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CARE OF THE PATIENT IN AUTOIMMUNE RENAL DISEASE. ASSESSMENT OF CLINICAL AND IMMUNOLOGICAL ACTIVITY

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174 patients suffering from various autoimmune renal diseases have been followed up for periods of one to four years. Repeated assessment of clinical and immunological activity is indispensable for therapy, prognosis and rehabilitation.

Determination of microscopic haematuria by the Addis count proved to be the best indication of clinical activity. Immunological activity was assessed by the CH_{50}, C3 and immunoconglutinine tests, the titer of the anti-glomerular basal membrane antibodies and the inhibition of leucocyte migration. Depending upon the nature and stage of the disease one or more positive tests indicated activity of the pathological process.

Consequently, the simultaneous application of several methods is recommended for assessment of immunological activity in autoimmune renal diseases.

The general lines of long-term care are independent of the type of nephropathy. There are none the less certain points to be kept in mind in case of autoimmune renal disease where a close study of the clinical and immunological activity is of utmost therapeutic and prognostic relevance and also predictive of the chances of rehabilitation.

Autoimmune renal disease includes the following conditions.

1. chronic glomerulonephritis,
2. Goodpasture's syndrome,
3. nephropathy collagen disease,
4. idiopathic nephrotic syndrome.

The present material included 121 patients with renal disease of strictly autoimmune character. In a wider sense, it amounted to 174 cases if the patients with acute glomerulonephritis of protracted course and those with subacute nephritis of rapid progression are also included.

It is obvious that certain forms of autoimmune renal disease, e.g. the Goodpasture-syndrome, polyarteritis nodosa, Wegener's granulomatosis, subacute glomerulonephritis hardly ever provide cases for long-term care owing to the rapid fatal outcome of the process.

Practice of long-term care

The cardinal factor of long-term care in chronic renal disease is an outpatient clinic provided with all necessary diagnostic facilities. It belongs to the practising physician to sort out the cases and to recognize unexpected sudden changes. The patients have, however, to be admitted to the nephrology ward at least once a year for closer analysis of the process.

A printed from was used by our Nephrology Clinic, on which beside the history, the physical status, including the ocular fundus following laboratory data were recorded (Table I). The tests and investigations selected for this purpose are to provide information on the clinical and immunological activity of the process and on renal function.

Table I

Laboratory investigations

ESR	Urine
ASO	Spec. gravity
Serum Na	pH
Serum K	Protein
Serum Cl	Esbach test
Serum cholesterol	Donné test for pus
Blood sugar	Sugar
Serum total protein	Addis count
Paper electrophoresis	RBC
BUN	WBC
Serum creatinine	Casts
4 hr endogenous creatinine clearance	Bacterial count
	Antibiogram
	Sternheimer—Malbin cells
Haemoglobin	Capillary resistance
Haematocrit	Tourniquet test
Cell counts	Coagulogram
Leukocytes	Euglobulin lysis time
Neutrophils	Thromboelastogram
Platelets	LE-cell phenomenon
Platelet ADP aggregation	
Platelet factor 3 availability	
Electrocardiogram	Nasal swab
Ballistocardiogram	Pharyngeal swab
X-ray of stomach	

The most reliable index of activity is microhaematuria estimated by the Addis count. The process is considered clinically active as long as the Addis count exceeds 10 million. Proteinuria is less informative, its decrease being not necessarily a sign of clinical improvement. Excretion over 3 g daily does, however, reflect an activity characteristic of the nephrotic syndrome. The informative value of hypertension as a sign of activity is limited by the occurrence of dual syndromes, for instance of glomerulonephritis in association with central (essential) hypertension. The red blood cell sedimentation rate is a highly informative index of activity.

Efficiency of the kidney is assessed by estimation of the glomerular filtration rate. Inulin clearance is the most reliable procedure of this kind but it requires clinical facilities. Endogenous creatinine clearance is satisfactory for routine purposes with the understanding that it is carried out under identical conditions. Actually, in our experience, the same patient generally shows a lower creatinine clearance when seen as on outpatient than he does in the course of hospitalization. This is probably because many patients have to make a fairly long

journey to be seen at the clinic and fail to observe bed rest. Similar observations have been reported by FISCHER and VARGA [3].

Close attention is being given to blood coagulation, since its disorders belong to the essential features of immune nephropathies. Investigation of the heart includes ECG and ballistocardiographic studies. In case of massive corticosteroid therapy, X-ray examination of the stomach is performed at three week intervals.

This follow-up scheme has been applied to every case of renal disease, regardless of its type. However, in renal disease with autoimmune features additional procedures have been adopted for the analysis of the immunological background. These are as follows.

1. Measurement of serum complement according to LANGE [16]; normal range, 1 to 3 U.

2. Measurement of the third component of complement according to MANCINI [21]; normal range 100 ± 22 mg per 100 ml.

3. Study of immunoconglutinin according to COOMBS and COOMBS [2].

4. Measurement of the anti-glomerular basement membrane antibody titres by complement fixation. It is only from dilutions of 1 : 16 onward that the sera can be considered positive.

5. Leukocyte migration test according to SOBORG and BENDIXEN [27], with human glomerular basement membrane antigen prepared by the method of KRAKOWER and GREENSPON [13] and of ROCKLIN [26].

Diagnosis of immunological activity

Serum complement, i.e. total haemolytic complement activity (CH_{50}). It was GUNN [7] who first recognized the fall in serum complement level accompanying acute glomerulonephritis, an observation confirmed since by numerous authors. Chronic glomerulonephritis is generally associated with a normal serum complement level. There are, however, cases in which the level decreases while the process remains clinically active: persistent hypocomplementaemic glomerulonephritis [4, 8, 9, 10, 11, 14, 22, 23, 30]. Of the collagen nephropathies it is particularly lupus nephritis of which a low serum complement level is typical [16, 28]. The oedematous stage of the nephrotic syndrome is often associated with low complement levels [14, 15, 28] and its variations reflect the clinical course.

Though we have failed to confirm the existence of a close relationship of the clinical course and the serum complement level [8, 9, 11] we certainly regard persistently low complement values as an unfavourable prognostic sign.

The third component of complement (C3, β_1C-globulin). There are nine thus far identified components of the complement; among them C3 has been found to be the most informative [5, 6, 12, 25, 29].

In the present material, with the exception of the cases of lupus nephropathy, the variations of the serum total complement level did not invariably go parallel with the value for C3 (Fig. 1).

The left lower quarter of Fig. 1 represents the cases in which the values for both CH_{50} and C3 were reduced, its left upper quarter those in which only C3 was low, the left upper quarter those with normal CH_{50} and C3 values, and the right lower quarter those exceptional cases in which only the CH_{50} level was low.

Lupus nephropathy was invariably associated with a decreased value for both CH_{50} and C3. In a number of patients with chronic glomerulonephritis only C3 was reduced. Similar results have been obtained in the nephrotic syndrome.

In our experience C3 is a more sensitive indicator of activity than CH_{50} but the reverse may also occur in exceptional cases.

A decline of C3 in the course of intermittent haemodialysis is not necessarily a sign of immunological activity. As it can be seen in Fig. 2, C3 diminished during haemodialysis and returned to normal values thereafter. This might be attributed to a loss of aminoacids interfering with complement synthesis.

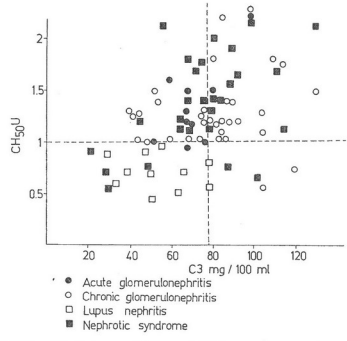

Fig. 1. Relationship between CH_{50} and C3 in autoimmune renal disease

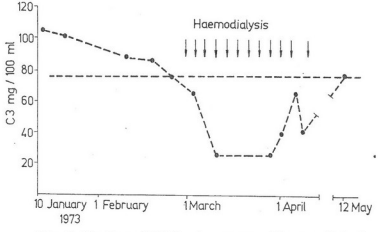

Fig. 2. Decline of C3 in the course of haemodialysis

Immunoconglutinin. Immunoconglutinin is an antibody to the concealed antigen-determinants of C3 and C4. Its level increases if it reacts with immune complexes. Increased levels have been found in sera of patients with acute nephritis [2, 24]. Immunoconglutinin is not demonstrable before the decrease of the complement level but it has been demonstrated even when the complement has ceased to decline [24].

The variations in C3 were compared with those of immunoconglutinin in 35 cases of immune renal disease. In 50 % of the cases no parallelism was found between the two values although both proved to be sensitive indices of immunological activity.

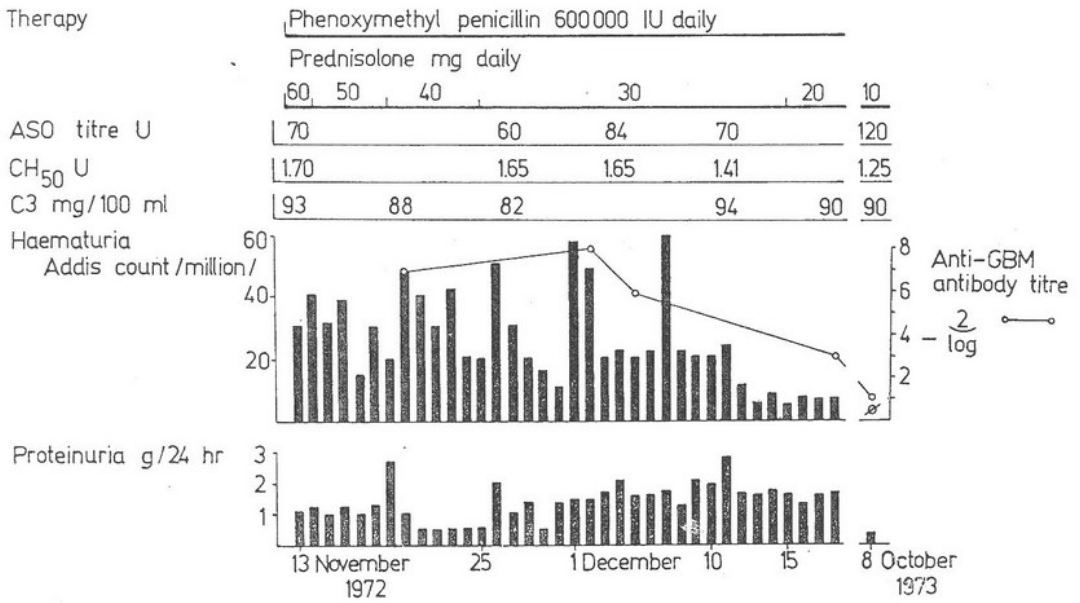

Fig. 3. Relationship of anti-glomerular basement membrane (CMB)-antibody titre and clinical course. Renal biopsy: proliferative glomerulonephritis

Anti-glomerular basement membrane antibodies. There are some data of anti-glomerular basement membrane antibodies being demonstrable in the sera of patients with various types of nephropathy [1, 17, 18, 19].

In the present material some relationship was observed between the anti-basement membrane antibody titres and the clinical course. This is obvious from Fig. 3. The patient was a 18 year old male with proliferative glomerulonephritis. All signs of clinical activity were present and the anti-basement membrane antibody titres were high. Prednisolone therapy resulted in regression of the symptoms and in normalization of the antibody titre. 10 months later proteinuria was minimal and the antibody titre had remained normal.

There are, however, some limitations of the method: circulating anti-basement membrane antibody was demonstrable in no more than 12 out of 66 cases of autoimmune renal disease, and antibody-positivity was confined

to 7 out of 25 cases of chronic glomerulonephritis. The possible explanations of the failure are that the sensitivity of the method may not be adequate or the anti-basement membrane antibody may not be the mediator of chronic glomerulonephritis in the majority of cases.

Cell-mediated immune response.

Sporadic data suggest that, in addition to humoral immunity, cellular immunity may also be involved in the pathogenesis of immunogenic renal disease [18, 20, 26]. On the evidence of our serial experiments, the migration index, with antigen derived from glomerular basement membrane, may serve as an indicator of the immune processes taking place at the cellular level.

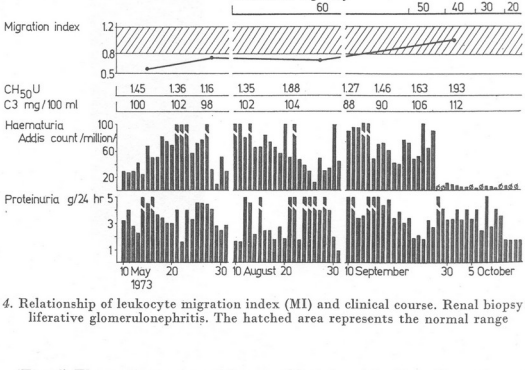

Fig. 4. Relationship of leukocyte migration index (MI) and clinical course. Renal biopsy: proliferative glomerulonephritis. The hatched area represents the normal range

(Fig. 4) The patient was a 39 year old male with clinically active proliferative glomerulonephritis. While the migration index was positive, no humoral anti-basement membrane antibody was demonstrable. In response to 60 mg prednisolone daily, haematuria subsided, the migration index returned to normal values and the biopsy also showed signs of improvement.

Inhibition of migration by the basement membrane-antigen was obtained quite unexpectedly in as many as 6 cases in a total of 7 patients with idiopathic nephrotic syndrome.

It is concluded from the present observations that assessment of the immunological activity requires the concurrent use of different procedures.

REFERENCES

1. Bach, J. F., Dardenne, M., Hinglais, N., Mahieu, P.: Actual. nephrol. Hop. Necker. 73. p. (1972).
2. Coombs, R. R. A., Coombs, A. M., Ingram, D. G.: The Serology of Conglutination and its Relation to Disease. Blackwell, Oxford, 1961.
3. Fischer, A., Varga, I.: Orv. Hetil. **107,** 681 (1966).
4. Gewurz, H., Pickering, R. J., Mergenhagen, S. E., Good, R. A.: Int. Arch. Allergy **34,** 556 (1968).
5. Gotoff, S. P., Fellers, F. X., Vawter, G. F., Janeway, C. A., Rosen, F. S.: N. Engl. J. Med. **273,** 524 (1965).
6. Gotoff, S. P., Isaacs, E. W., Muehrcke, R. C., Smith, R. D.: Ann. intern, Med. **71,** 327 (1969).
7. Gunn, W. C.: J. Path. Bact. **19,** 155 (1914).
8. Hámori, A.: Orv. Hetil. **106,** 2209 (1965).
9. Hámori, A.: Ther. hung. **14,** 83 (1966).
10. Hámori, A.: Curr. med. Digest. **34,** 573 (1967).
11. Hámori, A., Czirner, J., Bibor, Z., Gofman, L.: Acta med. Acad. Sci. hung. **22,** 225 (1966)
12. Humair, L. M.: Schweiz. med. Wschr. **100,** 1767 (1970).
13. Krakower, A., Greenspon, S. A.: Arch. Path. **51,** 629 (1951).
14. Lange, K., Graig, F., Oberman, J., Slobody, L., Ogur, G., LoCasto, F.: Arch. intern. Med. **88,** 433 (1951).
15. Lange, K., Slobody, L., Strang, R.: Proc. Soc. exp. Biol. (N. Y.) **82,** 315 (1953).
16. Lange, K., Wasserman, E., Slobody, L. B.: Ann. intern. Med. **53,** 636 (1960).
17. Macanovic, M., Evans, D. J., Peters, D. K.: Lancet **2**, 207 (1972).
18. Mahieu, P., Dardenne, M., Bach, J. F.: Amer. J. Med. **53,** 185 (1972).
19. Mahieu, P., Taieb, C. M., Bach, J. F.: Acta clin. belg. **26,** 183 (1971).
20. Mallick, N. P., Williams, R. J., McFarlane, H., Orr, W. McN., Taylor, G., Williams G.: Lancet **1,** 507 (1972).
21. Mancini, G., Carbonara, A. O., Heremans, J. F.: Imunochemistry **2,** 235 (1965).
22. Marosvári, I.: Mschr. Kinderheilk. **116,** 422 (1968).
23. Michael, A. F., Westberg, N. G., Fish, A. J., Vernier, R. L.: J. exp. Med. **134,** 208 (1971).
24. Ngu, J. L., Soothill, J. F.: Clin. exp. Immunol. **5,** 557 (1969).
25. Ogg, C. S., Cameron, J. S., White, R. H. R.: Lancet **2,** 78 (1968).
26. Rocklin, R. E., Lewis, E. J., David, J. R.: N. Engl. J. Med. **283,** 497 (1970).
27. Soborg, M., Bendixen, C.: Acta med. scand. **181,** 247 (1967).
28. Wedgwood, R. J. P., Janeway, C.A.: Pediatrics **11,** 569 (1953).
29. West, C. D., Northway, J. D. Davis, N. C.: J. clin. Invest. **43,** 1507 (1964).
30. West, C. D., McAdams, A. J., McConville, J. M., Davis, N. C., Holland, N. H.: J. Pediat. **67,** 1089 (1965).

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