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EDITORIAL

On The Pathogenesis of Uremia

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Neurobehavioral manifestations characterize early uremia. As renal failure progresses, such subtle disorders as decreased ability to focus attention, diminished attention span, speaking in shorter sentences and deficient performance of mental arithmetic regularly precede the conventional neurologic, pulmonary, cutaneous, gastrointestinal, hematologic and skeletal manifestations of the more florid uremic state [1–6].

The central problem confronting all investigations of the pathogenesis of uremia is to construct a test system which is at once quantitatively objective and relevant to uremia. The issue of relevance is further complicated by the fact that uremia is conventionally identified as a form of abnormal, whole organism behavior, i.e., as a clinical illness.

Prophylactic or maintenance dialysis technics prevent or correct the early neurobehavioral changes of uremia in patients with either acute or chronic renal failure [7,8] whereas they are much less successful in modifying the later findings [9]. This suggests that chemical changes which are corrected by dialysis procedures somehow cause these early uremic symptoms. However, chemical changes and clinical findings are often dissociated in patients with renal failure [10–13]. These observations have provided new incentives, and perhaps practical means, to distinguish between the alternatives (1) that uremia is caused by commonly measured chemical changes, i.e., the effects on cells and organs of abnormal extracellular concentrations of the principal electrolytes, urea, creatinine or urate, for example, or (2) that uremia is due to as yet unknown toxic substances which are eliminated in the dialysate [14].

Since the signal descriptions of Bright [15] the cause of the uremic syndrome has been sought at all levels of biological organization, i.e., at the level of biochemical analyses and in the measurable function of enzymes, cells, tissues, organ systems and whole organisms. Findings since publication of the encyclopedic discussion by Schreiner and Maher in 1961 [1] may be summarized as follows.

BIOCHEMICAL ANALYSES

Although this discussion will not rehearse the conflicting evidence regarding the toxicity of urea in uremia, attention has been refocused by Gilboe

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and Javid [16] on nonenzymatic conversion of urea to cyanate in aqueous solutions, on the potential of both substances as protein denaturants and on a demonstration that (compared to dialyzed controls) "uremic" symptoms and death were accelerated when either substance (in 1 per cent and 0.015 per cent concentrations, respectively) was added to peritoneal dialysates used to maintain bilaterally nephrectomized dogs. However, if the chemical equilibrium between urea and cyanate obtains in vivo, cyanate cannot logically be incriminated in those situations in which blood urea levels are elevated while symptoms are minimal.

Increased concentrations of other nitrogenous substances have been demonstrated in uremic plasma or dialysate by newer methods. These include certain free amino acids [17–21], other organic acids [22,23], aliphatic amines (especially dimethylamine and ethanolamine) [24], aromatic amines [25], phenols and their derivatives [18,26,27], indoles [18,28], guanidine derivatives [29], amino acid conjugates [19,30] and small peptides having a molecular weight less than 4,000 [19]. Hicks et al. [18] tabulate 94 different specific compounds and indicate some evidence for nearly 200.

SUBCELLULAR FUNCTIONS: ENZYMATIC DISTURBANCES IN UREMIA

Elevated blood levels of pyruvate, acetoin and 2,3 butyleneglycol suggested to Thölen and Bigler [31] that the normal metabolic transformations of pyruvate were partly diverted to synthesis of the latter compounds and implied diminished adenosine triphosphate (ATP) synthesis in uremia. In homogenates of brain and liver, but not of heart and small intestine, added tyramine increased acetoin biosynthesis. These investigators speculated that diminished consciousness in uremia could be due to cerebral ATP deficiency induced by several retention products, such as tyramine. In this way, deficiencies in enzymatic function might produce uremic symptoms in vivo and may also serve in vitro as quantitative assay systems. Recently reported examples of disturbed enzymatic functions as related to uremia are listed in Table I.

CELLULAR FUNCTION AND MORPHOLOGY IN UREMIA

As demonstrated by Markson and Rennie [41] and by Berman and Powsner [42], maturation of normoblasts in suspension cultures is inhibited when uremic serum (blood urea nitrogen, 69 to 168 mg per 100 ml) [41] was added to the culture medium. Erslev and Hughes [43] reported depressed ^{59}Fe incorporation per nucleated red cell and reticulocyte in rabbit marrow suspensions when the medium incorporated uremic serum (nonprotein nitrogen, 100 to 200 mg per 100 ml); but inhibition was not evident in autoradiographic studies by Markson and Moore [44] in which the per cell uptake of glycine-2-^{14}C, formate-^{14}C and methionine-^{35}S was similar whether the normoblasts were cultured in uremic serum (blood urea nitrogen, 61 to 170 mg per 100 ml) or in normal serum. This suggested that cellular hemoglobin and deoxyribonucleic acid (DNA) synthesis were not impaired.

Uremia may be associated with precisely measurable alterations in cellular compositional homeostasis, as shown by Welt and colleagues [45,46]. Erythrocyte sodium concentration was found to be elevated beyond the upper limit of 12 mM per L in approximately one-fourth of the uremic patients studied. The elevated cell sodium levels occurred despite elevated levels of erythrocyte ATP (the energy source for sodium efflux) and seemed related to decreased activity of glycoside-sensitive ATPase, with diminished glycoside-sensitive efflux rate constants for sodium. The associated defects could be induced in normal erythrocytes incubated in uremic plasma and then were shown to be reversible in time in patients treated by maintenance dialysis. Similar disturbances in intraerythrocytic homeostasis were discovered in patients with burns, metastatic carcinoma and in a patient with diabetes mellitus, infection and shock. Related erythrocytic abnormalities occur in patients with cystic fibrosis of the pancreas and their parents [47]. Welt speculates that "sick cells" may share one or more of these manifestations of molecular pathology.

Elevated ATP and 2,3-diphosphoglycerate levels in erythrocytes from uremic patients were also found by Hurt and Chanutin [48], with declines following dialysis. Kuroyanagi and colleagues [49] also demonstrated elevated erythrocyte ATP levels in uremia, together with augmented levels of adenosine diphosphate (ADP), a normal ATP:ADP ratio and diminished incorporation of radiophosphorus into polyphosphorylated compounds. The latter inhibition was inducible in normal erythrocytes by incubation in plasma from uremic patients and was attributed to inhibition of stromal ATPase, among several alternatives.

Cytotoxic morphologic effects were demonstrated by Henkin et al. [50] in HeLa cell cultures exposed to serum from some patients with chronic glomerulonephritis, occasionally in patients with a variety of other diseases but not in normal volunteer subjects. The rounding of cells, cellular degeneration and detachment, and refractile granularity were also observed in the absence of significant azotemia, and normal cell growth occurred in serum from patients with marked azotemia. Urinary flow in these patients is not recorded. The cytotoxic influence disappeared from the serum of patients treated with dialysis and thereupon appeared in the initial dialysates in all such cases.

Glucose utilization was found to be depressed in normal erythrocytes incubated in ultrafiltrates of plasma from patients with several types of azotemic, acute or chronic renal failure, according to Morgan and Morgan [51].

Although essentially normal phagocytic activity, complement levels and humoral antibody response to tetanus immunization have been reported in uremia [52], cellular evolution of the inflammatory response is altered from control as observed by means of the Rebuck window technic [53] and evidenced by reduction in lymphoid and macrophage response. Suppression of immunologic

TABLE I

Source of "Uremic" Material	Enzyme or Reaction	Effect	Reference
Urea; guanidine	Xanthine oxidase	Inhibition	32
Urea solutions, 0.05–0.2 M	Monoamine oxidase	Inhibition	33
Serum from human patients, blood urea nitrogen range 100–200 mg %	Glucose oxidation by rat brain mince	Acceleration	34
Ultrafiltrate through cellophane of serum from human patients, blood urea nitrogen < 100 mg % and > 150 mg %	Lactic dehydrogenase	Inhibition if blood urea nitrogen >150 mg%	35
Aqueous solutions, 10^{-2}–10^{-4} M, of 20–24 specific phenolic acids previously [16] identified in human uremic serum or dialysates	Respiration (guinea pig brain slice) Anaerobic glycolysis DOPA decarboxylase 5-hydroxytryptophan decarboxylase Monoamine oxidase Glutamic-oxalacetic transaminase Glutamic-pyruvic transaminase Glutamic acid decarboxylase 5′-nucleotidase Lactic dehydrogenase	10 to 58% inhibition 18 to 85% inhibition 10 to 98% inhibition 10 to 96% inhibition 0 to 100% inhibition 0 to 96% inhibition 0 to 100% inhibition 10 to 73% inhibition 0 to 80% inhibition 0 to 100% inhibition	36
N-methyl-2-pyridone-5-form-amidoacetic acid	^{3}H-leucine incorporation into protein by cell-free rat liver homogenate	Inhibition	37
Liver from uremic rats, blood urea nitrogen 181–269 mg %	L-(U-^{14}C)-leucine incorporation into protein by cell-free extract of liver homogenate	Accelerated	38
Serum from human patients, blood urea nitrogen 100–300 mg %, creatinine, 5.4–30 mg %	Oxidative phosphorylation by rat liver mitochondria	Inhibition with glutamate + malate as substrates	39
Plasma from uremic humans, (blood urea nitrogen (38–222 mg %)	ADP-induced platelet factor 3 activity (Stypven time, modified)	Elevates Stypven times	40
Guanidinosuccinic acid			64

responsiveness, reflecting further cellular dysfunction, characterizes uremia, as has been demonstrated in a variety of ways [e.g.,54].

DYSFUNCTION OF TISSUES, ORGANS AND ORGAN SYSTEMS IN UREMIA

The capacity of renal tubules to take up para-amino-hippurate (PAH) from the surrounding medium in vitro is readily measured and was found depressed to 28 to 57 per cent of normal by White [55] in rat renal cortical slices incubated in uremic rat serum (blood urea nitrogen, 240 to 312 mg per cent). This effect was confirmed by Hook and Munro [56] who also demonstrated a depressant influence of fasting and enhancement of transport when slices were incubated in serum from sham operated rats. Transport of an organic cation, N-methyl nicotinamide, was not affected in any of the experimental procedures. Pruess et al. [57] found similarly decreased PAH uptake by isolated rabbit renal tubules incubated in human uremic serum and peritoneal dialysate, and a lesser effect in the serum from the same patients treated with peritoneal or hemodialysis.

In a study of wound healing in dogs made azotemic by uranyl poisoning reported by Nayman [58], wound disruption occurred if renal failure was induced within five days of laparotomy but not after nine days or in dogs subjected to vigorous hemodialysis immediately after laparotomy.

In vitro oxygen consumption was measured by Lascelles and Taylor [59] utilizing the Warburg technic in cerebral cortex, whole kidney and liver slices incubated in media containing serum ultrafiltrates from uremic patients or various substances (singly or in combination) known to accumulate in uremic serum. Urea (500 mg per cent) and mixtures of various other metabolites, but not the single metabolites tested, inhibited oxygen utilization. The ultrafiltrates produced no inhibition, a disappointing result.

Using measurements of forearm blood flow and arteriovenous differences in solute concentration in uremic patients (blood urea nitrogen greater than 125 mg per cent) and normal subjects, Westervelt [60] described a reduction of glucose uptake in uremic patients to 25 per cent of normal (1.6 versus 8.3 μM per 100 ml forearm volume per minute), equal potassium

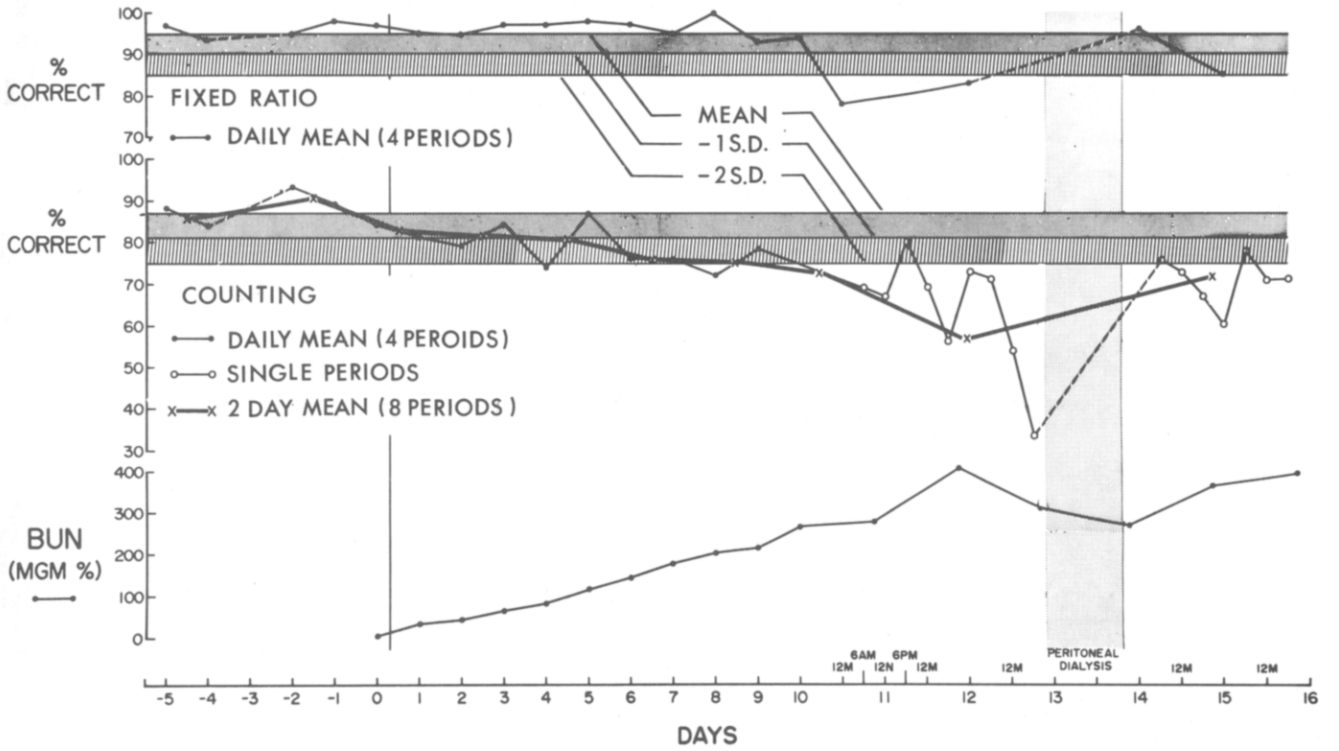

Fig. 1. Effect of acute renal failure induced by ureteral occlusion on motor (FR) and counting behavior in a rhesus monkey. With increasing azotemia counting accuracy decreases and becomes more variable while motor behavior is maintained. Both indices are abnormal as blood urea nitrogen exceeds 250 mg per 100 ml and are restored toward normal by peritoneal dialysis. In the latter, urea was added to a final dialysate concentration of 265 mg urea nitrogen per 100 ml. Counting data are plotted as daily and two day averages until day 11 when the scale is expanded into real time and session by session performance is shown.

fluxes, equal lactate release per micromole (μM) glucose uptake and reduced inorganic phosphate uptake to 40 per cent of normal. These results were interpreted to indicate a diminished responsiveness of intact forearm muscle to insulin in uremic subjects.

Kiley and Hines [61,62] have presented evidence from electroencephalograms of uremic patients, correlating increased severity of clinical uremia with an increased proportion of wave frequencies less than 8 cycles per second. Modal frequencies increased toward normal with recovery of renal function or with adequate therapy especially including dialysis, paralleling clinical improvement, but not in regular correlation with conventional plasma chemical values. Methods of automated reduction of electroencephalographic signals are in hand to render this method more readily available for clinical purposes.

WHOLE ORGANISM DYSFUNCTION IN UREMIA

The reader is referred to recent reviews [63,64] which appraise defects in erythropoiesis and in carbohydrate, lipid and bone mineral metabolism in uremic subjects. The characteristic metabolic defects of the uremic state which affect the whole organism involve the integration of organ systems. Such integrative defects may cause or be caused by biochemical or hormonal derangements which may also be detected at lower levels of biological organization. For example, impaired carbohydrate tolerance in the whole organism with features suggesting peripheral insulin unresponsiveness (impaired glucose uptake) has been linked by Cohen and Horowitz [65] to inhibition of ADP-induced platelet factor 3 deficiency in uremic patients. The latter defect, implicated in uremic bleeding, has been correlated with levels of guanidinosuccinic acid (GSA) before and after dialysis treatment. A GSA-induced defect in phosphorylating coenzyme function is postulated which inhibits the effect of ADP on platelet factor 3 release and upon hexokinase or other enzymes involved in cellular glucose uptake. Impairment of both glycogenesis and glycogenolysis points to the liver as a principal site of this defect in carbohydrate metabolism, a site in which the requirement for ATP is greatly enhanced by the increased requirement for urea synthesis from ammonia and deamination reactions. The latter point is also underscored by the report of Hutchings et al. who induced a degree of carbohydrate intolerance by adding urea to the dialysate during dialysis [66]. Impaired carbohydrate tolerance is otherwise usually improved by hemodialysis in chronic renal failure [67,68] or by diuresis and recovery in acute renal failure [69]. Uremic carbohydrate intolerance has been differentiated from the effects of starvation, infection, inactivity, electrolyte and hereditary factors, and appears to be independent of qualitative and quantitative defects in insulin or of circulating antagonists [66,69]. Abnormalities in

fat metabolism in uremia are reported [70]. The means by which the skeletal and hematopoietic systems contribute to the uremic state have been well reviewed elsewhere [63,64].

However, uremia continues to be most characteristically defined on clinical grounds in terms of neurobehavioral findings in the whole organism. Appropriate neurobehavioral manifestations may therefore serve in test systems having unique relevance to uremia. The precedent for such an approach is effectively illustrated in studies of the actions of various drugs [71–73].

After the initial experiments* in rats by Essman [74–76] several operant conditioning technics† have been employed in this laboratory for the behavioral evaluation of a variety of uremic states in primates [5,77–80]. Recently, use has been made of a counting task requiring sustained alertness. It appears to be a convincing analog of "higher mental processes" in man and has demonstrated significant sensitivity to the developing uremic state. Sessions involving the complex counting task are alternated throughout each twenty-four hour period with rest intervals and sessions in which much simpler, repetitive, motor (lever-pressing) behavior is required (FR). Representative data following bilateral ureteral ligation are exemplified in Figure 1. As blood urea nitrogen levels rose, counting accuracy deteriorated while the animal remained clinically well and concurrent motor (FR) performance remained unimpaired. Further deterioration in both indices preceded, and restoration followed, peritoneal dialysis despite small changes in blood urea nitrogen. The model thus appears able to detect changes inherent in renal failure with minor or moderate changes in such conventional indices as the blood urea nitrogen, and well in advance of clinically detectable illness.

Peritoneal dialysis in such uremic, trained animals returns counting accuracy virtually to the normal range. This occurred in the experiment in Figure 1 even though urea was added to the dialysate to maintain a high blood urea nitrogen. By so manipulating the chemical composition of the dialysate, each chemical change may be assayed separately at least for its acute contribution to the quantitative behavioral deficit.

The refinement of such quantitative behavioral test systems [73] contrasts with observer descriptions of gross behavioral abnormalities [81,82], in which the temptation is great to label as "uremic" whatever overt signs illness may follow an induced chemical change. Despite similar limitations of control and precision, psychologic testing has also been attempted in patients with uremia. In one study [83], patients whose blood urea nitrogen concentrations varied between 67 and 300 mg per 100 ml showed evidence of emotional disturbances and diminished performance in tasks "generally sensitive to cortical dysfunction." Test results did not correlate statistically with the degree of azotemia; and the study did not include clinical assessments, other chemical measures, urinary output data or a follow-up during the subsequent program of maintenance dialysis.

Clinical studies in man analogous to that in Figure 1 could be conceived in which dialysate composition is adjusted to prevent dialysis of one or more molecular species of interest in uremia. Apart from the ethical risks of such procedures in patients whose ability to give "informed consent" may be in doubt or jeopardy, the requisite, conceptually adequate objective and sufficiently precise criterion measures of "uremic" behavioral disturbances remain to be established for man and should logically precede such chemical manipulations in human patients.

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* The principles of laboratory animal care as promulgated by the National Society for Medical Research were observed.

† Operant conditioning involves establishing control of an organism's behavior by manipulating the consequences of that behavior especially with regard to reward and punishment.

REFERENCES

1. Schreiner GE, Maher JF: Uremia: Biochemistry, Pathogenesis, and Treatment, Springfield, Ill., Charles C Thomas, 1961.
2. Schreiner GE: Clinical manifestations of renal failure. Consciousness and the chemical environment of the brain. Report of 25th Ross Pediatric Research Conference, Columbus, Ross Laboratories, 1957, p 62.
3. Schreiner GE: Mental and personality changes in uremic syndrome. Med Ann D C 28: 316, 1959.
4. Grinell RG: The nature of the uremic state. Trans Amer Soc Artif Intern Organs 4: 182, 1958.
5. Teschan PE, Murphy GP, Sharp JC: Investigation of behavioral performance during urine reinfusion in the male primate. Amer J Physiol 206: 510, 1964.
6. Tyler HR: Neurologic disorders in renal failure. Amer J Med 44: 734, 1968.
7. (a) O'Brien TF, Baxter CR, Teschan PE: Prophylactic daily hemodialysis. Trans Amer Soc Artif Intern Organs 5: 77, 1959.
   (b) Teschan PE, Baxter CR, O'Brien RF, Freyhof NN, Hall WT: Prophylactic hemodialysis of acute renal failure. Ann Intern Med 53: 992, 1960.
8. Scribner BH, Buri R, Caner JEZ, Hegstrom R, Burness JM: The treatment of chronic uremia by means of intermittent dialysis:

a preliminary report. Trans Amer Soc Artif Intern Organs 6: 114, 1960.
9. Bluemle LW Jr: Current status of chronic hemodialysis. Amer J Med 44: 749, 1968.
10. Newburgh LH, Camara AA: Lack of correlation between symptoms and degree of renal impairment. Ann Intern Med 35: 39, 1951.
11. Meroney WH: Uremia-like symptoms not due to uremia in battle casualties. JAMA 158: 1515, 1955.
12. Scribner BH: Discussion. Trans Amer Soc Artif Intern Organs 11: 29, 1965.
13. Kay M, Comty C: Nutritional repletion during dialysis. Amer J Clin Nutr 21: 583, 1968.
14. Bradley SE: The Pathologic Physiology of Uremia in Chronic Bright's Disease. Springfield, Ill, Charles C Thomas, 1958, p 58.
15. Bright R: Cases and observations illustrative of renal disease accompanied by the secretion of albuminous urine. Guy's Hosp Rep 1: 338, 1836.
16. Gilboe DD, Javid MJ: Breakdown products of urea and uremic syndrome. Proc Soc Exp Biol Med 115: 633, 1964.
17. Woods KR, Rubin AL, Luckey EH: Effects of dialysis with the artificial kidney on plasma amino acids in uremic patients. Trans Amer Soc Artif Intern Organs 7: 83, 1961.
18. Hicks JM, Young DS, Wootton IDP: Abnormal blood constituents in acute renal failure. Clin Chim Acta 7: 623, 1962.
19. Lubash GD, Stenzel KH, Rubin AL: Nitrogeneous compounds in hemodialysate. Circulation 30: 848, 1964.
20. Muting D, Dishuk BD: Free amino acids in serum, CSF and urine in renal disease with and without uremia. Proc Soc Exp Biol Med 126: 754, 1967.
21. Gulyassy PF, Peters JH, Lin SC, Ryan PM: Hemodialysis and plasma amino acid composition in chronic renal failure. Amer J Clin Nutr 21: 565, 1968.
22. Seligson DL, Bluemle LW Jr, Webster GD Jr, Senesky D: Organic acids in body fluids of the uremic patient. (Abstract.) J Clin Invest 38: 1042, 1959.
23. Galloway R, Morgan JM: Serum pyruvate and lactate in uremia. Metabolism 13: 818, 1964.
24. Simenhoff ML, Asatoor AM, Milne MD, Zilva JF: Retention of aliphatic amines in uremia. Clin Sci 25: 65, 1963.
25. Morgan RE, Morgan JM: Plasma levels of aromatic amines in renal failure. Metabolism 15: 479, 1966.
26. Kramer B, Seligson H, Baltrush H, Seligson D: The isolation of several aromatic acids from the hemodialysis fluids of uremic patients. Clin Chim Acta 11: 363, 1965.
27. Muting D: Studies of the pathogenesis of uremia. Comparative determinations of glucuronic acid, indican, free and bound phenols in the serum, CSF, and urine of renal diseases with and without uremia. Clin Chim Acta 12: 551, 1965.
28. Ludwig GD, Senesky D, Bluemle LW Jr, Elkinton JR: Indoles in uremia: identification by countercurrent distribution and paper chromatography. Amer J Clin Nutr 21: 436, 1968.
29. Cohen BP, Stein I, Bonas JE: Guanidino succinic aciduria: An alternate route of ammonia detoxofication in uremia, (Abstract Proceedings) American College of Physicians, 1966.
30. Frimpter GW, Thompson DD, Luckey EH: Conjugated amino acid in plasma of patients with uremia. J Clin Invest 40: 1208, 1961.
31. Thölen VH, Bigler F: Die Pathogenese des Urämiesyndrome. Schweiz Med Wschr 94: 65, 1964.
32. Rajagopalan KV, Fridovich I, Handler P: Competitive inhibition of enzyme activity by urea. J Biol Chem 236: 1059, 1961.
33. Giordano C, Bloom J, Merrill JP: Effects of urea on physiologic systems. I. Studies on monoamine oxidase activity. J Lab Clin Med 59: 396, 1962.
34. Cummings NB, Stetten DEW Jr: The effect of human uremic serum and its fractions on rat brain glucose oxidation. (Abstract.) J Clin Invest 42: 927, 1963.
35. Morgan JM, Morgan RE, Thomas GE: Inhibition of lactic dehydrogenase by ultrafiltrate of uremic blood. Metabolism 12: 1051, 1963.
36. Hicks JM, Young DS, Wootton IDP: The effect of uremic blood constituents on certain cerebral enzymes. Clin Chim Acta 9: 228, 1964.
37. Clayton EM, Seligson D, Seligson H: Inhibition of protein synthesis by N methyl-2-pyridone-5-formamidoacetic acid and other compounds isolated from uremic patients. Yale J Biol Med 38: 273, 1965.
38. McCormick GJ, Shear L, Barry KG: Alteration of hepatic protein synthesis in acute uremia. Proc Soc Exp Biol Med 122: 99, 1966.
39. Glaze RP, Morgan JM, Morgan RE: Uncoupling of oxidative phosphorylation by ultrafiltrates of uremic serum. Proc Soc Exp Biol Med 125: 172, 1967.
40. Horowitz HI, Cohen BD, Martinez P, Papogoanou MF: Defective ADP-induced platelet factor 3 activation in uremia. Blood 30: 331, 1967.
41. Markson JL, Rennie JB: The anaemia of chronic renal insufficiency. The effect of serum from azotemic patients on the maturation of normoblasts in suspension cultures. Scot Med J 1: 320, 1956.
42. Berman L, Powsner ER: Review of methods for studying maturation of human erythroblasts in vitro: Evaluation of a new method of culture of cell suspensions in a clot-free medium. Blood 14: 1194, 1959.
43. Erslev AJ, Hughes JR: The influence of environment on iron incorporation and mitotic division in a suspension of normal bone marrow. Brit J Haemat 6: 414, 1960.
44. Markson JL, Moore JL: The anemia of chronic renal insufficiency: autoradiographic studies in normoblasts cultured in uremic serum. Brit J Haemat 8: 414, 1962.
45. Welt LG, Sachs JR, McManus JJ: An ion transport defect in erythrocytes from uremic patients. Trans Ass Amer Physicians 77: 169, 1964.
46. Welt LG, Smith EKM, Dunn MJ, Czerwinske A, Proctor H, Cole C, Balfe JW, Guitelman HJ: Membrane transport defect: The sick cell. Trans Ass Amer Physicians 80: 217, 1967.
47. Balfe JW, Cole C, Welt LG: Red-cell transport defect in patients with cystic fibrosis and in their parents. Science 162: 689, 1968.
48. Hurt GA, Chanutin A: Organic phosphate compounds of erythrocytes from individuals with uremia. J Lab Clin Med 64: 675, 1964.
49. Kuroyanagi T, Kuriou A, Sugiyaama H, Saito M: The ADP and ATP levels and the phosphorylating activity of erythrocytes in patients with uremia associated with chronic renal failure. Tohoku J Exp Med 84: 105, 1964.
50. Henkin RI, Levine ND, Sussman HH, Maxwell MH: Evidence for the presence of substances toxic for HeLa cells in the serum and in the dialysis fluid of patients with glomerulonephritis. J Lab Clin Med 64: 79, 1964.
51. Morgan JM, Morgan RE: Study of the effect of uremic metabolites on erythrocyte glycolysis. Metabolism 13: 629, 1964.
52. Balch HH: The effect of severe battle injury and of post-traumatic renal failure on resistance to infection. Ann Surg 142: 145, 1955.
53. Lang PA, Ritzmann SE, Merian FL, Lawrence MC, Levin WC, Gregory R: Cellular evolution in induced inflammation in uremic patients. Texas Rep Biol Med 24: 107, 1966.
54. Wilson WEC, Kirkpatrick CH, Talmage DW: Suppression of immunologic responsiveness in uremia. Ann Intern Med 62: 1, 1965.
55. White AG: Uremic serum inhibition of renal paraaminohippurate transport. Proc Soc Exp Biol Med 123: 309, 1966.
56. Hook JB, Munro JR: Specificity of the inhibitory effect of "uremic" serum on p-aminohippurate transport. Proc Soc Exp Biol Med 127: 289, 1968.
57. Preuss HG, Massry SG, Maher JF, Gilliece M, Schreiner GE: Effects of uremic sera on renal tubular p-aminohippurate transport. Nephron 3: 265, 1966.
58. Nayman J: Effect of renal failure on wound healing in dogs: Response to hemodialysis following uremia induced by uranium nitrate. Ann Surg 164: 227, 1966.
59. Lascelles PT, Taylor WH: The effect upon tissue respiration **in vitro** of metabolites which accumulate in uremic coma. Clin Sci 31: 403, 1966.
60. Westervelt FB Jr: Abnormal carbohydrate metabolism in uremia. Amer J Clin Nutr 21: 423, 1968.
61. Kiley J, Hines O: Electroencephalographic evaluation of uremia. International Congress Series No. 78, Proc. 2nd International Congress of Nephrology, New York, Excerpta Medica Foundation, 1963, p 745.
62. Kiley J, Hines O: Electroencephalographic evaluation of uremia. Arch Intern Med 116: 67, 1965.
63. Welt LG: Symposium on uremia. Amer J Med 44: 653, 1968.
64. Symposium: Proceedings on the conference on the nutritional aspects of uremia. Amer J Clin Nutr 21: 349, 1968.
65. Cohen BD, Horowitz HI: Carbohydrate metabolism in uremia: Inhibition of phosphate release, in Ref 64, p 407.
66. Hutchings RH, Hegstrom RW, Scribner BH: Glucose intolerance in patients on long-term intermittent dialysis. Ann Intern Med 65: 275, 1966.
67. Alfrey AC, Sussman KE, Holmes JH: Changes in glucose and insulin metabolism induced by dialysis in patients with chronic uremia. Metabolism 16: 733, 1967.
68. Hampers CL, Soeldner JS, Doak PB, Merrill JP: Effect of chronic renal failure and hemodialysis on carbohydrate metabolism. J Clin Invest 45: 1719, 1966.
69. Sagild U: Glucose tolerance in acute ischemic renal failure. Acta Med Scand 172: 405, 1962.
70. Bagdade JD, Porte D Jr, Bierman EL: Hypertriglyceridemia: A meta-

bolic consequence of chronic renal failure. New Eng J Med 279: 181, 1968.
71. Dews PB, Morse WH: Behavioral pharmacology. Ann Rev Pharmacol 1: 145, 1961.
72. Cook L, Kelleher RT: Drug effects on the behavior of animals. Ann NY Acad Sci 96: 315, 1962.
73. Boren JJ: The study of drugs with operant technics. Operant Behavior: Areas of Research and Application (Honig WK, ed) New York, Appleton-Century-Croft, 1966.
74. Essman WB: Correlates of behavioral deficit with an experimental induction of acute renal failure in rats. Clin Res 8: 175, 1960.
75. Essman WB: Effects of an experimentally induced acute renal failure on a learned maze response in rats. J Genet Psychol 67: 51, 1962.
76. Essman WB: Behavioral bioassay for experimentally induced uremic endotoxemia in rats. Percept Motor Skills 20: 115, 1965.
77. Murphy GP, Sharp JC: Timed behavior in primates during various experimental uremic states. J Surg Res 4: 550, 1964.
78. Murphy GP, Woodward SC: Uremia in the rhesus monkey: An experimental study. Invest Urol 2: 235, 1964.
79. Sharp JC, Murphy GP: Conditioned avoidance behavior in primates during various experimental uremic states. Nephron 1: 172, 1964.
80. Sharp JC, Murphy GP: A behavioral bioassay method using material from a uremic patient. Percept Motor Skills 22: 127, 1966.
81. Mandell AJ, Spooner CE: Psychochemical research studies in man. Science 162: 1442, 1968.
82. Giovanetti S, Balestri PL, Biagini M, Navalesi R, Giagoni P, de Matteis A, Ferro-Milone F, Perfetti C: Uraemic symptoms and complications induced in dogs chronically intoxicated with creatinine and methylgranidine. Transaction (Abstract) European Dialysis and Transplant Association, Dublin, 1968.
83. Blatt B, Tsushima WT: A psychological survey of uremic patients being considered for the chronic hemodialysis program: Intellectual and emotional patterns in uremic patients. Nephron 3: 206, 1966.