The Immunopathology of the Kidney

Boris Albini,
Jan R. Brentjens,
Giuseppe A. Andres,

The Immunopathology of the Kidney

Boris Albini,
M.D.
Associate Professor of Microbiology, School of Medicine
State University of New York at Buffalo

Jan R. Brentjens,
M.D.
Associate Professor of Pathology and Microbiology, and
Research Associate Professor of Medicine, School of Medicine,
State University of New York at Buffalo

Giuseppe A. Andres,
M.D.
Professor of Microbiology, Pathology and Medicine,
School of Medicine, State University of New York at
Buffalo, and Director of the Renal Research Laboratory,
Buffalo General Hospital, Buffalo, New York

Edward Arnold

First published 1979
by Edward Arnold (Publishers) Ltd
41 Bedford Square, London WC1B 3DQ

ISBN: 0 7131 4299 5
ISSN: 0141–3368

Text set in 10/11 pt IBM Press Roman, printed by photolithography, and bound in Great Britain at The Pitman Press, Bath

General Preface to Series

The impact of immunological thought on medical practice has been increasing at a steady rate now for nearly twenty years. There appear to be very few fields to which the immunologist cannot contribute. Initially the immunological approach was limited to assistance in diagnosis and in sera and vaccine production. New approaches in the field of therapy are not only in the use of vaccines, sera and immunosuppressive agents, but also in the more rational use of conventional therapeutic agents. Immunological knowledge is especially necessary in the field of tumour therapy, particularly in the balanced use of surgery and radiotherapy. Moreover, immunological knowledge in other fields has allowed us to understand more readily the mechanisms whereby a single aetiological agent can produce a wide range of different clinical manifestations. Different disease patterns occur depending on the nature of the immunological reaction causing tissue damage. A completely different symptom complex from reactions involving soluble immune complexes reacting with the complement cascade will be found in those involving the reaction of specifically sensitized lymphocytes with antigen as part of a cell-mediated or delayed hypersensitivity reaction.

As a massive amount of new scientific material accumulates in this field, the clinician is frequently left behind and perplexed. Each year a new scientific journal is published specializing in fields as diverse as immunogenetics, immunochemistry or immunological techniques. We have journals emanating from continents as well as countries. The wealth of material is often bewildering. Simple textbooks of immunology are often too simple, whereas review articles may be too complicated for the specialist physician or surgeon who wants a treatise on those aspects of the subject particularly relevant to his own field of interest. It is hoped that this series will fulfil some of these needs by giving comparatively short reviews that will lay emphasis on immunological subjects which should appeal to both clinicians and those working in clinical laboratories. The aim is to provide the busy clinician in a particular field of medicine with a short volume relevant to his practice written by a specialist. It should introduce the reader to the immunological approach to his subject and indicate how modern immunological thought might influence his day-to-day work in the wards or clinical laboratory.

JOHN TURK

The Royal College of Surgeons of England
London

Preface

Studies of the involvement of immune mechanisms in kidney diseases have contributed significantly to the shaping of modern nephrology. Immunologically oriented research on renal malfunction has also established many basic principles of general immunopathology.

This book is intended for clinicians, researchers, and students interested in the immunological aspects of kidney diseases. Excellent reviews on human and experimental kidney diseases are available. Similarly, extensive treatises are available on immunopathology. This book does not attempt to describe human disease and experimentally induced pathology in animals as extensively and completely, or to offer as thorough a discussion of their immunopathology, as those reviews. It endeavours, however, to bridge the gap between immunologically and clinically oriented texts. The involvement of immune reactions in kidney diseases is discussed according to the main types of immunologically mediated injury. An attempt has been made to outline the basic immunopathological mechanisms and to provide the reader with the most essential data on techniques used in immunopathology.

Buffalo, New York

B.A.
J.B.
G.A.

Acknowledgements

The authors very gratefully acknowledge Martin Milgrom, M.D. for reviewing the manuscript. Bert Arisz, M.D., Bernice Noble, Ph.D., and Elena Ossi, M.D. gave many helpful suggestions.

Excellent secretarial and editorial assistance was provided by Mrs Joan Watson, Mrs Mary Ann Bryant, and Mrs Nancy Cronk.

Mr Bruce Luders prepared the photographs. The schemes presented in Chapter 2 were drawn by Ms Barbara Evans.

This work was supported by Grants AI-10334 and AM-17317 from the National Institutes of Health, USPHS, and by Contract 91271 of the New York State Health Research Council.

Abbreviations

ALG	Antilymphocyte globulin
ANA	Antinuclear antibodies
BMDDD	Basement membrane dense deposit disease
BSA	Bovine serum albumin
C3NeF	C3 nephritic factor
DNA	Deoxyribonucleic acid
EBV	Epstein–Barr virus
ECF-a	Eosinophil chemotactic factor of anaphylaxis
ER	Effective radius
FITC	Fluorescein isothiocyanate
GBM	Glomerular basement membrane
GCW	Glomerular capillary wall
GFR	Glomerular filtration rate
HBAg	Hepatitis B antigen
HUS	Haemolytic uraemic syndrome
Ig	Immunoglobulin
LCM	Lymphocytic choriomeningitis virus
LPS	Lipopolysaccharides
MPGN	Membranoproliferative glomerulonephritis
MuLV	Murine leukaemia virus
MW	Molecular weight
NDNA	Native or double-stranded deoxyribonucleic acid
NTN	Nephrotoxic nephritis
NTS	Nephrotoxic serum
NZB	New Zealand black
NZW	New Zealand white
OS	Obese strain
PAF	Platelet aggregating factor
PEG	Polyethylene glycols
PMN	Polymorphonuclear leucocyte(s)
PSS	Progressive systemic sclerosis
PVP	Polyvinyl pyrrolidone
RES	Reticuloendothelial system
RNA	Ribonucleic acid
RPGN	Rapidly progressive glomerulonephritis
SDNA	Single-stranded deoxyribonucleic acid
SHP	Schönlein–Henoch purpura
SLE	Systemic lupus erythematosus
TBM	Tubular basement membrane
TI	Tubulointerstitial

Contents

1 Historical Review

In this first chapter it will be attempted to describe how the concerted efforts of clinicians, pathologists, and immunologists over the last 70–80 years resulted in the present concepts on aetiology and immunopathogenesis of renal disease.

The macroscopic appearance of the kidney with glomerular inflammation was characterized at the end of the middle ages by south Italian physicians as '*durities in renibus*' (hardness of the kidneys). In the first half of the 19th century, Bright, in London, described in great detail the anatomy, histology, and clinical symptoms of this condition.

With the foundation of immunology in the last decades of the 19th century and the first decade of this century, a search for the role of immune mechanisms in the pathogenesis of kidney diseases started. Since then, nephrology and immunology have been intensely interrelated. The majority of glomerulonephritides are nowadays interpreted as being caused or mediated to a variable extent by immune mechanisms. On the other hand, many concepts in immunology have arisen from studies of kidney diseases.

In the beginning, many findings, which now are recognized as immune phenomena, were not at all associated with immunity. Claude Bernard pointed out that injection of heterologous serum may induce proteinuria in the recipient; this observation was confirmed by Weiss (1896). Nephritis had been found to be a possible sequela of scarlet fever. But both pathological conditions were ascribed to toxic properties of proteins or infectious agents. Councilman (1898), in the late 1890s, described mononuclear and plasma cells in infiltrates present in kidney sections of patients with interstitial nephritis. But nobody at that time associated lymphocytes or plasma cells with immune reactivity and antibody production. Nevertheless, such studies provided the basis for more conscious and systematic immunological research in kidney diseases.

Already in the early days of the study of the immunopathogenesis of kidney diseases, two major mechanisms were described: the antibody-mediated, tissue-specific, lesions, and the pathology induced by the localization of antigen–antibody complexes unrelated to antigens present at the site of their deposition. Naturally, this dichotomy in the immunopathogenesis at first was only poorly recognized. It was the great achievement of Dixon in the late 1950s and early 1960s to formulate clearly and define these two immunopathological mechanisms of kidney diseases.

The first convincing demonstration of immunologically induced kidney injury came from experimental work, and was reported by a pathologist of St. Petersburg, Lindemann, in 1900. Following a suggestion of Metchnikoff, he injected rabbit kidney homogenates intraperitoneally into guinea-pigs. The serum obtained after some time from the guinea-pigs induced upon injection into rabbits proteinuria, uraemia, and death. The animals died 3–5 days after the injection. In analogy to the haemolytic sera described by Bordet, Lindemann proposed the term 'nephrolytic' for the sera inducing kidney damage. He suggested that certain specific substances were formed in the blood of guinea-pigs during the process of resorption of the injected rabbit kidney homogenate, and that these substances were responsible for the kidney pathology in the rabbits. Thus he gave to his nephrolytic activity three of the characteristics of an antibody: it was a serum component, it had specificity, and it was induced by an antigenic preparation. Reporting on similar experiments, Nefedieff in 1901 added to these characteristics the feature of memory: he reported that sera obtained from rabbits immunized with guinea-pig kidney were stronger if the rabbits were immunized more than once. Whereas Lindemann described only tubular lesions, Nefedieff also noted a hyperaemia of glomerular tufts in his animals. It was probably Nefedieff who for the first time used the now well-established term 'nephrotoxic serum'.

In the following two years, experiments with nephrotoxic sera gave only confusing and contradictory results. It was the time when the question of cytotoxic sera was ardently disputed. Some researchers claimed to have induced leucotoxic, spermatotoxic, hepatotoxic, and nephrotoxic sera; others vehemently denied the possibility of doing so. The use of impure tissue homogenate had already worried Nefedieff. The use of unfractionated sera for injection, and the lack of adequate immunological methods rendered the experimental findings very difficult to interpret.

In papers published in 1903 and 1904, Pearce presented an exhaustive study on nephrotoxic serum nephritis (NTN). He described glomerular lesions and pointed out that renal cortex was a better antigen to induce nephrotoxic sera than kidney medulla. He was unable, however, to separate completely haemagglutinating activities of the serum from nephrotoxic ones. This distinction was accomplished by Wilson and Oliver in 1920.

In the meantime, heterologous sera became a routine therapeutic agent in infectious diseases. By 1891, von Behring and Kitasato had introduced the serum therapy for neutralization of diphtheria toxin (von Behring and Kitasato, 1890; von Behring, 1892). Very soon, side effects of this therapy were recorded. The profession and the general public became dramatically aware of them, when the son of the German pathologist Langerhans died in what probably was an anaphylactic shock after such a passive immunization. Such lethal incidents, fortunately, were extremely rare. Milder symptoms, however, were reported with increasing frequency. As main complications of serum therapy, urticarial rashes, joint pain, enlargement of lymph nodes, and fever were noted, only seldomly was proteinuria reported. Clemens von Pirquet, a Viennese paediatrician, coined the term 'serum sickness' for this syndrome. His theory of the incubation period and his concept of allergy gave him an excellent basis for serious investigations on serum sickness. Nevertheless, it was Francioni in Florence who, in 1904, published the first monograph on serum sickness. On the basis of findings of Schick and von Pirquet, and using his vast experience, Francioni

implicated precipitins in the pathogenesis of serum sickness. In the classical review of serum sickness, published by von Pirquet and Schick in 1905, the authors expressed their opinion, that the interaction of antibody with the heterologous serum induces the symptoms of the disease. In 1911, von Pirquet published an article on allergy; in it, he stressed the appearance of proteinuria in some patients with serum sickness. He suggested that in serum sickness the combination of antibodies with the foreign protein may lead to a 'new toxic agent' capable of causing tissue injury. Thus the notion of a disease caused by immune complexes, was at least in theory, formulated. Interestingly the understanding of the basic phenomena of serum sickness all came from clinical studies.

The focusing on kidney pathology in serum sickness started with the experiments of Longcope (1913). He had noted that patients with glomerulonephritis very often had symptoms characteristic of serum sickness. When he repeatedly injected animals with foreign proteins, these animals developed proteinuria, had mononuclear cell infiltrates in the renal interstitium, but also marked glomerular lesions, i.e. crescent formation, and proliferation of endothelial cells, fibrosis, and glomerular sclerosis. Longcope explained his findings by assuming increased toxicity of proteins following repeated injections. This interpretation was analogous to that given for the Arthus phenomenon. In 1929, Hepler and Simonds found 'Arthus-like' lesions in kidneys of rabbits sensitized to horse serum or egg albumin, and then injected with the specific antigens directly into the kidney.

In the meantime, Boughton had confirmed Longcope's findings in 1916. The main stream of investigation at that time, however, was directed towards the possibility of a role of microorganisms in the pathogenesis of kidney diseases. Ophüls, in 1917, suggested a role for endotoxin in the pathogenesis of glomerulonephritis. He could, however, offer only unconvincing experimental data in support of his claim. Bell, Clawson, and Hartzell (1925) induced glomerulonephritis in monkeys by repeated intravenous injection of streptococci. Most researchers, however, reported negative results upon injection of animals with bacteria. Dural and Hibbard (1926, 1927), who in the late 1920s developed an interesting immunization procedure, claimed to have induced glomerulonephritis in rabbits. They sensitized rabbits to streptococci, and then injected streptococci into the peritoneal cavity; or they incubated streptococci *in vitro* with a specific antiserum and injected these preparations intravenously. Both procedures possibly produced immune complexes. Thus, it is possible that, indeed, they produced glomerulonephritis, despite the fact that their results could not be confirmed by other investigators.

In the early 1930s, Masugi and his group extensively studied the histopathology of both NTN and immune complex glomerulonephritis. The main characteristics of NTN were described by his group. Their study of immune complex glomerulonephritis seemed to indicate that rabbits did not develop chronic serum sickness upon repeated injection with egg albumin. The rabbits developed disease after intraperitoneal injection of rat organ homogenates, and, especially reproducibly and frequently, upon intravenous application of horse serum over prolonged periods of time. He noted that rabbits produced very variable amounts of precipitins and that in most animals the precipitin titre increased with the administration of larger doses of proteins. He stressed the observation that among individual rabbits the reaction to protein injections differed widely, a fact later confirmed by the work of Germuth and his group.

In the late 1930s, 1940s, and early 1950s, Smadel, Kay, Seegal, and Mellors demonstrated that NTN has a biphasic development (see Chapter 3). Immunofluorescence tests established that the antigen responsible for the induction of NTN resided in the glomerular basement membrane. This finding was confirmed by immunoelectron microscopic studies, and by the fact that purified glomerular basement membrane antigens prepared according to the procedures of Krakower and Greenspon could induce nephrotoxic serum formation if used as antigen for immunization.

Rich and Gregory studied in 1943 the pathology of acute serum sickness in animals using whole serum. A great methodological improvement was achieved by Hawn and Janeway in 1947 when they introduced pure plasma protein fractions (bovine gammaglobulin and albumin) as immunizing agents. In experimental acute serum sickness, they and, later on, Germuth and Dixon described acute glomerulonephritis, necrotizing arteritis, and endocarditis.

In the early 1950s, radiolabelled antibodies and antigens became available for the kidney research through the endeavour of the groups of Pressmann and Dixon. Blau and collaborators performed studies on the turnover of nephrotoxic sera (see Chapter 3). Latta, Gitlin *et al.*, Germuth, and Dixon *et al.* described a triphasic disappearance curve for radiolabelled antigens in experimental acute serum sickness. Germuth in 1953 demonstrated that the lesions of acute serum sickness develop during the phase of immune elimination of the antigen and proposed that serum sickness pathology is induced by immune complexes formed in the circulation.

In the late 1950s and in the 1960s, Dixon's and Germuth's groups achieved important results in the quantification of antibody binding in NTN and in the characterization of complexes in serum sickness type nephropathies. In the latter endeavour, the work of Christian on 'lattice formation' should be mentioned.

The link between the purely experimental models of NTN and serum sickness in rabbits, on the one hand, and human diseases of the kidney, on the other hand, was established by two models of autoimmune diseases: the autoimmune antiglomerular basement membrane nephritis described by Steblay in sheep, and the autoimmune immune complex nephritis established by Heymann in rats.

With the main models of immunologically mediated kidney diseases at hand, the two main questions to pose were on the aetiology of the diseases and on the mechanisms of actual tissue injury.

Before immune phenomena were implicated in the development of kidney diseases, toxic action of substances was shown to cause lesions in the kidneys. It was again Lindemann, in 1900, who claimed that serum from a dog treated with potassium bichromate could induce proteinuria in a normal dog upon transfer. Since then, many toxic agents such as gold and mercury salts and drugs have been implicated in triggering off autoimmune phenomena. The possibility that purely physical injury may induce autoimmune phenomena, cherished by some of the early researchers of kidney immunopathology, and then totally abandoned for more than half a century, becomes more plausible in the light of reports that heat or cold can induce autoimmune phenomena in some organs. Recently, it has been suggested that inhalation of hydrocarbons is associated with Goodpasture's disease. Further interesting data on aetiological factors may be expected from continued studies on New Zealand mice and their hybrids which develop spontaneously immune complex glomerulonephritis resembling human lupus nephritis. Similarly,

the endeavours of Oldstone and Dixon, and of Mellors and their groups to elucidate the role of viruses in kidney diseases may lead to a better understanding of the aetiology of human nephropathies.

The way immunological mechanisms induce tissue injury has been studied extensively but with little definitive result. Ehrlich and Morgenroth, and Moreschi had already noted a decrease of complement levels in rabbits injected with foreign antigens. Francioni in 1908 demonstrated the same phenomenon to occur in patients with serum sickness. Using immunohistological methods, localization of complement in kidney structures has been demonstrated in both antibody-mediated and immune complex mediated tissue injury. Complement seems to be essential for the induction of NTN in some species, but not in others; it seems not to be required for the development of acute serum sickness glomerulonephritis.

In 1904, Francioni had already suggested that antibodies may collaborate with leucocytes in the induction of serum sickness. In 1907, Bienenfeld investigated the behaviour of white blood cells in serum sickness. She noted a marked neutropenia during the active phases of the disease. The role of leucocytes has been studied by Cochrane and collaborators in both immune complex nephritis and NTN.

The possibility that derangements of the function of phagocytic cells may be involved in the pathogenesis of serum sickness was first expressed in 1908 by Menabuoni. He found a decreased phagocytic index in patients with serum sickness. This possibility has been reinvestigated by Wilson and Dixon and by Mannik and his co-workers.

Kraus and Biedl noted at the very beginning of research on serum sickness that the coagulation time was decreased in the wake of what they called 'serumanaphylaxis'. In 1932, Vaubel noted fibrin in his glomerulonephritic animals. Vassali and McCluskey more recently, stressed the importance of the coagulation in NTN, whereas Kincaid-Smith studied the involvement of the coagulation system in human glomerulonephritides.

Still, the mechanisms of tissue injury remain very poorly understood. It is especially discomforting that different species seem to use different mediators of inflammation in the same type of immunologically mediated reaction.

In the past, glomeruli were that much the centre of attention that interstitial nephritis was not taken much into account by immunonephrologists. Only in the last decade, Steblay, Rudofsky, Klassen, and many others have shown that immune phenomena similar to those involved in glomerular diseases can also affect the tubules and the interstitium.

With the exception of kidney allograft rejection, until very recently, no connection between cell-mediated immunity and kidney diseases could be established. Only in 1976 was the first experimental model for the induction of lesions characteristic of delayed hypersensitivity described (van Zwieten *et al.*, 1977).

The availability of the kidney biopsy as a relatively safe and simple procedure (Iversen and Brun in 1951) opened new ways for the study of human nephropathies. In combination with improved immunohistological techniques, better staining procedures for light microscopy, and the use of electron microscopy (Hall, Bergstrand, Farquhar, Movat, Folli, Churg, Jones, Habib, Kincaid-Smith, and many others), the kidney biopsy allowed for new classifications of human kidney diseases and for evaluation of therapy schedules. New clinicopathological syndromes were discovered: e.g., minimal glomerular lesions, Berger's disease, and membranoproli-

ferative glomerulonephritis.

Recently the transition of antiglomerular basement membrane disease into immune complex disease, and *vice versa* has been described. These findings establish a link between the two main immunopathogenetic mechanisms established for kidney diseases and allow for more unified concepts for their understanding.

What are the directions in the present research? Where will the research go in the future? Some of the most enthusiastically followed lines of investigation are the characterization of kidney antigens; attempts to identify antigens involved in immune complex glomerulonephritis (here the development of techniques to detect circulating immune complexes has greatly expanded the possibilities and hopes); to reach a better understanding of inflammatory mediator systems involved in immunologically induced nephropathies; the development of new techniques for diagnostic purposes, e.g., a radioimmunoassay for the detection of antiglomerular basement membrane antibodies in sera; investigations on the immune response in kidney diseases; and, most urgently needed, the pursuit of new therapeutic approaches as trials with new drugs.

References and bibliography*

Andres, G. A. and Seegal, B. B. (1957). L'ipersensibilita nella patologia umana. *Minerva nefrol.* **4**, 126.

Andres, G. A., Morgan, C., Hsu, K. C., Rifkind, R. A. and Seegal, B. C. (1962). Electron microscopic studies of experimental nephritis with ferritin-conjugated antibody. The basement membranes and cisternae of visceral epithelial cells in nephritic rat glomeruli. *J. exp. Med.* **115**, 929.

Andres, G. A., Seegal, C. B., Hsu, K. C., Rothenberg, M. S. and Chapeau, M. L. (1963). Electron microscopic studies of experimental nephritis with ferritin-conjugated antibody. Localization of antigen–antibody complexes in rabbit glomeruli following repeated injections of bovine serum albumin. *J. exp. Med.* **117**, 691.

Bell, T., Clawson, B. J. and Hartzell, T. B. (1925). Experimental glomerulonephritis. *Amer. J. Path.* **1**, 247.

Bernard, C. Cited in Creite, A. (1869). Versuche über die Wirkung des Serumeiweisses nach Injection in das Blut. *Z. rationelle Med. B* **36**, 90.

Biedl, A. and Kraus, R. (1909). Experimentelle Studien uber Anaphylaxie. *Wien. klin. Wschr.* **22**, 363.

Bienenfeld, B. (1907). Das Verhalten der Leukozyten bei der Serumkrankheit.' *Jb. Kinderheilk.* **65**, 174.

Blau, M., Day, E. D. and Pressman, D. (1957). The rate of localization of anti-rat kidney antibodies. *J. Immunol.* **79**, 330.

Blittersdorf, F. (1952). Zur Geschichte der Serumkrankheit. *Sudhoffs Arch. Gesch. Med.* **36**, 149.

Boughton, T. H. (1916). Kidney lesions in chronic anaphylaxis. *J. Immunol.* **1**, 105.

*The bibliography is not exhaustive. Only those publications which are, in the opinion of the authors, the most relevant ones, were selected. However, these references should give the interested reader access to additional literature on the various topics discussed in this book.

Bright, R. (1827–1831). *Reports of medical cases, selected with a view of illustrating the symptoms and cause of diseases by a reference to morbid anatomy*. Vol. I, p. 231. Longman, Rees, Orne, Brown, and Green, London.

Christian, C. I. and Lightfoot, R. W., Jr. (1970). Properties of immune complexes, p. 3. In: *Immune Complex Diseases*. Ed. by L. Bonomo and J. L. Turk. Carlo Erba, Milan.

Cochrane, C. G. (1971). Mechanisms involved in the deposition of immune complexes in tissues. *J. exp. Med.* **134**, 75s.

Councilman, W. T. (1898). Acute interstitial nephritis. *J. exp. Med.* **3**, 393.

Dixon, F. J. (1953). Use of I^{131} in immunologic investigations. *J. Allergy* **24**, 547.

Dixon, F. J., Vazquez, J. J., Weigle, W. O. and Cochrane, C. G. (1958). Pathogenesis of serum sickness. *Arch. Path.* **65**, 18.

Dixon, F. J., Feldman, J. D. and Vazquez, J. J. (1961). Experimental glomerulonephritis. The pathogenesis of a laboratory model resembling the spectrum of human glomerulonephritis. *J. exp. Med.* **113**, 899.

Dural, C. W. and Hibbard, R. J. (1926). Experimental glomerulonephritis induced in rabbits with the endotoxin principle of streptococcus scarlatinae. *J. exp. Med.* **44**, 567.

Dural, C. W. and Hibbard, R. J. (1927). Nature of the toxic moiety of streptococcus scarlatinae. *J. exp. Med.* **46**, 379.

Feldman, J. D. (1958). Electron microscopy of serum sickness nephritis. *J. exp. Med.* **108**, 957.

Francioni, C. (1904). La malattia da siero. *Sperimentale* p. 767.

Francioni, C. (1908). La diminuzione del complemento nella malattia da siero. *Rev. clin. Ped.* **6**, 321.

Germuth, F. G., Jr. (1953). Comparative histologic and immunologic study in rabbits of induced hypersensitivity of serum sickness type. *J. exp. Med.* **97**, 257.

Germuth, F. J. Jr., Flanagan, C. and Montenegro, M. R. (1957). The relationships between the chemical nature of the antigen, antigen dosage, rate of antibody synthesis and the occurrence of arteritis and glomerulonephritis in experimental hypersensitivity. *Johns Hopk. med. J.* **101**, 149.

Gitlin, D., Latta, H., Batchelor, W. H. and Janeway, C. A. (1951). Experimental hypersensitivity in the rabbit: Disappearance rates of native and labelled heterologous proteins from the serum after intravenous injection. *J. Immunol.* **66**, 451.

Greenspon, S. A. and Krakower, C. A. (1950). Direct evidence for antigenicity of the glomeruli in the production of nephrotoxic serums. *Arch. Path.* **49**, 291.

Hall, C. V. (1953). Studies of normal glomerular structure by electron microscopy. Proc. 5th. Ann. Conf. Nephrotic Syndrome, p. 1. Natl. Nephrosis Foundation, New York.

Hawn, C. V. Z. and Janeway, C. A. (1947). Histological and serological sequences in experimental hypersensitivity. *J. exp. Med.* **85**, 571.

Hepler, O. E. and Simonds, J. P. (1929). The production of allergic inflammation in the kidneys. *Amer. J. Path.* **5**, 473.

Heymann, W., Hackel, D. B., Harwood, S., Wilson, S. G. F. and Hunter, J. L. P. (1959). Production of nephrotic syndrome in rats by Freund's adjuvant and rat kidney suspensions. *Proc. Soc. exp. Biol. (N.Y.)* **100**, 660.

Iversen, P. and Brun, C. (1951). Aspiration biopsy of the kidney. *Amer. J. Med.* **11**, 324.

Kay, C. F. (1942). The mechanism of a form of glomerulonephritis. Nephrotoxic nephritis in rabbits. *Amer. J. med. Sci.* **204**, 483.

Kincaid-Smith, P. (1972). Coagulation and renal disease. *Kidney Int.* 2, 183.

Latta, H. (1950). Experimental hypersensitivity in the rabbit: Blood and tissue concentration of foreign protein labelled with radioactive iodine and injected intravenously. *J. Immunol.* **66**, 635.

Lindemann, W. (1900a). Sur le mode d'action de certains poisons renaux. *Ann. Inst. Pasteur* **13**, 49.

Lindemann, W. (1900b). Über das Wesen der toxischen Nephritis. *Zbl. allg. Path. path. Anat.* **7**, 308.

Longcope, W. T. (1913). The production of experimental nephritis by repeated protein intoxication. *J. exp. Med.* **18**, 678.

Mannik, M. and Arend, W. P. (1971). Fate of preformed immune complexes in rabbits and Rhesus monkeys. *J. exp. Med.* **134**, 19s.

Masugi, M. (1934). Über die experimentelle Glomerulonephritis durch das spezifische Antinierenserum. Ein Beitrag zur Pathogenese der diffusen Glomerulonephritis. *Beitr. path. Anat.* **92**, 429.

Masugi, M. and Sato, Y. (1934). Über die allergische Gewebsreaktion der Niere. Zugleich ein experimentellen Beitrag zur Pathogenese der diffusen Glomerulonephritis und der Periarteriitis nodosa. *Virchows Arch. path. Anat.* **293**, 615.

Mellors, R. A. (1962). Autoimmune disease in NZB/BL mice. I. Pathology and pathogenesis of a model system of spontaneous glomerulonephritis. *J. exp. Med.* **115**, 891.

Mellors, R. C., Siegel, M. and Pressman, D. (1955). Analytic pathology. I. Histochemical demonstration of antibody localization in tissues with special reference to the antigenic components of kidney and lung. *Lab. Invest.* **4**, 69.

Menabouni. Cited in Francioni, C. (1908). La diminuzione del complemento nella malattia da siero. *Rev. clin. Ped.* **6**, 321.

Moreschi. Cited in von Pirquet, C. (1911). Allergy. *Arch. intern. Med.* **7**, 259.

Movat, H. Z., Steiner, J. W. and Huhn, D. (1962). The fine structure of the glomerulus in acute glomerulonephritis. *Lab. Invest.* **11**, 117.

McCluskey, R. T. and Vassali, P. (1969). Experimental glomerular diseases. In: *The Kidney. Morphology, Biochemistry, Physiology*, Vol. 2, p. 83. Ed. by C. Rouiller and A. F. Muller. Academic Press, New York and London.

Nefedieff, N. (1901). Serum nephrotoxique. *Ann. Inst. Pasteur* **14**, 17.

Oldstone, M. B. A. and Dixon, F. J. (1971). Lactic dehydrogenase virus-induced immune complex type of glomerulonephritis. *J. Immunol.* **106**, 1260.

Ophüls, W. (1917). The etiology and development of nephritis. *J. Amer. med. Ass.* **69**, 1223.

Pearce, R. M. (1903). An experimental study of nephrotoxins. *Univ. Penn. med. Bull.* **16**, 217.

Pearce, R. M. (1904). Concerning the specificity of somatic cytotoxins. *J. med. Res.* **12**, 1.

Pressman, D. (1949). The zone of localization of antibodies. IV. The *in vivo* disposition of anti-mouse kidney serum and anti-mouse plasma serum as determined by radioactive tracer. *J. Immunol.* **63**, 375.

Rich, A. R. and Gregory, J. E. (1943). The experimental demonstration that periarteritis nodosa is a manifestation of hypersensitivity. *Bull. Johns Hopk. Hosp.* **72**, 65.

Sarre, H. and Wirtz, H. (1942). Geschwindigkeit und Ort der Antigen-Antikörper-Reaktion bei der experimentellen Nephritis. *Dtsch. Arch. klin, Med.* **189**, 1.

Seegal, B. C. and Loeb, E. N. (1946). The production of chronic glomerulonephritis in rats by the injection of rabbit anti-rat placenta serum. *J. exp. Med.* **84**, 211.

Smadel, J. E. (1936). Experimental nephritis in rats induced by injection of anti-kidney serum. I. Preparation and immunological studies of nephrotoxins. *J. exp. Med.* **64**, 921.

Steblay, R. W. (1962). Glomerulonephritis induced in sheep by injections of heterologous glomerular basement membrane and Freund's complete adjuvant. *J. exp. Med.* **116**, 253.

Steblay, R. W. and Rudofsky, U. H. (1971). Renal tubular disease and auto-antibodies against tubular basement membrane induced in guinea pigs. *J. Immunol.* **107**, 589.

Unanue, E. R., and Dixon, F. J. (1967). Experimental glomerulonephritis: immunologic events and pathogenetic mechanisms. *Advanc. Immunol.* **6**, 1.

Vassalli, P. and McCluskey, R. T. (1964). The pathogenic role of fibrin deposition in immunologically induced glomerulonephritis. *Ann. N.Y. Acad. Sci.* **116**, 1052.

Vaubel, E. (1932). Die Eiweissuberempfindlichkeit (Gewebshyperergie) des Bindegewebes. II. Teil. *Beitr. path. Anat.* **89**, 374.

Vollhard, F. (1918). Die doppelseitigen hämatogenen Nierenerkrankungen (Brightsche Krankheit). Springer, Berlin.

Vollhard, F. and Fahr, Th. (1914). *Die Brightsche Nierenkrankheit.* Springer Berlin.

Van Zwieten, M. J., Leber, P. D., Bhan, A. K. and McCluskey, R. T. (1977). Experimental cell-mediated interstitial nephritis induced with exogenous antigens. *J. Immunol.* **118**, 589.

Von Behring, E. (1892). *Die Blutserumtherapie.* Deuticke, Leipzig.

Von Behring, E. and Kitasato, S. (1890). Ueber das Zustandekommen der Diphtherie-Immunitat und der Tetanus-Immunitat bei Thieren. *Dtsch. med. Wschr.* p. 1113.

Von Pirquet, C. E. (1911). Allergy. *Arch. intern. Med.* 7, 259.

Von Pirquet, C. E. (1927). Zur Geschichte der Allergie. *Wien. med. Wschr.* **77**, 745.

Von Pirquet, C. E. and Schick, B. (1905). *Die Serumkrankheit*. Deuticke, Leipzig and Vienna. English translation by Schick, B. (1951). *Serum Sickness.* Williams and Wilkins, Baltimore.

Weiss, O. (1896). Ueber die Wirkungen von Blutserum Injectionen ins Blut. *Pflügers Arch. ges. Physiol.*

Wilson, C. B. and Dixon, F. J. (1976). The renal response to immunological injury. In: The Kidney, p. 838. Ed. by B. M. Brenner and F. C. Rector, Jr., W. B. Saunders Co., Philadelphia.

Wilson, G. W. and Oliver, J. (1920). Experiments on the production of specific antisera for infections of unknown cause. III. Nephrotoxins. Their specificity as demonstrated by the method of selective absorption. *J. exp. Med.* **32**, 183.

2

Basic Pathogenetic Mechanisms in Immunologically Mediated Renal Diseases

Immunopathology describes diseases in which immune mechanisms induce functional or morphological tissue injury. The extent to which immune reactivity determines pathological processes varies with different disease entities. Thus, in renal allograft rejection, the immune response of the recipient to histocompatibility antigens of the graft is the primary pathogenetic mechanism in tissue damage. In bacterial pyelonephritis, on the other hand, immune response to the infectious agents may cause tissue injury only as an epiphenomenon to the pathological processes induced directly by the invading microorganisms.

Immunologically mediated tissue injury is determined by the immune effector mechanism involved and by the inflammatory mediators recruited. Only under rare circumstances do immune effectors, i.e. antibodies or small lymphocytes, cause damage to tissues without activation of the protagonists of inflammation.

In the following, an attempt will be made to summarize some basic concepts of immune response and inflammation which seem to have relevance to kidney diseases. In view of the restricted space available, only a brief discussion of these complex processes can be given; the interested reader is referred to the detailed treatises on general immunology and inflammation listed in the bibliography. This chapter will be concluded with a section dealing with the mechanism of proteinuria in immunologically mediated renal diseases.

The immune response

General considerations

Immunity was first described in connection with infectious diseases. In antiquity it was already known that recovery from an infectious disease made the patient less susceptible to reinfection. In the middle ages, individuals who had survived the disease were chosen to nurse patients with plague. Intentional inoculation of healthy individuals with material from lesions of patients with contagious diseases has been practised for millenia in order to produce a mild disease in the recipient and thereby render him less prone to develop serious illness. Such practical approaches in handling infectious diseases make it obvious that the basic features of immunity were well understood long ago. These characteristics are 'specificity' and