In these experiments the marked leucopenia and febrile reaction observed for the typhoid filtrate did not occur, the reaction being comparatively slight. The lesions as a whole, both gross and microscopic were those of a toxemia but unlike the representative lesions produced by the typhoid toxin.

It would appear, therefore, that the toxic moiety obtained from *B. coli* wherein a peritonitis has been excited, does not demonstrate the effects analogous to human typhoid fever previously noted when the typhoid bacillus had been employed in a similar manner.

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Afebrile Post-Scarlatinal Nephritis.*

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In many cases of scarlet fever the symptoms of the infection have passed and recovery has apparently been established, when acute nephritic symptoms without fever appear about the third week. Of these, the signs of glomerular nephritis are the most prominent. It is generally thought that the new symptoms are not those of a secondary infection or late manifestations of scarlatina. In this connection Longcope[1] and his co-workers indicate that the late nephritis following scarlet fever is the result of existing foci of streptococci in the throat and other parts of the upper respiratory tract. They could not obtain evidence that the streptococci caused the glomerular nephritis by actual invasion of the kidney, as cultures of the blood and urine were negative. These authors suggest that toxin from streptococcal foci in the throat, sinuses, etc., is eliminated by the kidney, thus causing the acute glomerular nephritis.

Our experiments with 17 healthy young dogs support Longcope's contention and furthermore prove that the late acute glomerular nephritis (at least in the dog) is not the result of retained viable streptococci in the body but is due solely to the *in vivo* prepared streptococcal lysate (endotoxin) of Duval and Hibbard.[2] In the recovered experimental dogs which had been infected with living cultures of scarlatinal streptococci, a second or a third dose of

* Aided by a grant from the David Trautman Schwartz Research Fund.

[1] Longcope, W. T., *et al.*, *J. Clin. Invest.*, 1927, v, 7.

[2] Duval, C. W., and Hibbard, R. J., *J. Exp. Med.*, 1927, xlvi, 379.

"lysate" (toxin *in vivo* prepared) produce a severe and often fatal acute hemorrhagic glomerulo nephritis which in every way corresponds to the afebrile post-scarlatinal nephritis of man. These animals tested before administrating the "lysate" showed more or less lytic immunity: that is, a specific streptococcal lysin was demonstrable in the blood serum and the animals could not be infected with the same dosage of living culture that infected them originally.

The deductions drawn from these experiments are that the animals, though lytically immune, were not apparently anti-endotoxically protected against the toxic product of the scarlatinal streptococcus. The toxin was free to act and did so upon the kidney, particularly the glomeruli. Previous experiments by Duval and Hibbard[3] have shown that the hemolytic scarlatinal streptococcus or its endotoxin has a marked predilection for the kidney.

Experimental scarlatinal streptococcal infection in the dog is of infrequent occurrence unless the dose is large (5 cc. emulsion of the entire 36 hour growth from blood agar slant). On the other hand, young dogs are highly susceptible to the *in vivo* prepared and filtered toxin, and not at all affected by the so-called toxic filtrate from cultures. Dogs infected with the living culture or affected by the "lysate" invariably show acute lesions in the kidneys, and death is apparently due to the destructive changes in the glomeruli of these organs.

While Dick and Dick and others secure from scarlet cultures grown in broth a filterable toxin which reacts intradermally in the human non-immune, we have been unable to obtain any toxic effect with this same material employed upon the guinea pig, rabbit, and *macac rhesus* monkey. However, we have obtained striking skin and general toxic reactions in these animals with the filtered *in vivo* prepared product of hemolytic streptococci. Furthermore, we have elicited in the human non-immune the intradermal reaction to scarlatinal lysate which seems to be more specific than the Dick and Dick toxin of culture filtrate. We believe from the character of the reaction in humans, and the same kind of reaction obtained with non-specific protein products, that the Dick and Dick cutaneous test is not specific. In our hands a variety of bacterial proteins produce much the same reaction. It is interesting in this connection that Zlatogoroff and Derkatch[4] state that neither the toxin production nor the Schultz-Charlton test enable them to confirm the conception of the specificity of scarlet fever streptococci.

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[3] Duval, C. W., and Hibbard, R. J., *J. Am. Med. Assn.*, 1926, lxxxvii, 898.

[4] Zlatogoroff, S. I., and Derkatch, W. S., *J. Infect. Dis.*, 1928, xlii, 56.

So complex an organ is the kidney that an injury anywhere has far reaching results. If we consider the intricate histology and physiology of the kidney we can better understand the variety of lesions arising from a single injurious agent. In the same organ there occur great destructive changes, side by side with attempts at healing and compensatory hypertrophy. Though the injurious agent be the same, the lesions are of many different kinds, affecting all parts of the kidney parenchyme, but especially the glomeruli in the case of the scarlatinal streptococcus. Experimentally it is seen that the toxin primarily affects the capillary tufts while the viable organisms produce lesions in the interstitial tissues.

The experimental nephritis with scarlet streptococci in the dog is essentially of 2 types, parallel in every way to the 2 types described for man. The *in vivo* prepared toxin produces an acute glomerular lesion, while the living culture produces a type lesion of the stroma that is a lymphocytic infiltration.

The lysate of scarlatinal streptococci causes in the dog extraordinarily complex changes in the glomeruli. The simplest lesion seems to be an intense engorgement of the capillary whorl with the red blood cells becoming densely packed and appearing as though the hemoglobin was completely dissolved out. In many of the tufts the capillary loops become enormously distended with erythrocytic thrombi. Generally this happens only in parts of glomeruli. The occluded capillaries become further distended by masses of eosin staining material which is homogeneous and apparently formed from fused and destroyed red blood cells. These thrombotic capillary loops may become glued to the wall of Bowman's capsule. In older dead loops of capillaries, connective tissue may partially or completely organize them. In other glomeruli where the capillaries are not blocked by hyalin thrombi, their lumenae contain large numbers of lymphocytic or endothelial cells. It is difficult to determine the exact location and character of these cells since many appear to be outside of the capillaries. In no instance are these cells of the neutrophilic variety. We are inclined to regard these abnormal elements as endothelium because of their manner of staining and the character of the nucleus which is definitely vesicular and surrounded with considerable loosely arranged cytoplasm. In other glomeruli there is noted extensive hemorrhage which in some instances can be traced into the tubule. Sometimes the hemorrhage into Bowman's capsular space is so large as to misplace or crowd out the capillary whorl. When blood escapes into the capsular space the red blood cells fuse into a homogeneous pink staining mass and often become attached to the lining of Bowman's space.

In these masses there commonly occurs connective tissue and epithelial cell invasion, producing the socalled "crescent". With fibrous tissue ingrowth and replacement of the hyalinized capillaries the glomeruli become in part or completely obliterated.

The tubular epithelium is remarkably unaffected, at least until quite late in the glomerular process. Later the lining epithelium, especially that of the convoluted portion of the tubule, becomes swollen, granular and filled with fat droplets. Sometimes the epithelium desquamates and the tubules atrophy. All kinds of casts may at times be demonstrated.

A significant feature of the experimentally induced glomerular nephritis in the dog is the absence of any acute inflammatory products about the involved tufts and tubules. However, in dogs that have received repeated injections of streptococcal lysate, and the urine examination showed previously the existence of acute glomerular nephritis, there was seen upon microscopic study of the kidneys a well advanced sub-acute and chronic interstitial change. In these kidneys there was noted fibrous tissue increase in the areas where the greatest damage had occurred to the glomeruli. In such connective tissue areas many of the tubules were atrophic and the glomeruli destroyed. The less affected glomeruli were actually larger than normal, and certain tubules appeared large and others extremely small.

The experimental work carried out upon dogs with both the living culture of streptococcus scarlatinae and its *in vivo* prepared toxin induces an acute glomerular nephritis. The kidney lesion occurs during the infection and may also be induced in the recovered animal several weeks later, by injections of the *in vivo* prepared lysate.

Aside from the question whether the hemolytic streptococcus of Dick and Dick is the primary excitant of scarlet fever, there is abundant experimental proof that the streptococcus is responsible for the acute glomerular nephritis during the infection and the so-called afebrile nephritic period which occurs weeks later. Longcope's observations upon recovered cases of human scarlet fever certainly indicate that though they have recovered from the infection, they may maintain foci of hemolytic streptococci in parts of the upper respiratory tract, and that these foci may be responsible for post-scarlatinal nephritis of man.

It would appear from the results of our experiments that scarlatinal infection in the dog establishes a lytic rather than an antitoxic immunity. If this is true for the human infection it is logical to suppose that the persistence of hemolytic streptococci upon the mucous membrane of the upper respiratory tract, middle ears, sinuses.

etc., would be the source of an intermittent supply of toxin to the system; and though the lytic action of an already existing immunity render the absorbed streptococcal product more effective for the kidney where in greater part the toxin is eliminated.

A comparative study of the experimentally induced scarlatinal nephritis in the dog with the filtered *in vivo* prepared toxin shows a complete analogy with the afebrile post-scarlatinal nephritis of man.

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Serological Evidence of Identity of Duval and Hibbard Measles Coccus with that Isolated by Tunnicliff.

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In a recent paper Tunnicliff[1] has noted the close immunological relationship between the cocci isolated by her from patients with measles and those isolated by other workers, as evidenced by the phagocytic index. In the study she used 2 strains isolated in this laboratory by Duval and Hibbard[2] from the blood stream of human cases of measles during the height of the eruption; the blood in each case was filtered through a Berkfeld N filter before special media was inoculated, a coccus being obtained from every case cultured.

Similar evidence of this immunological relationship has likewise been demonstrated in this laboratory, based upon agglutination reactions. Three rabbits were immunized by 12 intravenous injections over a period of 70 days—one with a coccus sent us by Tunnicliff, another with a measles coccus isolated by Duval and Hibbard, and a third with a stock strain of *Streptococcus viridans*. The first 4 injections were killed cultures, the last 8 were living cultures.

As shown by the accompanying tables, the sera of the rabbits immunized against the measles cocci each agglutinated almost equally and to high dilutions both strains of the measles coccus, while the *Streptococcus viridans* was only slightly agglutinated by these sera. On the other hand, the serum of the rabbit immunized against the *Streptococcus viridans* very markedly agglutinated the homologous organism, whereas the measles cocci were practically not affected.

[1] Tunnicliff, Ruth, *J. Infect. Dis.*, 1927, xli, 267.

[2] Duval, C. W., and Hibbard, R. J., PROC. SOC. EXP. BIOL. AND MED., 1927, xxiv, 519.