TREATMENT OF NEPHRITIS, PYELONEPHRITIS AND NEPHROSIS

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Vast, practically boundless, is the literature I am to survey. My lecture cannot possibly be exhaustive. It must be limited to the therapeutic recommendations made on the basis of modern knowledge. Nor can it extend to technical details. Instead, I shall endeavour to sketch out the theoretical background, in the spirit of S. KORÁNYI.

Glomerular nephritis

The progress in the etiology and pathogenesis of glomerular nephritis, which has marked the last ten years, has had its effect on the treatment of the disease. A critical evaluation of the new therepeutic methods is a task of extraordinary difficulty as the data so far accumulated are insufficient for reliably evaluating the results. Nevertheless, it is possible, to formulate a programme of management.

The acute stage

Diet. To begin with, the latest drugs have outdated neither bed rest nor dietary measures. On the contrary, in the light of recent research rules of diet seem to be assuming a new significance. VOLHARD [119], during World War I, prescribed fasting and withholding all fluids, to avoid cerebral oedema which proved fatal in one out of every ten cases of acute nephritis. SARRE [98], even today, holds that the VOLHARD cure is no kidney cure. We are unable to share his view: the results call for an immunological explanation.

Glomerular nephritis is an expression of an antigen-antibody reaction. On the other hand, a correlation is known to exist between antibody formation and protein intake. Unequivocal evidence particularly shows that increased protein intake is conducive to antibody formation. FARR and SMADEL [25], and later DUTZ [22], demonstrated that a diet rich in protein aggravates the MASUGI type nephritis, which has an indisputable immunologic background. Starting from clinical experience made during the blockade of Leningrad, TSHERVJAKOVSKI and KOVALJOV [114] established that fasting is of beneficial effect in MASUGI nephritis. On these grounds, and in the hope of inhibiting thereby pathogenic antibody formation, the patients with acute nephritis

are kept at our Department on a fruit diet as long as they can tolerate it. Usually, they start revolting against it after eight days or so. They are then placed on a strictly low-protein vegetarian diet which is to last, preferably, as long as clinical and immunological signs of the active character of the disease (hematuria, decrease in serum complement, etc.) persist. In uremic patients a fruit diet is of course contraindicated on account of the danger of hyperkalemia.

Penicillin. Glomerular nephritis is an allergic disease, and so it is in principle amenable to causal treatment by elimination of the antigen. RAMMELKAMP and WEAVER [88], in 1953, claimed the existence of "nephritogenic" streptococcus strains, viz. types 4, 12, 25, and the Red Lake [87]. The last one — labelled recently type 49 — which they were unable to identify with any of the known types, was incriminated to be the causative agent of the scarlet fever and nephritis epidemics experienced in an Indian Reservation at Red Lake, Minnesota. The view has since been confirmed bacteriologically in numerous areas geographically remote from one another [90, 94, 105, 120]. Outstanding among these from the point of view of therapeutic value are the results of WILMERS et al. [121] who could isolate the type 12 streptococci from the throat or nose of 28 out of 31 patients with clinically acute glomerular nephritis, in various hospitals of England and Wales. This would appear to form a basis for regarding acute nephritic patients as carriers of "nephritogenic" streptococci, and so it seems advisable to treat them with penicillin without delay, not awaiting the bacteriological results. Throat cultures from about half the acute cases in our clinical material needed to particular efforts to yield beta hemolytic streptococci.

In glomerular nephritis, more than in any other disease, it is indispensable that before initiating penicillin treatment the patient should be tested for hypersensitivity, for in addition to anaphylaxis, parallergy threatens. Instead of the simple intracutaneous, the modern scratch test should be employed [54, 75, 104]. An intracutaneous penicillin injection might bring forth fatal anaphylaxis. In established cases of hypersensitivity to penicillin, erythromycin should be administered, in full doses.

Removal of infective foci. Are we still justified in removing foci in the present antibacterial era?

Dental foci have lost much of the importance that had formerly been attributed to them as centres of infection. According to SEELEMANN [103], mostly *Str. salivarius* only can be cultivated from them, an organism devoid of antigenic function. In the available literature I have failed to find a single report of "nephritogenic" streptococcus having been cultured from a periapical abscess.

Tonsillectomy is seen in an entirely different light. In SARRE's [98] opinion, it is still in place; we too consider it indicated in view of the possible

residual hematuria or residual proteinuria. In our experience the operation, although performed under penicillin protection, often aggravates the symptoms. The reaction abates in a few days, but a dramatic improvement is seldom seen. It is as yet impossible to predict in an individual case what effect tonsillectomy will have on acute nephritis. The general view is that the tonsils should be removed because they might harbour hidden infective foci. However, the matter is not as simple as that; in our clinical material the inside of the tonsil was in each case found to be free from beta hemolytic streptococci and showing no sign of acute inflammation (RAUSS, ROMHÁNYI). At present we have nothing but suppositions to guide us in interpreting the effects of tonsillectomy. What we know for certain is that there are extrarenal antigens capable of starting immunologic processes that result in nephritis. Nephrotoxic serum was produced in animals of another species by SEEGAL and LOEB [102], using placenta; by HÁMORI and OLÁH [42, 43], using stomach; and by STREHLER [109], using aorta antigen. An autosensitization in human disease is conceivable not only within the kidney, but also at the site of the "first" disease, i.e. of direct contact between the bacteria and the capillary antigen, where the former interfere with the latter, or the two combine to form complete antigen [39].

Corticosteroids. Penicillin has failed to bring us the solution of how to treat nephritis, probably because the disease is the clinical manifestation of an intricate immunological mechanism. Studying the literature makes one feel convinced that each of the presently presupposed allergic mechanisms comes to play a part in the origin or in one or the other process of the disease (the slow progression of chronic nephritis, acute exacerbations, etc.). The chain of such allergic mechanisms comprises streptococcal sensitization, soluble antigen-antibody complex, inverse active anaphylaxis, and, as its last link, auto-immunization [37, 38, 39]. Penicillin exerts no influence on the autoimmune reactions wherefore it is advisable to apply general antiallergic therapy. Particularly, I am having in mind the corticoid hormones and the many variants which have been developed from them such as prednisone, prednisolone, dexamethasone, etc.

The most extensively debated question of the treatment of glomerular nephritis is that concerned with the use of corticosteroids. In our experiments carried out in collaboration with CZIRNER, BIBOR and GOFMAN [44], prednisone as well as prednisolone failed to bring about a sudden favourable change in acute nephritis running a protracted course or in immunologically active chronic nephritis. The results obtained in acute nephritis fluctuated widely; some were favourable, others unfavourable, yet others perhaps too good to be true, but — to all appearances — all conformed with the original dynamism of the pathologic process. Please note my emphasis on apparent conformity!

If interrupted before complete recovery from acute nephritis, prednisolone was found by us to enhance microhematuria as determined by ADDIS's method [1]; moreover, in one case visible hematuria was noted one day after discontinuance of the drug. This seems to prove its efficacy.

REUBI [93] considers corticosteroid therapy contraindicated in general. Among the American workers there is divergence of opinion. DANOWSKI and MATEER [20] assert that ACTH and cortisone, if administered in the proper doses (200 I. U. of ACTH, respectively 300 mg of cortisone, daily, divided in equal quantities, over a period of four weeks) inhibit transition from acute to chronic forms. Other authors are not enthusiastic about the use of corticosterone in the treatment of acute glomerular nephritis [15, 51, 62, 113]. Reports concerning prednisone and prednisolone treatment are remarkably scarce, and do not seem to have as yet been worked up statistically. To shape a definitive opinion would require the study of a large case material, in view of the marked tendency for spontaneous recovery of glomerular nephritis.

The following points emerge as main conclusions to be drawn from animal experiments.

The first indifferent findings [33, 65] were followed by reports of SPÜHLER et al. [106, 107, 123] that in rabbits injected with nephrotoxin huge doses of cortisone (25 mg/kg, daily) inhibited the formation of antibody against foreign protein, and practically prevented the development of MASUGI nephritis. ACTH was found to act similarly [118]. MOENCH and VOGT [80] advise great caution in the determination of doses, having found that MASUGI nephritis in rats is influenced favourably by small doses but adversely by large doses of prednisolone.

In our experiments carried out with CZIRNER and GOFMAN [46], prednisolone (Di-Adreson-F Aquosum, Organon, Oss), irrespective of dosage, neither prevented MASUGI nephritis nor inhibited antibody formation against foreign protein, but is apparently moderated the pathologic process.

According to LANGE et al. [71] triamcinolone (9-alpha-fluoro-16-alpha-hydroxy-prednisolone) is of value in avoiding uremia. In interesting experiments JULESZ et al. [56] showed that implantation of pituitary favourably affects MASUGI nephritis.

To summarize, we incline to the view that steroid therapy should be applied in all active cases of glomerular nephritis. We consider the disease active as long as routine ADDIS [1] counts reveal hematuria or the complement level is low. Steroid preparations that cause no sodium retention should be given preference. The medium dose is recommended as the dose of choice. Treatment should be continued, if necessary, for months, until the clinical and immunological signs of active disease have disappeared.

Steroid therapy is not without danger. Its prescription must be preceded by the same deliberations as go before a major surgical operation. Its risks

must be carefully weighed against the benefits to be expected. What dangers does entail prolonged treatment with steroid hormones? There are three occurrences to consider, *viz.*

1. Perforation of the stomach, gastric hemorrhage.
2. Adrenal atrophy.
3. Infection.

The greatest threat are gastric complications. To obtain direct information we studied the effect of cortisone and prednisolone on the gastric mucous membrane (HÁMORI, NEMES and HAL; 48). Cortisone did not enhance the ulcerogenic action of vagotomy in the rabbit; and prednisolone (Di-Adreson F, Organon, Oss), most interestingly, induced ulcers but exceptionally in the stomach of the dog. It did, however, greatly advance progression of cincophen ulcers. Prednisolone in combination with cincophen was found to give rise to extensive ulcers. In view of these observations all our patients are first subjected to an X-ray examination and those showing an ulcer are not treated with prednisolone. Responsable security might be attained by combining the administration of steroids with antacid drugs. Potassium deficiency must of course be prevented by adequate doses, provided the patient is not uremic. We recommend 40—50 mg of prednisolone daily, a sufficient quantity of sodium bicarbonate, and 1 g of potassium chlorate t.i.d.

Adrenal atrophy may be lethal, as in the cases reported by HAJÓS [34] and FARKAS [24]. But the feedback effect is perhaps not as dangerous as it was formerly thought to be. VECSEI and KEMÉNY [117] established that prednisolone, whether administered continuously or at intervals, reduced endogenous corticoid production in the rat, but the feedback effect began to wear off after some time. This means that prolonged steroid therapy does not enhance this untoward effect. Our method of shielding the patient against the carency syndrome is to discontinue prednisolone gradually, in the course of about two weeks. In our opinion ACTH does little, if anything, to reduce the feedback effect, and so its administration is unnecessary, and may even be harmful (parallergy).

Infection is extremely rare, but at times of epidemic influenza it may be a severe threat, as could be seen during the recent outbreak of "Asiatic" influenza in this country. In non-viral infections wide-spectrum antibiotics have proved beneficial in every one of our cases.

The evidence at hand strongly indicates that it is possible to diminish the side effects of steroid therapy. Hyperacidity and established peptic ulcer mentioned in the history contraindicate treatment with steroids, yet many other ways are known by which to depress antibody formation.

X-radiation. It has been known for more than 50 years that X-radiation inhibits antibody formation. BRAUN and MOELLER [11] attempted the treatment of glomerular nephritis with X-rays and reported favourable results

provided not more than two years had elapsed since the onset of the disease. X-radiation is capable of preventing the type of MASUGI nephritis which is supposedly caused by a biphasic mechanism [60, 61, 89].

Nitrogen mustard. In model experiments with bovine serum gamma globulin pathogenic antibody formation could be inhibited by nitrogen mustard [100]. Trials with the compound in humans were not convincing [6]; its use may cause dangerous complications.

Antihistamines. The intricate immunological mechanism of glomerular nephritis requires our efforts to stop the pathological process at every point. The antigen-antibody reaction releases diverse chemical mediators from the tissues. Little is known of these, though their neutralization might form a sound therapeutical approach. The most important of these mediators are histamine, serotonin, and what are termed the "wild" polypeptides. So far research has been concentrated mainly upon histamine. DIECKHOFF [21] found that nephrotoxin increased the histamine content of renal venous blood to from three to four times its normal. Using JANCSÓ's gelatine-India ink method, I demonstrated in collaboration with TOMPA [49] the release of histamine in the glomeruli of rabbits injected with nephrotoxic duck serum. REUBI [91, 92] observed the beneficial effect of antazoline in acute glomerular nephritis; however, HALPERN et al. [35] denied the value of antihistaminics because they found that promethazine was unable to prevent MASUGI nephritis. Artificial hibernation with chlorpromazine-promethazine-pethidine cocktail and physical cooling, contrary to expectation, was found to hasten the development of MASUGI nephritis [115]. In summing up the REUBI vs. HALPERN dispute one may say that promethazine is devoid of effect but certain antihistaminic substances can be conceived as being capable of producing beneficial results.

In collaboration with CZIRNER and GOFMAN [45] we have studied the effect the potent antihistaminic preparation chlorpheniramine maleate (Chlortrimeton SCHERING) in rabbits injected with nephrotoxic duck serum. The drug has been found to have no effect.

No definite conclusions can be drawn from clinical experience. Reports on the effects of the antihistaminic drugs are conflicting; some results have been said to be favourable [5, 10, 18, 66], others unfavourable [72, 112].

In sum, the true value of the antihistaminic drugs has still to be established; what seems to be certain is that the range of preparations exerting a favourable influence on nephritis cannot be particularly extensive.

Anticoagulants. An intriguing question is that of a correlation between blood clotting and inflammation. JANCSÓ and KOVÁCS [55] has recently reported that by the use of some new anticoagulants (quaternary polyammonium compounds of polypeptide structure) he mostly succeeded in preventing, in a number of experimentally induced inflammatory processes, the pathological phenomena which interfere with permeability. Other authors found that

heparin was capable of preventing the local [27, 85] as well as the generalized [27] SHWARTZMAN reaction. On the other hand, according to SARRE [97] heparin affords no protection against experimental glomerular nephritis.

Pathologists have long ago pointed to the presence, occasionally in vast numbers, of fibrin thrombi in the glomerular loops of humans with REICHEL type glomerular nephritis. Fibrin thrombi were also found to be present in renal glomerular lesions of rats [74] and dogs [101] injected with nephrotoxic serum. Working with nephrotoxin-treated rabbits, we produced indirect evidence of the clotting disturbance. Following nephrotoxin treatment, the animals were given an intravenous injection of India ink stabilized with gelatine according to JANCSÓ. Autopsy revealed India-ink thrombi in the renal arterioles, provided the nephrotoxic action had been violent. Precipitation of exogenous colloid was interpreted as a sign of latent clotting disturbance [41]. It is improbable that intravascular coagulation should be responsible for all inflammatory phenomena; nevertheless, one might conceive of it as a pointer in the direction of new therapeutic possibilities, i.e. of the right type of coagulant, applied at the right moment, and for the right period of time.

The chronic stage

As has already been stated, the treatment of chronic nephritis differs in dependence on whether the pathological process is in the active or inactive phase. The inactive phase requires strict observation of dietary rules and a mode of life that spares the kidneys. The active phase calls for steroid therapy.

Kidney denervation. Encouraged by favourable clinical results, BROD and ANTONIN [14] recommend denervation, but animal experiments show that it has no decisive effect on the immunological process in the kidney. HÁMORI and KORÁNYI [47] found that bilateral denervation fails to prevent the onset of MASUGI nephritis, and unilateral denervation involves the dysfunction of both kidneys. An explanation of the favourable clinical results reported is, perhaps, that spasm of the innervated arterioles adds itself to the glomerular lesions as a secondary factor in maintaining the nephritic symptoms. It is certainly not easy to determine the right time for surgery; performed prematurely it is unnecessary, and done too late it is unreasonable.

What can be done in the terminal stage? Uremia, though the fifth act of a Shakespearean tragedy, still leaves some room for hope, justified by two new promising methods, the artificial kidney, and kidney transplantation.

Artificial kidney. The problems of the artificial kidney have been discussed in detail at the Congress of Hungarian Internists in 1960. Here I would only emphasize that the artificial kidney must not be used unless there is reasonable hope that after uremia has been relieved there will be improvement in renal function.

The technical progress in this field is amazing. At the congress just mentioned we have learned from SARRE [99] that thin polyvinyl tubes are now inserted in the artery and the vein of the forearm, and left in them for days, and allow extracorporeal dialysis to be performed repeatedly and conveniently. A small receptacle, not unlike a tin for preserves, can hold the new-type artificial kidney which is discarded after use. However, even with the modern technique extracorporeal dialysis is of no avail in the terminal stage of patients with aglomerular kidneys.

Kidney transplantation. The idea of kidney transplantation had arisen more than 50 years ago. The technical details for its performance were soon elaborated, but biological incompatibility of the transplant with the recipient organism was for a long time an impediment. The experiments of MERILL et al. [76, 77, 82] are known to all of us; they have transplanted kidneys with success between identical twins. The results achieved in Boston have not been published in detail but at least one transplanted kidney is known to have retained its perfect functional capacity for three years. Unfortunately, it happens very rarely that one of a pair of uniovular twins should be perfectly healthy while the other suffers from chronic nephritis. The latest progress is to be credited to American [78] and French [36, 70] clinicians who achieved immunological tolerance in the recipient by subjecting him to sublethal whole-body irradiation with 400—460 r. This procedure has made kidney transplantation possible between twins who have not developed from a single ovum.

There is another impressive possibility. Kidney transplantation may be successful if the recipient suffers from agammaglobulinemia. To this at any rate points the experience acquired in skin transplantations [28].

SARRE [98] praises cortisone as the drug of choice in the terminal stage: it relieves the patients' anxiety and keeps them soothed to the end.

Prevention

Antibiotic treatment of coccogenous infections. Glomerular nephritis is a "second" disease, the "first" being usually some infection of the upper respiratory tract, or pyoderma. The "first" disease is the prelude to the tragedy. It is best prevented by competent antibiotic treatment. According to KERPEL-FRONIUS et al. [63], in children early treatment of scarlet fever with penicillin prevents involvement of the kidneys.

Epidemiological observations revealed that treatment with penicillin of carriers of type 12 streptococcus and type 12 streptococcal pharyngitis prevents spread of nephritis [86, 108]. On the other hand gamma globulin treatment of the patients with type 12 streptococcal infections not only valueless, but may even be harmful [108]. Let me point to bovine gamma globulin nephritis! Prolonged penicillin treatment, as far the prevention of rheumatic

relapses, is in my opinion unnecessary in nephritis, where it involves certain risks (parallergy).

Detection of "nephritogenic" streptococcus carriers. For the prevention and control of epidemic outbreaks of nephritis the ideal solution would be a systematic detection of carriers of "nephritogenic" streptococcus strains. Unfortunately, typing is an intricate task. For the time being we can only suggest some practical measures. Persons in contact with acute nephritic patients should frequently be examined bacteriologically for the presence of beta hemolytic streptococci in the throat and the nose, and those found positive should be treated with penicillin. Each patient should be considered an infective source, and therefore be isolated and made to wear a face mask until residual infection has been controlled.

Pyelonephritis

Pyelonephritis has been known for over a hundred years, but it was only in the last decade that we became painfully aware of its frequency, gravity, and the deplorable insufficiency of its therapy.

The acute stage

The treatment of acute pyelonephritis apparently presents no challenging problems. According to COLBY's statistics [17], antibiotics are efficaceous in 90 per cent of the cases.

The chronic stage

Regrettably, the condition frequently develops into the chronic stage. Apparent recovery is followed after a few months by relapses or the infection remains latent for long periods, leading ultimately to a total destruction of the kidney. Chronic pyelonephritis proves curable in one third of the cases at the utmost. The cause of relapses or the persistence of an infection is not always obvious. It is at this point that we come into conflict with the weighty general problems of organ disposition and organ immunity.

Removal of foci and surgical correction of urological changes. The problem of organ disposition may lose some of its intricacy if it is contemplated in the light of the fact that, while inserted as a filter in the blood path, the kidney, by way of the urinary tract, communicates directly with the external world. What is strange is not that a person should have pyelonephritis, but why not everybody has it. In fact there is evidence that in one of every five autopsies changes are found which point to varying degrees of this disease [95]. The special position of the kidney in the organism explains the distinction of two types of pyelonephritis, viz. the ascending and the hematogenous type. In the

first type, some urologic change, such as developmental anomaly, calculus, prostatic hypertrophy, etc., is responsible for the persistence of the pathologic process; in the second, this is due to some active infective focus. It follows that recovery from pyelonephritis is inconceivable without the elimination of the underlying cause. Sucessful therapy imperatively requires the elimination of infective foci and the surgical correction of urologic changes.

Numerous authors have studied the relationship between pyelonephritis and hypertension. The question is whether nephrectomy is justified in chronic pyelonephritis when hypertension can be interpreted on the basis of the GOLDBLATT mechanism? Hypertension developing in pyelonephritis not infrequently reminds one of the malignant form. This underlines the significance of the question. Some authors regard nephrectomy as a lifesaver. Others, whose number is growing, keep pointing out that pyelonephritis is very exceptionally unilateral and that the functioning renal parenchyma is diminished by nephrectomy.

Evaluating the data on hand I cannot escape the impression that nephrectomy performed in order to lower blood pressure is in most cases a will-o'-the-wisp scheme. In COLBY's statistics [17], for instance, we see that only three of twenty such operations were successful. It would appear that nephrectomy in case of a GOLDBLATT type hypertension is unrewarding except in patients with stricture of the renal artery verified by lumbar aortography. GÖMÖRI and SZENDEI [30] recommended SMITHWICK's operation in several cases of hypertension supposed to be of pyelonephritic origin; the results were variable.

Patients with nothing for which to operate on them, constitute peculiar problems. These cases requiring medical treatment represent, according to BROD [13], at least one third of all the cases. The histories sometimes point to cystopyelitis, at other times they give no or not specific information. The prognosis of these non-obstructive forms is much poorer than that of the obstructive forms. I would once more refer to COLBY [17] whose statistics show that 28 per cent of the complicated forms of chronic pyelonephritis are curable against only 15 per cent of the non-complicated forms. To provide an explanation for this paradoxical observation, BROD [13] suggests that most patients suffering from one of these latent forms undergo treatment much too late. One may agree with those who say that the chance of curing chronic pyelonephritis is the greatest if it is acute.

Approaching the question from the Pavlovian standpoint, BROD [13] in his monograph underlines the possibility that some minor neurogenic functional disturbance imitates anatomical obstruction of the urinary system. The consequences of severe disturbances of nervous origin are well known. For instance, pyelonephritis following paraplegia leaves no hope of recovery, and is mostly lethal. Lesser disturbances of nervous origin acquire significance if there occurs some inflammatory process near the urinary system. Procain

block is known to have been recommended to relieve spasms of reflex origin, and injection of pituitrin, to regulate weakened dynamism [31]. In my view, etiological treatment of regional inflammations is to be preferred to such symptomatic treatment.

Control of bacteriuria. The chronic forms are usually treated by prolonged administration of sulphonamides relatively well soluble in the urine, of which doses of 1 to 2 g daily are prescribed intermittently for months, until the patient is symptomless and repeated analyses show the urine to be permanently sterile. In acid urine the acetylated sulphonamides assume a crystalline structure. To prevent crystallization, alkalies should be prescribed and it should be remembered that the combination of hexamine and sulphonamides forms a formaldehyde compound and the mass of precipitate obstructs the renal tubules; the result is anuria and uremia. The alternative is a prolonged course of some tetracycline preparation in 100-mg doses b.i.d. The choice of the antibiotic may be a subject of dispute; not so the ultimate end, which is to control bacteriuria by some means or other, irrespective of whether or not it is accompanied by pyuria. Subclinical infections may likewise cause irreversible renal damage [59, 69]. Bacterial counts prove the etiologic significance of the bacteria discharged [57, 58, 73, 81]. They afford the best indication of the presence of an infection in the urinary tract [19].

In view of the above, we cannot possibly be satisfied with the current methods of treating chronic pyelonephritis. Obviously some new ways must be found to approach the problem.

Electrolyte balance. There are several therapeutical possibilities that have not yet been put to the full proof. Foremost among them stands a careful control of the electrolyte balance, and the immediate restoriation of its changes. Until recently, the problem had been the "retaining" kidney; now, the concept of the "losing" kidney is being much expounded. Perhaps the most frequent loss is that of salt, particularly in pyelonephritis, where potassium deficiency may also occur, though less frequently. KERPEL-FRONIUS et al. [64] found tubular dilatation in rabbits kept on a potassium-free diet. From the therapeutical point of view this finding is not without interest in pyelonephritis. Tubular dilatation due to potassium deficiency intensifies the infectious process, and a vicious circle may develop. Correction of the deficiency might, on the other hand, start a benignant circle. The vicious circle is reversible, as S. KORÁNYI [67, 68] had frequently pointed out in other connexions.

Antihistamines. Another therapeutical possibility seems to be the use of antihistamine drugs. On the basis of the convincing experimental evidence produced by BABICS and RÉNYI-VÁMOS [3, 4] there seems every reason to assume that in the chronic forms urine is absorbed by the adipose tissue around the renal pelvis, whence it finds its way into the interstitial space, causing vast release of histamine. Another therapeutical result of the work of these

authors is the removal of the scarred adipose tissue in the renal sinus. Occlusion of the lymph ducts automatically causes the lymph flow to fall short of normal; the adverse effect of this on protein transport is heavily responsible for renal destruction and contraction.

Exogenous and endogenous poisons. Organ immunity would certainly afford full protection from pyelonephritis. Unfortunately, its mechanism is still imperfectly known. Perhaps local antibody formation plays a part in it. Observance of general hygienic and sanitary rules, rest and administration of vitamins, are undoubtedly beneficial measures, but most important is to eliminate every factor that might interfere with renal immunity. This equally includes exogenous and endogenous poisons. A commonplace example is the extremelly severe clinical manifestation of pyelonephritis in diabetics, developing not infrequently into necrotizing renal papillitis.

It is certain that exogenous poisons also impair renal immunity. In the first place, I am thinking of chronic damage due to acetophenetidin. Although the pathologic findings are the same as those seen in interstitial nephritis, animal experiments supply unequivocal evidence that the compound only destroys the kidney in association with an infection [79, 110].

Corticosteroids. ZOLLINGER [122] states that flooding of the kidney with foreign protein may produce interstitial nephritis. In his view the lesion can be interpreted on the basis of an allergic mechanism.

It may be assumed that the lesion can be induced by various mechanisms, and should this prove true, the treatment of pyelonephritis would have to be placed on a wider than its present basis; in this case the corticosteroids might become one of the components of a complex therapy.

Prevention

The urologist's responsibility. Growing emphasis is now being layed upon the urologist's responsibility in reference to iatrogenic infection. There has been considerable discussion about the question whether catheterization had not better be abandoned. In the initial portion of the male, and the outer two thirds of the female, urethra, bacteria are present, which the catheter is likely to transport into the bladder. The risk incurred is still more serious in ureteric catheterization because the delicate instruments used in this manoeuvre are difficult to sterilize. Urological departments are habitats of antibiotic-resistent pathogenic agents, of which the most dreaded are the *B. proteus* and *B. pyocyaneus* strains. COLBY [17] discards the ureteral catheters used in patients found to be infected with these strains. BABICS and RÉNYI-VÁMOS [3, 4] describe with dramatic force the catastrophe which may occur during manipulations involving the use of internal instruments in ureteric occlusion due to a calculus. The urologist inserts the ureteral catheter past the stone. He want

to obtain information by retrograde pyelography. He injects the contrast medium. This gives rise to considerable overpressure in the dilated pelvis and so enables the infected urine to enter the interstitial space through the cracked calyces, causing foudroyant renal inflammation. I think that the right treatment of calculus obstruction is one of the most provocative questions in clinical practice. Whether he takes his time or is in a hurry, the urologist in any case may make a mistake.

The pediatrician's responsibility. The responsibility the pediatrician has to bear is not small either. In childhood the incidence of pyelonephritis is known to be high and to account for 2 per cent of all deaths, primarily because of developmental anomalies [16]. In the presence of the latter particular care must be taken in eliminating infectious foci.

The gynecologist's responsibility. Recent research has revealed the special problem of pyelonephritis in pregnancy and puerperium. During pregnancy there is physiological ureteral dilatation, but functional disturbances of the urinary tract are known to equal an obstructive disorder. Pregnant women often harbour microorganisms in their urine [52, 59]); the bacterial counts should decide their significance, and antibiotics must be prescribed accordingly.

The internist's responsibility. He must know that asymptomatic bacteriuria, too, can be of consequence, that its absence is to be preferred, and that he must keep his patient under careful observation for it. We subscribe to GÖMÖRI's [30] demand for early diagnosis and treatment. Prompt and energetic treatment of infections of the urinary system must go beyond the control of pyuria, and must aim at the eradication of the organisms. Even this is not enough. In consultation with the urologist, all structural and functional changes must be corrected. If nevertheless there are recurrent attacks, the points of entry of the invasive bacteria must be found, especially in women.

The nephrotic syndrome

Since it has been introduced by MÜLLER [83], the term "nephrosis" has undergone many conceptual changes. The term accepted at present is the "nephrotic syndrome". The nephrotic syndrome may occur in any of a variety of conditions, such as lipoid nephrosis, nephritis with traits of nephrosis, amyloidosis, systemic lupus erythematosus, KIMMELSTIEL—WILSON's disease, renal vein thrombosis, constrictive pericarditis, etc. These conditions cannot be amenable to the same treatment.

Experimental and clinical data suggest an allergic mechanism of lipoid nephrosis, and that it is possibly a form of chronic glomerular nephritis. In its treatment a decisive role is played by adrenal cortical hormones. Ultimately,

lipoid nephrosis is as much a clinical manifestation of vascular allergy as is a systemic lupus erythematosus, and this consideration prompts and encourages intensive and consistant application of steroid treatment [40]. Steroid preparations, mainly prednisone and prednisolone, can now be administered for months [2, 8, 9, 23, 26, 29, 32, 50, 53, 84, 111, 116). Formerly short-term steroid therapy was applied generally, but today prolonged either continuous or intermittent treatment is preferred. The results are statictically valid [96].

Amyloidosis is reversible, provided the chronic infection has been eliminated in time, if necessary by surgery, as for instance by amputation of a limb in osteomyelitis, or by lobectomy in bronchiectasis.

The problem of treating the KIMMELSTIEL—WILSON syndrome still awaits solution. There are several reasons for assuming that nodular hyalinosis, which in the rabbit appears after a 3-week course of cortisone, is in humans the result of endogenous hypercorticism. In Hungary, this has been pointed out by BRETÁN [12]. Accordingly, the administration of corticosteroids is inadvisable. Nor does it seem to be of value in conditions with symptoms due to renal congestion. Thrombosis of the renal vein calls for nephrectomy, and anticoagulant treatment has been recommended for bilateral thrombosis [7]. Perhaps antialdosterone preparations should also be given, since there is experimental evidence pointing to the important role of aldosterone in renal oedema formation — or else kidney transplantation should be performed. In patients with chronic constrictive pericarditis surgery is the only promising intervention.

Conclusion

Glomerular nephritis, nephrosis, and pyelonephritis have the feature in common that all issue from infections. On this ground, it may be reasonably hoped that with the general progress of man's struggle against infectious diseases, they will be wiped off.

Summary

I. Nephritis

Modern drugs have outdated neither bed rest nor rules of diet. Patients should be kept on strictly vegetarian diets, preferably as long as the pathologic process is active.

Patients with acute nephritis should be treated with penicillin immediately, without waiting for the bacteriological result, but not without scratch testing for hypersensitivity. If the test yields a positive reaction, erythromycin should be administered in full doses.

Tonsillectomy is justifiable if residual proteinuria or residual hematuria has been diagnosed.

Corticosteroid therapy is indicated in every clinically or immunologically active case, provided there are no complaints pointing to hyperacidity, and no established signs of peptic ulcer. Steroid preparations that cause no sodium retention should be given preference over others. The medium dose is recommended as the dose of choice. The most important signs of activity are microhematuria and a low complement level.

The true value of the synthetic antihistamines has still to be established. The use of anticoagulants has not yet passed the experimental stage.

Kidney denervation, recommended by some authors in chronic nephritis, involves the difficult problem of determining the right time for its performance, because if it is performed prematurely it is unnecessary, and done too late it is unreasonable.

The use of the artificial kidney is only justifiable in cases where there is hope of an improvement in renal function.

Kidney transplantation is now possible between twins who have not developed from a single ovum, if immunological tolerance has been ensured by sublethal whole-body irradiation.

Early treatment of coccogenous infections with antibiotics is most effective in prevention of nephritis. The patient with acute nephritis is an infective source; he should be isolated and made to wear a face mask. To prevent epidemic outbreaks the ideal solution is a systematic detection of carriers of "nephritogenic" streptococcus strains.

II. Pyelonephritis

The principles of treatment are (i) the administration of suitable antibiotics; (ii) the removal of the infective foci; (iii) the surgical correction of urological deformities; (iv) the control of exogenous and endogenous poisons; (v) the correction of the electrolyte balance; (vi) the general observance of hygienic rules.

The use of antihistaminic drugs and corticosteroids is still in the experimental stage.

With regard to prevention, the responsibility rests with the urologist, the pediatrician, and the gynecologist. Catheterization, and manipulations involving the use of instruments, must be preceded by grave deliberation and performed under antibiotic protection. On recognizing some developmental anomaly, eventual infective foci must be eliminated at once. Urinary bacterial counts are the best indicator of urinary infection. If the number of coliform organisms exceeds 1000 per ml, antibiotic treatment is advisable in pregnancy and the puerperium.

III. The nephrotic syndrome

Treatment of the nephrotic syndrome varies with the cause eliciting it.

An allergic mechanism calls for prolonged corticosteroid treatment.

The latest development in symptomatic treatment is the administration of antialdosterone preparations.

In unilateral renal vein thrombosis nephrectomy is indicated; in bilateral thrombosis anticoagulants should be prescribed.

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