

May 11, 1967

KIMMELSTIEL-WILSON SYNDROME

Case

Case No. 1

The patient, a 28-year-old Negro male, was a juvenile-type diabetic with a history of two episodes of diabetic acidosis, one associated with a lung infection. Diabetes was diagnosed at age 15. He had been on insulin therapy since that time on various doses ranging from 40 to 120 units daily.

At age 26, he was first noted to have diabetic retinopathy. At that time, BUN and urinalysis were normal; blood pressure was 140/90. He was not seen from that time to the present at which time he presented with a three month history of progressive edema. The edema began in the legs; it was not accompanied by shortness of breath nor orthopnea. However, as the amount of edema increased exertional dyspnea was noted.

Examination disclosed a blood pressure of 160/110, retinopathy and anasarca. Laboratory results included a BUN of 60, albumin of 2.4, cholesterol of 368, blood sugar 180.

Over a three month period there were several admissions, primarily because of increased edema. Although measures directed toward diuresis were moderately successful, he was never edema free. Moreover, there was a continued slow rise in azotemia and the development of metabolic acidosis.

The final admission disclosed signs and symptoms of uremia. The patient's heart which had been slightly enlarged was markedly dilated. Oliguria was present. The patient expired some 36 hours after admission.

Case No. 2

The patient was a 60-year-old Negro man who presented with an indefinite history of mild diabetes, probably of ten years duration, and marked pitting edema of both lower extremities. On that admission, there was no evidence of cardiomegaly nor congestive heart failure. There was a mild diastolic hypertension together with funduscopic changes consisting of old exudates and an occasional microaneurysm. There was mild azotemia and the serum albumin concentration varied between 3.7 and 4 gm% during that admission. Occasional random urine specimens showed at most a 2+ reaction for protein, but many urine samples were negative. On bedrest and a low salt diet, the patient eventually diuresed losing all his edema and was discharged with a diagnosis of, in addition to diabetes, idiopathic edema.

Almost one year later the patient was readmitted. At that time, there was no serious impairment of carbohydrate metabolism, but again he presented with marked edema without signs of congestive heart failure. At the time of admission, there was again no evidence of congestive heart failure (See Figure 1). Note that a 24-hour urine collected beginning the day of admission contained almost 12 grams of protein. However, thereafter the 24-hour excretion of protein was much lower, usually below the 3.5 to 5 gram per day limit for the nephrotic range. On admission, the serum albumin concentration was 3.2 g/100 ml and quickly rose to 4. The serum cholesterol concentration continued to rise after admission, but fell to 200 mg% by the time of discharge. Frankly evident edema was present for about 10 days. Thereafter, he was edema free. He was asymptomatic throughout and manifested only mild azotemia, having a BUN varying between 20 and 26 mg%.

Because of the very high urine protein excretion on the day of admission, it was considered possible that this patient might from time to time have a massive outpouring of protein into the urine resulting in the nephrotic syndrome. Attempts were made therefore to follow the patient closely in the clinic, in an attempt to pick up these sporadic nephrotic episodes. Figure 2 discloses the data obtained in following this patient. As can be seen, only

very few 24-hour urines were obtained during the patient's outpatient course. However, he was instructed to test his urine daily with albumin sticks, and if there was a very positive reaction, to return to the hospital for admission. Approximately 5 weeks after discharge, the patient returned to clinic with marked edema; again without any signs of heart failure. He stated that for the past week his test for urine protein had shown a very strong reaction. However, since he had a clinic appointment he saw no reason for returning before that date. Note that at the time of admission his serum albumin concentration was just under 2 gm per 100 ml. Note also that the initial 24-hour urine sample contained in excess of 14 grams of protein. Again the massive proteinuria quickly subsided and the serum albumin concentration rather more slowly returned towards normal. Note however, that clinically evident edema persisted even though the serum albumin concentration was within the normal range. Some 18 days after admission, the patient was edema free.

Case No. 3

The patient was a 20-year-old white girl who had been a known diabetic since 18 months of age. For the most part, her control with respect to carbohydrate had been poor, her insulin dosage varying tremendously, well over 140 units to as low as 50 units of insulin daily. This patient was followed closely as an outpatient in our clinic, and was felt to manifest a continued low grade nephrosis with sudden bursts of massive protein excretion. She maintained a mild azotemia throughout with diastolic blood pressures in the 90 to 100 mm range. Figure 3 discloses data obtained in this patient during clinic visits over a nine week period. Unfortunately, very few 24-hour urines were collected. However, it can be seen that at least on one occasion there was a massive proteinuria recorded and accompanied by an increase in edema, an abrupt lowering in serum albumin concentration and a later rise in serum cholesterol. Figure 4 depicts her clinical course during a hospitalization that was brought about for an elective full mouth extraction. Again 24-hour urine protein excretion rose and then fell to very low levels. This resulted in a fall of serum albumin concentration to 2.0 gm per cent and was associated with increased clinical edema. Thus, a pattern similar to the patient in Case No. 2 is demonstrated.

Case No. 4

The patient was a 58-year-old white man who had diabetes of the adult onset type of nine years duration. At the time of admission, he was markedly edematous, dyspneic and orthoptic; blood pressure was 160/110. There was cardiomegaly and a right pleural effusion. Venous pressure was 22 cm of water and circulation time was 18 seconds. The serum albumin was 3.6 gm%. On the day following admission, a 24-hour urine disclosed an excretion of 8.7 grams of protein. Subsequently, several urines for protein disclosed a 24-hour urine of less than 2.5 gms per day. The patient had modest azotemia with a BUN varying between 25 and 30 mg% and a creatinine varying between 1.5 mg% and 2.0 mg%. He was treated with a low salt diet, bed rest and diuretics and had an uneventful recovery.

Rogers and co, 1952, 1953, 1954, 1955, 1956, 1957, 1958, 1959, 1960, 1961, 1962, 1963, 1964, 1965, 1966, 1967, 1968, 1969, 1970, 1971, 1972, 1973, 1974, 1975, 1976, 1977, 1978, 1979, 1980, 1981, 1982, 1983, 1984, 1985, 1986, 1987, 1988, 1989, 1990, 1991, 1992, 1993, 1994, 1995, 1996, 1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025, 2026, 2027, 2028, 2029, 2030, 2031, 2032, 2033, 2034, 2035, 2036, 2037, 2038, 2039, 2040, 2041, 2042, 2043, 2044, 2045, 2046, 2047, 2048, 2049, 2050, 2051, 2052, 2053, 2054, 2055, 2056, 2057, 2058, 2059, 2060, 2061, 2062, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2070, 2071, 2072, 2073, 2074, 2075, 2076, 2077, 2078, 2079, 2080, 2081, 2082, 2083, 2084, 2085, 2086, 2087, 2088, 2089, 2090, 2091, 2092, 2093, 2094, 2095, 2096, 2097, 2098, 2099, 2100, 2101, 2102, 2103, 2104, 2105, 2106, 2107, 2108, 2109, 2110, 2111, 2112, 2113, 2114, 2115, 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TABLE 1

Morphology of Glomerular Lesions

1. Discrete Nodular Lesions - The true Kimmelstiel-Wilson lesion - nearly specific.
2. Diffuse Lesion - Mesangial proliferation - not specific.
3. Exudative Lesion - So-called fibrin caps and capsular drops - non-specific.

Morphology of Vascular Lesions

1. Afferent arteriolosclerosis - non-specific.
2. Efferent arteriolosclerosis - probably specific.
3. Large vessels atherosclerosis - non-specific, but very common in diabetic kidneys.
4. Interstitial nephritis - with round cell infiltration - non-specific, but common.

TABLE 2

Incidence of Nephrotic Syndrome

	<u>%</u>
Kimmelstiel and Wilson, 1936 (1)	Undetermined
Laipply, Eitzen, and Dutra, 1944 (4)	Under 10
Henderson, Sprague, and Wagener, 1947 (5)	6.3
Kimmelstiel and Porter, 1948 (2)	6.6
Mann, Gardner, and Root, 1949 (9)	± 20.0
Rogers and Robbins, 1952 (11)	Under 2.0
Bell, 1953 (6)	20.0
Lambic and MacFarlane, 1955 (13)	20.0
Gellman, <u>et al</u> , 1959 (20)	26.0
Hatch, <u>et al</u> , 1961 (23)	12.0

REFERENCES

1. Kimmelstiel, P. and C. Wilson. Intercapillary lesions in the glomeruli of the kidney. Amer. J. Pathol. 12:83, 1936.

Presents renal pathology on 8 patients, all autopsies, 7 had diabetes. Mainly presents pathology, little clinical data to go on; but from history of long-standing edema - assumes that 7 had nephrotic syndrome. All had hypertension. No true assessment of renal function, but states that all had renal failure.

2. Kimmelstiel, P. and W.B. Porter. Intercapillary glomerulosclerosis. New Eng. J. Med. 238:876,908, 1948.

Shows some reluctance to accept the diffuse glomerulosclerotic lesion of Bell. Admits that syndrome may not be complete, but in these patients with severe renal lesions, nephrosis is common.

3. Newburger, R.A. and Peters, J.P. Intercapillary glomerulosclerosis; a syndrome of diabetes, hypertension and albuminuria. Arch. Int. Med. 64:1252, 1939.

Presented 4 autopsied cases, 3 of which were considered to have the nephrotic syndrome. Concluded that the syndrome as described by Kimmelstiel was real.

4. Laipply, T.C., Eitzen, O., and Dutra, F.R. Intercapillary glomerulosclerosis. Arch. Int. Med. 74:354, 1944.

In 332 autopsied diabetics, nephrosis had been present in only 6.3%. An early description of the diffuse glomerular lesion. Noted no relationship to it and severity of clinical picture. Doubted that there was a syndrome.

5. Henderson, L.L., R.G. Sprague, and H.P. Wagener. Intercapillary glomerulosclerosis. Amer. J. Med. 3:131, 1947.

The syndrome is often not complete. Noted a "high incidence" of cardiac decompensation in those patients with IGS. 33% as opposed to 11%. In only 4 of 29 patients was the nephrotic syndrome present. Albuminuria present in 95% of 29. "Serum proteins - there were only four determinations of total serum proteins among the cases of intercapillary glomerulosclerosis, the values being 6.7, 6.6, 5.5 and 4.3 gm per 100 cc of serum. These meager data, and the fact that this determination was not made more frequently, suggest that hypoproteinemia of marked degree is probably not a common manifestation of intercapillary glomerulosclerosis."

6. Bell, E.T. Renal vascular disease in Diabetes Mellitus. Diabetes 2:376, 1953.

A study of 1465 autopsies in diabetic patients. First strong emphasis of the diagnostic importance of sclerosis of the efferent arteriole. "There is, however, no close correlation between the degree of edema and the severity of the hypoproteinemia."

7. Hall, G.F.M. The significance of atheroma of the renal arteries in Kimmelstiel-Wilson's syndrome. J. Pathol. and Bacteriol. 64:103, 1952.

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for the severe clinical forms of K-W syndrome.

8. Hall, G.F.M. Factors in the etiology of diabetic glomerulosclerosis. *Quart. J. Med.* 21:385, 1952.

Report on autopsy findings in 120 diabetic patients. Incidence of glomerulosclerosis was 37.5%. No significant new data. No mention of the incidence of nephrosis.

9. Mann, G.V., Gardner, C., and Root, H.F. Clinical manifestations of intercapillary glomerulosclerosis in diabetes mellitus. *Am. J. Med.* 7:3, 1949.

Concludes from the study of 83 diabetics with "renal disease" that the K-W syndrome is a true clinical entity. Of these 83 patients with mixed renal disease, 20.5% were said to have nephrosis.

10. Wilson, J.L., Root, H.F., and Marble, A. Diabetic nephropathy. *New Eng. J. Med.* 245:513, 1951.

Believes the term "diabetic nephropathy" better than K-W syndrome or ICGS. Notes that a high percentage of cases have acute and chronic pyelonephritis at autopsy. Many have arteriosclerotic changes. Most have arteriolosclerosis.

11. Rogers, J. and S.L. Robbins. Intercapillary Glomerulosclerosis: A clinical and pathologic study. I. Specificity of the clinical syndrome. *Amer. J. Med.* 12:688, 1952.

Clinical-pathologic correlation (autopsy material) in 229 diabetics. Only 4 had nephrotic syndrome (basis of this diagnosis not described). From clinical diagnosis 57% were not correctly diagnosed as having the pathologic lesion. Also 32% were diagnosed as having lesion on clinical grounds when it was absent pathologically.

12. Rogers, J., Robbins, S.L. and H. Jeghers. Intercapillary glomerulosclerosis; a clinical and pathologic study: II. A clinical study of 100 anatomically proven cases. *Amer. J. Med.* 12:692, 1952.

One hundred diabetic patients with a pathologic diagnosis of ICGS were compared with 176 diabetic patients not having this lesion. Concluded that many, if not most, of patients with ICGS do not have the classic syndrome. The classic syndrome is occasionally seen in diabetics that do not have ICGS. However, the clinical diagnosis of the pathologic lesion is more often missed than incorrectly diagnosed.

13. Lambie, A.T. and A. MacFarlane. A clinico-pathological study of diabetic glomerulosclerosis. *Quart. J. Med.* 24:125, 1955.

A pathologic study of 120 diabetic patients that came to autopsy. 46% had renal lesion. A total of 11 patients were diagnosed as having the nephrotic syndrome. In these 11 patients - urine albumins given as gms/liter only varied from 1 to 12. Serum albumin concentration in all but one case over 3.0 gms%. Four of these patients died of "uremia." Massive albuminuria was associated principally with the "exudative lesion."

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Study of 137 autopsied cases. Thirty-seven had nodular lesions. Twenty-three had serum albumin below 3.0 gm%. Thirty had edema; however, 31 had signs of CHF when edema present.

15. Zubrod, C.G., Enersole, S.L., and Dana, G.W. Amelioration of diabetes and striking variety of acidosis in patients with Kimmelstiel-Wilson lesions. *New Eng. J. Med.* 245:518, 1951.

Reviewed the clinical history of 190 post mortem diabetics and concluded that by some means, K-W lesions lower the insulin requirement in these patients.

16. Runyan, J.W. Jr., Hurwitz, D. and Robins, S.L. Effect of Kimmelstiel-Wilson syndrome on insulin requirements in diabetics. *New Eng. J. Med.* 252:388, 1955.

Concluded that insulin dose tended to be lower in those patients that had the "full-blown K-W Syndrome" and thought this was due to a decreased food intake.

17. Marble, A. Diabetic nephropathy. In Diseases of the Kidney, Eds., Strauss, M.B. and Welt, L.G. Little, Brown and Co., 1963. pp. 620-626.

A review stressing the incompleteness of the K-W syndrome.

18. Heptinstall, R.H. Pathology of the Kidney. Little, Brown and Co., 1966. pp 465-490.

Stresses the point that pathologically lesions previously thought to be due to chronic renal infection (pyelonephritis) are, for the most part, the result of vascular disease. Believes that term "K-W syndrome" should be dropped.

19. Thomsen, A.C. The significance of renal biopsy for the diagnosis of pyelonephritis in diabetic patients. In *Ciba Foundation Symposium on Renal Biopsy*, Eds., Wolstenholme, G.E.W. and Cameron, M.P. Little, Brown and Co., 1961, Boston, p 281.

Concludes that moderate to severe interstitial infiltration with round cells, and periglomerular fibrosis were non-specific changes that could be the result of vascular disease.

20. Gellman, D.D., Pirani, C.L., Soothill, J.F., Muehrche, R.C. and Kark, R.M. Diabetic nephropathy: A clinical and pathologic study based on renal biopsies. *Medicine*, 38:321, 1959.

21. Kark, R.M. and Gellman, D.D. Renal disease in diabetes. In Diabetes, Ed. R.H. Williams, P.B. Hoeber, New York, 1960, p 569.

22. Gellman, D., Pirani, C.L., Soothill, B.M., Muehrche, R.C., Maduros, W., and Kark, R.M. Structure and function in diabetic nephropathy. *Diabetes* 8:251, 1959.

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1. Most common lesion (biopsy) was diffuse diabetic glomerulosclerosis (75% of 53 selected patients).
 2. Nodular lesions seen in 48% - is specific.
 3. Classical pathology of acute and chronic pyelonephritis not seen in this series.
 4. Severity of the nodular lesion did not correlate with the clinical status.
 5. Severity of the diffuse lesion did correlate with the clinical picture.
 6. Nodular lesion does not cause nephrosis.
 7. The term "K-W Syndrome" should be dropped.
23. Hatch, F.E., Watt, M.F., Kramer, N.C., Parrish, A.E., and Howe, J.S. Diabetic glomerulosclerosis: A long-term follow-up study based on renal biopsies. *Am. J. Med.* 31:216, 1961.
- Only report with good criteria for diagnosing nephrotic syndrome. On this basis, 5 of 41 patients had nephrosis, but 19 other patients were possible nephrotics. Noted edema present with relatively high serum albumin concentration. Also thought clinical state correlated best with the severity of the diffuse, but not nodular glomerular lesion.
24. Shapiro, A.P., Perez-Stable, E., Moutsos, S.E. Coexistence of renal arterial hypertension and diabetes mellitus. *J. Amer. Med. Assoc.* 192:813, 1965.
- Patients found to have "renal artery hypertension" were tested for diabetes. Of 55 patients, 24 were considered diabetic. Suggested that hypertension in diabetics may be more reasonably ascribed to renal artery disease (pressor hypertension) than K-W lesions in the kidney.
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- From normal adult biopsy and autopsy material the mean width of BM was found to be $3146 \pm 983 \text{ \AA}$. A maximum mean width of 5112 \AA was still considered normal. No variation with sex or age.
26. Kimmelstiel, P., Osawa, G., Beres, J. Glomerular basement membrane in diabetics. *Am. J. Clin. Pathol.* 45:21, 1966.
- Width of $5373 \pm 2280 \text{ \AA}$ with nodules. Width of $3293 \pm 1260 \text{ \AA}$ without nodules. Concludes that thickening of G.B.M. is not an early lesion in diabetes.
27. Harrington, A.R., Hare, H.G., Chambers, W.N., and Valtin, H. Nodular glomerulosclerosis suspected during life in a patient without demonstrable diabetes mellitus. *New Eng. J. Med.* 275:206, 1966.
- No glucose intolerance could be detected in this patient with a family history of diabetes, who clinically manifested nephrosis, hypertension, and renal failure. Renal pathology classical for diabetes.

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Shows that albumin catabolism is reduced by removal of kidneys in nephrotic rats.

32. Nussle, D., Barandun, S., and Witschi, H.P. Pertes digestives de proteines et syndrome nephrotique. In Plasma Proteins and Gastrointestinal Tract in Health and Disease. Williams and Wilkins, 1963, Baltimore, p 180.

Describes 4 children with nephrotic syndrome that have marked loss of albumin into gastrointestinal tract.

33. Yamuchi, H. and Hopper, J. Hypovolemic shock and hypotension as a complication in the Nephrotic Syndrome. Ann. Int. Med. 60:242, 1964.

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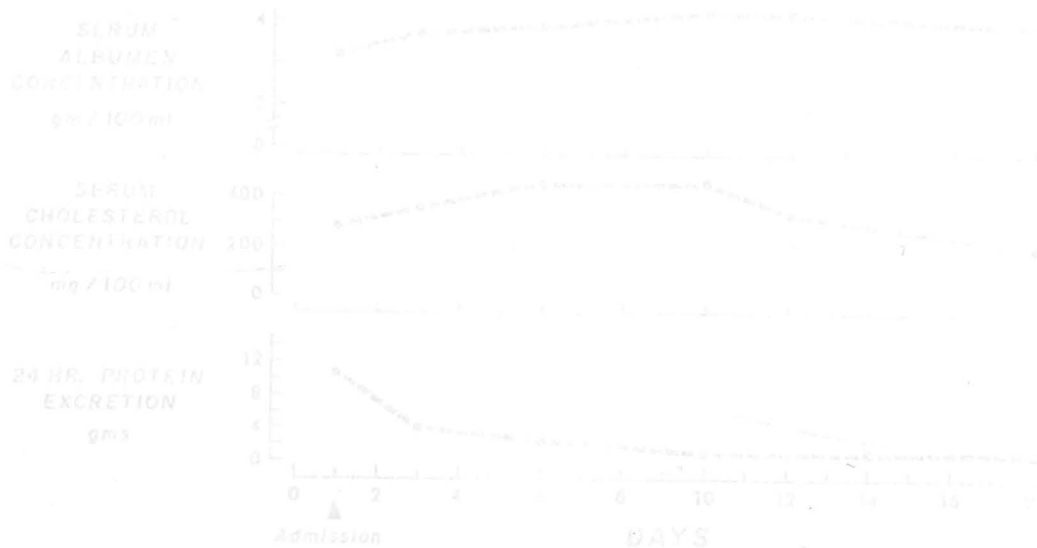
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W.C. 60 yr. old

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CLINICAL COURSE - P-W

W.C. 60 yr. old

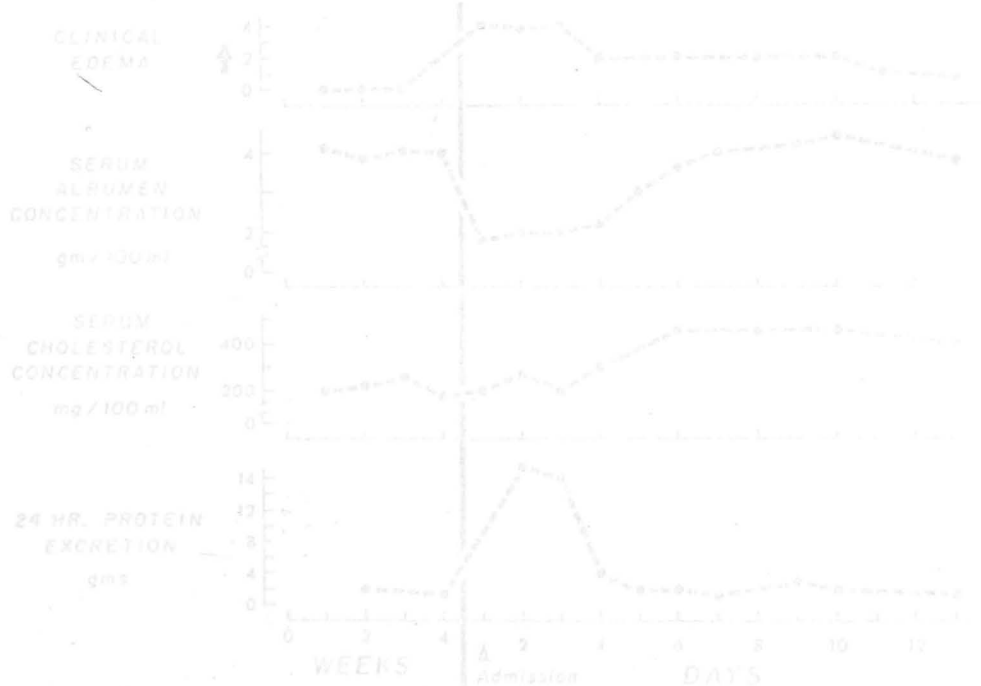


FIGURE 2

CLINICAL COURSE - K-W

W.C. 60yr. old

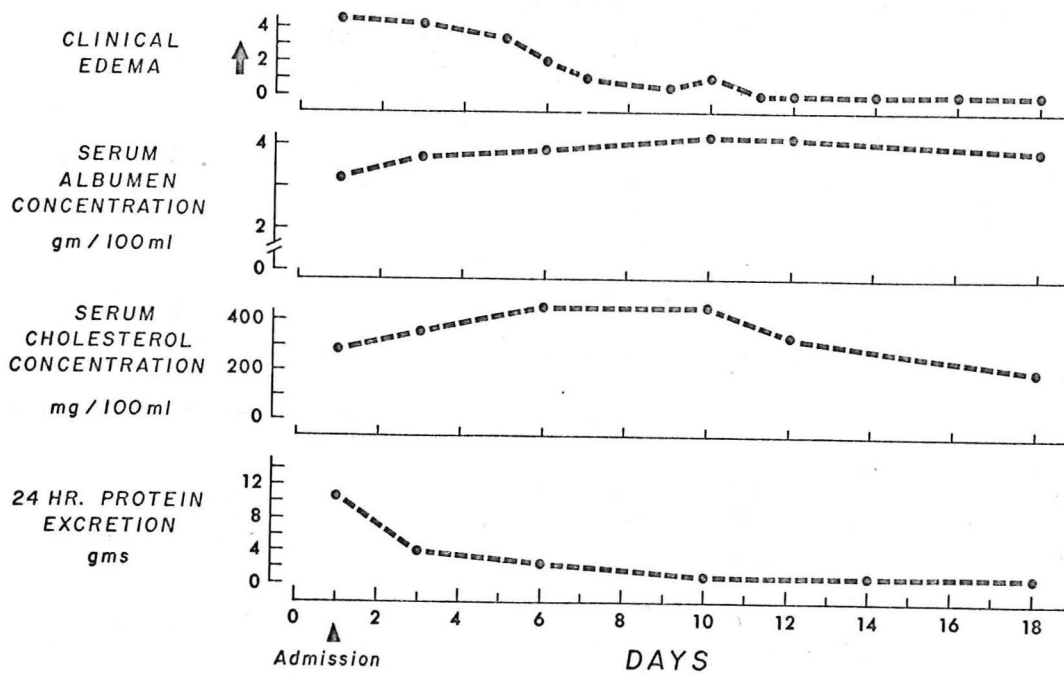


FIGURE 1

CLINICAL COURSE - K-W

W.C. 60yr. old

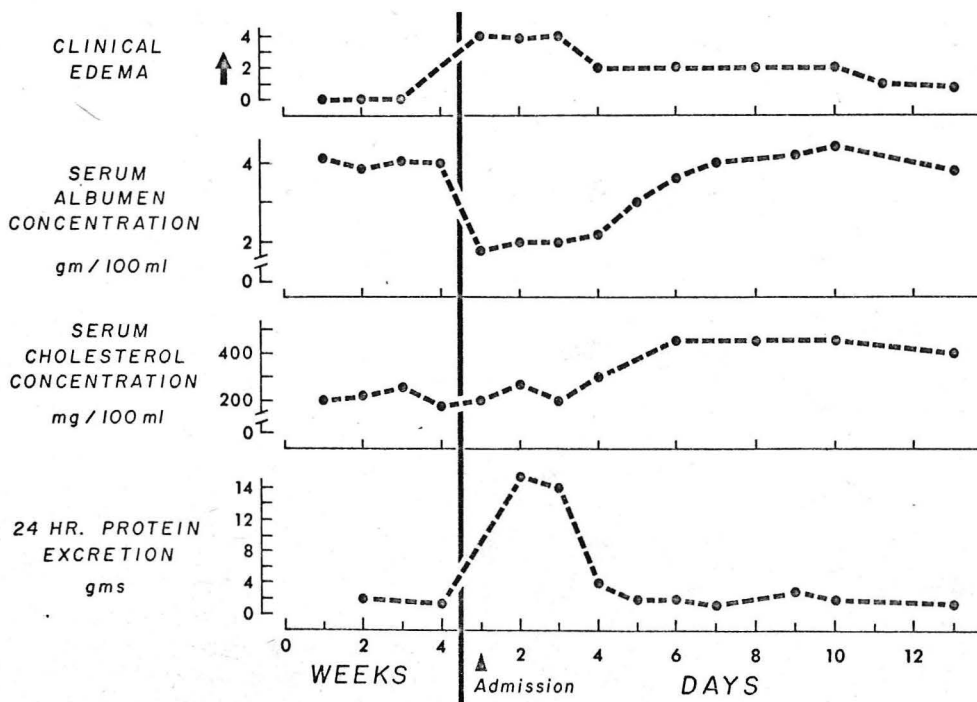
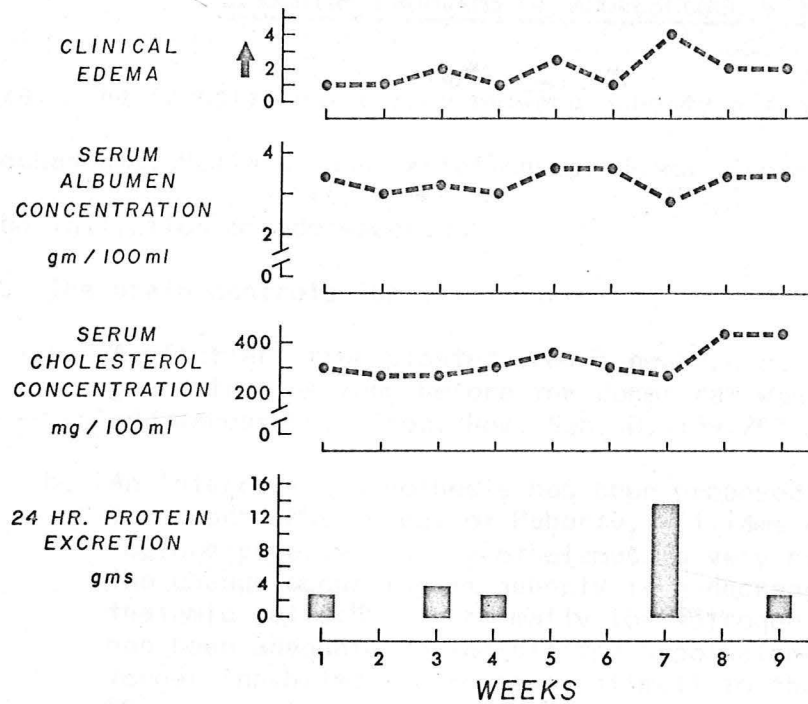


FIGURE 2

CLINICAL COURSE - K-W

C.S. 20yr. old

FIGURE 3



CLINICAL COURSE - K-W

C.S. 21yr. old

FIGURE 4

