# Geographical pathology

## The Scientific Basis of Medicine

**Presented by Professor Hutt, St Thomas's Hospital Medical School, London.**
**Introduced by Dr Ian Gilliland.**

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**Black-and-white**
**Duration: 00:36:58:18**

**00:00:00:00**

**<Opening titles>**

**<Dr Gilliland to camera>**

Professor Hutt is Professor of Geographical Pathology at St Thomas's Hospital Medical School, London. Before that he spent a good many years as Professor of Pathology in Makerere University, Kampala, Uganda. He has written extensively on tropical medicines and on the influence of geography on disease and it is this last subject that forms the title of today's discourse, Geographical Pathology. Professor Hutt.

**<Hutt to camera>**

I would like to introduce the topic of geographical pathology by asking two questions of the type that might be found in any multiple choice examination.

**<Hutt narrates over slides showing question and answers>**

The first question: what is the commonest histological type of bladder cancer? Several alternative answers are given of which normally one only would be chosen. But, as you see here, a tick has been put both against transitional cell carcinoma and squamous cell carcinoma.

**<Hutt to camera>**

The correct answer depends upon the area in which this question is asked. As you all know, transitional cell tumours are the common ones seen in the bladder in Europe and in North America. However, if these questions were asked to a student sitting an examination in many parts of Africa, the correct answer would be squamous cell carcinoma. If I asked a subsidiary question, that is, why should there be these differences between Africa and Europe, I think that many of you would reply that schistosomiasis is common in Africa, that this is accompanied by an increase in bladder cancer in haematobium infections and that the squamous cell pattern is due to preceding metaplasia. This is perfectly true if we are talking about the situation in Egypt and a few other parts of Africa. However, in Uganda, over 50% of bladder tumours are squamous in origin and yet schistosomiasis of the bladder is extremely rare. These differences in histological pattern in different parts of the world illustrate the value of geographical pathology for they certainly indicate different aetiological factors in the different areas. In Uganda, it seems likely that the squamous cell type of carcinoma is due to urinary obstruction and urinary infection rather than to the schistosomiasis seen in Egypt. It indicates that we must look for different aetiological agents in these different areas.

**00:04:49:13**

I would now like to ask another question about the behaviour of a common bacterial disease. Following a staphylococcal bacteraemia or septicaemia, pyogenic abscesses may be formed in many organs. If one was to ask which organs were

least likely to be involved in pyogenic abscesses, I think that many of you would point to voluntary muscle.

**<Hutt narrates over photograph showing legs of patient with pyomyositis>**

The picture that you are now seeing of a patient is of a condition known as pyomyositis. This is a common disease in many parts of Africa and in other tropical areas. In this patient, the muscles of the thigh are almost completely replaced by a large abscess, which contained staphylococci.

**<Hutt to camera>**

Here is a situation where a common organism behaves quite differently in another environment. There is no evidence that the organism itself is different from the ones found in Europe. There's no evidence that there is a genetic background to this condition. There are, however, some pieces of information which suggest that geographical factors may play a role, that disease is not uniformly distributed in East Africa. It seems possible that some other condition affects the muscle and produces a focus in which the organisms may colonise. And we believe it possible that this is some virus infection or possibly a parasitic infection. These two examples that I have given you, one of a non-infective disease, a tumour, and the other of a common infective disease, show great differences in incidence and behaviour in different areas.

The principles of geographical pathology, which really forms part of epidemiology, are not new. They were outlined over a hundred years ago by Dr August Hirsch.

**<Hutt narrates over photograph of title page of *Handbook of Geographical and Historical Pathology*>**

He produced a three volume treatise, which was published in London in 1883, entitled the *Handbook of Geographical and Historical Pathology* and in this he pointed to the principles on which modern epidemiology is now founded.

**<Hutt to camera and then reads from book>**

I would just like to read to you the introduction to this book. He states:

> 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 upon them from without. The form and fashion of this process are determined by the kind of individuality (he refers here to genetic factors) and by the character of the environment. Each of these two factors shows many differences in time and in space. As regards the human species, the differences are expressed for the first factor 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 kingdom, insofar as these are brought into direct relation with man, and further in the vicissitudes of politics of social affairs of the food supply and of the mental training.

He concludes:

> In these considerations lie the germ of a science which in an ideally complete form would furnish a medical history of mankind.

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**<Hutt to camera and then over cartoon illustration, on display board, depicting people, time and place>**

If we try and summarise this in a diagrammatic form in this picture up here, we will see that there are three components that we look at when we are talking about the incidence of disease. We are interested in differences in disease frequency in different places. This may be between two different continents or it may be within a relatively small country. And this essentially is geographical pathology, however, as

Hirsch emphasised, we are also interested in differences in the incidence of disease over a period of time. And finally, to complete the triad, we are concerned with differences in the incidence in different groups of people, be these ethnic or socioeconomic, living in different places and at different periods of time.

**<Hutt to camera>**

There are, of course, many difficulties in obtaining accurate figures for disease frequency, particularly in the developing countries, but in the last 20 years, we have been able to obtain useful figures which are sufficiently accurate for us to draw some deductions. Supposing we find a difference in the incidence of a disease between two places, what should we look at in terms of determinants? Well, first of all, we should have to consider genetic and ethnic factors, but more important are those in the environment.

**<Hutt narrates over slide listing environmental factors>**

And we see in this next list the environmental factors that we would have to consider. These are the basic geographical factors of humidity, temperature, etc.; the socioeconomic factors; and cultural factors. And, of course, the interrelationship of all three of these.

**<Hutt to camera and then over photographs showing bird's-eye views of various cities>**

In the modern Western world and particularly in the big cities, the environment, the natural environment, has been completely replaced. And as we look at these pictures of large cities, which may be found in any part of the world, one is aware that there is a certain sameness between them and one would expect that the disease patterns would be very similar, except perhaps in groups of a very low socioeconomic status.

**<Hutt to camera>**

However, even in the advanced countries with extensive urbanisation, differences due to geographical factors may still play some role in the incidence of disease. One might think, for example, of the differences in the incidence of heart disease which have been shown recently in this country between areas of soft water and of hard water, or in the difference in the incidence of dental decay in areas with low and high fluoride intake.

**00:14:12:06**

Now, by contrast, if we turn to the areas such as those of Central Africa, we find situations in which groups of people of varying ethnic origin and with varying cultural patterns remain in separate areas, retaining their customs, in a wide variety of environmental circumstances which have been little modified by man.

**<Hutt narrates over photographs of: a nomadic woman in a rural setting in North East Uganda; hut in East Ugandan village>**

We see here a scene in North East Uganda with a nomadic tribe living in a semi-desert area in which the effect of man on the environment is minimal and, by contrast, we see another picture taken in Uganda, only about 50 miles away, where the vegetation and the level of general socioeconomic advance is slightly different.

**<Hutt to camera>**

Only 100 miles away from either of these two places is a large modern city in which many of the environmental factors seen in our own cities will still operate. These unmodified environments, of course, produce very great differences in the disease patterns between Central Africa and those found in Europe. However, the local differences that I have shown you also lead to variations in disease pattern over quite small distances. For example, it was the observation by Burkitt that the tumour, that now bears his name, was very rare in South West Uganda that led to him to make the various safaris to define the geographical distribution upon which our knowledge of its cause is based.

I would like to illustrate some of the problems in geographical pathology with special reference to some of the studies made during the time I was in Africa.

**<Hutt narrates over film showing life in an African village>**

The film that you are just going to see shows life in a typical African village. The young child born into this environment is exposed, from a very early age, to a variety of infectious diseases such as we get in this country, but in addition to malaria, to multiple intestinal parasites, and on top of this, there is nearly always some degree of malnutrition. There is a great variety in terms of the actual environmental factors that operate in a particular area, but in nearly all these situations, […]

**<End of film clip>**

**<Hutt to camera and then over slide listing diagnoses of an acutely ill, 5-year-old child admitted to hospital in Central Africa>**

[…] disease is multiple. And in the next diagram that we see are illustrated the diagnoses made on a young child of 5 admitted to hospital in a village in Central Africa. As you will see, the child had kwashiorkor, some degree of protein malnutrition. The reason for acute admission was that it had developed measles with complicating bronchopneumonia and there is evidence that measles is more severe in children who are malnourished. On top of this and almost as incidentals, the child had ankylostomiasis – hookworm disease, ascariasis – roundworm disease, and a background of malaria which dates from an early age.

**<Hutt to camera>**

The effect of these multiple infections and also malnutrition on the child's immunological system is very considerable and the effects last into late life. If one looks at the gamma globulin level of any group of Africans living in rural areas, they

are nearly always raised. And if we look at their immunoglobulin levels, we will also find abnormalities.

**<Hutt narrates over chart showing effects of geography on immunoglobulin levels in various groups of people>**

In this diagram, the levels of IgG, IgA, and IgM are expressed as percentages of the normal Caucasian level, shown across here. And we see these figures in three groups: a group of Tanzanians and of indigenous people from New Guinea; a group of Nigerians living in the rural areas; and then in a group of Tanzanians and Nigerians who have been resident in London for some time. You will see that the IgG and IgM levels are raised in these groups and in the Nigerians, but there is some decline in the groups who have lived for a long period of time in London.

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**<Hutt to camera>**

These figures are produced probably in the main by the result of malarial infection, though other infections play a part, and in certain groups of people, they lead to other abnormalities and I have listed these in the next diagram.

**<Hutt narrates over slide listing abnormalities resulting from malarial infection>**

These people, who are sometimes referred to as having the tropical immunological syndrome, have a high titre of malarial antibodies, a high level of IgM, the presence of rheumatoid factor, thyroid antibodies, antibodies against gastric parietal cells and speckled antinuclear factor in the serum.

**<Hutt to camera and then over photograph of woman with gross splenomegaly>**

A certain group of patients present these abnormalities in extreme degree and these are characterised clinically by gross splenomegaly as we can see in the picture of this next case. This young lady presented with gross splenomegaly and some enlargement of the liver, without any obvious cause being found on routine examination. The features of this syndrome, which we refer to as tropical splenomegaly syndrome, are now outlined.

**<Hutt narrates over slide listing features of tropical splenomegaly syndrome>**

There is hepatosplenomegaly with a high titre of malarial antibodies, although with very few parasites present, and when they are found, they're only intermittent; a high level of IgM and an infiltration of the hepatic sinusoids by lymphocytes.

**<Hutt to camera>**

The spleen is also enlarged due to a proliferation of lymphoid cells and of mononuclear phagocytic cells. We now believe that this is an extreme individual reaction to recurrent malaria, for if prolonged antimalarial treatment is given, the spleen will eventually go down, though it may take at least a year's treatment to effect this. Paradoxically, this high incidence of abnormal antibodies is associated with a very low incidence of autoimmune disorders. Rheumatoid arthritis, disseminated lupus erythematosus and Hashimoto's disease are all uncommon in Africa. It would appear that the stimulus to the immunological system may in some ways be protective of the autoimmune phenomenon seen in European countries, though the mechanism is still not clear.

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Malaria also has other effects upon the immunological system and this may be relevant to the aetiology of Burkitt's lymphoma.

**<Hutt narrates over photograph of a boy with Burkitt's lymphoma, then over map of Uganda on display wall>**

This next picture is that of an African child suffering from the lymphoma known after Denis Burkitt. The tumour affects the jaw and a number of other sites. We now know that this condition in Uganda is very uncommon in this southwest corner, although it occurs with frequency in all the rest of the country. These two cases indicated by a cross and an inverted V here, in fact, had spent some time in the areas up here <*indicates area north of symbols*>. What are the environmental factors that determine this distribution?

**<Hutt to camera and then over photograph of mountainous area in Southwest Uganda>**

The next picture is taken from Southwest Uganda and I think you can see the very great contrast between this terrain and that shown earlier on in the Northeast. This is high mountainous country, mostly above 5000 feet and at this point, malarial transmission rarely occurs.

**<Hutt to camera>**

Burkitt and his co-workers have suggested that the geographical distribution of this tumour is related to endemic malaria, but if this is so, what might be the mechanism by which this operates? Recently, it has been shown by experimental workers that if malaria is given to animals who are then infected with an oncogenic virus, there is a much higher yield of tumours. This suggests that malaria has an effect on the immunological system which results in an increase take of tumours when the animals are exposed to a particular virus. And it has been suggested by Burkitt that malaria influences the human and so following an infection by a virus, possibly EB, tumours develop in a small proportion of cases.

Now, in these examples, I've been trying to show the complex effect of infections and their late results on the immunological system and in turn the influence of this on non-infective diseases, such as cancer. I would now like to turn to a different sort of

environmental effect, namely the one of diet. And to do this, we're going to consider some disorders of the large bowel.

**<Hutt narrates over slides showing age standardised rates, in different countries, for carcinoma of the colon and of the rectum>**

Cancer of the large bowel is relatively uncommon in Africa and the next slide that one sees shows the age standardised rates for carcinoma of the colon. You will see that there is a gradation of incidents from the westernised countries down to those of rural Africa, as shown by Uganda. The figures from South Africa refer to the indigenous people of that area. You will also see that there are intermediate rates in places like Jamaica and India. Similar figures are obtained for carcinoma of the rectum and you can see that the pattern range is the same as in carcinoma of the colon.

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**<Hutt to camera>**

It is often useful in looking at the causation and pathogenesis of disease to compare incidents of related conditions. We know that adenomatous polyps of the large bowel are frequently associated with carcinomas of the large bowel in this country, both in groups and in individuals. It would be useful to see whether this operated in the areas where there was a low incidence.

**<Hutt narrates over table showing results of a post mortem study of the large bowel for the presence of adenomatous polyps, conducted in Uganda 1964-1968>**

These figures are taken from a postmortem series conducted in Uganda, where we were specifically examining the large bowel for the presence of adenomatous polyps. As you can see here, none were seen in over 2000 adult post mortems.

**<Hutt to camera>**

It would appear therefore that the incidence of carcinoma of the large bowel and adenomatous polyps parallel one another, either both are high or both are low. And this points to similar aetiological factors. We might extend this a little further and look at some other disorders of the large bowel, and diverticular disease would be a good example. This condition, which is very common in European populations in old age, is very uncommon in the elderly people living in rural Africa. It seems likely that dietary factors may be incriminated to account for these differences. There are many differences in the diet between the rural dweller in an area such as Africa and in Europe. These main differences involve the amount and type of fat, the amount and type of sugar and the amount of unabsorbable fibre. These differences give rise to alterations in the bowel physiology and there are two particular abnormalities that I would like to illustrate on this next diagram.

**<Hutt narrates over chart showing intestinal transit time and average daily stool weight in African and UK populations>**

This shows the intestinal transit time in hours and also the figures for the average daily stool weight in grams. Africans on an unrefined diet have a very short transit time with a large bulky stool, whereas the average European on a refined diet has a long transit time with a small and often hard stool.

**<Hutt to camera>**

These abnormalities in bowel function are also associated with other changes. There is, for example, a difference in the bacterial content of the stool of a rural African and somebody on a normal European diet. There is, incidentally, a profound difference in the bacterial content between a normal diet and a vegetarian in this country. These alterations in bacterial content have been associated also with alterations in the content of acid and neutral steroids and the possibility that the bacteria, produced by the dietary pattern here, lead to the production of carcinogens which, in turn, leads to

the higher incidence of carcinoma of the large bowel is one which is now being investigated.

During the last 30 years, there has been a marked increase in our knowledge of the disease patterns throughout the world and particularly in the developing areas such as Africa. The knowledge of these differences has enabled us to investigate many conditions, particularly in the field of cancer and heart disease, and the geographical patterns have given us new clues as to the aetiology. And, perhaps, there is no better example of this than Burkitt's lymphoma. However, the environmental conditions in all these areas are changing rapidly and they're changing to produce a somewhat similar pattern. We need to take advantage of these various natural experiments, firstly to define the disease patterns in terms of incidence and secondly their determinants. But to do this requires a lot of people and a lot of hard work and it is essentially a multidisciplinary approach. Not only do we need the various members of the medical profession but this is something where we need medical geographers and also social workers for, as I've tried to show, the inter-reaction of geography, socioeconomic and cultural factors are all important in the causation of disease. There is the added advantage of this approach that discovery of the aetiological factors may be one of the best methods of preventing these diseases, both in the developing and the developed worlds.

**<End credits>**