A THEORY CONCERNING THE MECHANISM OF ALLERGIC DISEASES

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The causes of human glomerular nephritis and nephrosis usually have been considered to involve an allergic mechanism. Both diseases occur more commonly in those who have other manifestations of allergy, often members of families with an allergic diathesis. Acute nephritis usually follows infection with certain strains of hemolytic streptococcus, with a latent period like that which would be necessary for antibody formation. During the nephrotic stage of glomerular nephritis the serum complement level falls precipitously, then rises as the nephrotic activity subsides. Some have attributed nephritis to the immunologic effects of a hypothetical autogenous antibody to kidney tissue, but the demonstration of autoantibodies to kidney tissue has been elusive. There has always been a stumbling block in this explanation: Why should an autogenous tissue ever become antigenic? The association of streptococcal infection with nephritis has been invoked to overcome this stumbling block, and the antigenicity of autogenous kidney protein has been attributed to some interaction with streptococcal protein. Experiments to find out whether such an interaction can create autogenous or even homologous antigenicity have led to doubtful or negative conclusions.

Two types of experimental immunologic procedure will produce nephritis in animals. In one type, usually called "Masugi-type nephritis" (although the work of Masugi was antedated by that of Lindemann as well as by that of Wilson and Oliver), antikidney antibodies are formed in a heterologous species and then administered to produce nephritis in experimental animals. Obviously, this mechanism cannot be the natural one involved in the production of human nephritis. The second type of experimental nephritis is produced by administration of various foreign proteins, not themselves antibodies or extracted from kidney tissues. Hawn and Janeway speculated provocatively concerning the reason why such foreign proteins, not themselves directly related to or derived from the kidney, should have the capacity to induce nephritis.

In 1940 Kay observed that experimental nephritis in the rabbit followed a latent period after the administration of duck anti-rabbit-kidney serum and that the development of nephritis came simultaneously with appearance in the rabbit serum of antibodies to duck serum. Indeed, he suggested that the duck anti-rabbit-kidney antibody combines with rabbit kidney tissue to produce a harmless combination (DAK-RK) which is fixed in the kidney tissue and that the rabbit anti-duck-serum antibodies, when formed, then combine with the harmless DAK-RK combination to produce a harmful antigen-antibody complex, which causes nephritis. Both types of experimental nephritis may be inhibited or enhanced by general factors affecting the response to any antigen-antibody reaction (state of adrenal function, complement availability, etc.). Kay's experiment may be considered as a special case of the second type of experimental nephritis, since the specific antikidney antibody produced no immediate effect, possibly as the result of a low antibody titer, and the subsequent nephritis seemed to result from the foreign character of duck serum protein.
By a slight extension, expressed in the following three hypotheses, the suggestions of Kay can be applied to explain the second type of experimental nephritis in a general way and can be applied, further, to human nephritis and even to other immunologic phenomena and diseases that follow the introduction of foreign antigens into the body.

**First Hypothesis:** When a foreign antigen is introduced into the body, it may accumulate at certain local sites of predilection which are determined by the nature of the antigen, the route of introduction, and the amount of antigen. It is evident that the sites of accumulation will be determined in part by the nature of the antigen. For example, a particulate antigen (such as a suspension of killed bacteria) might be expected to accumulate in the reticulo-endothelial system, while a soluble antigen might be expected to accumulate in the liver, lymph tissue, or kidney. The route of introduction will determine the order in which the antigen reaches potential sites of accumulation. For example, an antigen that gains entrance to the peripheral circulation will travel to the lung through the pulmonary circulation; an antigen that is absorbed through the intestinal tract will travel mainly to the liver and, perhaps, partly through the lymph system and the systemic veins to the lung. The amount of antigen will determine in part the sites of accumulation, since a very small amount of antigen, regardless of its nature, might be fixed entirely in the first site reached; a very large amount of antigen might saturate the site of greatest affinity and accumulate thereafter in sites of secondary affinity.

**Second Hypothesis:** The antigen persists at the sites of predilection during the period when antibodies are formed. Persistence of antigen for several weeks has been demonstrated by McMaster et al. in the rabbit and in the mouse. Garvey and Campbell have demonstrated persistence of antigen for 8 weeks in the rabbit; the persistence may be the result of an inability to utilize or destroy the antigen or may be the result of a slow rate of destruction. Following a single introduction, the amount of antigen at the sites may diminish; but the amount of antigen at these sites may be maintained or even increased through continuous or repeated introduction. The antibodies may be formed at the sites of antigen accumulation or in remote locations.

**Third Hypothesis:** After the antibodies are formed and released into the circulation, they react with the antigen, which is in greatest concentration at the sites of predilection, and thus produce a localized anaphylactoid (reversed Arthus) phenomenon, with inflammation, exudation, and other consequent results.

The work of Smetana, Oliver, Rather, and others has shown that the kidney is a site of predilection for the deposition of some proteins, among which are those which have been used to produce various forms of experimental nephritis. For example, Oliver, Moses, MacDowell, and Lee demonstrated protein droplets in the tubular epithelium of rat kidney after the intraperitoneal administration of horse serum, and Wissler, Smull, and Lesh found that glomerulitis, along with some other cardiovascular lesions, could be produced in the rabbit by a single intravenous administration of horse serum. In the latter experiment, and in other similar experiments concerning the second type of experimental nephritis, only pathologic criteria for glomerulitis were used, applied to the specimens obtained at autopsy when the experiment was concluded. However, Waugh and More observed also the time when proteinuria appeared, after rabbits were given bovine serum gamma
globulin. They found a latent period of 8 days, consistent with the time required for the formation of antibodies to the foreign antigen. All these observations agree with the above theory.

If certain other foreign proteins, such as one produced by the proper strain of streptococcus, were also found to have a predilection for deposition in the kidney, the theory would then explain the pathogenesis of human nephritis as well. In view of the suspected relationship between streptococcal infection and such human diseases as rheumatic fever and rheumatoid arthritis, in addition to nephritis, it would seem profitable to investigate the deposition and disposal of streptococcal antigens as a next step.

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5 P. Cavelti and E. S. Cavelti, Arch. Pathol., 40, 158, 1945.