of the intracellular pool for the precursor amino acid in the 2 tissues had been rendered similar by a suitable preincubation procedure. Under these conditions, swelling markedly enhances the rate of incorporation of C^{14}-glycine into protein, and this increase is still present when no appreciable inward transfer of amino acid across the cell membrane takes place. A faster incorporation rate of C^{14}-leucine into protein of swollen liver slices has also been observed. These results indicate that a real stimulation of protein synthesis occurs in swollen liver and suggest that this stimulation may explain, at least in part, the increase in cell protein content found in liver with cloudy swelling.

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Uremic Toxicity Correlated with Unidentified Anions. (28661)

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It is known that experimental administration of urea, creatinine or uric acid does not reproduce the clinical manifestations of the uremic syndrome, even though blood levels of these nitrogenous wastes often parallel uremic toxicity. The identity of the "uremic toxin" is still not clear. Seligson(1) and Hyman(2) analyzed serum and dialysis fluid from patients with acute renal failure: clinical signs and symptoms of uremia were present in these persons when an organic anion moiety was increased in their body fluids. The data suggested a pathogenic role of unidentified organic anions in uremia.

Ten patients with terminal chronic uremia underwent enterostomy here, to be reported elsewhere. After the enterostomy had become established, the fluid discharged from it sufficed to maintain water balance; it was helpful in controlling serum cation levels; for weeks at a time the discharge contained enough urea and other non-protein nitrogen to achieve nitrogen equilibrium. Critical deficits of blood volume, hemoglobin or plasma proteins were absent; liver function was well maintained. When the patients suffered from distressing symptoms or signs these could not be explained by "pseudo-uremic overlay" (such as overhydration)(3). Representative data from 2 patients support earlier tentative conclusions of other authors(1,2).

Case reports: J. B., a 40-year-old man,

TABLE I.
J.B., 40, polycystic kidneys; ileostomy 2/6/63, transection 90 cm proximal of ileocecal valve.

Days postop.	−1	+37	+65	+75	+86	+90	+93	+96
Body wt, kg	74	54	54	55½	55½	54		
BP, mm Hg	200/120	105/75	142/114	142/78	110/80	100/60	135/85	120/65
Blood								
hematocrit, %	12½	25	40	33	35	32	31	
hemoglobin, g %	4.4	8.7	13	12	10	10.3	10.3	
urea N, mg %	204	120	126	159	126	140	115	138
creatinine, mg %	14	7.7	13	13.5	15.9	19	15	15.3
serum Na, me/l	138	140	135	136	141	135	140	131
serum K, me/l	3.7	6.0	5.8	4.5	3.8	4.6	4.6	4.5
CO_2 content, me/l	10	17	12	13	12	17	19	10
chloride, me/l	100	105	95	91	88	68	64	59
uric acid, mg %		10	9.5	9.3		11.2		12.5
Urine								
ml/24 hr	500	1250	500	300	50	0	0	0
urea N, mg %		320	260	318				
urea N, g/24 hr		4.6	1.3	1.0				
"creatinine," mg %		49	70	48				
"creatinine," g/24 hr		.6	.35	.15				
"uric acid," mg %		25	32	46				
"uric acid," g/24 hr		.3	.16	.15				
Ileost. fluid								
ml/24 hr		3500	1800	1500	2900	4200	3800	3200
urea N, mg %		130	142	204	138	134		170
urea N, g/24 hr		4.6	2.6	3.1	4.1	5.6		5.5
"creatinine," mg %		11.5	21.5	14	24	9.8		
"creatinine," g/24 hr		.4	.4	.2	.7	.4		
"uric acid," mg %		45	50	26		35		
"uric acid," g/24 hr		1.6	.9	.4		1.4		

Arterial blood pH within normal limits until May 12. Plasma albumin above 3.0 during last 30 days. Liver function (Rose Bengal) normal 80th day postop.

had congenital polycystic kidneys. On Feb. 5, 1963 he was stuporous, twitching and edematous. The blood chemistries (Table I) showed severe azotemia and acidosis. On Feb. 6, 1963, the ileum was transected 90 cm proximal from the ileocecal valve and an ileostomy was made. After several complications the patient recovered consciousness and reason, ate, took care of the ileostomy and other physical needs, and was dismissed from the hospital 4 weeks after the operation. Ileostomy (Table I) resulted in substantial loss of edema fluid, markedly reduced azotemia, and excretion of large quantities of nitrogenous waste with the enteric discharge. The improvement was sustained for about 10 weeks. During this period his heart rate remained above 100, the WBC was consistently elevated, episodes of fever and dysuria supervened several times and were controlled with antibiotics. Virtual anuria set in April 27 and lasted until his death May 13. He was readmitted to the hospital April 29 because of flank pain, fever, weakness and paresthesias. Convulsions occurred with increasing frequency after May 6th. He became comatose May 9th. Autopsy showed bilateral polycystic kidneys with massive abscesses and hemorrhages in each.

Comment: In Jan. 1963, this patient with irreversible renal failure was terminally ill; distressing signs and symptoms were associated with retention of edema fluid, azotemia and acidosis. "Serum base" (Na + K = 140 me/l) and "serum acid" (Cl + HCO_3 = 110 me/l) showed a concentration difference of about 30 me/l — about 10 - 15 me/l in excess of the normally measured difference between "total cations" and "measured anions" (called "delta" hereinafter) which is attributed to proteins and normally present organic radicals. The ileostomy operation was followed by striking clinical improvement, loss of edema fluid, fall of the elevated blood pressure, and decrease of blood levels of urea and other nitrogenous waste. The patient did not recover fully. About 3 months after the operation signs and symptoms of uremia

TABLE II.
D.E., 45, chronic glomerular nephritis; ileostomy 3/16/63, transection 120 cm proximal of ileocecal valve.

Days postop.	−7	+11	+27	+51	+60	+66
Body wt, kg	73.4		63	65.2		
BP, mm Hg	190/106	140/85	150/90	160/90	145/90	138/75
Blood						
hematocrit, %	39	26	32	24	32	25
hemoglobin, g %	12.8	9.7	11.8	8.0	11.3	10.0
urea N, mg %	150	126	120	141	140	132
creatinine, mg %	9	11	15	17	17	17
uric acid, mg %	12	8	9	6		5
serum Na, me/l	138	138	141	142	142	144
serum K, me/l	3.7	4.9	4.5	4.7	7.5	6.3
CO_2 content, me/l			23	16	24	21
chloride, me/l	95		88	95	70	74
Urine						
ml/24 hr	500	460	470	300	100	0
urea N, mg %		485	449			
urea N, g/24 hr		2.2	2.1			
"creatinine," mg %		192	124	112		
"creatinine," g/24 hr		.9	.6	.3		
"uric acid," mg %		40	41	50		
"uric acid," g/24 hr		.18	.19	.15		
Ileost. fluid						
ml/24 hr		2000	2200	3400		2900
urea N, mg %		170	180	141	180	168
urea N, g/24 hr		3.4	4.0	4.8		5
"creatinine," mg %		27	30	44	30	23
"creatinine," g/24 hr		.54	.66	1.5		.7
"uric acid," mg %		142	20	35		35
"uric acid," g/24 hr		2.8	.44	1.2		1.1

Arterial blood pH within normal limits on several occasions. Plasma albumin above 3.2 g % throughout.

reappeared, became progressively more severe and ended his life. The end was considered inevitable because of the uncontrolled infection.

Unlike the earlier "terminal" state, the final episode of clinical uremia was not associated with edema, abnormal cation concentrations in the serum, or steadily rising serum non-protein nitrogen. Although elevated, the blood levels of urea, creatinine and uric acid remained fairly stable and he appeared to be in nitrogen equilibrium, as evident from the quantity of urea and other nitrogenous matter recovered from the ileostomy fluid. Liver function, blood volume and plasma proteins remained normal or nearly normal to the end. The terminal stage of uremia was characterized by hyperactive reflexes, progressing to twitching and convulsions, and by mental confusion which progressed to stupor and coma. The symptomatology was not influenced in this (and the other) patient by the retention of sedatives; while the patient was conscious the convulsions were mitigated only with injections of 25% magnesium sulfate. The terminal stage of uremia coincided with an inexorable fall of the measured serum anion concentration, which decreased from 119 me/l (April 5) to 69 me/l (May 13). Oral (or tube) administration of anion-absorbing resin, intentional increments of the ileostomy fluid volume (sorbitol by mouth or tube), alcali by mouth were of no avail. Intravenous sodium chloride caused a temporary increment of serum chloride and a corresponding decrease of HCO_3, while the "delta" remained unchanged.

D. E., a 45-year-old man, had chronic glomerular nephritis, hypertention and azotemia and was suffering from exertional chest pains and dyspnea, headaches, nausea and vomiting (Table II). On March 16, 1963 his ileum was transected 120 cm proximal of the ileocecal valve and an ileostomy was made. During the initial postoperative period

he lost weight, felt much improved and performed part of his regular work; his blood pressure fell to normal levels. Troublesome pruritus was controlled with an antihistaminic. Seven weeks after the operation his condition deteriorated, as evident from increasing involuntary muscular twitching and beginning mental confusion. The downhill course was temporarily reversed by repeated peritoneal dialyses: each procedure afforded relief for about 2 days. The patient became despondent; dialyses were not repeated and he died.

Comment. The initial clinical improvement of this terminally ill patient (weight of both kidneys at autopsy: 50 g) was evident from the absence of dyspnea and chest pain and gradual disappearance of nausea and vomiting. Clinical deterioration was evident from malfunction of the central nervous system. Clinical improvement or deterioration were not related to changes of weight (*i.e.* edema), blood pressure, hematocrit, or abnormal serum cation patterns. The severity of uremic symptoms paralleled the magnitude of the unknown serum anion moiety.

Discussion. Mechanisms that bring about the typical clinical signs and symptoms of severe uremia will be understood only when the toxic molecules have been identified. It is shown here that true clinical uremia (as distinct from the chemical entity azotemia and from pseudouremic syndromes) was associated with the rise of an unknown fraction of serum anions above a concentration of 25 me/1. The patients described here had nearly normal serum cation patterns; serum phosphate and sulfate were measured and accounted for only a small fraction of the unknown anionic radicals; serum urea varied independently; serum creatinine and uric acid remained highly abnormal but relatively stable. Serum amino acid levels are not known to increase in uremia above 1-2 me/1 (4). The data support the concept that central nervous manifestations of true uremia are caused by unknown anions of low molecular weight.

Summary. In 2 patients the central nervous signs and symptoms of uremia were associated with rising serum levels of unidentified anions, but not with parallel changes of other chemical or physiologic parameters.

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Brain Hormone Activity in *Bombyx mori* of Sterols and Physiologically Vital Active Substances. (28662)

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In the silkworm, *Bombyx mori,* imaginal differentiation is brought about by 2 hormones, one secreted from neurosecretory cells in the brain and the other from glandular cells in the prothoracic gland(1-2) as in other insects(3). Extraction of the hormone from insect brains was first reported by Kobayashi and Kirimura(4). Recently, it was determined that one of the active principles of the brain hormone was cholesterol(5-7). Therefore, considering the importance of sterols as insect hormone, we have investigated the brain hormone activity of compounds known as the steroid hormones in mammalian organisms, of sterols related to cholesterol and of other sterols. Furthermore, the brain hormone activity of some compounds known as physiologically vital active principles