Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Annotations

Viruses in Balkan nephritis

That Balkan nephritis (BN)—a familial, slowly progressive degenerative disorder of the kidneys—might be of viral etiology, was not suspected until Georgescu and colleagues[7] demonstrated by electron microscopy the presence of reoviruslike particles in renal parenchymal cells of patients dying of this condition. The round particles observed in the cytoplasm of tubular epithelial cells, varied in size from 50 to 90 nm. and exhibited an electron-dense central core, surrounded by a distinct peripheral layer. Formerly, clinical and laboratory findings failed to suggest an infectious etiology. The afebrile clinical course (except for intercurrent or terminal infection), the lack of a regularly antecedent illness and of typical pathological reactions, spoke against infection.[6]

Encouraged by this preliminary evidence, we initiated systematic search for hidden viruses in the kidneys of BN patients. In the last several years an increasing number of viruses have been found to be carried in the urine of man. However, we succeeded to recover only an adenovirus strain from the urines of clinically confirmed BN patients, and there was circumstantial evidence that this strain was an accidental passenger virus, with no relationship to the patient's illness at the time of demise. Our attempts at uncovering latent viruses by cell cultivation have been handicapped by lack of satisfactory virus harboring tissue. We were not successful in propagating autopsy material, and biopunctures often failed to provide renal tissue because of the advanced atrophy and sclerosis of this organ. Moreover, fragments were frequently obtained from fibrous connective tissue rather than from the renal parenchyma, and resulted in monolayers of fibroblast-type cells in culture. However, long-term organ cultures and co-cultivation of kidney fragments and trypsin-dispersed human embryo kidney cells also yielded negative results, and it became thus apparent that the major obstacle in isolating the involved agent consisted in the fastidious, difficult nature of the virus. On the other hand, we have recovered several cytopathic agents from throat swabs and urine specimens of family members sharing the housing and living conditions of BN patients. Some of these agents could readily be identified as adenovirus or echovirus strains, whereas other isolates still await identification.

Current epidemiologic data with the highest incidence of BN in women of the child-bearing age, suggested that a vertically transmitted agent of low-grade infectivity might be involved. With maternal infection progressing during pregnancy, the fetus may become chronically infected and this infection may persist through birth and for a variable period afterwards. Serological diagnosis of intrauterine infections is based on the fact that the fetus can respond immunologically already from the twentieth week of gestation. As IgA and IgM antibodies are not transferred from the mother, their presence in the cord blood indicates a fetal response to a prenatal antigenic stimulus. We used the immunodiffusion method to test this possibility by screening sera of newborns from the endemic and a control area for raised IgA and IgM levels suggestive of intrauterine infection. The non-specificity of this method rendered it suitable for checking infections of unknown etiology. However, this study did not disclose any statistically significant difference of the incidence of infection in the endemic and the control area.

The assumption that BN might be a late post-infectious phenomenon or a chronic state of childhood illness, was hardly tenable, since we could establish no regularly antecedent disease. The contention that the antecedent infection might be inapparent, was disturbingly difficult to investigate and could only be tested sero-epidemiologically. The hypothesis implied that all viruses are suspected which are able to cause mild or inapparent, but persistent infection in children. However, sera from 35 patients with BN, 35 cases of lupus nephritis, and 105 selected healthy controls matched for age, sex, and residence, yielded no consistent pattern of antibody to echovirus and adenovirus, *herpes virus hominis* Types 1 and 2, ground squirrel herpes virus, human, murine-, and ground squirrel cytomegalovirus, mumps, respiratory syncytial, parainfluenza, influenza A and B, sindbis, west-Nile, hypr, tribeč, and reovirus antigens.

The existence of natural foci of viral infection in areas endemic of BN, would afford an attractive explanation for the very restricted geographical distribution of this disease. Epidemiological search for possible natural foci led to the isolation, identification, and characterization of a tribeč-type arbovirus strain from *Haemaphysalis punctata* ticks,[8] of several novel cytomegaloviruses from wild mice of the *Mus musculus* and *Microtus arvalis* genera[2, 3] and from the ground squirrel *(Citellus citellus)*,[4] as well as to the recovery of a ground squirrel herpes virus.[5] All these viruses had features which appeared relevant to the implication of viruses in renal disease. The tribeč-like arbovirus induced in mice focal degenerative lesions in the tubular segment of the nephron.[8] Cytomegalovirus of *Mus musculus* mice caused glomerulonephritis and was found to be under genetic control of the natural host,[3] etc. Nevertheless, none of these viruses shared morphological and/or biological features of the viruslike particles seen by electron microscopy,[7] and there was no evidence to link any of them with the etiology of BN.

In spite of the fact that our studies failed to elicit a recoverable virus from the kidneys of BN patients, and that

the influence on the carrier host of the reoviruslike agent is not yet understood, the possibility of an infectious etiology of BN was further supported by the demonstration of virus-like particles in renal biopsy specimens of three further BN patients, as well as by the findings of Apostolov and colleagues[1] who lately described corona virus particles in the cytoplasm of renal cells obtained by biopsy from patients with clinically confirmed BN (corona viruses have previously been named "reo-like," "reovirus-like," or "difficult viruses," etc.). Since no *in vitro* serologic procedure has been developed as a useful diagnostic tool in this disease, and the involved virus has not been cultivated in tissue culture or laboratory hosts, little is known of the nature of this agent. Repetition of such attempts and extension of the studies to embrace most of the modern techniques of virology are prerequisite to any progress in this field. Meanwhile, evidence of viral etiology in BN is still entirely morphological.

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Marked decline in serum digoxin concentrations during an episode of severe diarrhea*

During the past several years numerous studies involving digoxin pharmacokinetics and bioavailability have been reported.[1, 2] However, relatively few studies have been directed to the actual mechanism of digoxin absorption and in particular to the influence of factors such as altered intestinal motility and transit time,[3] intestinal disease,[4-6] and the role of the enterohepatic circulation.[7, 8] From these studies it does seem apparent that disturbances of normal gastrointestinal function might well result in a significant alteration of digoxin bioavailability. We would like to report such a circumstance involving an individual who demonstrated profound differences in serum digoxin levels during an acute transient diarrheal illness.

A 24-year-old healthy male volunteer received four 0.25 mg. digoxin tablets (Lanoxin, Burroughs Welcome, Lot 022-1) as part of a more extensive study of digoxin absorption and pharmacokinetics. Three hours after ingesting the drug the patient developed repeated episodes of watery diarrhea which persisted throughout the subsequent 24 hours. A total of 15 serial blood samples were drawn during the first 24 hours following which a single blood sample was obtained every 24 hours for three days. Six weeks following this illness the patient was restudied in a healthy state using the same protocol with tablets from the same lot. The serum digoxin concentrations were determined in duplicate using an I^{125} radioimmunoassay (Schwarz/Mann) with the subject's digoxin-free control plasma serving as the blank for the standard curve done simultaneously with experimental samples. The resultant serum levels were plotted against time for both treatments (Fig. 1). Since the patient was involved in a larger study which involved intravenous administration of 1 mg. of digoxin, it was possible to calculate the absolute bioavailability of the tablets by the area under the curve method.[9] Although the time to reach peak serum levels did not differ, and the peak levels were similar, the calculated absolute bioavailability of the tablets given when the patient developed diarrhea (16 per cent) was substantially less than when the drug was administered under normal circumstances (84 per cent).

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