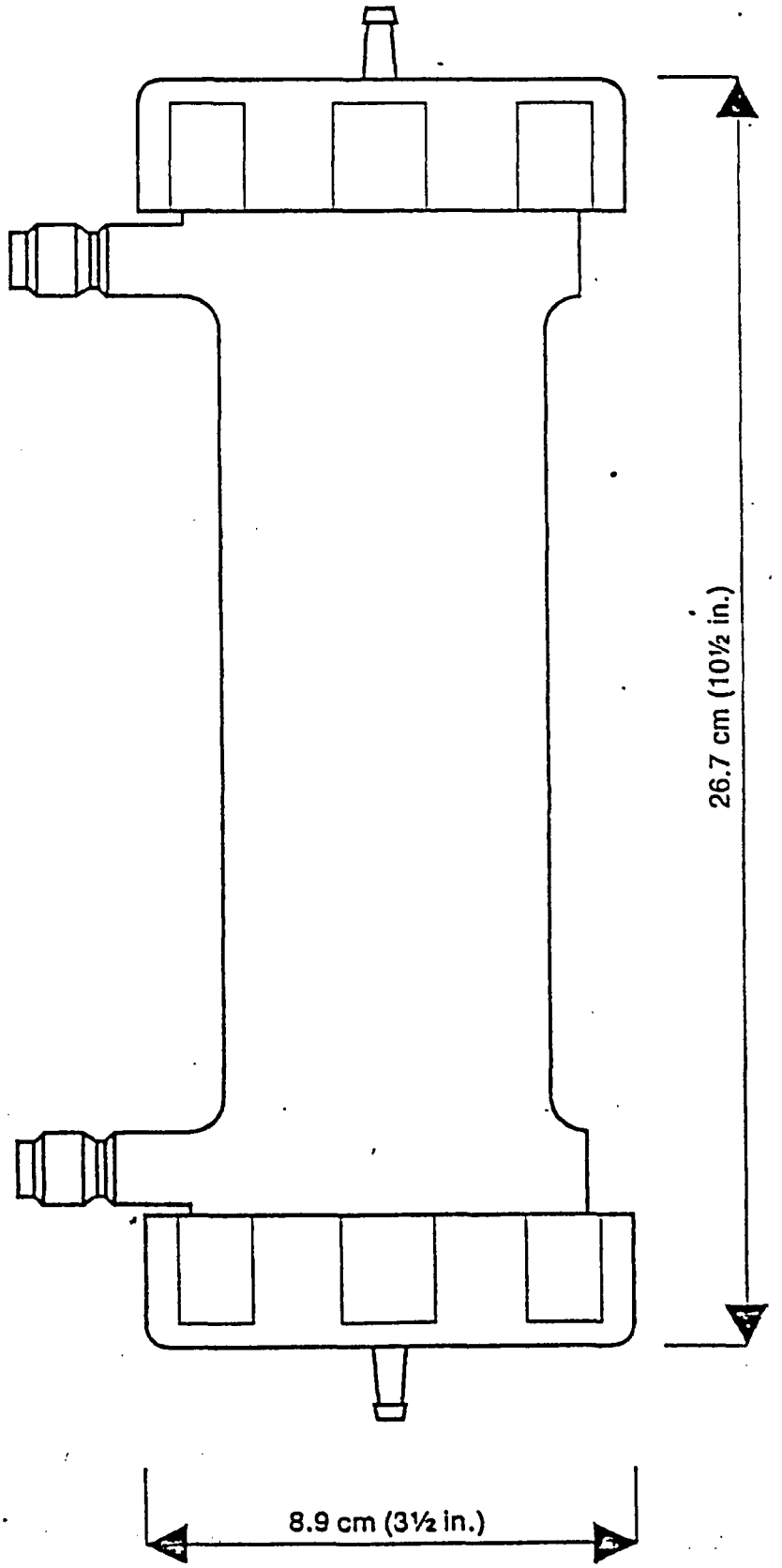
Specifications

C-DAK Model 5

Dimensions:	26.7 cm (10½ in.) long x 8.9 cm (3½ in.) diameter
Weight (filled):	1080 gm (2½ lb, approx.)
Blood volume:	180 ml average
Dialysate volume:	320 ml average

Fibers

Material:	Regenerated cellulose
Quantity:	20,000
Effective length:	21 cm
Inside diameter:	200 μ
Wall thickness:	30 μ
Effective surface area:	2.5 m^2 (approx.)



Performance Characteristics

1. Typical flow resistance in blood compartment at blood flow rate of 200 ml/min whole blood of hematocrit 20: 15 to 20 mm Hg.

2. Typical flow resistance in dialysate compartment at dialysate flow rate of 500 ml/min: 20 mm Hg.

3. Typical clearances at 200 ml/min blood flow and 500 ml/min dialysate flow (see Fig. A):

Urea	184 ml/min
Creatinine	154 ml/min
Uric acid	148 ml/min
Phosphate	140 ml/min

4. Typical clearance of Vitamin B_{12}. as measured in vitro, is 40 ml/min with an ultrafiltration rate of 10 ml/min.

5. Typical in vitro ultrafiltration: 3.0 ml/hour/mm Hg transmembrane pressure. For example, at 300 mm Hg ultrafiltration will be 900 ml/hour. See Fig. B.

Figure A

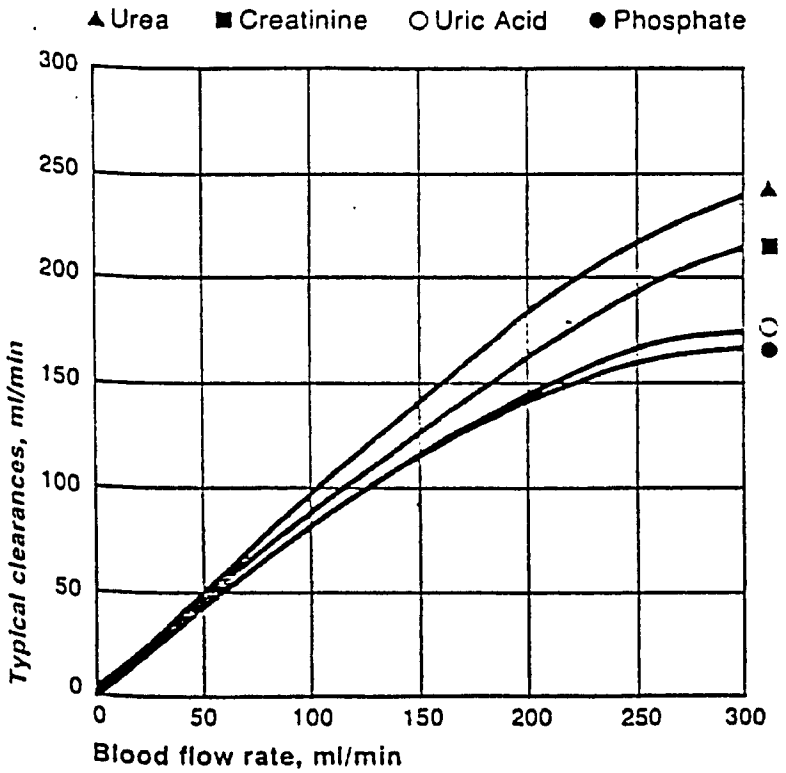
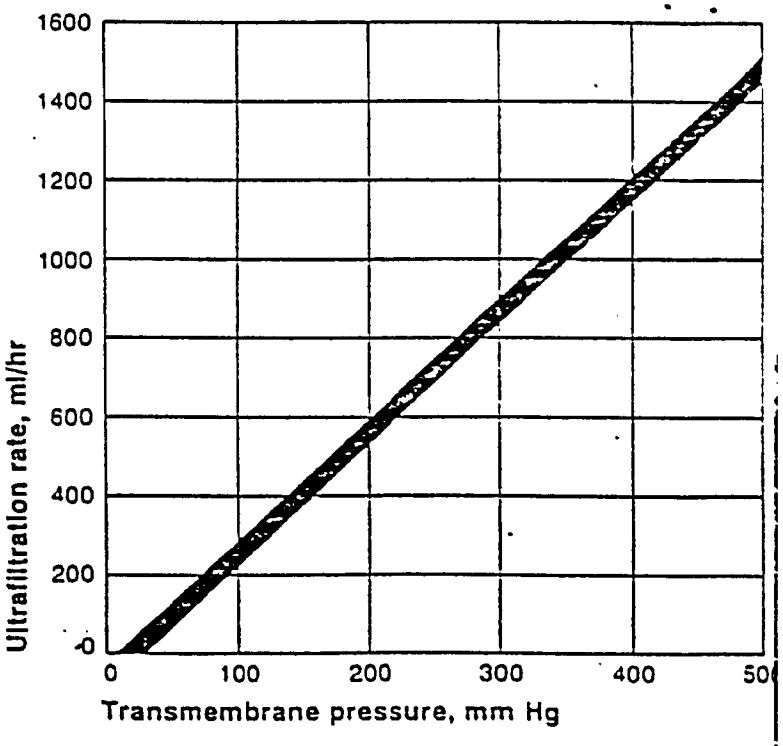


Figure B

Effect of transmembrane pressure on ultrafiltration rate at 37°C.



range. If the delta pressure increases significantly from the initial reading, more frequent readings are recommended. In circumstances of grossly inadequate heparinization or large air inclusions in the fibers, higher delta pressures may be seen. In these instances, an increased delta pressure of 45 mm Hg over the initial reading indicates that replacement of the dialyzer should be considered.

Monitoring Negative Pressure in the Arterial Line (Fistula Pressure)

If the negative pressure in the arterial line (fistula pressure) is monitored instead of the delta pressure (ΔP), a rigid drip chamber must be positioned before the blood pump. Fistula pressure will be monitored as a negative pressure value, while the venous pressure reading will remain positive.

Machine Requirements. In delivery systems with two blood pressure monitors, one gauge typically has a pressure range of −150 to −150 mm Hg and the second gauge has a range of −50 to −300 mm Hg. Because the operating range of negative pressure can approach −150 mm Hg, the monitor with the lower negative pressure range (that is, −150 mm Hg) should be used. Delivery systems without a monitor that measures to −150 mm Hg cannot effectively monitor low fistula pressure. In these cases, an auxiliary monitor that measures to −150 mm Hg is required.

Ultrafiltration Rate. When monitoring fistula pressure, the pressure of the venous drip chamber is used to determine total transmembrane pressure.

Determining Negative Pressure to Be Used for Ultrafiltration

Ultrafiltration is the result of transmembrane pressure (TMP) and occurs in the Model 5 C-DAK at the rate of 3.0 ml/hr/mm Hg TMP. Transmembrane pressure is the sum of the applied negative pressure in the dialysate compartment and the positive pressure in the blood compartment. Positive pressure is normally monitored at the venous drip chamber and is dependent upon such variables as blood flow rate, the condition of the shunt or fistula, hematocrit, the size and position of the venous needle, and the position of the patient.

To determine the negative pressure setting for ultrafiltration:

1. Add the weight (or equivalent volume) of all fluids to be removed during dialysis, including:
   a. patient's weight to be removed.
   b. fluids given orally or intravenously during dialysis.
   c. the prime, if administered.
   d. saline rinse back.
   Approximate equivalents: 1 lb = 500 ml*
   1 kg = 1000 ml

*1.1 lb = 500 ml. However, for easy computation, 1 lb = 500 ml.

2. To obtain the amount of fluid to be removed per hour, divide the total amount of fluid to be removed by the number of hours.

3. To obtain the TMP needed to remove the weight, divide the amount of fluid to be removed per hour by the ultrafiltration rate (3.0).

4. When the desired blood flow rate is reached, subtract the positive pressure on the blood pressure monitor(s) from the TMP. The number obtained is the negative pressure needed for ultrafiltration.

   Note: The desired maximum blood flow rate and negative pressure should be obtained within 10 to 15 minutes after the start of dialysis or the patient may not lose the desired weight. The ultrafiltration rate is based on total treatment time.

Example:

1. Patient to lose 3 lb ..... =1500 ml
   Saline prime including blood lines (when infused) ..... = 340 ml
   Lunch ..... = 320 ml
   Saline rinse back ..... = 300 ml
   Total fluid to be removed during dialysis ..... =2460 ml

2. $\frac{2460}{4 \text{ hr}}$ = 615 ml/hr/of fluid to be removed

3. $\frac{615 \text{ ml/hr}}{3 \text{ ml/hr/mm Hg}}$ = 205 mm Hg TMP

4. 205 mm Hg TMP
   −50 mm Hg positive pressure (measured at venous drip chamber)
   155 mm Hg negative pressure

Blood Leak Procedure

When the blood leak monitor is activated, check the dialysate outflow to see if the dialysate has a red or pink color.

1. If the dialysate doesn't appear to be red or pink, check the dialysate effluent with a Hemastix.

2. If the Hemastix test is positive (indicating the presence of blood in the dialysate) but the dialysate appears colorless or only faintly pink, leakage from one or a few fibers often will stop if the negative pressure is reduced to less than 50 mm Hg for 15 minutes. After running 15 minutes at the lower negative pressure, recheck the dialysate effluent with a Hemastix. If the test is negative, the fibers have sealed off and the negative pressure can be *slowly* increased to the previous setting and dialysis continued. Recheck the dialysate effluent with a Hemastix after 15 minutes at the higher negative pressure setting. If the test remains negative, dialysis can be continued. If the test is positive, it is recommended that the procedure be started again with a new C-DAK.

APPENDIX F

SUBJECTIVE RATING SCALE

SUBJECTIVE RATING SCALE

DIRECTIONS:

Each pair of statements you see below is separated by the numbers 7-6-5-4-3-2-1. If you agree completely with the statement on the left side of the page circle the number 7. If you agree completely with the statement on the right side of the page circle the number 1. If your agreement lies somewhere in between circle the number 6,5,4,3, or 2 depending upon which number expresses your feeling.

For example in item one:

If you had no cramps at all circle 7.
If you had mild cramps circle 6 or 5.
If you had moderate cramps circle 4.
If you had bad cramps circle 3 or 2.
If you had very bad cramps circle 1.

Read each item very carefully before you circle a number. In this way you will be sure that the number you chose accurately expresses your feeling on a given question. Your cooperation in filling out this questionnaire is greatly appreciated.

THESE STATEMENTS REFER TO HOW YOU FEEL RIGHT NOW:

I am in a very good mood.	7-6-5-4-3-2-1	I am in a very bad mood.
I feel very anxious and nervous.	7-6-5-4-3-2-1	I feel very relaxed.
I feel physically very strong.	7-6-5-4-3-2-1	I feel physically very weak.
I feel very sleepy.	7-6-5-4-3-2-1	I feel fully awake.
I have alot of energy to do things.	7-6-5-4-3-2-1	I have almost no energy to do things.
My thoughts are very confused.	7-6-5-4-3-2-1	My thoughts are very clear.
If I were to do something I could keep my mind on it easily.	7-6-5-4-3-2-1	If I were to do something I would have much trouble keeping my mind on it.
I feel very sad.	7-6-5-4-3-2-1	I feel very happy.

People enjoy being with me.	7-6-5-4-3-2-1	People dislike being with me.
I feel different than most people.	7-6-5-4-3-2-1	I feel I am like most other people.
I feel physically very healthy.	7-6-5-4-3-2-1	I feel physically very sick.
My body is full of pain.	7-6-5-4-3-2-1	My body is free from pain.
I do not have a headache.	7-6-5-4-3-2-1	I have a very bad headache.
I feel like my blood pressure is either much too high or much too low.	7-6-5-4-3-2-1	I feel like my blood pressure is normal.
I feel like I am breathing normally.	7-6-5-4-3-2-1	I feel like I am grasping for breath.
My feet burn severely and/or feel very numb.	7-6-5-4-3-2-1	I do not have any burning of numbness in my feet.
My muscles are free from cramps.	7-6-5-4-3-2-1	My muscles cramp very badly.
I itch very badly.	7-6-5-4-3-2-1	I am not itchy at all.
I have no chest pain.	7-6-5-4-3-2-1	I have very bad chest pain.

APPENDIX G

SPEARMAN CORRELATION OF DISCOMFORT INDEX AND INDIVIDUAL ELEMENTS OF THE SUBJECTIVE RATING SCALE

Spearman Correlation of Discomfort Index and

Individual Elements of the Subjective Rating Scale

(N = 20)

Pair	Day	Spearman Coeff.	Sig. Level
Discomfort With Mood	0	.6218	.003
	1	.7517	.001
	2	.8133	.001
Discomfort With Anxiety	0	.7588	.001
	1	.5552	.011
	2	.8396	.001
Discomfort With Weakness	0	.7801	.001
	1	.8548	.001
	2	.8219	.001
Discomfort With Sleepiness	0	.3824	.096
	1	.6199	.004
	2	.6479	.002
Discomfort With Energy Level	0	.9297	.001
	1	.7638	.001
	2	.8240	.001
Discomfort With Confusion	0	.5586	.01
	1	.8826	.001
	2	.8965	.001
Discomfort With Sadness	0	.5813	.007
	1	.7267	.001
	2	.8638	.001
Discomfort With Self-Concept	0	.5701	.009
	1	.6890	.001
	2	.6341	.003
Discomfort With Comparison of Self with Others	0	.5390	.014
	1	.5676	.009
	2	.6085	.004
Discomfort With Overall Health	0	.7861	.001
	1	.8098	.001
	2	.8257	.001
Discomfort With Pain	0	.7783	.001
	1	.8712	.001
	2	.7127	.001.
Discomfort With Headache	0	.2024	.392
	1	.2325	.324
	2	.4793	.032

(N = 20)

Pair	Day	Spearman Coeff.	Sig. Level
Discomfort With Blood Pressure	0	.7200	.001
	1	.4716	.036
	2	.6679	.001
Discomfort With Breathing Difficulty	0	.6863	.001
	1	.6332	.003
	2	.7214	.001
Discomfort With Burning	0	.4862	.030
	1	.1734	.465
	2	.2170	.358
Discomfort With Cramping	0	.5818	.007
	1	.4363	.054
	2	.4594	.042
Discomfort With Itching	0	.7465	.001
	1	.4581	.042
	2	.7869	.001
Discomfort With Chest Pain	0	.6608	.002
	1	.3239	.164
	2	.5470	.013

APPENDIX Ho

PEARSON INTERCORRELATION OF SENSORY-MOTOR AND COGNITIVE MEASURES, DAY ZERO

PEARSON INTERCORRELATION OF SENSORY-MOTOR AND

COGNITIVE MEASURES DAY ZERO*

(N = 20)

Sensory-Motor & Cognitive Measure Pair	Pearson Corr. Coeff.	Sig. Level
Digit Symbol/Trails A Time	-.6027	p = .005
Digit Symbol/Trails B Time	.6240	p = .003
Trails A Time/Trails B Time	.7458	p ≤ .009
Trails A Time/Trails B Error	.5827	p = .007
Trails A Error/Trails B Time	.7421	p ≤ .009
Trails B Time/Trails B Error	.6953	p = .001
Grooved Peg-Board Time In Non-Dominant/ Grooved Pegboard Time In Dominant	.6398	p = .002
Grooved Pegboard Dominant Time Out/Trails A Time	.6076	p = .004
Grooved Pegboard Dominant Time Out/Trails A Error	.8995	p ≤ .0009
Grooved Pegboard Dominant Time Out/Trails B Time	.7490	p ≤ .0009
Grooved Pegboard Non-Dominant Time Out/Trails A Time	.5854	p = .007
Grooved Pegboard Non-Dominant Time Out/Trails A Error	.8607	p ≤ .0009
Grooved Pegboard Non-Dominant Time Out/ Trails A Error	.8607	p ≤ .0009
Grooved Pegboard Non-Dominant Time Out/ Trails B Time	.6958	p = .001
Word Fluency/Trails A Error	.6047	p = .005
Word Fluency/Trails B Error	.6841	p = .001
Seashore Rhythm/Color Naming Error	-.5817	p = .007
Choice Reaction Time/Trails A Error	.6190	p = .004

Sensory-Motor & Cognitive Measure Pair	Pearson Corr. Coeff.	Sig. Level
Grooved Pegboard Non-Dominant Time Out/ Grooved Pegboard Dominant Time Out	.9639	p .0009
Speech Sounds Perception/Grooved Pegboard Error In Dominant	-.5430	p = .013
Choice Reaction Time/Grooved Pegboard Dominant Time Out	.5946	p = .006
Choice Reaction Time/Grooved Pegboard Non-Dominant Time Out	.5750	p = .008

*Only Sensory-Motor & Cognitive Pairs with Pearson correlations of $p \leq .01$ are included.

APPENDIX H_1

PEARSON INTERCORRELATION OF SENSORY-MOTOR AND COGNITIVE MEASURES - DAY ONE

Pearson Intercorrelation of Sensory-Motor and Cognitive Measures - Day One*

(N = 20)

Sensory-Motor & Cognitive Pair	Pearson Correlation Coeff.	Significance Level
Trails B Time/Trails B Error	.8279	$p \leq .0009$
Grooved Pegboard Time In Non-Dominant/Grooved Pegboard Time In Dominant	.7609	$p \leq .0009$
Grooved Pegboard Non-Dominant Time Out/Trails B Time	.7469	$p \leq .0009$
Grooved Pegboard Dominant Time Out/Trails B Error	.6918	$p = .001$
Seashore Rhythm/Color Naming Error	-.5867	$p = .007$
Grooved Pegboard Dominant Time Out/Quick Test	.5604	$p = .01$
Quick Test/Proverbs Test	.6751	$p = .001$

*Only sensory-motor and cognitive pairs with Pearson correlations of $p \leq .01$ are included.

APPENDIX H_2

PEARSON INTERCORRELATION OF SENSORY-MOTOR AND COGNITIVE MEASURES-DAY TWO

Pearson Intercorrelation of Sensory-Motor & Cognitive Measures-Day Two*

(N = 20)

Sensory-Motor & Cognitive Measure	Pearson Correlation Coeff.	Significance Level
Trails B Time/Trails B Error	.6979	p = .001
Digit Span Backward/Trails B Error	-.6869	p = .001
Benton/Trails B Time	-.5587	p = .010
Benton/Trails A Time	-.5582	p = .011
Proverbs Test/Trails A Error	-.5440	p = .013
Finger Tapping Dominant/Trails A Error	.5458	p = .013
Finger Tapping Dominant/Color Naming Time	-.5629	p = .010
Finger Tapping Dominant/Finger Tapping Non-Dominant	.6463	p = .002
Digit Span Forward/Digit Span Backwards	.6065	p = .005
Quick Test/Proverbs Test	.6954	p = .001
Speech Sounds Perception/Proberbs Test	.6359	p = .003
Grip Strength Dominance/Grip Strength Non-Dominant	.8956	$p \leq .0009$
Quick Test/Digit Span Forward	.6165	p = .004
Grooved Pegboard Dominant Time In/ Grooved Pegboard Non-Dominant Time In	.7171	$p \leq .0009$
Grooved Pegboard Dominant Time Out/ Grooved Pegboard Dominant Time In	.5858	p = .007
Grooved Pegboard Non-Dominant Time In/Word Fluency	-.5508	p = .012
Grooved Pegboard Dominant Time Out/ Grooved Pegboard Non-Dominant Time Out	.6834	p = .001

*Only sensory-motor and cognitive pairs with Pearson correlations of $p \leq .01$ are included.

APPENDIX I

IMPAIRMENT RANGES

Impairment Ranges*

Test	High Normal	Normal	Mildly Impaired	Moderately Impaired	Severely Impaired
Benton Visual Retention	8 - 10	6 - 8	4 - 5	2 - 3	1 - 0
Digit Symbol (Scaled)	> 12	12 - 8	7 - 5	4 - 3	3
Digit Span (Scaled)	> 11	11 - 8	7 - 6	5 - 4	4
Trailmaking A Time (Sec.)	< 24	24 - 30	31 - 51	52 - 71	> 72
Trailmaking B Time (Sec.)	< 46	46 - 64	65 - 90	91 - 120	> 120
Word Fluency	> 20	20 - 16	15 - 12	11 - 6	< 6
Grooved Pegboard Dominant Time (Sec.)	< 60	61 - 66	67 - 75	76 - 110	> 110
Grooved Pegboard Non-Dominant Time (Sec.)	< 65	66 - 73	74 - 81	82 - 115	> 115
Color Naming Time (Sec.)	< 110	110 - 133	134 - 179	180 - 239	> 240
Grip Strength (Kg.):					
Male Dominant	> 55	55 - 35	34 - 20	11 - 6	< 6
Female Dominant	> 40	40 - 25	24 - 15	19 - 6	< 6
Male Non-Dominant	> 45	45 - 30	29 - 17	14 - 5	< 5
Female Non-Dominant	> 35	35 - 22	21 - 13	16 - 5	< 5
Speech Sounds Perception (Errors) (60 items)	0 - 3	4 - 7	8 - 14	15 - 25	> 25
Seashore Rhythm (Errors)	0 - 2	3 - 5	6 - 9	10 - 13	> 13
Finger Tapping:					
Male Dominant	> 54	54 - 50	49 - 43	42 - 20	< 20
Female Dominant	> 50	50 - 46	45 - 39	38 - 17	< 17
Male Non-Dominant	> 48	48 - 44	43 - 38	37 - 18	< 18
Female Non-Dominant	> 44	44 - 41	40 - 34	33 - 15	< 15

*Adult norms as utilized in the Hamilton Psychiatric Hospital Neuropsychology Laboratory.

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VITA AUCTORIS

1950	Born March 26 in Brooklyn, N.Y. to Nathan & Marian Ratner
1971	B.A. Philosophy, Brooklyn College
1973	Married Roberta Sue Elkin
1975	M.S.W. Clinical Social Work, University of Michigan
1975	Registered As A Full Time Student In The Ph.D. Program In Clinical Psychology At The University of Windsor
1976	Four Month Internship - Forensic Unit, Hamilton Psychiatric Hospital
1977	Four Month Internship - Adolescent And Pediatric Service, Kitchener-Waterloo Hospital
1977-1978	Half Time Internship - Psychological Services Centre, University of Windsor
1979	Ph.D. Clinical Psychology, University of Windsor.