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CHAPTER 6

The Geography of Disease (Nosogeography)

Throughout the many centuries of human history, people have died most often of hunger, war, and (especially) infection. Culminating in dirty and densely populated cities, conditions for spreading of infections were created with the formation of settlements. Change can be brought about through improvement of living conditions, especially by ensuring a supply of bacteriologically sound drinking water and by introducing safe ways of waste disposal. Even greater influence on decline of mortality from previously fatal infections was erted by great medical discoveries made for the most part in the first half of the last century, above all by the devising and widespread application of vaccines and serums, insecticides, and (particularly) antibiotics.

Changes in the structure of illness and mortality of the population and prolongation of life expectancy in the last decades have put non - infectious somatic ailments in the group of leading diseases. Scientific forecasting on questions of health protection has now become impossible without detailed research on diseases of the heart and blood vessels (infarct, etc.), malignant tumors, and cerebrovascular diseases (stroke, etc.)[88]. Such research provides new data on the etiology and pathogenesis of these diseases and can open up new possibilities in developing programs of prevention and organized treatment of diseases that take into account the geographical and geological characteristics of their distribution.

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[88] In Serbia (as in the Western world), the main causes of death are as follows: cardiovascular diseases (infarct, etc.), 40%; malignant tumors, 15-20%; cerebrovascular diseases (stroke, etc.), 15%; inadequately defined symptoms and states, 7-8%; chronic lung diseases, 5%; and injuries and poisonings, 5%. It follows that more than half of all deaths by illness result from diseases of the blood vessels, especially those of the heart and brain (Z. Radovanovic et al., 1995).

There can be no doubt as to the need for application of medico - geographical methods in the field of *non - infective epidemiology*, whose theoretical foundations are unquestionably weaker than in the case of classical *infective epidemiology*. A complex approach to research is obligatory, inasmuch as the relationship between man and the environment is very complex and environmental influence on human health and life expectancy is extremely diverse. It thus becomes imperative for investigators to elaborate the geological and geographical foundations of a territory of interest to them. In other words, they need to evaluate the chemical composition of rocks, soil, and water in it; ascertain the level of radiation; determine the nature of climatic and meteorological factors; establish characteristics of food and the manner of food preparation; evaluate social and hygienic conditions; determine the presence of anthropogenic pollutants; etc. Of great importance here are information on cases of disease, demographic data on the population, and data on the economic state of the territory.

A more comprehensive treatment of the geography of disease is given by Keller, Shchepin, and Chaklin (1993). We shall dwell briefly on the most widespread diseases of the present day: diseases of the heart and blood vessels, malignant tumors, infectious and parasitic diseases, and some diseases whose causes most likely originate in the geological environment.

NON - INFECTIOUS SOMATIC DISEASES

Diseases of the Heart and Blood Vessels

Among diseases of the heart and blood vessels, the most important are heart disease (affecting blood vessels of the cardiac muscles) and cerebrovascular disturbances, i.e., damage to blood vessels of the brain, which most often are a consequence of hypertension (high blood pressure) as the third - ranked pathological state in this group of diseases. Also of great epidemiological significance are rheumatic disease of the heart valves, congenital heart defects, and cardiomyopathy (diseases of the cardiac muscle itself).

Diseases of the heart and blood vessels are considered to be the tax (albeit not unavoidable) man pays for development of his civilization. Taken together, those diseases in many countries are the cause of every other death that occurs. However, considerable differences exist within the group of diseases as a whole. There are many more cases of cardiomyopathy in developing countries, whereas coronary and hypertensive heart diseases - together with cerebrovascular disturbances (stroke above all) - are dominant in developed countries.

The leading risk factors include the following: 1) ingestion of cholesterol and other animal fats as the cause of *atherosclerosis* (accumulation of fatty substances on the walls of arteries) in conjunction with factors that accelerate the process itself (smoking, high blood pressure, exposure to psychic stress); 2) high consumption of kitchen salt, obesity, and hereditary factors as causes of *high blood pressure* (hypertension); and 3) increased consumption of sugar and fats as the cause of the sudden expansion of *diabetes* and *obesity*, which are very important risk factors where cardiovascular diseases are concerned. The relationship between the incidence of cardiovascular diseases and hardness of water represents one of the most intriguing, but still undefined, aspects of the problem (Bernardi et al., 1995).

In study of the geography of heart and blood vessel diseases, a number of important data have been obtained indicating the significance of diet along with climatic and meteorological factors in the occurrence primarily of infarct, atherosclerosis, and ischemic heart diseases. For example, mortality from myocardial infarct is highest in regions where saturated fats and refined sugars are heavily present in the food and where the drinking water contains little calcium and magnesium; in temperate and high latitudes, deaths caused by coronary diseases occur most frequently during the cold season of the year; a sudden drop of atmospheric pressure can lead to cardiac disasters; and so on. Held in especially high esteem are the studies of A. Keys (1957, 1963) on the link between development of the process of atherosclerosis and excessive consumption of animal fat in different countries of the world: these studies enabled the author to establish that a correlation exists between the two values. An international project whose work was published under the title "**The Geographic Pathology of Atherosclerosis**" (1968) dealt with atherosclerosis, one of the mass diseases of mankind. Stressed among other things was the dependence of atherosclerosis on the total number of calories in food (which is linked with fat intake) and the level of cholesterol in the blood serum. According to the authors of the project, geographic differences (in occurrence of atherosclerosis) are more significant than differences of race and sex.

Geographic characteristics of the distribution of heart and blood vessel diseases are discussed in greater detail in the book of Keller, Shchepin, and Chaklin (1993).

Malignant Tumors

Perhaps the first observation of a professional carcinogen was that made by P. Pott, who already in 1775 described the susceptibility of chimney sweeps to tumors of the scrotum. The beginning of the epidemiological way of thinking about malignant tumors (cancer) dates from a much later time with the work of R. Stern, who at the outset of 1842 gathered statistical data on mortality from cancer in the city of Verona. The geographic distribution of cancer was a subject that attracted increasing attention in the second half of the 19th Century and in 1915 Hoffman wrote a book on the rates of mortality and geographic pathology of cancer throughout the world. This was followed by a large number of urban investigations.

In the last half century, there have been many studies in the world devoted to the geography of malignant tumors. Registration of patients in many countries has made it possible to achieve a more comprehensive approach in studying these serious diseases and mortality caused by them. This has resulted in the discovery of local (regional) characteristics of their distribution.

The latest research indicates that cancer is (after cardiovascular diseases) the greatest killer in many industrially developed countries, and that it originates for the most part from environmental causes. Investigations for now are based on the hypothesis that the environment can be assumed to affect the incidence of cancer until it is proven otherwise. This means that geochemistry plays an important role in the etiology of this disease (Dissanayake and Changrajith, 1999). A good example is contamination of drinking water with nitrogenous substances (human and animal waste, nitrogen - containing fertilizers, etc.) in developing countries, where diseases caused by excessive nitrate content (cancer of the stomach and esophagus, metahemoglobinemia) are prevalent. Since penetration of the food chain by these chemical ingredients is for the most part a geochemical process, *medical geochemistry of cancer* has developed into a special area of research (Dissanayake and Werasooriya, 1987).

About five million people in the world die every year of malignant tumors, which means that approximately every tenth person to die was a victim of cancer. The number of new cases is almost twice as great, even not counting very early forms of certain tumors and slowly developing types of malignant tumors of the skin. More than half of all malignant tumors occur in developed countries, despite the fact that not even a third of the world's population lives in them (Z. Radovanovic et al., 1995). This can be attributed in part to the considerably longer life expectancy of the population of more developed countries, due to which more favorable conditions exist for tumors to act on the organism (to develop in them), and in part to other factors (chemical, radioactive, and other pollutants of air, soil, water, and food; viruses; smoking).

As for the location of malignant processes, the stomach is most often affected (close to 700 thousand new patients throughout the world annually), followed by the lungs (600 thousand), breasts (550 thousand), large intestine (more than 500 thousand), cervix (460 thousand), etc. Malignant tumors of the lungs and stomach are most frequent in men, while breast and cervical cancers are most common in women. Of the many possible factors leading to the occurrence of malignant tumors, diet and tobacco smoking are held to be responsible in the greatest number of cases (35 and 30%, respectively).

Characteristic of most of the 20th Century, the trend toward increased mortality from malignant tumors is especially noticeable in more highly developed countries. These diseases rank second among all illnesses of the present day in the majority of civilized countries: the USA, Canada, the greater part of Europe, Australia, and New Zealand.

A significant difference is present in the distribution of various kinds of malignant tumors in different countries. The greatest affliction among males is recorded in Uruguay, Scotland, and Belgium, while the greatest affliction among females occurs in Uruguay, Denmark, and Hungary. Appreciable differences are also evident in the frequency of distribution of individual forms of these diseases by regions. Thus, the frequency of incidence of liver cancer varies a thousandfold, being highest in blacks of the Bantu tribe in South Africa and lowest in the inhabitants of many regions of Canada, the USA, the Scandinavian countries, and the European part of Russia. The indices for cancer of the esophagus are also quite variable, the highest values being recorded in several countries of southeastern Africa, the lowest ones in Holland, Canada, and countries bordering the Baltic Sea. Hundredfold differences are recorded in the indices for cancer of the sexual organs: the highest values here are recorded in South China, Vietnam, Jamaica, and Uganda, the lowest ones in Israel and several Arab countries (Keller, Shchepin, and Chaklin, 1993).

There are many examples of direct or indirect correlation between the frequency of occurrence of cancer in different parts of the body and environmental conditions (Keller, Shchepin, and Chaklin, 1993). Intensive onco - geographic research is being conducted in the world due to the linkage of groups of malignant tumors with natural geographic and socio - economic factors. Thus, numerous maps of the distribution of different forms of cancer by regions were drawn up in the former Soviet Union, and attempts at onco - geographic regionalization were given in the **"Atlas of Cancer Mortality in Districts of the USA: 1950 - 1969" and the "Atlas of Mortality from Malignant Tumors in Cities and Districts of Japan: 1969 - 1971." The "Atlas of Cancer Mortality in China"** (1981) contains *basic maps* (with data on mortality by districts and by provinces in the case of rarer forms of the disease for the period of 1973 - 1975) and *auxiliary maps* (with data on administrative divisions, population density, climate, soil, etc.). The purpose of the authors was to isolate regions with increased risk of contracting cancer.

Study of the geographical and geological preconditions for occurrence of human diseases as an attribute of territorial comples can be widely used in onco - geographic research. However, a great deal of multi - disciplinary research is still needed in order to solve the *enigma of cancer*, one of the greatest of modern - day riddles. For example, medical geography has not been able to answer why lung cancer ranks first among all forms of cancer in England; stomach cancer in Japan, Russia, and Iceland; cancer of the oral cavity in India; skin cancer in Australia; cancer of the esophagus and liver in certain regions of Africa; and cancer of the urinary bladder in Egypt. *We probably need to learn more about certain natural (geological) and anthropogenic factors as causes of the disease. Perhaps a significant advance could be made using methods of medico - geological (geochemical, eco - geological) research.*

Infectious and Parasitic Diseases

The great *plague of Justinian*, which began in the East in 532 A.D., moved around the Mediterranean over the course of four long periods, each of them lasting 15 years. When the epidemic finally passed, previously inhabited countries resembled a desert. Mortality from the *Black Death* - as plague was often called on account of its severity and fatal outcome in many cases (in which the lungs were frequently attacked and the lips turned blue due to impaired breathing and facial cyanosis) - was extremely high. It is estimated that as much as a fourth of the population of Europe sometimes perished in the waves of greatest expansion of the disease (J. R. Paul, 1966). It was generally agreed that plague originated in the Far East (in China), but nobody had any idea as to the cause or nature of the disease, which attacked rich and poor alike.

For all that, *cholera* is believed to have caused the greatest number of deaths of all infectious diseases. India was long the homeland of this dangerous disease, and its spreading to other countries probably became more frequent after an East Indian firm started trading with Great Britain. Cholera epidemics and pandemics were discussed earlier in the text.

It is difficult to estimate the toll taken by infectious diseases - whether epidemic or endemic - among non - immune or semi - immune populations in the course of the past six or seven centuries. *Smallpox, measles, scarlet fever*, and *diphtheria* are only some of the diseases that are known to have existed. With introduction of the smallpox or measles virus among the non - immune population of North American Indians, some tribes were virtually wiped out. Two other terrible curses of colonial America were diphtheria and yellow fever, which raged through its colonies in great waves.

For centuries epidemiologists and other investigators tried to find the cause and attempted to classify various infectious diseases. Two significant discoveries were as follows: 1) that the local diet affects the incidence of pellagra; and 2) that infectious diseases can be spread by polluted drinking water. However, the turning point occurred in the era of Pasteur (from 1860 to 1890), when the *germ theory of infectious diseases* was formulated. The whole concept of the causes of infection then underwent a radical change, with stress being placed on microbes and bacteria, and Pasteur and Koch soon thereafter developed methods of coping with these agents (J.R. Paul, 1966).

During the first 50 years of the *bacteriological era*, a great deal of emphasis was placed on the role of parasites as causes of disease, while much less attention was paid to human resistance and the role of the environment in transmission or retention of infectious diseases.

Together with the development of epidemiology, opinions changed both as to the essence of the infectious diseases and the role of geographical and geological factors in formation of the epidemic process. However, those factors never disappeared from the field of vision of doctors engaged in research on causes of the spreading of epidemics. As I.A. Okhotin stated in 1889: "*In order to exist, every form of microorganism requires certain climatic, soil, meteorological, and other conditions, in short has its own geography.*" Today no textbook, manual, or monograph on the special epidemiology of any infectious disease fails to characterize the geographic distribution of that disease, and geographic maps and atlases devoted to the geography of infectious diseases have been published.

The main goal of *epidemiological geography* is to discover objective laws governing the spatial distribution of infectious diseases[89]. At the current stage of development of that discipline, several basic laws can be singled out according to Keller, Shchepin, and Chaklin (1993):

1. *Dispersion and concentration of epidemiological occurrences in space.* This regularity arises from two mutually opposed tendencies in the development of epidemics of infectious diseases: a) the widest possible dissemination among people; and b) adaptation of special nosological forms to certain territories;
2. *Spatial unevenness in the development of epidemiological processes.* This is obvious if we look at a map of the range of any infection (Fig. 6.1.) and is a consequence of many things, above all different biological and socio - economic factors. As an example of the influence of customs of the population, we cite the disease kuru (fatal encephalopathy caused by a slow virus), whose only endemic focus in the world (in Papua New Guinea) owes its existence to the custom of ritual cannibalism, which was until recently practiced by members of one of the local tribes (Fore);
3. *Suitability of the complex of geographical conditions for elements of the epidemiological process.* To be specific, it is known that the existence of a

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[89] Proceeding from the premise that medicine is the basic subject and geography an auxiliary concern, A.P. Avtsin (1972) concluded that **geographic epidemiology** is a more correct name.

natural focus of disease is dictated by a certain climate, soil, vegetation, and fauna, and that destruction of the focus occurs when some member crucial to biocenotic interrelations drops out of the picture. In keeping with this regularity, the probability of spreading of malaria in France by agents imported from the tropics is exceptionally low on account of their non - adaptation to local carriers. Also, *Anopheles hyrcanus sinensis* is a carrier of malaria in China, on the Malay Peninsula, and in Eastern India, but does not transmit the disease to other parts of India; and

4. *Zonality and azonality of prerequisites and manifestations of the epidemiological process.* As a law, this is expressed fairly clearly. For example, as we approach the tropics, increases are observed in the number of parasitic, communicable, and infectious diseases; the degree of epidemiological tension; and the index of linkage between foci.

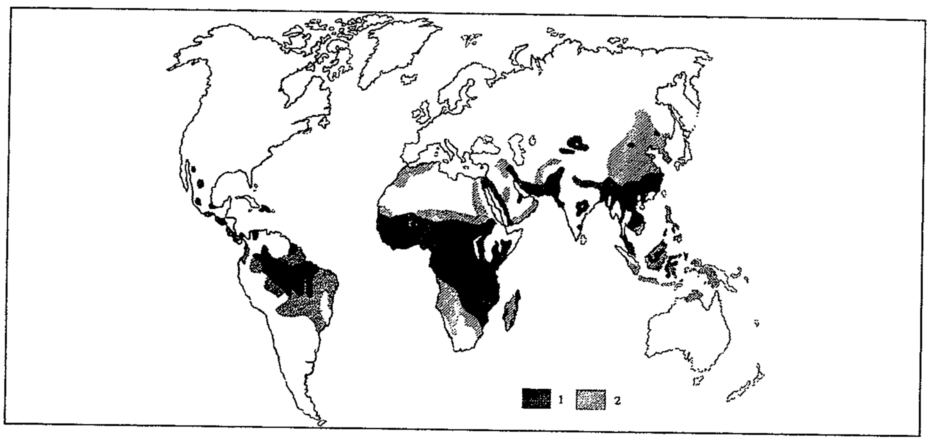

Fig. 6.1. Risks of malaria epidemics. 1 - high and average; 2 - low.

All of these laws influence formation of the epidemiological status of different territories, which determines the world's epidemiological geography (global epidemiology). By the term *epidemiological status,* we mean the sum total of typical (relatively constant) epidemiological occurrences that characterize a concrete territory.

RARE AND STRICTLY LOCALIZED DISEASES

In the history of culture and natural sciences, interest in *strictly localized diseases* remained for a long time in the shadow of *rare diseases* in the wider sense. Increased attention was devoted to those rare diseases that led to a noticeable change in the external appearance of people, to significant deviations in their behavior, and sometimes to completely inexplicable death. Until the advent of the first indications of *scientific teratology*, giants and dwarfs, immensely fat people, and bearded ladies were important attractions for the curious at fairs and carnivals. These unusual examples were generally imported from some distant land where such persons are completely ordinary or constitute a majority of the population there. The history of anthropology and travel contains familiar information about the "long - legged" tall Patagonians, who were exterminated by the colonizers of Argentina; and about the pygmies of Central Africa, who have survived to the present day.

Among the many *rare diseases* with their unusual complications, special attention of investigators has been attracted by illnesses that with greater or lesser justification are classified as *strictly localized* or endemic diseases. The causes of such endemism are sometimes clearly linked with a certain factor of the geographical or geological environment[90].

For specialists in the area of geographic pathology and especially medical geology, so - called *rare* and *strictly localized diseases* are particularly important because there is the real hope of linking their incidence or characteristics with some factor of the geographic or geological environment in the broader sense. This hope is known to have been justified in study of many *biogeochemical endemias*, natural infectious and parasitic diseases of the focal type, as well as certain pathological reactions associated with residence in extreme zones. For support of these notions, we could perhaps dwell on such well studied diseases as endemic goiter or yellow fever, which in no case can be counted among rare diseases.

Our attention will be focused on several *strictly localized diseases*, which are closely linked with the natural environment in which they are systematically registered (Fig. 6.2.). The still puzzling *Balkan endemic nephropathy* is without doubt one of them.

Examples of Rare and Strictly Localized (Endemic) Diseases

Kashin - Beck Disease. This disease was described in 1895 by N. I. Kashin and in 1906 by E. V. Beck, who called it *Osteoarthritis deformans endemica*[91]. Encountered in the Chita and Amur Provinces of the former Soviet Union, it occurs in strictly limited focal areas. Its main symptoms affect the system of the bones and joints, predominantly among younger persons. With the passage of years, sharply expressed deformation of the entire skeleton and especially the joints occurs in natives of the region. The first studies of this disease already indicated that it is endemic. Several hypotheses were suggested to explain its etiology. Among other explanations were the following: a) that the disease is caused by chronic poisoning of the population by spores of the toxin - bearing fungus *Fusarium sporothrycoides*;

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[90] Our discussion of strictly localized diseases is given for the most part according to the book "**Introduction to Geographic Pathology**" by A.P. Avtsin (1972), with the reservation that we divide the examined factors into geographical and geological categories.

[91] *Hondroosteoarthritis deformans endemica* according to L.F. Kravchenko (1965).

and b) that it is an endemia of biogeochemical origin resulting from deficits of calcium, potassium, and sodium in soil and water in the presence of excessive amounts of strontium and barium.

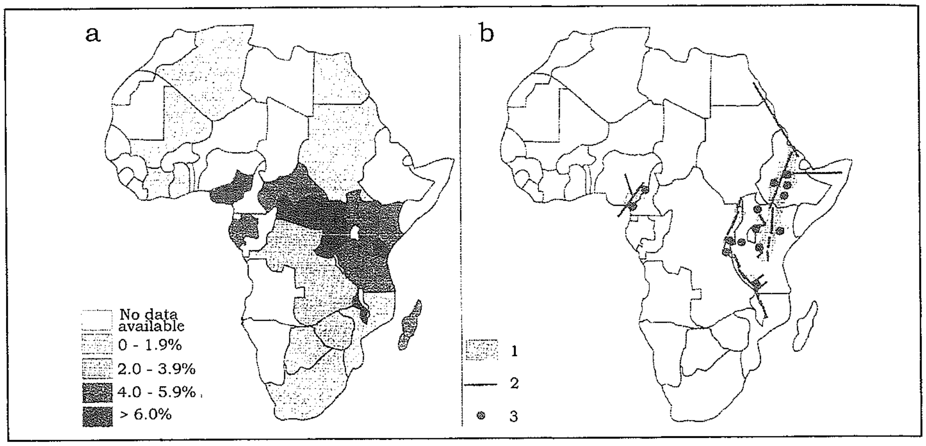

Fig. 6.2. The geographic distribution of Kaposi's sarcoma (**a**) and basalt (**b**) in Africa. 1 - Ultrabasic basalts; 2 - Rift systems; 3 - Area of podoconiosis.

According to Avtsin (1972), it is highly probable that Kashin - Beck disease is a biogeochemical endemia[92]. A disbalance of calcium, strontium, and barium is a very important feature of it. Climatic conditions also play a significant part in occurrence and especially manifestations of the disease.

Kuru sickness. This endemic disease of unclear nature was discovered in high - mountain regions of the eastern half of New Guinea (Papua). It was entirely clear that kuru sickness is disseminated among members of the Fore linguistic group of one of the Melanesian tribes. The sickness affected women primarily, as well as children of both ses, and it invariably culminated in death. The population suffering from this disease lived in forested regions at elevations of from 1500 to 2,000 m. Starting from 1960, the level of mortality in the given zone has declined, with no increase in territory on which the disease is present. Since that time, the whole tribe has in effect been in quarantine.

Kuru is manifested essentially as a wider ailment of the central nervous system, a serious disease with fatal consequences. The cause of this puzzling disease has been the subject of many investigations. Avtsin believes that it cannot be explained in purely geographic terms. The only known environmental factor is the high - mountain relief of the terrain where the disease is prevalent, which obviously promoted natural isolation of part of the Melanesian tribe in question.

[92] The disease was also discovered in the remains of inhabitants buried thousands of years ago, which indicates that similar biogeochemical conditions in which the disease occurred existed in ancient times.

Avtsin therefore concludes that large allowance must also be made for the influence of some other factors of a non - geographic nature.

New facts have been obtained using various research techniques, namely pathohistological, ecological, and experimental - virological methods. It is now clear that important facts of an ecological nature must unquestionably be taken into account in studying the epidemiology of kuru. Most important among them is the practice of ritual cannibalism, in which mainly women and children take part. In addition to other organs, it was the custom to eat the brain of the deceased. *Culinary treatment* of tissues of the deceased was extremely primitive, so that in the opinion of R. Glasse (1967) it was possible for the disease agent to be transmitted in appreciable quantities.

An interesting idea was put forward in 1966 by J. Hotchin. According to this idea, the kuru virus can be transmitted to man through domestic pigs and their parasites. The author did not exclude the possibility that the indicated virus was imported into this high - mountain region, where it encountered a genetically sensitive population and the favorable absence of hygienic conditions.

Vilyui encephalitis. The range of greatest distribution of this disease is confined to riverside localities and embraces a limited area where the Vilyui River empties into the Lena, a region characterized by very low winter temperatures. Here it predominately affects the residents of rural settlements formed on low - lying swampy terrains. The population of this region is mainly engaged in the raising of livestock. Mice and other rodents are very numerous in endemic localities. The disease is registered every year and is therefore of an endemic nature.

Inasmuch as Vilyui encephalitis mainly attacks the working population, it was logical to seek the source of infection in those forms of nature with which the inhabitants come into contact in various ways. The epidemiological significance of the hay gathering period and muskrat trapping season was stressed by A. N. Shapoval (1959).

In 1954 studies were initiated in which attempts were made to isolate the possible agent of the disease. Experiments were carried out by E.S. Sarmanova on white mice. Since that time, it has been assumed that Vilyui encephalitis is an independent viral disease, one that can only be understood by clarifying pathways of transmission of the virus to man and investigating its reservoir in nature. The question of the etiology and epidemiology of this disease remains a subject of discussion.

Buruli pustules. This disease is predominantly distributed on the banks of the Nile in Northern Uganda and on the shores of a number of lakes and rivers (including the Nile and Lake Victoria) in Central Uganda. The disease takes its name from one of the settlements where it has occurred most frequently. Special interest in this disease was shown by G. T. O'Conor and F. Lunn (1966).

The pustules appear primarily on the limbs and very often in the vicinity of joints. Extensive and deep pus fields embracing the muscles are formed in the course of further development of the disease. In some cases, the process of supporation extends even to the bones. MacCallum encountered such a disease in Australia and called it a *mycobacterial infection of man.* Two years later, Belgian investigators in the Congo rediscovered the disease agent and gave it the name

Mycobacterium ulcerans. O'Conor and Lunn indicated the possibility of infection by polluted water and stressed that increase of the disease is dependent on a high water level in rivers and lakes of Central Africa[93].

Biogeochemical Endemias (Microelementoses) of Man

We have already discussed the role of chemical elements in the vital activity and pathology of plants, animals, and man. Characteristics of some biogeochemical provinces or major biogeochemical endemias (microelementoses) of man will now be considered[94]. Here we draw on the book of Keller, Shchepin, and Chaklin among other sources.

Many large regions throughout the globe are known today where the soil and water are characterized by significant deficits of certain microelements or by their increased concentrations, circumstances that have an unfavorable effect on the health of living beings and which lead to the appearance of endemic diseases. It goes without saying that the manifestations of human pathology linked with microelements are themselves also extremely varied. This has served as the basis for isolation of a "*new class of diseases, viz., microelementoses, i.e., diseases in whose etiology the main role is played by a deficiency or excess of microelements in the human organism or their disbalance in the sense of anomalous ratios of micro - and macroelements*" (A. P. Avtsin, A. A. Zhavoronkov, and L. S. Strochkova, 1983).

The term *microelementosis* was introduced in the literature relatively recently, although many diseases and pathological states of the given nature were known previously. Deliberations about the role of deficits or excesses of certain metals and non - metals in the human organism were stimulated by the study of vitamins, as a result of which avitaminoses and hypovitaminoses became classical examples of deficit - induced diseases. It can be said with complete justification that they have now been joined by hypomicroelementoses.

Because they have a pronounced natural or anthropogenically dictated localization, many microelementoses are of great interest from the standpoint of both medical geography and medical geology. As we shall see, they are primarily dependent on geological factors (geochemical factors, to be more precise).

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[93] It is interesting to note that in all four examples of rare and strictly localized diseases given in Avtsin's book, no mention is made of a possible geological factor in explaining any of them. Among other omissions, nothing is said about the geological (geochemical) composition of the studied region.

[94] With elevated content of Pb, As, F, Hg, Cd, Mn, Ni, and other elements, significant areas are occupied today by technogenic biogeochemical provinces formed around industrial concerns and urban settlements.

According to the classification of Keller et al. (1993), the microelementoses of man belong to four basic groups:

I. *Natural endogenous ones,* congenital (1) and hereditary (2);
II. *Natural exogenous ones,* caused by a deficit (1), excess (2), or disbalance (3) of microelements;
III. *Technogenic ones,* of the industrial - professional (1), neighborhood (2), and transgressive (3) types; and
IV. *Medico - elementoses* (microelementoses associated with intensive therapy).

Natural Endogenous Microelementoses

A microelementosis of the mother is usually responsible for *congential microelementoses,* accompanied by defects in development. The case of zinc deficit can serve as an example of such pathology: when a zinc deficit is present during pregnancy, congenital anomalies are observed in a significant percentage of the progeny. Together with zinc, deficiencies of copper, manganese, iron, iodine, and selenium can also be accompanied by certain anomalies.

Zones of distribution of goiter and cretinism represent the best - studied examples of the influence erted by anomalous biogeochemical situations on the fetus. Large regions in the Himalayas, Southeast Asia, Central Africa, the Andes, Oceania, and the Alps are such zones. Endemic cretinism has practically disappeared in Europe, together with improvement of socio - economic conditions. In many other regions, conditions for the appearance of endemic cretinism - manifested in mental retardation, deaf muteness, blindness, cross - eye, and growth lag - are created where pregnancy occurs in the presence of an iodine deficit.

In contrast to congenital microelementoses, in *hereditary microelementoses* the deficiency, excess, or disbalance of microelements is caused by damage to the genetic apparatus on the chromosome or gene level. *Wilson - Konovalov disease* can serve as an example. In this disease, profound disturbances are recorded in the metabolism of copper and copper - containing proteins in the organism.

Natural Exogenous Microelementoses

Deficits of elements registered in humans and animals can serve as examples of exogenous microelementoses. They include iodine deficits, selenium deficits, iron deficits, and zinc deficits.

Iodine deficit. Endemic goiter occurs not only in mountainous regions, but also on plains in tropical zones of South Asia, Africa, and South America, as well as in the valleys of the great rivers of Siberia and other parts of the globe (Fig. 2.39.). The wide dissemination of this endemia is determined not only by iodine deficit, but also by disbalance of other elements (Mn, Co, Cu, etc.). According to data of the World Health Organization, 200 to 400 million peoples suffer from endemic goiter throughout the world.

Selenium deficit. The problem of the selenium - deficit state in man began to receive attention following publication of a paper on *Keshan disease* in 1979. It was established that Keshan disease (endemic cardiomyopathy) occurs in a wide zone across Chinese territory from the northeastern to southwestern border. Low content of selenium in rocks, soil, and groundwater is recorded in the indicated zone. Administration of selenium to children with their daily meals significantly reduced occurrence of the disease.

The problem of carcinogenesis is another important aspect of the selenium - deficit state. Epidemiological investigations have demonstrated the existence of a pronounced negative correlation between consumption of selenium with food and mortality from cancer of the large and small intestines, mammary gland cancer, cancer of the esophagus, and lung cancer (Schrauzer et al., 1977).

Iron deficit. The iron - deficit state represents the most widespread microelementosis of mankind. The frequency of this microelementosis varies from 20 to 95% in different populations. In India and Central Africa, more than 50% of the population suffers from anemia. Very high indices of iron deficit in the population are registered among inhabitants of the Philippines, Pakistan, and Turkey. Iron - deficit anemias are especially pronounced in regions with extreme living conditions, such as high mountains and the Far North, where *acclimatization iron deficit* occurs.

Zink deficit. The zinc - deficit state was first registered in Iran (A. Prasad et al., 1961), where it occurred in young males in the form of a complex of symptoms: retardation of growth and sexual maturation, testicular atrophy, and other accompanying manifestations. An analogous complex of symptoms was discovered somewhat later in settlements near Cairo in Egypt. In both cases, the diet of patients was characterized by deficiency of animal proteins.

Endemic fluorosis represents a classical example of diseases and syndromes caused by an *excess of certain microelements in the biosphere.* It occurs when too much fluorine enters the organism. We have already discussed this question this and now only mention the fact that foci of endemic fluorosis are found on all continents (Fig. 2.6.). The problem of fluorine excess is of national significance in India, where a so - called *fluorosis belt* exists. The southern part of what was formerly the Soviet Union is characterized by fluorine - rich groundwater, whereas much of the northern part, Siberia, and the Far East represent a gigantic biogeochemical zone of hypofluorosis.

Endemic arsenosis is a disease caused by excessive entry of inorganic forms of arsenic into the organism with water and food. The best - known endemic provinces and foci are in Argentina, China, the USA, Mexico, and Japan. Arsenic - induced skin cancer does not differ histologically from other forms of the disease.

The already mentioned *Kashin - Beck disease* can serve as a typical example of a biogeochemical endemia linked with a disbalance of micro - and macroelements. The etiology of this disease has not yet been established, but great significance is assigned to high content of strontium, copper, molybdenum, and phosphorus in the biosphere, and low concentrations of calcium (disbalance of calcium, strontium, and barium according to Avtsin, 1972).

Technogenic (Anthropogenic) Microelementoses

Professional microelementoses are caused by an excess of certain microelements and their compounds in the zone of production itself. They have been known for a long time to professional pathologists and have been studied fairly thoroughly.

Neighborhood microelementoses (endemias) are diseases and syndromes that develop as a result of environmental pollution in the neighborhood of industrial concerns. Familiar throughout the world, the already discussed Mina Mata disease (mercuriosis) and Itai - Itai sickness (cadmiosis) can serve as examples.

Transgressive technogenic diseases of a chemical nature are linked with the transport of chemical pollutants over great distances as a result of atmospheric processes or water circulation (A. P. Avtsin, 1983). *Acid rain* is a classical example of transgressive occurrences in the biosphere.

It must be kept in mind that the pathology of technogenic pollution with microelements is characterized not so much by sharply expressed severe diseases as by latent forms that often show minimal symptoms. This is the case, for example, with microsaturnism (poisoning by low doses of lead of from 0.6 to 0.07 mg/day, the norm being 0.3 mg/day).

Medico - elementoses

These diseases are encountered practically everywhere in the world, especially in countries with a high level of medical protection. The given paradox is attributable to the fact that modern methods of treatment are becoming increasingly invasive, while the assortment of medicines has grown precipitously. Some medicines can be contaminated by certain microelements, admixtures of aluminum for instance. A survey of this type of microelementoses is given in the book "**Microelementoses of Man**" (A. P. Avtsin et al., 1991).

Urolithiasis

One of the oldest diseases of mankind, *urolithiasis* in its nature represents a broad group of various diseases and syndromes accompanied by formation of stones. Urolithiasis is characterized by very wide distribution throughout the world and is endemic in some regions. In spite of significant research on many questions, this still remains an inadequately studied area of theoretical medicine because the tasks themselves have turned out to be considerably more complex than appeared at first glance. Inclarities are especially present in study of this group of diseases from the standpoint of geographic pathology. *It is logical to hope that medical geology will throw additional light on the nature of most rare and strictly localized diseases, since the basis of their occurrence* (the geological environment with its factors) has not been clearly established. For example, there have been no precise statistical analyses revealing correlations between occurrences of urolithiasis on the one hand and chemical components of drinking water and food from soils of various compositions on the other, and no correlation has been found with the geological (mineral) composition of terrains in general[95].

Zones with greatly increased frequency of stones in the urinary ducts have been discovered in Syria, the southern provinces of China, India, lands bordering the Mediterranean and Caspian Seas, the Volga basin, Sweden, Northern Australia, parts of Madagascar, the southern states of America (especially Florida), the eastern part of Mexico, and Argentina. However, beyond the establishment of clear foci of urolithiasis, not enough progress has been made in clarifying the cause of this medical phenomenon, although many hypotheses have been put forward to explain it. There is a relatively voluminous literature on this question. We shall dwell only on certain points of interest to us.

Earlier authors classified stones in the urinary ducts on the basis of the presumed leading role of anions in stone formation and singled out oxalate, phosphate, carbonate, and urate stones. It was later clarified that cations, especially calcium cations, are responsible in the majority of cases of inorganic stones. In his tabular presentation of diseases that develop with formation of stones in the urinary ducts, Avtsin (1972) indicated that the created stone is often composed of calcium phosphates. It is evident from our examination that the occurrence of urolithiasis is linked to a significant extent with regions having the limestone composition typical of the calcium - bicarbonate type of groundwater (the Mediterranean region or southern provinces of China, for instance). Here it should be kept in mind that magnesium content can be appreciable on such terrains, a circumstance that is reflected in perceptible reduction of calculus formation (E. Trimmer, 1987).

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[95] Avtsin rightly concludes that study of the geography of urolithiasis solely from the statistical data of urologists must be considered unpromising due to the complexity of the problems involved. It would be far more correct to organize multi-disciplinary expeditions in already registered endemic foci. This would make it possible to study prelithiasis more closely and clarify the factors that cause it. In this sense, experiments with animals are justified. For example, it would be interesting to test the potential lithogenicity of hard water.

Endemic silicon urolithiasis was singled out by V. V. Koval'skii and V. L. Suslikov (1980). According to these authors, the indicated disease is a consequence of human non - adaptation in special biogeochemical provinces to increased intake of silicon into the organism in combination with high content of fluorine, calcium, manganese, nitrates, sulfides, and chlorides in the biosphere. If this view is confirmed, then silicon urolithiasis can join the list of polymicroelementoses. Figure 6.3. presents the distribution of siliceous rocks and endemic urolithiasis on territory of the former Soviet Union. Characterized by decline of phosphorus reabsorption in the kidneys, disturbances of phosphoro - calcium metabolism are recorded in silicon biogeochemical provinces here.

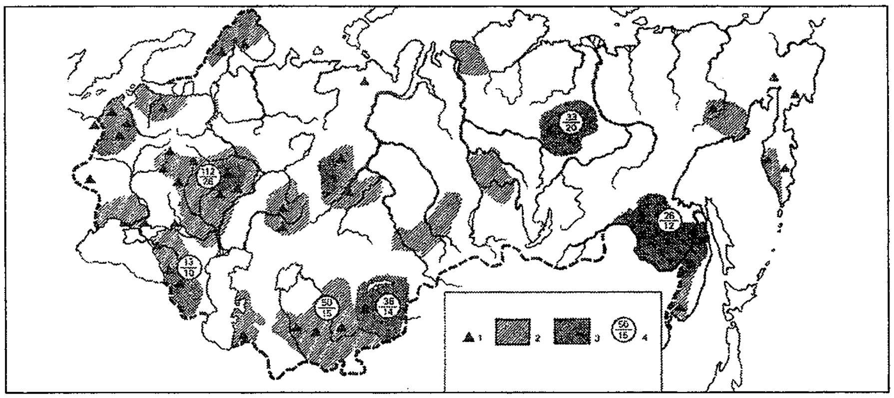

Fig. 6.3. Space distribution of silica rocks and endemic urolithiasis in the territory of former USSR. 1 - exploitated silica deposits; 2 - territories with endemic urolithiasis; 3 - specifically endemic urolithiasis; 4 - marker of public illness.

Questions Connected with the Etiology of Endemic Nephropathy

Up until 1957, nothing was known about Balkan endemic nephropathy as a special kind of chronic nephropathy. The disease was then described for the first time on the basis of medical examinations of inhabitants of the village of Sopic near the Serbian town of Lazarevac (V. Danilovic et al., 1957). By examining church records, Danilovic was able to verify that endemic nephropathy first appeared in this region around 1922[96].

According to S. Strahinjic (1985), endemic nephropathy represents a chronic slowly progressive disease that occurs in endemic foci and endemic regions and has a family - linked nature, unknown etiology, and

[96] In the last two decades, the qualifier Balkan has been used for the nephropathy described in that part of the world to distinguish it from other nephropathies described at the same time in Nigeria, Japan, and elsewhere.

inadequately clarified pathogenesis. It is accompanied by progressive and gradual degradation of the mass of functional nephrons, together with reduction in the anatomical volume of renal tissues, which after long - term evolution of the pathological process leads to terminal insufficiency of the kidneys. Endemic nephropathy is today accepted and described as a special nosological unit.

The existence of endemic foci has been described in all three parts of Serbia (Serbia proper, Vojvodina, and Kosovo), as well as in FYROM, Republic Srpska, Croatia, Bulgaria, and Romania (Z. Radovanovic, 1985).

On the territory of Serbia, the most complete data are available for villages in the valley of the Kolubara River in the vicinity of Lazarevac (Petka, Sopic, and Cvetovac) and the village of Pridvorica (near the town of Lajkovac). The percentage of sufferers here is very high and ranges from 10.23% (Petka) to 6.94% (Pridvorica). The endemic region in the valley of the Southern Morava River embraces villages in the area between Aleksinac and Leskovac (Fig. 6.4.). The following rural areas are conspicuous for the number of patients: Pukovac, Brestovac, Pecenjevci, Moravac, Orlane, and Donje Brijane. The villages with the highest percentage of sufferers are Mezgraja (6.2%), Donja Trnava (2.8%), and Kutles (2.6%). Known endemic settlements in Vojvodina border on the municipalities of Sid and Sremska Mitrovica. The only nephritis focus in Kosovo and Metohija to be described so far in the literature is Vitina with the surrounding settlements. The total number of settlements in Serbia that have been linked with endemic nephropathy comprises 376, which amounts to 6.2% of all settlements in the republic.

In Republic Srpska, the only region under threat is land along the Sava River in the northeast. In 1982 the municipalities of Bosanski Samac and Beeline had the greatest incidence of the disease (0.72 and 0.71%, respectively), which was also significant in Brcko (0.50%).

Foci of endemic nephropathy in Croatia are primarily found on territory of the municipality of Slavonski Brod. The disease has been recorded in 14 villages located in a lowland region with a high level of groundwater.

In Bulgaria, endemic nephropathy occurs on the territory of two districts, Vraca and Mihajlovgrad: in 52 settlements (or 38.5% of all settlements) in the former and four settlements (or 3.0%) in the latter.

The Romanian foci are found in the neighborhood of the Danube on both sides of the Carpathians. The disease occurs on the territory of five districts, with a total of about 40 endemic settlements.

In former Yugoslavia, all of the endemic settlements identified to date are located in close proximity to river courses belonging to the Danube watershed. Those in Serbia are for the most part in floodable regions built of alluvial deposits. Another characteristic feature of endemic nephropathy is their confinements to rural settlements, i.e., patients with this disease as a rule are farmers. The periodic nature of its appearance represents a significant characteristic of the disease.

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The causative factor is the crucial question in the case of endemic nephropathy. In order to establish it, living agents (bacteria, viruses, fungi) were tested initially, followed heavy metals. Significant efforts have been devoted to testing the eventual etiological role of drinking water. Experiments have been conducted on animals, heredity has been considered, and immunity aspects have been tested.

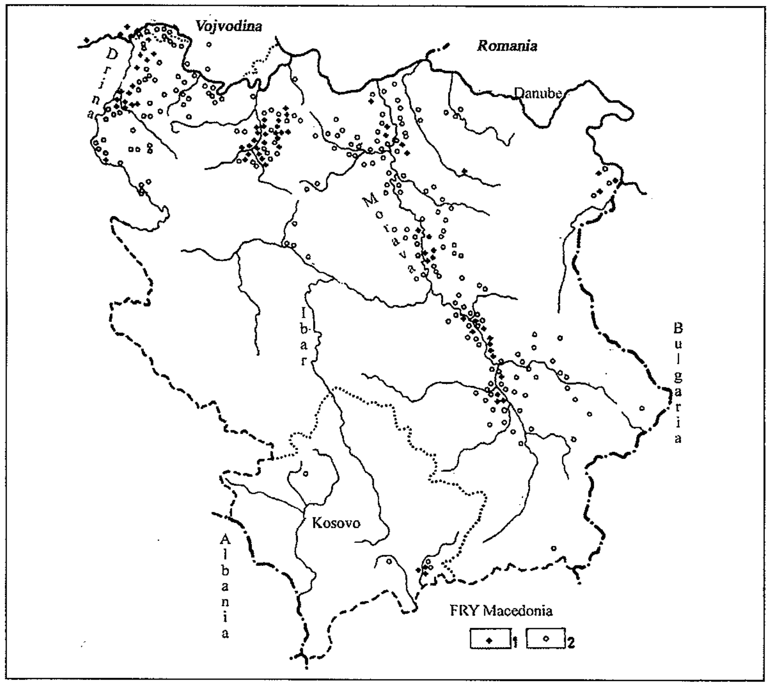

Fig. 6.4. Position of villages with certain and uncertain diseases foci in Serbia
1 - certain foci; 2 - uncertain foci (J. Peric, 1985).

According to Z. Maksimovic (1985), the geographic distribution of endemic nephropathy indicates that this disease is linked with the geochemical environment, as is also the case with other well - known endemic diseases of man, which is sometimes treated as *geochemical diseases*. Most investigators of the etiology of endemic nephropathy have suspected chronic intoxication as a consequence of ingesting subtoxic doses of one or more microelements. In connection with this, lead, nickel, chromium, silicon, uranium, and other radioactive elements have been mentioned as possible causes of this disease, followed by cadmium, boron, beryllium, and nitrates. However, testing of water from wells, rocks, and river sediments in focal regions indicates that practically all of the analyzed microelements are present in amounts significantly below hygienic norms. According to Maksimovic, these data suggest that the possible cause of the disease may lie among chemical elements deficient in water and food of the affected villages. He recommended systematic analysis of rocks, soil, water, and crops in regions threatened by the disease and proposed the compilation of geochemical maps of microelements, primarily ones with anomalously low content.

Hydrogeological factors have been analyzed over the course of many years by J. Peric (1985), who investigated the regions around the villages of Petka and Stubica (in the vicinity of Lazarevac) and Kaniza - Klakar (in the neighborhood of Slavonski Brod). In both endemic and control villages, the electroconductivity of water and its temperature were measured repeatedly; depth to the level of groundwater was determined; and the content of radon, nitrates, boron, and silicon dioxide in water of all dug wells was tested. Also tested were the levels of microelements in water of selected wells. It was concluded that the probability of occurrence of endemic nephropathy increases significantly if the water is mineralized, if polluted water from shallow wells is used for drinking purposes, and when the water has high content of silicon dioxide, boron, and radon. Due to the extremely low rate of real movement of groundwater, in areas where wells are used there is practically no exchange of water during the year in the investigated region, or else its circulation depends on the amount of polluted water. On the other hand, pollution of groundwater by organic substances - which is amplified when flood waves and states of high water occur - is exceptionally great and constantly growing.

Living agents (bacteria, viruses, and fungi) have also been tested as a possible etiological factor in occurrence of the disease. Among other things, it has been observed that fungi of the genus *Aspergillus* are considerably more frequent in materials taken from households where someone suffered from nephropathy or died of it. According to B. Birtasevic et al. (1985), the clinical course of sickness, pathomorphological findings on the kidneys and (especially) significant epidemiological characteristics of the disease suggest an infectious (viral) nature of endemic nephropathy as a disease of the group with natural foci.

We mention in conclusion that V. Momcilovic (1995) investigated the focus of endemic nephropathy in the village of Brestovac near Leskovac. She reached the conclusion that the disease occurs in residential buildings located on privileged hydrogeopathogenic routes of alluvial sediment, which is unlikely in the case of an intergranular water - bearing medium.

Despite the considerable efforts of many Yugoslav and foreign investigators, the causes of Balkan endemic nephropathy (EN) are still unknown even after several decades of multi - disciplinary research. Such a conclusion was reached at the Fourth Symposium on Endemic

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Nephropathy (Belgrade, October 1982). At this meeting, Z. Radovanovic (1985) closed the introductory lecture with the following remarks: "*It can be concluded with no shame that we have not yet discovered the cause(s) of EN. The etiology of many other diseases in whose study thousands of experts throughout the whole world are engaged likewise remains unknown. Still, there is a sense of frustration that no basic facts about the epidemiology of EN have been established in the course of 25 years.*"

In our opinion, all that can be said is that a certain geological (hydrogeological, geochemical) environment - an overlying horizon of alluvial sediment in which water probably transmits the unknown agent(s) - plays a part in occurrence and maintenance of the disease. Until we learn the true etiology of endemic nephropathy, it is imperative that water from shallow wells not be used for drinking purposes, and that some new source is found in the threatened villages. Capping of the main (deeper) alluvial aquifer is a rational solution in the given conditions.