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# THE GEOGRAPHICAL APPROACH IN MEDICAL RESEARCH

M. S. R. HUTT

"When interpreted with proper scientific passion, pathology can be not only fascinating but beautiful". This is a quotation from a recent book review in the *Observer*. I cannot guarantee to show you the beauty of pathology but hope to reveal some of its fascination.

There are, I believe still some laymen who associate the word 'pathologist' only with crime, the law court and amazing deductions in detective fiction. These forensic brothers, however, represent only a small part of the pathological band and most pathologists are as concerned with diagnosis in the living patient as they are with causes of death. In a medical school the various branches of pathology should form a bridge between the preclinical scientists concerned with a study of normal structure and function and the clinicians studying their individual patients.

The importance of pathology in the medical curriculum is well established and in the new curriculum designed for the medical school at Makerere, we have aimed both at maximum relevance to the local medical scene and at maximum integration with our clinical collegues. Here however, I would like to consider one aspect of medical research in which, I believe, the Pathology Department has a major role to play.

In any university it is desirable that research workers should be free within bounds of the financial situation to pursue research along the lines of their own choice. Nevertheless, in the circumstances of East Africa it is right that we should consider our obligations to the community who support us. This means that, particularly in the medical field, research should be mainly, though not exclusively, directed to the local medical scene. It is important, however, to point out that the opportunities for medical research available here have a significance not only for East Africa but also for many of the major disease scourges which affect other parts of the world.

The medical research worker is faced with one of two possibilities. Firstly, he may aim to become highly proficient at some specialised technique, such as electron microscopy, and having mastered this he can proceed to utilise this technique to try to solve a variety of problems in different fields or disease processes. Secondly, he may choose a disease process or particular group of diseases to study and then apply a variety of techniques to try to elucidate the problem; in doing this he will often need to fall back on the technical specialist just mentioned. Geographical medicine or pathology is in this second category.

To the newcomer from Europe or America it is soon evident that the disease pattern in East Africa is very different from that of western countries. Firstly, there are those diseases that are usually, though often erroneously, considered as specifically tropical, such as malaria, schistosmiasis, trypanosomiasis, yellow fever, leprosy and hookworm infestation. In these examples a combination of geographical factors such as ambient temperature, flora and fauna together with socio-economic factors combine to maintain these diseases. It is important to remind ourselves, however, that for most of these diseases the socio-economic factor is now the dominant one determining this prevalence. In previous centuries,

for example, malaria was a major problem in areas such a southern Europe, particularly in Italy and the Balkan countries. Until only recently most of the medical research in Africa has been predominantly concerned with these tropical diseases, and their geographical distribution has been of vital importance in delineating the vectors concerned with their transmission and the local conditions under which such transmission occurs. The spread of trypanosomiasis from West Africa to East Africa along the transcontinental river routes of the Congo basin, which were followed by explorers such as Stanley, is a classical example of a geographical and a historical factor combining to produce the great Uganda epidemic at the beginning of this century. It was, of course, here in Uganda that Castellani and Bruce discovered the causal organism, the trypanosome. The spread of the disease from West to East was occasioned by the fact that the rivers harboured not only the necessary vector, the tsetse fly, in the vegetation along their banks but also because they were trade routes. Here were foci of sufficient population concentration to allow transmission.

Let me now turn to the second major difference in the disease pattern between East Africa and Europe. This is the dominance of acute and chronic infectious disease in African practice. Tuberculosis, meningitis, acute lobar pneumonia, typhoid and small-pox are all major problems here but they are now rarely seen in western countries. In the majority of parasitic and infectious diseases the immediate causes are known and it is mainly socio-economic and cultural factors which now account for their geographical distribution. There remain, however, a large group of diseases, many whose cause is unknown, which occur with quite different frequencies in Europe and East Africa or between East Africa and India. These differences in incidence of diseases between different parts of the world form the basis of what is called geographical pathology or geographical medicine. This type of study is not new and the first complete textbook of geographical pathology was written by a German, Dr. Hirsch of Berlin in 1883. Let me quote from his introduction:- "The life of the organic world is the expression of a process called forth and sustained in organisms that are capable of life by the sum of all the influences which act on them from without. The form and fashion of this process accordingly are determined by the kind of individuality and by the character of the environment". He is saying here that a living organism is the product of the seed and the soil, or genes and environment. He goes on: "Each of these two factors shows many differences in time and in space. As regards the human species, the differences are expressed in the first factor (genes) in the distinctive qualities of generations separated by years, and of races and nationalities scattered over the globe; for the second factor they are expressed in peculiarities of the climate and the soil, and of the animal and vegetable kingdoms in so far as these are brought about in direct relation to man, and further in the vicissitudes of politics, of social affairs, of the food supply and of mental training". He is repeating here the many factors that represent our environment, all of which must be considered when we consider geographical differences in disease incidence.

The aim of geographical pathology is firstly to determine who has *what* and *where* but once this has been established the all important question is *why*. Let me give two examples of diseases which vary in incidence in different parts of the world and then consider the reasons.

A not uncommon disease in East Africa is sickle cell anaemia which is due to a genetic abnormality inherited from both the mother and father which leads to a defect in the constitution of the haemoglobin of red cells; this defect can be



shown by a simple relatively new technique, in paper electrophoesis. Sickle cell anaemia does not occur in Europeans in Europe or America, however, it does occur in people of negro extraction in America and the U.K. This appears, therefore, to be a simple genetic problem unrelated to environment. However, studies have shown an unduly high incidence of sickle cell trait (a symptomless heterozygous state) in East and West Africa where malaria rates are high. Alison has shown that people with the sickle cell trait are more resistant to the malaria parasite. Thus an environment factor combines with a genetic one to determine the geographical distribution.

One of the best known examples of the geographical approach in medical research is in the study of endemic goitre. This is a condition in which the thyroid gland in the neck becomes enlarged. Hirsch in his handbook on the distribution of disease devotes over 80 pages to this condition. He quotes the works of Pliny and Juvenal to show that there were areas of high incidence of goitre in the Alps as far back as the first century A.D. By 1883 when his book was published Hirsch was able to detail the Alpine areas in Italy and Switzerland which had a high incidence of goitre and also to outline its distribution in England; here he refers particularly to the country of Derbyshire where the condition was so common as to be referred to as Derbyshire neck. He also describes a series of reports from the Himalayas, now well known as a goitrous area. It is fair to say that Hirsch's study of the geographical distribution was nearly complete for the whole globe, excluding only the central areas of Africa. Nevertheless, his interpretation of the distribution was wrong in that he dismissed the idea that it might be due to a deficiency of iodine in the diet. It is now well known that endemic goitre is closely related to the intake of iodine in the diet. The intake is dependent firstly on the local geological conditions and secondly on the nutritional customs. For example, a diet rich in fish may compensate for a low iodine level in the water. A very good example of this comes from western Canada where there are two closely related Indian tribes. One of these groups has goitres the other does not; the latter are protected because they are fishermen and their predominantly fish diet compensates for the lack of iodine in the water. Recently Latham has reported a high incidence of goitre in the Ukinga area of Njombe in southern Tanzania. He has shown that 76% of 3,000 patients examined in this area had goitres; this is the highest incidence reported on the African continent. Latham showed also that there was a rapid improvement in the smaller goitres when the population was given iodised salt. A survey in Uganda carried out by Connor and Follis in 1963 showed that in certain areas there was a low excretion of iodine in children attending school. In one area this was associated with the finding of goitres in the adult population.

With these two examples of diseases, one dominantly due to genes and the other to environment, may I return to quote Dr. Hirsch. "In these considerations lie the germs of a science which, in an ideally complete form, would furnish a medical history of mankind, but which treated more narrowly and so as to embrace only the pathological side of human life, will give firstly, a picture of the occurrence, the distribution, and the types of the diseases of mankind, in different epochs of time and at various points of the earth's surface; and secondly, will render an account of the relations of those diseases to the external conditions surrounding the individual and determining his manner and life. And this science I have named the science of geographical or historical pathology". This science forms today part of the wider branch of medicine known as epidemiology.

If we are to show differences in disease incidence between different goegraphical envirnments it is, of course, of vital importance that we have accurate figures and this means not only accurate diagnosis and case finding but also a knowledge of the population at risk. This immediately poses considerable problems in the African scene; indeed, many people have suggested that no meaningful figures can be obtained here. However, I believe that in Uganda and in Kenya and Tanzania we have an unrivalled opportunity to use the geographical approach despite the formidable difficulties. The reasons for this so far as Uganda is concerned are that here in a relatively small country environmental factors affecting groups of individuals vary very considerably. Firstly, there is a great variation in the basic nuttion of different groups which is partly due to the geographical environment and partly to social customs; some groups have a dominantly carbohydrate diet and others a dominantly protein one. Secondly, the varying altitude which affects temperature, humidity and the vegetation has an effect in determining the presence and behaviour of insect vectors, as shown, for example, by the low incidence of malaria in parts of Kigezi. Thirdly, there are people of different ethnic origin (a genetic factor) with very different social customs which may influence the disease pattern. Fourthly, although it is now dated, Uganda has had a census which provides some idea of the population density, structure and rate of increase. Then, finally, we have a medical school which has close links with both government and missionary hospitals throughout the country and in the field of pathology we have an open service for diagnostic material, particularly in the field of such diseases as cancer.

In most technologically advanced countries with very mobile populations the majority of people live under very similar circumstances in terms of their overall environment and apart from specific industrial or habit hazards the pattern of disease is uniform. This is certainly not so in Uganda nor probably in any country in Africa.

I would like to turn now to consider some specific diseases in which geographical variations are significant; and to look firstly to heart diseases. In the United Kingdom and the United States the commonest single cause of death is a condition known as *coronary thrombosis* or *mycardial infarction*. By contrast this disease is a very rare cause of death among Ugandan Africans, though it is quite common in the Asian population. These marked differences are not explicable by the age structures of the populations and represent a real difference in incidence. In South Africa it has been shown that the South African White has an incidence rate of coronary thrombosis similar to that of American Whites while the rate in the African population is low, with the Asians having an intermediate rate. It has long been known that coronary thrombosis is associated with a thickening in the walls of the coronary artery which supplies the heart and that this thickening predisposes to clotting of the blood in the artery and so to its occlusion. During the last six years an extensive research programme has been carried out by workers in the Makerere medical school in co-operation with the Albany Medical College, New York State, and also with workers in Korea. It was first established that coronary thrombosis and myocardial infarction was almost non-existent in Ugandan Africans and that it was uncommon in the lower socio-economic group in Korea. It was then established by direct measurements that in age and sex matched groups from Uganda and New York, the latter showed more and large thickenings of their coronary arteries and that this diference was apparent by the age of twenty. Few such lesions were seen in the Ugandan Africans. It was further shown that these differences could not be



accounted for by the associated diseases. In more recent studies Professor Shaper has shown that in addition to the changes in the arterial wall there are significant differences in the blood coagulation processes between Ugandan Africans who have the low incidence of coronary thrombosis and Ugandan Asians who have a a high incidence. It has been shown that the arterial lesions are associated with changes in the lipids of the blood and also of cholesterol. Our studies here confirmed that Ugandan Africans have low serum lipid levels and a low fat intake which contrasts with the Americans, or with the Asian group in Uganda. Recent studies suggest that the amount and type of fat intake may affect not only the vessel wall but also the coagulation mechanisms. These geographical studies suggest that incidence of coronary thrombosis and myocardial infarction are mainly dependent on cultural and socio-economic factors with particular emphasis on the dietary pattern. However, there have been reports of different incidence rates in different geographical areas but in a population with a fairly uniform cultural pattern. These differences may depend on other physical factors in the environment.

By contrast to coronary thrombosis which is common in America but rare in Uganda, let us consider a form of heart disease known as *endomyocardial fibrosis*. This disease, first delineated by my predecessor, Professor Davies, in one of the commonest forms of organic heart disease in Uganda but is rarely or never seen in the U.K. or U.S.A. Dr. Connor, who spent two years working on this condition in Uganda, visited a large number of African countries to define the geographical picture. Needless to say, he had first laid down reasonably rigid criteria for its pathological diagnosis; it is no good plotting the geography of something whose recognition is difficult or uncertain. Dr. Connor showed that endomyocardial fibrosis occurred in Uganda and other parts of East Africa; it was also seen in Nigeria and Ghana but not in South Africa. A recent study by Professor Shaper and Mrs. Coles pointed out that an unexpectedly high proportion of the cases occurring in Uganda were of Rwanda origin. Conversely, the incidence in the Buganda was lower than expected. These results suggest that while some general physical factor may operate in its causation, cultural and/or socio-economic factors must play a part. Unfortunately, at the moment we have no information as to the incidence of this condition in Rwandans who remain in their country. Although more geographical evidence is needed, the information already provided affords some clues as to the information we need from individual patients and also the type of tests which may reveal differences which point to an aetiological factor.

I would like to turn now to another curious clinical problem long known to clinicians in East Africa; *big spleen disease*. These patients present with a very large spleen, but investigations fail to reveal the cause. Although some people suspected the cause might be malarial, no supporting evidence was available and material parasites were rarely demonstrated. In the last few years investigations at Mulago Hospital using certain new techniques have shown that most of these cases almost certainly have a malarial aetiology and also that there are specific abnormalities in the liver which enable this group to be separated from other causes of enlarged spleen. Using these techniques, we have been able to show that the distribution of cases in Uganda follows the overall pattern of malarial incidence. There are very, very few cases in Kigezi and there is a very high incidence in areas where quartan malaria is prevalent, such as Karamoja. The histological appearances in the liver has also been described from the Sudan, Aden, India and Hong Kong. If this disease is indeed malarial it should be

prevalent elsewhere in tropical Africa and in the Far East. I have recently reviewed slides from Zambia, Nigeria, French West Africa, Papua and New Guinea. Typical cases have been found in all these countries and malaria is found in them all. Although these observations do not prove a causal relationship between malaria and 'big spleen disease', they do prove a good example of the geographical approach on a world basis, and they open up new avenues of experimental work designed to establish the aetiology of these cases. It is important, however, to note that without the use of new techniques we would not be able to define these cases and therefore no studies could have been made.

I would like to end by discussing the geographical approach to the problem of cancer. For many years it was considered that cancer does not occur in underdeveloped countries. Professor Davies has shown that when allowance is made for the age structure of the population, the overall incidence of cancer is very similar in Uganda to that in most western countries. However, although the overall incidence is similar, the types of cancer are quite different. For example, cancer of the lung, the commonest type of cancer in British men is very rare in Uganda where atmospheric pollution and heavy cigarette smoking do not occur. Conversely, cancer of the liver is common in Uganda and most parts of tropical Africa but uncommon in U.K. and America.

Many of you are, I am sure, familiar with the studies carried out by Mr. Burkitt into the geographical distribution of the tumour that occurs commonly in this area and is now known throughout the medical world as *Burkitt's tumour*. This unusual tumour was first described by Sir Albert Cook in 1904 at the Mengo Hospital, Kampala. Nevertheless, it was not until 1958 that Burkitt defined the clinical features and 1963 when Dr. Dennis Wright showed it to be a pathological entity. As a result of extensive safaris and correspondence with hospital throughout Africa, Burkitt showed that the tumour occurred endemically in a belt across central Africa but that it was rarely, if ever, seen in north or south Africa. Moreover, it was noted that within the tumour belt, cases did not occur in people residing over 5,000 feet and that this altitude barrier fell as the distance from the equator increased. Haddow then pointed out that cases of yellow fever rarely, if ever, occurred over 5,000 feet because at such altitude the temperature falls to 60° — 65°F. at certain times of the year and that at this point viruses cease to grow in the mosquito. He went on to suggest that as the limiting factors for virus transmission were temperature and rainfall, the distribution of Burkitt's tumour might be related to these parameters. He then showed that if a map of Africa was drawn outlining the area where the annual rainfall was 20 inches or below and the mean temperature of the coolest month was 60°F or less, these areas were practically free of cases of Burkitt's tumour. The remarkable correspondence of the tumour with certain zoogeographical areas provide very strong circumstantial evidence that the tumour might be caused by a virus born by a vector such as a mosquito. Further support came for this idea when Burkitt and Wright observed that the majority of cases occurring in adults in Uganda (a rare phenomenon) were immigrants from the high country of Rwanda, Burundi or Kigezi, these are areas conditions are unfavourable for virus transmission by vector. If this unpleasant and fatal tumour is, in fact, due in some manner to a vector-borne virus infections, why is it that so few children are affected? The answer to this may lie in using the anlogy of infantile poliomyelitis — a virus disease which is wdespread in the community but one in which fortunately only a few infected people develop paralysis. It is possible that a virus causing Burkitt's tumour also infects the greater part of the population but only a few develop tumours. The



absence of cases in children under the age of two suggests that they may be protected by maternal antibody. It is now known that cases of Burkitt's tumour occasionally occur in Europe or America. However, the only other area with an incidence comparable to Africa is New Guinea, and there the geographical factors are very similar to tropical Africa. We are now attempting to investigate the immediate environment of each case in more detail; in particular we are trying to establish whether cases of Burkitt's tumour occur in 'clusters'. The term 'cluster' here refers to cases occurring within both a limited distance of one another in time and in place. It is important not to under-estimate the difficulties of the geographical approach, firstly in obtaining accurate figures of incidence but also in their interpretation once the disease pattern has been mapped.

*Cancer of the oesophagus* is a tumour which has a very variable incidence in different parts of the world. There are at least two areas of very high incidence, one in Russia and one in South Africa. In the latter country it has been shown that in the Transkei not only has cancer of the oesophagus an unsually high incidence but also that the prevalence is increasing and that the male dominance usually found in this disease is disappearing. These facts suggest strongly that a carcinogen or a tumour provoking agent has been introduced into this community during the last twenty years. One might imagine that it would be easy to track down such an agent but this has not proved to be so. Unfortunately, the cause of most diseases is a complex of factors rather than a single agent. It was soon proved that a simple explanation such as the use of fermented liquors or contamination of beverages prepared in tar barrels, could not be correlated with the disease pattern. In a recent study Dr. Burrell and his colleagues has drawn attention to the fact that the gardens or shambas attached to the house of cancer patients were different from those of non-cancer controls. The cancer gardens were less productive and this was thought to be due to a deficiency of molybdenum in the soil which led to leaf changes in several plants and particularly maize and beans. It was further demonstrated that correlation of the molybdenum deficiency corrected these growth deficiencies and also increased the plants resistance to fungal attack. It is possible that the carcinogen is a toxin produced by a fungus which grows preferentially on molybdenum deficient plants. Experimental work has shown that certain fungi produce toxins which are carcinogenic. Liver cancer which has an abnormally high incidence throughout most of African can be produced in certain animals by feeding groundnuts infected by the fungus *Aspergillus flavus*. The active principal Aflatoxin extracted from the fungus is a potent carcinogen. Ahmed and Burkitt have recently shown that there is a focus of high incidence of oesophageal cancer around Kisumu. It would be of interest to look into the problem of molybdenum deficiency and fungus contamination there. We are also attempting to map within Uganda the incidence of *liver cancer* and to correlate this with groundnut consumption and also to conditions of storage. Fungal contamination is most likely when the nuts are moist. For those of you who, like myself, are groundnut addicts let me say that to date there is no proof yet that fungal contamination of these nuts is related to cancer in man.

In Uganda among many other problems I would refer briefly to the localisation of *Buruli* or *mycobacterial ulcer* to the immediate environs of the Nile, the higher frequency of *gall bladder disease* in Ankole, the localisation of *subcutaneous phycomycosis* (a fungus disease of the skin) to the northern area and to the enormous problem of *trachoma* in Karamoja. In trying to resolve why these geographical distributions occur we should come nearer to a better understanding of the diseases and an approach to their prevention.

These are a few examples of the geographical approach. We are engaged in trying to plot more accurately the geography of disease in Uganda. Unfortunately, disease knows no political barriers and a knowledge of the pattern in our neighbours is very important. For example, southern Sudan and northern Uganda have a very similar disease pattern. On the other hand Burkitt has described the desert zone in the Sudan as the greatest pathological divide he has encountered.

It is impossible to give more than a brief glimpse of the medical problems in which this geographical approach is applicable. I hope, however, that I have indicated the value of the geographical approach in medical research and the opportunities that Africa and particularly East Africa offers for this approach. We have in the local situation a golden opportunity which has already led in the case of Burkitt's tumour not only to benefits locally, but to the whole world. Further, this geographical approach by linking the university departments with those working up-country should lead to immediate benefits in terms of co-operation and improvement in diagnosis throughout the country. A more precise knowledge of our disease pattern should also be of value to our medical planners.

*Note*: This essay is an abbreviated version of a lecture given by Professor Hutt on his inauguration to the Chair of Pathology at Makerere University College.

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# ECOLOGICAL PROBLEMS OF CATTLE RANCHING IN COMBRETUM SAVANNA WOODLAND IN UGANDA

BRENDA J. TURNER

An investigation of the Bunyoro Ranching Scheme, undertaken between 1960 and 1962, has provided a preliminary study of the ecological problems involved in ranch management of moist savanna woodland areas of Uganda. A 100 square mile cattle ranch was established in 1956 by Agricultural Enterprises Ltd., a subsidiary of the Uganda Development Corporation. Its inauguration followed two years after the apparent eradication of tsetse from the area and aimed at developing a relatively unpopulated and unproductive region. By 1960 game had been drastically reduced in the interests of tsetse fly control and the number of cattle increased from a few to approximately 4,500. Despite many problems the area now supports a more permanent and dense population of cattle than at any time earlier in the century, and probably more than in earlier centuries when it formed part of the ranchlands of the royal herds of the Mukama of Bunyoro. The overall picture in recent years is one of change from the widespread, varied and less intensive grazing and trampling of game to the more local, intensive and uniform effect of the domestic animal. This has had an immediate impact on the soil and vegetation, the practical implications of which will be discussed.

The ranch is located in southeast Bunyoro, 1°·30' north of the Equator and approximately 100 miles northwest of Kampala and 14 miles southeast of Masindi. The rainfall is unevenly distributed throughout the year with a tendency to two maxima, one in April and the other in September, and a relatively dry season from December to February. The average annual rainfall over a period of 47 years to 1961 was 36 inches at the nearest recording station at Masindi Port. The ranch area probably receives an average of about 40 inches a year although the amount and seasonality is very variable. The vegetation is predominantly broadleaved deciduous savanna woodland[23] with tussocky perennial grasses 5-8 feet high. It has been variously described as high-grass, low-tree savanna"[2], "tropical open woodland"[25] and "Combretaceous savanna"[28]. It is characterised by the prevalence of *Combretum* trees associated with tall grasses such *Hyparrhenia* and *Loudetia* species, and is found in a large area of central Uganda where other cattle ranches are being developed. (Fig. 1)

The ecological problems of ranch management may by grouped into three broad categories, which will be considered in turn:

1. the control of disease,
2. the provision of a suitable habitat,
3. the maintenance of the carrying capacity of the land.

1. Disease has threatened the survival of this scheme ever since its establishment and a brief review of the known history of disease in the area shows how this problem has developed. Cattle have probably grazed the present ranch area for nearly 600 years. Disease is reported to have periodically caused mortality [12] and since the advent of the European the introduction of new diseases, such