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

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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 of 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][1]. 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

[1] 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 histocompatibiiity 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 looses 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 β_{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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