

A LOW MOLECULAR WEIGHT PROTEIN (β_2 -MICROGLOBULIN) AND RENAL DISEASE IN SPINAL CORD INJURY PATIENTS

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CLINICAL observations indicate that renal disease is one of the major complications and causes of death in patients with spinal cord injuries. Effective therapeutic and preventive measures depend upon the earliest possible detection of deterioration of renal function, before extensive and irreversible damage has occurred. The development of newer and more sensitive techniques for measuring changes in renal function is therefore of particular interest to physicians caring for patients with spinal cord injury.

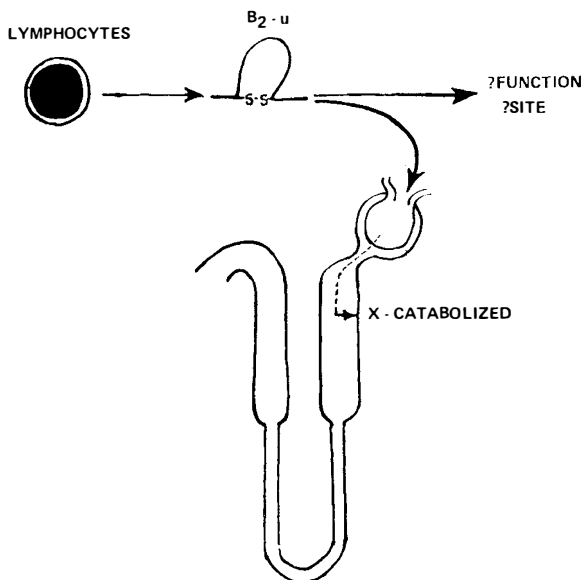


FIG. 1

Probable normal origin and fate of β_2 -microglobulin.

Of the standard tests of renal function, creatinine clearance is generally accepted as the most reliable, but owing to the ability of the kidney to compensate, even this test does not detect anything less than a 40 per cent. loss of functioning units. Anatomical changes in kidney size or shape as detected by X-rays are signs of gross changes which have already taken place. The increased urinary excretion of protein is also a somewhat crude indicator of renal disease. However, it may be made more meaningful by fractionation of the protein and subsequent identification and measurement of the specific protein fractions.

In recent years Berggård and others (1964, 1968) have described a low molecular weight globulin fraction, β_2 -microglobulin, which is present in only trace amounts in normal human serum and urine. It is increased in patients with renal disease (Bernier *et al.*, 1968; Harrison *et al.*, 1968), the level of increase being proportional to the degree of failure present. The urinary excretion is markedly increased in patients with renal tubular dysfunction (Peterson *et al.*, 1969). As far as is known at present this low molecular weight protein is produced in the body by lymphocytes (fig. 1), and can be artificially produced in tissue cultures, by stimulation of lymphocytes with phytohemagglutinin, at the phenomenal rate of 3000 mol./cell/min. (Bernier & Fenger). Its function is still unknown, although it seems probable that a substance which can be produced with such speed, and removed with such dispatch by the normal renal mechanisms, must have some significant

TABLE I
Parameters of Renal Function studied in 25 Patients with
Spinal Cord Injury

1. Creatinine clearance (normal: > 100 ml./min.)
2. 24 hr. urinary excretion of total protein (normal: < 150 mg.)
3. I.V.P. & cystogram
4. Serum β_2 -microglobulin (normal: < 2 ug./ml.)
5. 24 hr. urinary excretion of β_2 -microglobulin (normal: < 0.2 mg.)
6. β_2 -microglobulin clearance (normal: < 0.1 ml./min.)

TABLE II
Analysis of 25 Patients with Spinal Cord Injury studied for
Abnormalities of β_2 -Microglobulin

| Patient age (14-82) | | | Sex | | Injury | | Years since injury | | |
|---------------------|-------|-----------|-----|---|--------|------|--------------------|-----|-----|
| < 20 Yrs. | 21-40 | > 40 Yrs. | M | F | Quad | Para | < 1 | 1-2 | > 5 |
| 4 | 14 | 7 | 24 | 1 | 13 | 12 | 15 | 4 | 6 |

activity in the body. There is experimental evidence (Bernier & Conrad, 1969) to say that it is normally destroyed or catabolised by the cells of the renal tubules, so that dysfunction of the renal tubular cells results in an abnormally high urinary excretion.

We have used a radio-immuno assay method to detect $\beta_2\mu$ levels in the serum; measure the 24 hour urinary excretion and calculate the renal clearance in 25 patients with spinal cord injuries, and correlate the results obtained with those of the three standard renal function tests (Table I). The make up of the patient group studied, with respect to level and duration of injury, age and sex, is shown in balanced automatic bladders. The rest still wore indwelling urethral catheters. Only two had documented evidence of pyelonephritis, but most of the group had bladder infections at some time.

TABLE III
Analysis of Abnormalities in Handling of β_2 -Microglobulin
(in Patients with Spinal Cord Injury (17 cases))

| Abnormalities of β_2 microglobulin | Number of patients |
|--|--------------------|
| ↑ Serum only | 6 |
| ↑ Urinary excretion only | 1 |
| ↑ Clearance only | 1 |
| ↑ Serum and urinary excretion | 0 |
| ↑ Serum and clearance | 0 |
| ↑ Urinary excretion and clearance | 3 |
| ↑ Serum, urinary excretion and clearance | 6 |

TABLE IV
Comparison of Standard Renal Function Tests with $\beta_2\mu$
Assays in Patients with Spinal Cord Injuries

| Standard renal function tests | | | β_2 -microglobulin assays | |
|-------------------------------|----------|----------|---------------------------------|-------------------------------|
| All normal | Abnormal | | Normal | Abnormal |
| | ↓ Cr Cl | X-ray | | |
| × × × × × × × × × × × × | | | × × × × | × × × × × × × × (66%) |
| Single abnormalities | × × | × × | × × × | × × × × × × |
| Multiple abnormalities | × × | × × × | × × × × | × × × |
| SUBTOTAL: | | | × × × × | × × × × × × × × × (66%) |

RESULTS

Seventeen of the patients were found to have abnormalities with respect to their handling of β_2 -microglobulin (Table III). Serum levels were high in 12 of these, and nine patients showed increased urinary excretion and clearances. In each of eight patients only one parameter was found to be abnormally high.

When these results were compared with those obtained with the standard renal function tests, it was apparent that of 12 patients whose kidney function would be judged normal by the standard tests, two thirds showed abnormalities of β_2 -microglobulins (Table IV). Thirteen patients, on the other hand, had abnormalities of one, two or three standard test parameters, and two thirds of this group also showed abnormalities in the handling of β_2 -microglobulin. It was of interest to find that of 21 spinal cord injury patients with normal creatinine clearances, a test on which most physicians rely strongly as an indicator of abnormal renal function, only five patients were normal in all other parameters. This would seem to indicate the need for a battery type test approach to renal function studies.

What precise role β_2 -microglobulin assays will eventually assume in the early detection of renal impairment in spinal cord injury patients will, it is hoped, emerge as the result of continued follow-up of the present group of patients, and the data reported at this stage must be regarded as the beginning of a long-term study.

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