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Review
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ANIMAL STUDIES RELATED TO BALKAN ENDEMIC NEPHROPATHY

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Basic field studies related to the animal population were performed in the region of Slavonski Brod, Republic of Croatia, where Balkan endemic nephropathy is an endemic disease. Pathological changes in several animal species from the locality were examined. The pig population in the area is numerous. Morphologically and physiologically pigs make an excellent animal model for studies of human diseases. Their use in studies should be encouraged, especially because there is a possibility that pigs and humans suffer from the same type of intoxication with a specific xenobiotic of natural origin. According to the mycotoxin theory about the aetiology of Balkan endemic nephropathy, pork meat might be one of the possible hazards for humans. Experiments on laboratory animals provide an excellent possibility to monitor several aspects of pathogenesis and all stages of pathomorphological changes which might then be correlated with Balkan endemic nephropathy. However, the experimental species should be critically chosen because some spontaneous, species-specific lesions of the kidneys are easily mistaken for changes induced experimentally.

Key terms: animal population, endemic disease, field studies, rural area.

Despite an unknown aetiology, different aspects of Balkan endemic nephropathy (BEN) have been studied very thoroughly, and are actually well described in a number of convincing papers. Probably the best known is the epidemiology of the disease, owing to extensive investigations performed in the endemic areas during a long period of time (1–4). Those areas with their topological, hydrological, pedological and climatic features have been well recognized and described. The epidemiological pictures concerning the populations from different endemic areas described by several independent groups of authors are generally comparable.

In this paper we shall first give a brief overview of our preliminary field studies and then discuss research on animals. The data are related to the well-known hyperendemic area of Slavonski Brod in the Republic of Croatia. The area is entirely rural. It is based on farm-type production, where each household owns a small piece of land and tends to be self-supporting. Traditionally, food supply comes almost exclusively from people's own farming. People grow cereals, mostly corn for animal feed and wheat for own consumption. The area is comparatively rich. Corn was used as a foodstuff only during World War II and a few years after the war, but since then its use has by no means been extensive.

Generally, each household keeps several species of domestic animals. The area is rich in surface waters. The most frequent among the fowl are ducks and geese, which at least partially depend on own food supply from within the reach of a house. Diary cattle is the commonest large animal. Years ago each household used to keep several of those animals, but today they are encountered less frequently. However, most households keep at least one. Horses, once very numerous, are rather scarce today (the area was one of the horse producing regions for marketing). Dog and cat populations are generally similar to those in the other rural areas, and are found in each house. Finally, there is a large number of pigs, which are the most important and most numerous domestic animals. They are farm-bred, and have been produced for several generations in the area. Actually, the area has been known for pork production; only a small amount of pork will be consumed by the farmer. Animal production is generally extensive, but the feeding and keeping conditions are rather traditional. There are still some villages, close to oak woods, where pigs are fed for a month or two almost exclusively on acorn crop. Whole herds will be left in a nearby wood, brought home afterwards, fattened with corn and slaughtered. During the »acorning« period animals freely get in contact with wild animals. Pigs are fed home-produced feed, which consists largely of corn, with the seasonal addition of pumpkins, potatoes and clover. In our experience, daily human table left-overs, although readily given to pigs, are not of any meaningful amount (a pound or two), because the farmer usually keeps more than five animals. There is a practice of producing larger quantities of corn than is necessary for one year, to prevent the consequences from possible failure of the next year's harvest. The corn from the previous year then will be used first, the fact which might have certain implications if a mycotoxin is involved in the aetiology of BEN. The pigs for the people's own need are slaughtered when they reach the weight of 150–200 kg. As the farmers slaughter and process pigs in their own backyards, the meat is not subject to veterinary inspection, and many disease processes might be overlooked.

Finally, close to humans and their food mice and rats live inevitably, feeding on the same cereals as man and domestic animals, and frequently contaminating them with their excreta. Every late autumn the human habitats are invaded by fluctuant mice populations. The rats are of the sedentary type and belong to black rat (*Rattus rattus rattus*). They mostly live in the attics. It seems that these commensalistic animals are no more numerous in endemic than in non-endemic (control) areas.

It is possible that some members of a certain species carry the same disease process as humans having BEN, if some xenobiotic deriving from the fields, or produced during the storage of grain is involved. Some of those animals, through their products, may enter the human nutritional chain, and thus get involved in the disease causation. During agricultural activities in the fields, farmers get indirectly in contact with several wild animal species, most notably with micromammals. A possibility of such contact was much more real a few decades ago, when for lack of machinery farmers spent much more time working on the land and were in closer contact with it.

In the proximity of agricultural fields large woods offer habitat to several wild animal species. Direct contact with animals from the ecosystem (through hunting and meat consumption) or an indirect one are relatively frequent. Since all the endemic areas are normally located in the immediate vicinity of rivers, the arthropod charge of the area is a very rich one, and cannot be neglected. As a matter of fact, some of the presently hyperendemic areas were foci of endemically occurring malaria many years ago.

The question of possible involvement in BEN of a species other than human has remained open until today. If the fact that some other animal species might suffer from

this disease is established, a reliable animal model for human disease could be made and studied. The aetiological agent could then be recognized enabling the prevention and control of human disease, which in the last three decades has already taken too many lives, and still seems to be entirely out of control. By analogy with biocenosis, where all species have to be considered as a unique, interrelated life phenomenon, observing the pathology of a certain human population during a given period of time without taking into consideration the pathocenosis of all possibly related species from the given area is artificial, and a definite conclusion about human pathology cannot be drawn.

The data gathered during the past 30 years of research indicate two main possibilities regarding the aetiological agent of BEN. One refers to a hypothetical infectious agent, mainly supported by the specific epidemiological picture of the disease, closely resembling the infectious disease of natural foci. The other theory advocates involvement of some toxin, but the researchers disagree as to the xenobiotic in question. With those two main pathways all proposed theories about the aetiology of BEN are by no means exhausted. However, we are not going to refer to all those theories where animal research is without possible implications, as it is for instance with the genetic theory. The followers of the infectious agent theory believe that the humans get infected during their agricultural activities through contact with wild animals, most probably micromammals. The hypothetical infectious agent could be a virus, slowly inducing a progressive tubular disease, finally resulting in specific clinical and morphological manifestations in the late phase of the disease. Some authors observed virus-like particles in the kidney material taken from patients with BEN (5), others used chickens as a possible model for corona-virus kidney infection (6, 7). However, there has been neither conclusive morphological nor virological support from studying human material favouring virus as aetiological agent of BEN. That fact does not exclude a possible virus implication, because at the late stages of the disease, when the tissues are usually examined, the virus will not necessarily be present. The possibility of some animal species acting as vector for the hypothetical viral agent has not been sufficiently examined, and larger, well conducted field animal investigations are called for. In order to obtain reliable information, several profiles of laboratory research including morphological, virological, bacteriological and some combined immunological techniques should be performed in a sufficient number of animals during a longer period of time. Speaking about a possible infectious agent contracted from micromammals to humans, one cannot avoid leptospires, the organisms so frequent among the rodents, which are known to »flourish« in water ponds during the warm weather. It has to be mentioned, without any prejudice, that the lesions of chronic leptospirosis in dog kidneys, generally bacteriologically negative, remind a great deal of the kidney morphology in people having BEN. Years ago, researchers knowing that fact, investigated the incidence of leptospirosis in the human population in endemic areas obtaining positive results (8). Although the work is not conclusive, it will be interesting to compare the incidence and the strain of leptospirosis infection in wild as well in commensalistic micromammals and domestic animals, especially pigs from the endemic and control areas. Once again we have to emphasize the need for long-term studies, because of the specific occurrence of infection, depending largely on the weather and the number of micromammals. *Rozhaju and co-workers* (9) performed a histopathological study of the wild rat kidney, and although certain pathological findings were stated, they are considered to be non-contributory to the problem resolution. The other theory, favouring a toxicological aetiology, is largely supported by epidemiological observation, this time interpreted as the »disease of the house«, where the members of certain households are more frequently diseased, regardless of consanguinity. Lately, the accumulated evidences have indicated a possible role of

some mycotoxic agent in the aetiology of BEN. Definitely, one of the most strongly suggested xenobiotics has been ochratoxin A, a secondary metabolite of some moulds growing as contaminants of grains, food and feed.

A progressive kidney disease of pigs, caused by ochratoxin A, has been reported from different countries (10–13). Because of remarkable morphological and functional similarities between porcine ochratoxicosis and BEN, it was postulated that both processes were induced by ochratoxin A, and a possible animal model for BEN was established (14). In the meantime, new evidences and supports have accumulated. A few studies (15–19) were performed with the intention to demonstrate the morphological changes similar to human nephropathy in domestic animals but without satisfactory results (20, 21). Taking into consideration that the incidence of BEN among the human population of the hyperendemic villages is about 4 per cent, it might be supposed that the incidence among pigs would not exceed this rate. Presumably, the works mentioned failed to demonstrate possible changes because of a relatively small number of animals observed. Although the lifespan of domestic pigs is much shorter in relative biological expectance when compared with humans, the lesions due to ochratoxin A intoxication have been demonstrated in many thousands of farm-growing pigs of short lifespan. We therefore think that research on pigs should be more extensive and should receive a great deal more encouragement. On the other hand our knowledge of the changes in human kidneys at the early stage of disease is relatively poor, which makes comparison with the changes observed on slaughter pig kidneys even more complex. The positive correlation of heavy rainfalls with the increased mortality of patients with BEN in certain years is interpreted by some authors as the result of higher contamination of grains with mycotoxins (22). Thus, the failure to demonstrate specific lesions in pig kidneys one year cannot be a decisive proof for excluding the endemic aspect of intoxication, for it can occur next year, depending on weather conditions as well as on specific way of grain storage. The results of several laboratory animal studies related to ochratoxin A toxicity are in accordance with clinical findings recognized in humans affected with BEN, such as the oncogenic properties (23) and suppression of haemopoetic tissue (24–26). Although ochratoxin A is definitely the best known and the most thoroughly investigated among nephrotoxic mycotoxins, possibly involved in the aetiology of BEN, it is not the only one suspected. *Peristianis and co-workers* (27) published an excellent paper on unidentified mycotoxin showing a potent nephrotoxic activity. The strain of the *Penicillium* used in this experiment with rats was obtained from a hyperendemic area in Bulgaria. Similar lesions on rat kidneys have been induced and described recently (28). The *Penicillium* strain producing the toxin applied has been isolated from corn collected in the endemic area near Slavonski Brod. The main lesions in both experiments involved the proximal tubule epithelium which is known to be damaged in patients with BEN. As there is strong evidence of synergistic effects among different mycotoxins in laboratory animals (29), it is of major importance to investigate a possible synergistic effect of all discovered mycotoxins from the area in question. Furthermore, possible synergistic effects of mycotoxins and other nephrotoxic agents, some of which may act as a non-specific initiating factor, must be investigated.

Based on the results of field investigations in domestic animals from endemic villages and on experimental data the monitoring of pig kidney pathology from the endemic areas should be conducted over a period of several years. Hundreds of samples from the hyperendemic region near Slavonski Brod and from the surroundings of Kosovska Vitina (another endemic region) have been collected over two consecutive years. By comparison of the results for each year, possible differences in the kidney pathology could be recognized.

Correlating BEN with some other, naturally occurring animal disease with a possible value in further investigation, bovine enzootic haematuria cannot be avoided. Although

the kidney lesions due to that disease are not comparable with those caused by BEN in humans, the diseases have certain similarities (30). Bovine enzootic haematuria is a very well-known bovine disease causing considerable economic losses and its strict enzootic distribution has been recognized in several countries (31–33). The enzootic areas of the disease do not overlap with the endemic nephropathy areas in former Yugoslavia. The suspected, though not definitely proved aetiology of bovine enzootic haematuria is poisoning with a certain plant (bracken fern). A remarkable pathological feature of that disease is the incidence of urothelial tumours, quite comparable to those caused by BEN. It is interesting to note that urothelial tumours are characterised by the same histological appearance as those in BEN (32, 34). It will be necessary to perform some epidemiological studies as well as some analytical work in order to determine the presence of a possibly similar agent in both endemic and epizootic areas inducing urothelial neoplasms. Considering the specific type of bovine digestion which is largely dependent on the microflora in their digestive tract, and their specific potentials of detoxification, it might be that the same agent is involved.

Regardless of the investigated animal species deriving from the endemic area, and the material and methodology used, some general principles should be respected in all further investigations, which will facilitate the use of data, and approach to a definite answer. Crucial for success in such type of work is establishment of a bank, where all material, including fixed and frozen tissue specimens will be kept for an indefinite period of time, available for all consecutive analytical procedures and comparison of results. Should some so far unknown evidence of a possible aetiological agent appear, the material could be analysed in that direction. An interdisciplinary scientific approach is imperative. The financial basis will thus be better focussed, enabling the processing of a larger number of samples, offering more precise answers.

Our considerations on the role of animals in the studies related to BEN cannot, of course, be completed without stressing the importance of experiments on laboratory animals. Essentially, there is no suspected agent which is not involved in some type of experiment on animals in laboratory conditions. A paper has been published (35) encouraging researchers in the use of laboratory animals. The author performed quite ingenious experiments with rats giving them concentrated water from the endemic area in order to discover a possible mineral xenobiotic (36). *Marković* (37) compared the guinea pig kidney lesions previously treated with silicates with morphological findings in BEN. *Macanović* (38) informed about possible immunological aspects of BEN, when the process takes place in the kidney interstitium.

A guinea pig animal model (39) has been registered for the study of human kidney disease, where an immunologically induced basal membrane disorder is the underlying aetiology. We advocate the use of this animal model in further research, rather than of rat models because rats are prone to develop degenerative kidney lesions as a spontaneous age-related disease (40), which is easily confused with the effects of some xenobiotic tested. A number of papers refer to different experimental animal species as a model to study specific problems concerning BEN (41–43). The other aspects of investigation imply the use of animals living in the proximity of inhabitants in the BEN region. No less attention should be paid to the species living free in the area. Such field studies being rather scarce more efforts should be concentrated in that direction.

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Sažetak

ISTRAŽIVANJA NA ŽIVOTINJAMA U VEZI S BALKANSKOM ENDEMSKOM NEFROPATIJOM

Obavljena su osnovna terenska ispitivanja životinjskih populacija u okolici Slavonskog Broda, u kojoj je balkanska endemska nefropatija endemska bolest, i ispitane su patološke promjene na različitim životinjskim vrstama. Populacija svinja u promatranom području vrlo je brojna, a zbog svoje morfološke i fiziološke sličnosti čovjeku svinja je odličan model za bolesti ljudi. Treba poticati studije na svinjama, osobito zbog mogućnosti da su svinje i ljudi izloženi intoksikaciji istim ksenobiotikom prirodnog podrijetla. U suglasju s mikotoksičnom teorijom o etiologiji balkanske endemske nefropatije, svinjsko meso moglo bi biti opasno za čovjeka. Pokusi na životinjama pružaju odličnu mogućnost promatranja različitih vidova patogeneze i patomorfoloških promjena u svim stadijima razvoja, koji tako mogu biti uspoređivani s balkanskom endemskom nefropatijom. Ipak, eksperimentalne vrste moraju biti kritički izabrane, jer neke spontane lezije bubrega specifične za pojedine vrste mogu biti protumačene kao one izazvane eksperimentalno.

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Ključne riječi: endemska bolest, ruralno područje, terenska ispitivanja, životinjska populacija.