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**3**

**Clinical Nephrology, Immunology**



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Vol. 3

# Clinical Nephrology Immunology

Editors: N. ALWALL (Lund), F. BERGLUND and B. JOSEPHSON (Stockholm)

134 figures and 92 tables



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S. KARGER · BASEL (Switzerland) · MÜNCHEN · NEW YORK

Volume 1. Embryology, Ultrastructure, Physiology  
Volume 2. Endocrinology, Metabolic Aspects  
Volume 3. Clinical Nephrology, Immunology

*In conjunction with the Fourth International Congress of Nephrology*

Regulation of Body Fluid Volumes by the Kidney

Symposium on 'Natriuretic Hormone', Smolenice Castle 1969  
Edited by J. H. CORT, Prague and B. LICHARDUS, Bratislava  
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# Contents

## *Volume 3 – Clinical Nephrology, Immunology*

### *I. Recent Advances in Nephrology*

HAMBURGER, J. (Paris): Recent Advances in Nephrology . . . . .	1
MERRILL, J. P. (Boston, Mass.): Recent Advances in Nephrology-Immunology . .	8

### *II. Immunological Aspects on the Pathogenesis of Glomerulonephritis*

DIXON, F. J. (La Jolla, Cal.): Introduction . . . . .	23
HOLM, S. E. (Göteborg): Relationship between Streptococci and Glomerulonephritis	26
MARKOWITZ, A. S. and LANGE, C. F. (Chicago, Ill.): Antistreptococcal Antibodies, Glomerular Basement Membrane Antigens and Glomerulonephritis . . . . .	33
LERNER, R. A.; MCPHAUL, J. J., and DIXON, F. J. (La Jolla, Cal.): Glomerulo- nephritis Mediated by Antiglomerular Basement Membrane Antibodies . . . .	40
LAMBERT, P. H. (Liège): Glomerulonephritis in NZB/W Mice . . . . .	44
KOFFLER, D.; AGNELLO, V.; CARR, R. I., and KUNKEL, H. G. (New York, N.Y.): Different Patterns of Glomerular Deposits of Gamma Globulin and Complement in Patients with Systemic Lupus erythematosus . . . . .	51

### *III. Immunosuppressive Treatment of Glomerular Disease*

MIESCHER, P. A. (Genève): Immunosuppressive Therapy for Systemic Lupus erythematosus . . . . .	57
HERDMAN, R. C.; MICHAEL, A. F., and GOOD, R. A. (Minneapolis, Minn.): Immuno- suppressive and Anticoagulant Therapy of Renal Disease . . . . .	62
DRUMMOND, K. N. (Montreal): Treatment with Cyclophosphamide of Resistant and Relapsing Nephrosis in Childhood . . . . .	72
SOOTHILL, J. F.; BARRATT, T. M. (London), and MCLAINE, P. N. (Montreal): Controlled Studies of the Treatment of Steroid Resistant, and Steroid Sensitive Relapsing Nephrotic Syndrome . . . . .	88

MICHELSEN, P.; VERBERCKMOES, R., and HEMERIJCKX, W. (Leuven): Treatment of Chronic Glomerulonephritis with Indomethacin . . . . .	92
LANGE, K. (New York, N.Y.): Immunosuppressive Treatment of the Nephrotic Syndrome and Glomerulonephritis . . . . .	102

#### *IV. Intermittent Hemodialysis for Chronic Renal Failure*

SCRIBNER, B. H. (Seattle, Wash.): Maintenance Hemodialysis in Perspective – 1969	110
DALY, R. J. (Edinburgh): Psychiatric Aspects of Maintenance Haemodialysis . . .	121
MOORHEAD, J. F.; BAILLOD, R. A., and HOPEWELL, J. P. (London): Home Dialysis	131
BURTON, B. T. (Bethesda, Md.): Socio-Economic Aspects of Hemodialysis . . . .	141
KAYE, M.; CHATTERJEE, G., and COHEN, G. F. (Montreal): Bone Disease and Chronic Hemodialysis . . . . .	151
ESCHBACH, J. W., Jr. and FINCH, C. A. (Seattle, Wash.): Anemia and Hemodialysis	165
GINN, H. E. (Nashville, Tenn.): Removal of Serum Components by Hemodialysis	174
LINDSTEDT, E. (Lund): Use of Arteriovenous Shunts (External and Internal) for Hemodialysis . . . . .	188
LEONARD, E. F. (New York, N.Y.): Artificial Kidneys. Processes, Designs and Materials . . . . .	198
KLINKMANN, H. (Rostock): Dialysis Membranes in Clinical Use . . . . .	211

#### *V. Kidney Transplantation*

CALNE, R. Y. (Cambridge): Introduction . . . . .	219
MURRAY, J. E. (Boston, Mass.): Seventh Report of the Human Kidney Transplant Registry . . . . .	221
ROOD, J. J. VAN; LEEUWEN, A. VAN; TAN, L. B.; LUBBERS, W., and EERNISSE, J. G. (Leiden): Histocompatibility Testing for Kidney Transplantation . . . . .	231
BACH, F. H. and BACH, MARILYN, L. (Madison, Wis.): Donor-Recipient Pairing for Transplantation . . . . .	233
BRENDEL, W. (München): Clinical Experiences with Antilymphocyte Globulin in Kidney Transplants. Essential Advantages of the Intravenous Route . . . . .	245
TRAEGER, J.; FRIES, D.; REVILLARD, J. P.; BROCHIER, J.; PLAN, M.; ARCHIMBAUD, J. P.; SAUBIER, E., and PERRIN, J. (Lyon): Studies of Antilymphocyte Globulins Made from Blood and Thoracic Duct Lymphocytes . . . . .	256
HERBERTSON, B. M. (Cambridge): The Pathology of Renal Transplantation . . .	260
CROSNIER, J.; LESKI, M.; KREIS, H., and DESCAMPS, B. (Paris): Non-Renal Complications of Kidney Allotransplantations . . . . .	270

#### *VI. Modern Radiology of the Kidney*

HODSON, C. J. (London): Adult Atrophic Pyelonephritis . . . . .	282
MEANEY, TH. F. (Cleveland, O.): Renal Arterial Disease in Patients with Hypertension. Radiological Diagnosis, Classification, Natural History and Results of Surgical Therapy . . . . .	284
NILSON, A. E.; BERGENTZ, S.-E., and OLANDER, R. (Gothenburg): The Use of Angiography in Kidney Transplantation . . . . .	287
BOJSEN, E. (Lund): Roentgenologic Findings in Hemangioma of the Kidney . . .	294
FRY, I. K. and SPIRO, F. I. (London): Upper Urinary Tract Dilatation in Non-Pregnant Women . . . . .	301



CRAVEN, J. D. (London): Atypical Post-Obstructive Kidneys . . . . .	308
BROWN, J. N. and MCILRATH, E. M. (Belfast): Renal Vein Thrombosis. An Evaluation of the Radiological Diagnosis . . . . .	313
STEIN, H. L. (Manhasset, N.Y.): Direct Serial Magnification Renal Angiography . . . . .	322

### *VII. Treatment and Prevention of Pyelonephritis*

BROD, J. (Hannover): Factors Affecting Pathogenesis and Course of Chronic Pyelonephritis . . . . .	329
BUCHT, H. (Gothenburg): Long-Term and Short-Term Therapy . . . . .	334
ANDRIOLE, V. T. (New Haven, Conn.): Factors Affecting Antibiotic Concentrations in Urine and Kidney Tissue . . . . .	338
KUNIN, C. M. (Charlottesville, Va.): Binding of Antibiotics to Tissues . . . . .	342
BRUMFITT, W. (London): Treatment of Pyelonephritis: Some Factors Influencing the Course of the Disease and the Results of Treatment . . . . .	347
SMELLIE, J. M. (London): The Disappearance of Reflux in Children with Urinary Tract Infection during Prophylactic Chemotherapy . . . . .	357
KASS, E. H. (Boston, Mass.): Bacteriuria and Renal Disease . . . . .	360
Subject Index . . . . .	365

## *Volume I – Embryology, Ultrastructure, Physiology*

### *I. Addresses at Opening Ceremony*

ALWALL, N. (Lund): Presidential Address at Opening Ceremony . . . . .	1
MOBERG, S. (Stockholm): Inaugural Address . . . . .	3
MERRILL, J. P. (Boston, Mass.): Address Delivered at Opening Ceremony . . . . .	6

### *II. Recent Advances in Nephrology*

ULLRICH, K. J. (Frankfurt a. M.): Recent Advances in Nephrology, Physiological Aspects . . . . .	8
HAMBURGER, J. (Paris): Recent Advances in Nephrology, Clinical Aspects . . . . .	see Vol. 3
MERRILL, J. P. (Boston, Mass.): Recent Advances in Nephrology-Immunology . . . . .	see Vol. 3

### *III. Developmental Renal Physiology and Embryology*

BARNETT, H. L. (Bronx, N.Y.): Introduction. Part I . . . . .	20
EDELMANN, CH. M., Jr. (Bronx, N.Y.): Glomerulo-Tubular Balance in the Developing Kidney . . . . .	22
SAXÉN, L. (Helsinki): The Determination and Differentiation of the Metanephric Nephron . . . . .	29
METCOFF, J. (Chicago, Ill.): Introduction. Part II . . . . .	39
SCHÄRER, K. (Heidelberg): Adaptive Mechanisms in Renal Metabolism . . . . .	41

SCRIVER, C. R.; BAERLOCHER, K.; MACKENZIE, S., and MOHYUDDIN, F. (Montreal): Membrane Transport of Amino Acids in Mammalian Kidney. Mutation, Differen- tiation and Ontogeny . . . . .	50
--	----

#### *IV. Renal Excretion of Macromolecules*

LAMBERT, P. P. (Brussels); HULME, B. (London); GASSÉE, J. P.; ASKENASI, R.; FICHEROULLE, P.; FAFCHAMPS, R., and VERNIORY, A. (Brussels): Physiological Basis for Glomerular Sieving of Macromolecules . . . . .	60
SOOTHILL, J. F. (London): Clearance Studies of Proteins in Renal Disease . . . .	77
KARNOVSKY, M. J.; VENKATACHALAM, M. A.; GRAHAM, R. C., Jr., and COTRAN, R. S. (Boston, Mass.): Ultrastructural Basis of Glomerular Permeability to Macromolecules . . . . .	81
MCPHAUL, J. J., Jr. and DIXON, F. J. (La Jolla, Cal.): Urinary Excretion of Immuno- reactive Basement Membrane Antigens . . . . .	83

#### *V. Correlation of Renal Function and Ultrastructure*

TRUMP, B. F. (Durham, N.C.): Ion Movements in Cell Injury. Effects of Inhibition of Sodium Transport on Ultrastructure of the Nephron and Related Systems . .	88
MAUNSBACH, A. B. (Aarhus): Ultrastructure and Digestive Activity of Lysosomes from Proximal Tubule Cells . . . . .	102
OSVALDO-DECIMA, LYDIA and LATTA, H. (Los Angeles, Cal.): The Renal Medulla of Diuretic and Antidiuretic Rats Studied by Electron Microscopy . . . . .	116
ERICSSON, J. L. E. (Stockholm): Phylogenetic Differences in Renal Tubule Structure in Vertebrates . . . . .	126

#### *VI. Renal Medullary Function*

THURAU, K. (München): Introductory Remarks . . . . .	134
KRIZ, W. and DIETERICH, H. J. (Münster): The Supplying and Draining Vessels of the Renal Medulla in Mammals. Light and Electron Microscopic Observations .	138
MOFFAT, D. B. (Cardiff): Morphological Studies and Renal Medullary Function .	145
MARSH, D. J. (New York, N.Y.): Countercurrent Properties of the Renal Medulla .	149
MORGAN, T. (Bethesda, Md.): Movement of Solute and Water in the Countercurrent System of the Medulla . . . . .	156
MOREL, F. (Saclay): Permeability Properties of the Thin Descending Limb of the Loop of Henle . . . . .	165
JAMISON, R. L. (St. Louis, Mo.): The Function of the Thin Loops of Henle in the Urinary Concentrating Mechanism . . . . .	170

#### *VII. Renal Control of Acid and Ammonia Secretion*

RELMAN, A. S. (Philadelphia, Pa.): The Control of Acid Excretion . . . . .	175
GIEBISCH, G. (New Haven, Conn.) and MALNIC, G. (São Paulo): Some Aspects of Renal Tubular Hydrogen Ion Transport . . . . .	181
PITTS, R. F. (New York, N.Y.): Non-Ionic Diffusion and Ammonia Secretion . .	195
ALLEYNE, G. A. O. (Kingston): The Metabolic Control of Ammonia Production . .	206

Subject Index . . . . .	213
-------------------------	-----

*Volume 2 - Endocrinology, Metabolic Aspects**I. Renin, Angiotensin and Juxtaglomerular Cells*

HATT, P.-Y. (Limeil-Brévannes) and ROJO-ORTEGA, J.-M. (Montreal): The Ultra-structure of the Juxtaglomerular Apparatus . . . . .	1
GOMBA, SZ.; SOLTÉSZ, B. M.; SZOKOLY, V., and ENDES, P. (Debrecen): Histochemical Characterization of the Juxtaglomerular Apparatus . . . . .	7
COOK, W. F. (Oxford): Juxtaglomerular Cells, the Storage Site of Kidney Renin . . . . .	12
LJUNGQVIST, A. (Stockholm): Sympathetic Innervation of the Juxtaglomerular Cells of the Kidney . . . . .	14
KANEKO, Y.; TAKEDA, T.; IKEDA, T., and UEDA, H. (Tokyo): Hepatic Inactivation of Renin in Hypertensive Patients and Patients with Nephrotic Syndrome . . . . .	19
THURAU, K.; DAHLHEIM, H., and GRANGER, P. (München): On the Local Formation of Angiotensin at the Site of the Juxtaglomerular Apparatus . . . . .	24

*II. Angiotensin, Aldosterone, Hypertension*

PEART, W. S.; BOYD, G. W.; JAMES, V. H. T.; MACDONALD, G. J., and ADAMSON, A. R. (London): Angiotensin and Aldosterone . . . . .	31
BLAIR-WEST, J. R.; CAIN, M. D.; CATT, K. J.; COGHLAN, J. P.; DENTON, D. A.; FUNDER, J. W.; SCOGGINS, B. A.; WINTOUR, E. MARELYN, and WRIGHT, R. D. (Melbourne): The Mode of Control of Aldosterone Secretion . . . . .	33
LARAGH, J. H.; SEALEY, J. E.; NEWTON, M. A., and LEDINGHAM, J. G. G. (New York, N.Y.): Aldosterone and Renin Secretion in Hypertensive Disease: Low Renin Hypertensions: Studies of the Effects of ACTH and Cortisol . . . . .	45
MUIRHEAD, E. E.; BROWN, G. B.; GERMAIN, G. S., and LEACH, B. E. (Memphis, Tenn.): The Renal Medulla as an Antihypertensive Organ . . . . .	57
DUCROT, H.; KLEINKNECHT, D.; JUNGERS, P.; VANTELON, J.; AUVERT, J.; ZINGRAFF, J., and FUNCK-BRENTANO, J. L. (Paris): Blood Pressure, Hemodynamics, Renin and Body Fluid in Renoprival Man . . . . .	65

*III. Natriuretic Hormone*

NIZET, A. H. (Liège): Autonomous Renal Mechanisms and Hormonal Control of Sodium Excretion . . . . .	76
PEARCE, J. W. (Toronto); LICHARDUS, B. (Bratislava); SONNENBERG, H., and VERESS, A. T. (Toronto): Attempts to Transfer Natriuresis of Volume Expansion in Cross-Circulated Rats . . . . .	80
KLAHR, S.; BOURGOIGNIE, J.; MILLER, C. LINDSEY; LUBOWITZ, H., and BRICKER, N. S. (St. Louis, Mo.): Studies in Search of a Natriuretic Hormone in Uremic Patients . . . . .	88
BERLINER, R. W.; BRENNER, B.; FALCHUK, K., and KEIMOWITZ, R. (Bethesda, Md.): Which Factor is Third? . . . . .	99
CORT, J. H.; SEDLÁKOVÁ, E.; LICHARDUS, B., and DOUŠA, T. (Prague): The Nature, Source and Mode of Action of the Natriuretic Activity in Plasma Resulting from Volume Expansion and Pressor Stimuli in Animals . . . . .	107

*IV. Metabolic Aspects and Action of Diuretics on Sodium*

HEIDENREICH, O. (Aachen): Introductory Remarks: Problems of the Mode of Action of Diuretics on the Cellular and Subcellular Level . . . . .	116
---	-----



FÜLGRAFF, G. (Aachen): Effects of Diuretics on the Relation between Oxygen Consumption and Sodium Transport . . . . .	119
LANDON, E. J. and FITZPATRICK, D. F. (Nashville, Tenn.): The Action of Diuretics on Respiration and Glycolysis in the Kidney . . . . .	127
KESSLER, R. H. (Chicago, Ill.): The Effects of Glucose and Inhibitor Compounds on Renal Nucleotides <i>in vivo</i> . . . . .	137
WILLIAMSON, H. E. (Iowa City, Ia.): Relationship between ATPase Activity and Sodium Transport and Action of Diuretics . . . . .	144

#### *V. Calcium Metabolism in Renal Disease*

LEMANN, J., Jr. (Boston, Mass.): Acidosis and Calcium Metabolism in Chronic Azotemic Renal Disease . . . . .	153
REISS, E. and CANTERBURY, J. M. (Chicago, Ill.): Parathyroid Hormone in Renal Insufficiency . . . . .	164
AVIOLI, L. V.; BIRGE, S. J., and SLATOPOLSKY, E. (St. Louis, Mo.): The Nature of the Vitamin D Resistance of Patients with Chronic Renal Disease . . . . .	175
RUSSELL, R. G. G. (Oxford); BISAZ, SYLVIA, and FLEISCH, H. (Bern): The Possible Role of Pyrophosphate and Phosphonates in Calcium Homeostasis and in Renal Failure . . . . .	182

#### *VI. Nitrogen Metabolism and Nutrition in Uremia*

SWENDSEID, MARIAN E. (Los Angeles, Cal.): Protein Nutrition and Metabolic Regulation . . . . .	190
GIORDANO, C.; PASCALE, C. DE; SANTO, N. G. DE; ESPOSITO, R.; CIRILLO, D., and STANGHERLIN, P. (Napoli): Disorder in the Metabolism of Some Amino Acids in Uremia . . . . .	196
JOSEPHSON, B.; BERGSTRÖM, J.; BUCHT, H.; FÜRST, P.; HULTMAN, E.; NORÉE, L.-O., and VINNARS, E. (Stockholm): Intravenous Amino Acid Treatment in Uremia . . . . .	203
MAXWELL, M. H. and FRANKLIN, S. S. (Los Angeles, Cal.): Low Protein Diet in Uremia . . . . .	212
BERLYNE, G. M.; LAETHEM, L. VAN; BREWIS, R. A.; SIMONS, P. J.; THURSTON, H.; MALLICK, N. P., and BOOTH, E. M. (Manchester): Low Protein Diet in Conservative Management of Chronic Renal Failure . . . . .	220
SHEAR, L. (Philadelphia, Pa.): Selective Alterations of Tissue Protein and Amino Acid Metabolism in Uremia . . . . .	233

#### *VII. Uremic Toxicity*

TESCHAN, P. E. (Washington, D.C.): Approaches to the Study of Uremic Toxicity: An Experimental Model . . . . .	242
RENNER, D. and HEINTZ, R. (Aachen): Metabolic Changes in Uremia . . . . .	248
GIOVANNETTI, S.; BIAGINI, M.; BALESTRI, P. L.; NAVALES, R.; GIAGNONI, P.; MATTEIS, A. DE; FERRO-MILONE, P., and PERFETTI, C. (Pisa): Uraemic Symptoms in Dogs Chronically Intoxicated with Methylguanidine . . . . .	253
COHEN, B. D.; STEIN, I. M., and KORNHAUSER, R. S. (Bronx, N.Y.): Guanidine Retention and the Urea Cycle . . . . .	255
WELT, L. G. (Chapel Hill, N.C.): Erythrocyte Transport Defect in Uremia . . . . .	263

BITTAR, E. E. (Madison, Wis.): The Effect of $\text{Na}^+\text{-K}^+\text{-ATPase}$ Inhibitors and Uremic Plasma on Na Efflux from the Toad Oocyte . . . . .	267
WILSON, D. M. (Rochester, Minn.) and SCHWARTZ, F. D. (Chicago, Ill.): Cellular Transport of Iodopyracet (Diodrast): Studies in Erythrocytes from Normal and Azotemic Individuals . . . . .	272
PODEVIN, R.; PAILLARD, F., and RICHEL, G. (Paris): Action of Uremic Serum on Uric Acid Transport by Isolated Renal Tubules . . . . .	278
Subject Index . . . . .	283

## I. Recent Advances in Nephrology

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### Recent Advances in Nephrology

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Chronic dialysis and renal transplantation have probably been the most striking recent advances in clinical nephrology. Hundreds of men and women are alive today in spite of destruction or removal of their own kidneys.

#### *1. Chronic Dialysis*

Chronic dialysis has now been in use for more than nine years. We may well say now that the pioneers in this field were men of faith when they presumed that they knew enough of renal functions to imitate them for years with an artificial machine and that a simple membrane, commonly used as a wrapping paper could replace one of the most complex living organs. May I recall for you that the first of these men of faith was the President of this Congress, NILS ALWALL, who, exactly 20 years ago, designed an arterio-venous shunt for chronic dialysis in the rabbit [1]<sup>1</sup>. This does not diminish the merit of BELDING and SCRIBNER, who – on March 9, 1960 – were bold enough to dare what most of us thought hopeless [12]. Thousands of patients in Europe and thousands in America are now under this treatment. In my center, for example, the number of dialyses performed daily has increased tenfold between the last Congress and this one. In a majority of these patients, the main uremic manifestations are controlled. Many of them lead an active life. Better shunts, disposable kidneys and clever devices

<sup>1</sup> Chairman's comment at session: Arterio-venous shunt was applied in treatment of patients, too [ALWALL, N. *et al.*: On the artificial kidney. VII. Clinical experiences of dialytic treatment of uremia. *Acta med. scand.* 132: 587-602, 1949].

for individual monitoring have considerably improved the machinery of chronic dialysis. The scope of home dialysis is expanding in many countries. Last but not least, chronic dialysis greatly helps transplantation by providing a large enough number of potential recipients, so that each cadaver kidney may be used in the most histocompatible patient. An organization has been, for example, developed in Paris under the name of 'Paris Transplant', where all centers have placed in common the list of their patients under chronic dialysis waiting for kidney transplantation.

However, this method has clearly shown its limits in the last few years. Few major advances in medicine have at the same time raised so many questions, including entirely new psychological and economical problems. These, however, will not be discussed at this time since they will be studied later on, in this Congress. We are undoubtedly very far away from the true artificial kidney which the doctors of the 21st century will perhaps be able to insert into the body as a permanent and invisible part of it. For the moment the anephric patient treated with chronic dialysis is quite different from a man with normal kidneys. In fact, the study of this new type of patient – one who has passed the point where the destruction or removal of his kidneys should normally cause death – is about to increase enormously our knowledge of normal renal functions. I might give evidence for this by quoting studies on erythropoietin, on calcium metabolism, on hyperlipemia, on polyneuritis, on pericarditis, on gynecomastia or on immunologic defects in uremic patients. I would like to choose just one example, concerning a matter which has defied so many previous physiological studies and that has been remarkably clarified by the observation of anephric patients: the relationship between blood pressure and the kidney. First of all it is quite evident now that removing both kidneys is not sufficient to promote hypertension: the so-called renoprival hypertension cannot be explained solely by the absence of renal tissue. However, the antihypertensive function of the normal kidney can no longer be questioned as it is easy to show that the anephric man has a very much increased sensitivity to many hypertensive agents, and in particular to the balance of sodium. On the other hand, the actual role of the renin-angiotensin system in high blood pressure, a role which remained debatable in spite of so many studies, is now supported by two new and unexpected facts: first the fact that severely damaged kidneys may still produce large amounts of renin, and secondly, the demonstration that peripheral vascular resistance is closely correlated with the amount of renin secreted, in some patients with advanced uremia [10].

## *2. Renal Transplantation*

Advances in renal transplantation also have been remarkable during recent years. The first successful transplantation between identical twins was made by JOHN MERRILL, JOSEPH MURRAY and their associates, 13 years ago. Three years later, the first two cases between non-identical twins were performed, one in Boston and one in Paris, and both patients are surviving and well, more than 10 years after transplantation. The first successful transplantation between persons who were not twins was carried out on February 2, 1962, and the graft is functioning well seven and a half years later, the patient working hard now as a medical student. 2,347 kidney transplantations had been reported to the world registry at the beginning of the present year. About half of these patients are still alive [11]. The percentage of successes is now not far from 80% of those cases with related living donors and  $42 \pm 5\%$  of transplantations using cadaver kidneys. Progress is so rapid and so complex that a detailed account would demand far more time than we have now. I would like to make one statement only. During the last 3 or 4 years the advances in the concept of histocompatibility have been far more effective than those in immunosuppression.

Advances in histocompatibility have been striking. Since the description of the Mac antigen [4], the knowledge of the whole HL-A system, similar to the H2 locus in the mouse, is rapidly progressing. Two subloci of HL-A are now more or less well known. A good example of how this clarified the problem can be seen in renal transplantations between siblings. The brother or the sister of a patient may be HL-A-identical, when he has inherited the same two alleles (or better, haplotypes) as the patient, HL-A-semi-identical if they share only one of the two haplotypes, or HL-A-different when both haplotypes are different. In our series HL-A-identical siblings give successful allografts in all cases while others have a proportion of failures which is not far from that of unrelated donors. Since we are no longer speaking of siblings as a group, but considering separately HL-A-identical or non-identical, the correlation of clinical results with histocompatibility typing is easier to define and, in my opinion, really convincing for the first time. This does not mean that the problem of donor selection is completely solved. Far from it. In fact there are at least two reasons that make us suspect that leukocyte typing will never solve more than, let us say, three quarters of the problem. First the study of renal allografts with elaborate nephrological techniques shows that chronic rejection may induce several types of lesions, interstitial, or arterial, or glomerular, suggesting that specific tissue antigens may be

involved, which could hardly be predicted on the sole basis of the antigenic pattern common to all cells and tissues as detected by conventional leukocyte typing [7]. Furthermore, some transplantations fail despite perfect matching (this might be explained by antigenic systems still unknown) but some transplantations are perfectly successful despite gross mismatch – a fact which cannot be explained in the same way and which suggests that the reactivity of the recipient may be a variable factor. This is supported by the striking correlation that we have observed between the results of transplantations performed in my group since January 1966 and an overall test of lymphocyte reactivity such as the mixed lymphocyte culture. Studies are now in progress to explore new ways of predicting success or failure in one given donor-recipient pair.

Compared with remarkable advances in the area of donor selection, the status of recipient immunosuppression appears unsatisfactory. The side effects of the long-term use of drugs are more and more serious [8]. ALG, the most powerful agent in the experimental animal, is relatively disappointing in man, perhaps not in itself, but certainly in contrast with the considerable hope that it had raised three years ago. This situation may be improved with the discovery of new ways for *in vitro* evaluation of the immunosuppressive power, such as the rosette inhibition test described by JEAN FRANÇOIS BACH [2]. This test is: (a) extremely sensitive, and (b) well correlated with the effect of the drug on graft survival. As a very sensitive test, it permits us to follow immunosuppressive efficiency after the administration of a drug such as Imuran. As a test correlated with the survival of graft, it will lead to an easy screening of new drugs and also to a precise comparison between various ALG whose actual capacity to prolong graft survival is extremely different from one specimen to another. The fact remains, however, that all these non specific immunosuppressive agents have the great handicap of facilitating infectious or viral complications, which represent at the present time an important cause for failure. Clearly enough, the creation of a specific tolerance for the graft antigens will be the only satisfactory method. This may be achieved in simple immunological models involving an experimental animal and a pure antigen. The purification of human histocompatibility antigens is now on the way. But no one can predict if and when we will be able to use specific immunosuppression in human organ grafting.

Lastly, may I point out that we have no evidence that renal transplantation may cover the treatment of all uremic patients. In other words, we do not know whether we can ever provide a kidney for every patient without a complete and hypothetical transformation in our techniques of organ procurement and storage.



### 3. Renal Diseases

In any case, grafting a new kidney or using chronic dialysis cannot be considered the ideal solution in the treatment of uremia. The real aim is to cure – or even to prevent – renal diseases. This is evident for the doctor, for the patient and even for the economist. Treatments such as chronic dialysis are, in fact, so expensive that they might serve as a strong incentive to channel more funds into the field of research on renal diseases. In effect the only way to discover proper methods which will cure or prevent renal diseases is to know more about their nature.

From that point of view, many recent advances have been made. First in the description of new entities. As early as one century ago, many authors had suggested that chronic nephritis should be classified into a number of different diseases. This has become much easier because of the routine practice of renal biopsy, together with the use of modern methods in histochemistry, electron microscopy and immunofluorescence. The careful observation of clinical and pathological facts remains the basis for all nephrological research. It looks as if some nephrologists are no longer interested in this type of study, apparently considering the description of renal diseases to be complete. This, in my opinion, is a false and dangerous idea. In fact a number of new pathological entities are still brought to light, year after year, and this information is crucial to any further research. Recent examples may be found in the following lesions:

(a) *Intercapillary deposits of IgA*. They are discovered in a large number of so-called focal nephritis. They are diffuse in contrast with the focal and limited visible lesions. The clinical manifestations and course are quite different from other types of focal nephritis, so that the very concept of focal nephritis loses its individuality [3].

(b) *Renal microangiopathy*. It is a rather frequent cause of acute renal failure in the adult, since we have recently observed 13 cases. It has many similarities to the hemolytic-uremic syndrome described in children [9].

(c) Renal lesions due to an excessive *storage of pathological material*, such as lipids in new familial renal diseases [6] or polyvinyl pyrrolidone in patients treated with long-acting intra-muscular products.

These are only some examples of renal lesions recently described. Any suggested interpretation of the various types of nephritis is questionable if it is not based on a correct inventory of clinical facts.

It is clear, however, that each discovery of new pathogenic processes constitutes an important advance. A striking recent example concerns glo-

merulonephritis. New experimental models have been described by FRANK DIXON and others [5]: one is due to an antibasement membrane antibody and another is induced by the intrarenal deposits of antigen-antibody complexes. We still have to find to which extent these experimental models may be applied to human nephritis. Several authors have suggested that the pathological classification of nephritis may now be forsaken and replaced by a quite simple pathogenic classification into three types : non-immunological glomerulonephritis, complex-type nephritis and anti-basement membrane-type nephritis. This attractive simplification is unfortunately open to serious criticism. The whole history of medicine has demonstrated the risk of simplified explanations based on experimental models. This risk is greater in nephrology since it has been clearly shown that the effects of a drug such as aminonucleoside or phenacetin or cortisone may be quite different from one species to another. Furthermore, some facts suggest that the significance of immunoglobulin deposits in the kidney is not entirely clear. For instance in the nephrotic syndrome with minimal glomerular changes, no deposits are seen and this situation is classified as non-immunological; however, if not cured, the disease follows a natural course towards glomerular lesions, which are then covered with IgM, IgG and  $\beta_{1c}$ . On the other hand, including acute glomerulonephritis, lobular glomerulonephritis, membranous glomerulonephritis and intercapillary IgA deposits under the same heading of complex-type nephritis will certainly not satisfy the clinician, since it would merge entities that appear quite different in their causes, manifestations, prognosis and even treatment.

In fact, the course of our ideas concerning the identification of renal diseases is the center of a deep nosological crisis, similar to that which takes form in other field of modern medicine. In the first place the classification of pathogenic processes does not coincide with the clinical pathological classification. Secondly, other nosological approaches, such as those based on the causes of nephritis, again lead to a different classification. For example, membranous glomerulonephritis, with IgG deposits on the outer side of the basement membrane, may be due to a streptococcal infection as well as to penicillamine poisoning, or to disseminated lupus, or perhaps even to a thrombosis of the renal vein. Mercurial poisoning may cause a nephrotic syndrome as well as an acute renal failure and so on. Hence it is more and more evident that we shall not reach a nosological classification of renal diseases which will cover at the same time the causes, the clinical and pathological facts and finally the pathogenic processes. In this respect, the very concept of autonomous diseases, a concept on which the whole of conven-

tional nosology is founded, looks seriously shaken. We must become accustomed to the idea that the nosological analysis of facts has no scientific significance without previous definition of a precise reference programme. The programme, in turn, must be predominantly pathological, clinical, etiological, or immunological, or even based on prognosis or criteria of treatment. Several groups are currently studying this more scientific approach in the nosology of renal diseases. Such studies are based mainly on recent advances in a new field born from statistics and computer methods and called the technique of 'form recognition'. Here again, nephrology will perhaps be able to open new vistas which will be profitable to the rest of medicine.

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