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The Origin of the Treponematoses

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An attempt is made to explain along Darwinian lines the steps by which the treponematoses evolved and how they came to have their present distributions and characteristics. The original ancestors of the treponemes would have been free-living organisms, but various forms of symbiosis with larger creatures would in time lead to the development of parasitism with varying degrees of pathogenicity. Modern man may have acquired his treponemes from his ungeneralized primate ancestors and taken them with him on his migrations over the world. Isolation of man in different continents, especially after the end of the Ice Age, would lead to speciation in both man and his parasites; this would account for the features of pinta in Central America. Ecological isolations would produce syphilis and yaws, the latter being successful in warm areas where no clothes were worn or overcrowding was gross, and syphilis being successful in colder climates but not in endemic yaws areas where so many people were immune by puberty.

A syphilis organism has little chance of survival if it fails to infect the genitalia. This is perhaps the reason for congenital infections in that disease. The organotropic properties of syphilis treponemes may be the results of repeated passage through the foetus; the conditions for survival in the foetus are much different from those in the mother, so that organotropic rather than genitotropic strains would be selected.

THE EVOLUTIONARY BACKGROUND

" Species " is difficult to define, and the accepted concept keeps changing; a few decades ago it meant a single type-specimen with which all other specimens were compared, but now it is defined usually as a population with a wide range of characters. For larger animals and plants, the standard definition of a species with this population concept emphasizes the importance of sexual interchange of genetic material. A widely quoted definition is that of Mayr: " Species are groups of actually or potentially interbreeding natural populations which are reproductively isolated from other such groups ". Since individual bacteria and viruses were thought until quite recently not to interbreed at all but to multiply by various forms of fission, these definitions were simply not applicable to the microbiological world at large. In the last two decades, a vast change has taken place, and it has been demonstrated not only that actual mating of bacteria and protozoa takes place, but that genetic material is also transferred by viruses from one bacterium to another. In other words, the micro-organisms are not unique, but like larger creatures can also share their genetic material within their specific populations. The result of this is to bring the microbiological world within the limits of the species definition of Mayr. A bacterial species, like that of larger creatures, is a population which is isolated from other species, in which genes are exchanged, and where individuals may show great variations.

The modern classification of all living things is phylogenetic in character; when a name is given to an organism, an attempt is made to locate that organism in its proper place in the evolutionary tree. The specific name implies that all species in the genus are descended from one common ancestor, just as all genera in a family are similarly descended from one ancestor and so on all through the various groupings of living organisms. To apply these concepts to the treponemes, all species of the genus *Treponema* must be regarded as having been descended from one ancestral species, and all species in the genus are potentially interbreeding groups that are reproductively isolated from one another.

The concept of natural selection was Darwin's great contribution to biology. He observed that al

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organisms varied a little from one another and that many of these variations were inherited; since obviously far more organsims were born than could possibly survive, the ones that failed to survive must be those least adapted to the environment. The ones that did survive would pass on their successful characteristics to their offspring, and this would result in the species becoming more and more adapted to its environment. If one species invaded a number of different environments, the selections made by the differing environments from the great mass of individuals within the population would vary from one place to another, but interbreeding between the groups and the sharing of genetic material would cancel out differences to a large extent. If the interbreeding were prevented by any form of isolation, then the differences would accumulate, and new strains, and eventual new species, would evolve. The isolation that would cause this interruption of interbreeding could be of various kinds, of which the most important would be geographical isolation, where the populations of the organisms are physically removed from one another, and ecological isolation, where they live in the same geographical location but where by reason of habit they do not come into contact with one another. In this fashion, geographical and ecological isolations lead to an " adaptive radiation " from a single common stock. The possibility that the treponemes have " radiated " in this fashion in response to geographical and ecological isolations has been described in a previous paper (Cockburn, 1959; theory 7).

All evolutionary change is based on inherited variation. The variations come by mutations, the distribution through the population being through the various forms of genetic spread mentioned earlier. The rate of mutation differs from one gene to another, but a mean value is somewhere of the order of once per half a million divisions. Unfortunately the treponemes have not yet been grown *in vitro*, so that precise knowledge on the mutation rates of their various genes is not available. However, when it is realized that in one single yaws lesion there are very many millions of organisms, each with many genes, it is obvious that in that lesion in the course of a single day very many mutations must appear, and that throughout the world the total daily count of mutations in treponemes must be colossal. The vast majority of these will die out, some because they themselves are lethal to their hosts, and others because they cannot stand the competition in the struggle for existence. So long as the environment stays unchanging, the predominant organisms will be those chosen by previous selective processes, and these will be better fitted to survive than the majority of newly arriving mutants; as a result the chance of any new mutant becoming established and replacing the existing ones is extremely remote. Some mutants will survive if they cause no handicap. When, however, the environment changes, the position is different, and existing predominant genes may be at a disadvantage in the new conditions and may be liable to be replaced by mutants already existing in the gene pool or being created *de novo*. Such an environmental change could be the invasion of an unusual host animal or type of tissue, a new means of spread, the migration of the host to a fresh climate, or the adoption of new customs. When this happens, provided the organism is isolated from the main mass of genes, a new strain of parasite evolves.

THE TREPONEMATOSES

The treponemal infections form a group of closely related diseases, with curious clinical, epidemiological and distributional differences between the individual entities. The reasons for these differences have intrigued investigators for many years, and indeed the argument over the possible import of syphilis from America by Columbus has been fought over the past two or three centuries. The orthodox approaches to the problems have failed to provide satisfactory answers, and we do not know, for example, why there are nervous lesions and congenital infections in syphilis, but not in the other treponematoses, nor why pinta should be confined to America. Recently the author attempted to explain along Darwinian lines certain features of the evolution of infectious diseases in general (Cockburn, 1959). The initial brief description of the treponematoses contained in the previous communication has been expanded, and the present paper explores to what extent the so far unexplainable characteristics of the treponematoses can be accounted for in such a way. The ideas presented are of a philosophical nature and some at least may have to be greatly modified or rejected; yet the exercise will be worth while of it stimulates thinking along new lines.

THE REMOTE ORIGIN OF THE TREPONEMES

It is regarded as axiomatic that all parasites are descended from free-living forms (Cockburn, 1959;

theory 1), so that it is in the soil or water that one must look for the original ancestor of the treponemes. It is unlikely that the free-living ancestors of *Treponema* still exist, but probable that some free-living descendants still survive with the same basic characters.

The genus *Treponema* belongs to the family Treponemataceae, which includes the genera *Borrelia* and *Leptospira*. In the order Spirochaetales (Buchanan) to which the genus *Treponema* belongs, only the family Spirochaetaceae has free-living species.

The family Spirochaetaceae has three genera, *Spirochaeta*, *Saprospira* and *Cristispira*. The latter two genera are commonly found in molluscs, and at least one species, *Saprospira grandis*, is free-living in sand. The genus *Spirochaeta* is free-living in water and is obviously very adaptable, for the various species are found in a marked range of habitats. *S. plicatilis* lives in either fresh or salt water; *S. marmia* is probably a variant of *S. plicatilis* and also lives in salt water; *S. eurystrepta* is adapted to swamp water and grossly polluted water containing H_2S, as also is *S. strenostrepta*. *S. dexensis* is found in hot springs, its optimum temperature being 44°-52°C.

It will be seen therefore that within the order Spirochaetales there is no lack of free-living organisms which resemble the treponemes morphologically and which provide analogies for the type-specimen of a free-living ancestor for our present pathogens. It is not, of course, suggested that one of the species mentioned was the actual precursor, but rather that some free-living ancestral organism of the family Spirochaetaceae gave rise to the family Treponemataceae and all the parasitic genera in it.

The development of symbiosis between the free-living forms and the larger animals undoubtedly took place many millions of years ago, and probably the first sites to be occupied were the skin and orifices of the bodies of animals living in or ingesting the soil or water contaminated with the free-living forms. For a free-living form to jump at one stage to be a pathogen is probably a rare event, and the most likely possibility is that in the course of millions of years parasitic variants of the commensals slowly evolved in a number of different animals and orifices until there developed the families, genera, and species of the present-day order.

Once symbiosis has become established between a large animal and a microbe, there are two main ways in which the smaller partner can spread to new species of the animal. There can be direct horizontal spread to other animal species in the same ecology, or vertical spread throughout an adaptive radiation as the larger partner divides into new species over periods of millions of years. This latter process has been described elsewhere (Cockburn, 1959; theory 2), and results in related animals having the same or similar parasites. If man inherited his treponemes vertically from his remote primate ancestors, then a survey of the primate order would show that apes, monkeys, and other members were also hosts to species of *Treponema*. These would not necessarily be pathogens. If, however, he has been infected from some other animal in recent times, the other animal stock will have the related ancestral treponemes and the primate order would not generally be infected. Unfortunately, our knowledge of the distribution of treponemes throughout nature is extremely scanty, so that we cannot tell which of these two possibilities is correct. The rabbits have a treponeme closely related to that of man, but until further surveys have been done, we cannot tell whether man was parasitized from the rabbits or the rabbits from man, or both from some reservoir as yet unknown.

TREPONEMES AND THE GENUS *HOMO*

It is generally accepted that before the days of Columbus there were treponemal infections both in the Old World (which included Africa and Asia) and in the New World of the Americas. No one can doubt that pinta has been in Central America for a very long time, while ancient bones with some form of treponemal pathology have been uncovered in various parts of the Old World. Since the organisms responsible for the diseases must have descended from a common ancestor, as tacitly assumed by placing the treponemal species in one genus, there must have been some connexion between the infections; the difficulty is in finding some link between the populations on the two great land masses. It is possible to imagine that some recent group of migrants—such as the Eskimos, or the Vikings who crossed the North Atlantic to Greenland, or some hypothetical travellers of the Pacific—were responsible for introducing the treponemes to the New World, but there is no evidence to support such an idea. The only other likelihood is that the original settlers of the New World were already infected when they first crossed the Behring land bridge some tens of thousands of years ago. Before exploring the matter further, a brief review of conditions prevailing in those early days is necessary.

Modern man, *Homo sapiens*, seems first to have appeared about 100 000 years ago, most probably in Africa. He was not the only species of man, for another, Neanderthal man, had been in existence for a long time, and continued to co-exist until about 30 000 years ago. We do not know how much the two associated with each other, but there is a distinct possibility that modern man assisted in or contributed to the extinction of Neanderthal man. This was the time of the Ice Age, and because so much water was locked up in ice sheets one or two miles thick, the sea level was some hundreds of feet lower than it is today. This meant that it was much easier to walk over the world than it is today, for Asia was linked to America by dry land at the present-day Behring Straits, England was part of the European continent, Ceylon was part of India, and Australia was almost joined to South-East Asia. Modern theory has it that from his place of origin—either in Asia or Africa—modern man wandered to all parts of the world; presumably he took many of his parasites with him, and among these would be the ancestor of the treponemes.

Once man had occupied the world with its vast range of different climates, flora, fauna and physical conditions, both he and his parasites would undergo adaptive changes in response to local conditions. Since interbreeding would be sharply limited merely by reason of the vast distances separating the various groups, soon new strains and races of men would appear, so that all the present-day human racial characteristics would become established. Naturally there would be parallel evolution in their parasites, with new strains or species appearing. With the end of the Ice Age about 10 000 years ago, this process would be markedly accentuated, for the melting of the ice released enormous quantities of water that raised the level of the seas, and cut land bridges all over the world. The two most important locations affected were those joining Asia and America at the present-day Behring Straits, and the narrow strait separating Australia from Asia which became an almost impassible barrier. Also formed at this time were the islands of the British Isles, Ceylon, and the Indonesian Archipelago, while the Mediterranean Sea became more extensive and a greater barrier to migration. The populations of these places now became increasingly isolated and the rate of speciation must have been greatly increased. In Africa, the very fertile land north of the tropics became a desert as a result of the change in the rainfall pattern, and the land to the south of it was cut off from the rest of the world to a substantial extent.

Elsewhere (Cockburn, 1959; theory 3), it has been proposed that a host exposed to a parasite becomes genetically resistant to that parasite, the resistance being handed down from one generation to another and increasing or decreasing according to the amount of handicap given it by the parasite in the struggle for existence. If the host is severely handicapped, the genetic resistance might reach considerable proportions in only a few generations. From these generalities it can be concluded that, after a few thousand years of isolation from one another, the various human races would differ in their reactions to the treponemes infecting them. Similarly the pathogens would also produce differences, so that the disease picture could be expected to differ from one isolate to another.

The group of people geographically isolated for the longest period were those in America, for even when the Behring land bridge was still open, the number of individuals travelling by it must always have been small. The addition of such small quantities of new human genetic variants to the general mass of those already in Central America could have had little effect for some thousands of years before the land bridge was broken. It is suggested that pinta is the result of this process of geographical isolation, and the reason for its existing in so limited an area as Central America is that not only does the organism differ from those in other parts of the world, but so also does the human host and his reaction to his parasite.

This concept is supported by two facts: first, that the pinta organism varies from all other treponemes by a greater degree than others do, being the only one that has so far resisted all efforts to adapt it to a laboratory animal; and secondly, that pinta is still confined largely to its original home in Central America in spite of ample opportunity for it to spread in modern times. Pinta-like lesions are found in treponemal disease all over the world, but the full picture of the disease spread through a population is found only in Central America, and no other satisfactory explanation for this is forthcoming except that the full disease is produced only when the proper human host is infected. Such a host is found only in Central America.

Geographical isolation as a cause of speciation in parasites of the human races is of course not confined to the treponemes. A good example of the same process occurring at the same time as the

variations in the treponemes is found in the body lice. Studies have shown that the lice vary from one human race to another, with those of the white races of the Eurasian land mass differing from those of all other races. The ones of the American Indian are distinctive and most closely resemble those of the yellow races. The African lice differ most of all, being black and only half the size of those of the white races (Ewing, 1926; Ferris, 1951).

Ecological separation as distinct from geographical separation is well demonstrated by the incidence of yaws and venereal syphilis in the temperate regions. There is no geographical barrier separating these two infections. In certain locations in the syphilis sectors, a non-venereal yaws-like treponemal infection exists in populations where the hygiene is bad; in endemic yaws regions, groups with high standards of living such as Europeans rarely have yaws but can acquire venereal syphilis. Some hundreds of years ago, non-venereal syphilis, usually called " sibbens ", was not uncommon in the remoter parts of Great Britain.

The explanation given here is that, since the treponeme is a very delicate organism that cannot exist for long periods away from its human host, it must have almost direct routes of transmission from body to body, and the wearing of clothes must interfere drastically with this process and cut down the survival potential of the organisms. In warm climates where clothes are not worn, skin to skin transmission is obviously practical, but it is suggested that where clothes are worn, in such places as the temperate climates or among wealthier classes (such as the European) in the tropics, the yaws type of organism cannot survive. Exceptions to this would be in communities where overcrowding is intense and many people sleep together, as they did in the old days in Great Britain, or where special customs and rites provide for almost direct transmission, as in the " custom syphilis " in Russia and the Balkans.

If a yaws treponeme were imported to Europe, as indeed must happen frequently in these days of air and sea travel, it would find itself at a biological disadvantage and would soon die out. The syphilis organism in highly endemic yaws areas, such as West Africa, will find only a limited cultural group of persons for its permanent survival, for as soon as it is taken to peoples in which yaws is highly endemic, it will either itself become transmissible by non-venereal means, or soon die out since most of the population will have become immune to yaws before puberty. Intermediate zones would occur where the conditions were not fully favourable to either infection and both would exist side by side.

Australia was also isolated, but not to the same extent as America. The inhabitants of that continent almost certainly arrived there by boat, island-hopping over the original narrow channel, and the process must have continued as the channel grew wider. The Polynesians arrived on the scene with ocean-going craft in that general area about one and a half thousand years ago and undoubtedly visited Australia; indeed there is evidence that even earlier the Romans were vaguely aware of a southern land with strange animals like kangaroos. How far the irkinja of Australia is due to isolation and how much it has been affected by later importations, it is difficult to say.

The treponemal infections of man in the very early days would differ from those of the present time, because the populations were so much smaller. One of the theories expressed elsewhere (Cockburn, 1959; theory 4) is that the nature of an infection is influenced by the size of the population, being chronic in small populations and acute in large ones. In migrant groups of small size dependent on hunting for food, only infections of a saprophytic nature or low-grade pathogenicity could survive, but as agriculture and the domestication of animals were discovered, the populations increased and more acute strains of pathogens could exist. Even then, it must be remembered that the total population of both Americas at the time of Columbus did not exceed about eight million people (Means, 1952; Mooney, 1928), and that the fastest rate of travel was that of a man's legs, for there were no horses. Under these conditions, only chronic infections like pinta or low-grade sores could survive. Yaws is a relatively acute infection probably because it had a huge population to support it. At the time of Columbus there were possibly as many people in West Africa alone as in the whole of the Americas.

THE INFECTIONS IN MODERN TIMES

By about A.D. 1000, the position was probably as follows. Treponemes would exist either as commensals or parasites on all continents of the world, but because of the smallness of the populations in most parts, any disease would be of a mild type and chronic in nature. As the numbers of people in the Old World rose, more acute infections would be selected, and because of the unhygienic conditions prevailing these would be spread by direct

personal contact at an early age. The squalor in both the towns and the countrysides of those days was considerable, and in areas exposed to warfare the people crowded into fortified towns under conditions of overcrowding that were appalling. This continued until the discovery of gunpowder made city walls no longer a refuge from attack, so that towns expanded beyond their previous confines and overcrowding diminished; until the Crusades opened the eyes of Europeans to higher standards of personal comfort; and until the Renaissance opened men's minds to new ways of thinking and living. By 1492, unhygienic environments still prevailed, but living conditions had made a big advance on what had gone before, and this must have affected the transmission of treponemes. Gone were the days when most of the inhabitants of a castle huddled up together on the filthy rushes on the stone floor of the main hall in an effort to keep warm, for now there were spacious chateaux or mansions with separate living-rooms for family groups, and with glass at the windows. No longer, in the depth of winter, did the family in the rural areas all share the same bed, often in the same room as the sheep or cattle.

Such changes could well affect the passage of treponemes from one person to another, and it is suggested here that, in the changing circumstances, those treponemes in the temperate zones that depended on direct skin-to-skin transmission were at a biological disadvantage and largely died out. Those that would survive would be the hardier saprophytes and a strain that had developed venereal transmission. Such a venereal strain would have always been a potential possibility, but would not emerge as a distinct entity so long as it was not isolated from the other treponemes, for it would interbreed with them and lose its identity. Once the others

ism, such infections are of no obvious importance. The chances are infinitely small of an individual treponeme in a gumma of the liver or brain ever reaching the outside world and finding a new host to infect.

So far as the congenital infections of syphilis are concerned, it is not too difficult to imagine a possible sequence of events. Basically, the syphilis treponeme exists by transmission during sex contact, and if any particular strain regularly fails to infect the appropriate section of mucous membrane in the sex organs, it will become extinct. The mere fact that venereal syphilis exists as a distinct and separate entity (with only the occasional extragenital transmission) indicates that a genitotropic strain of treponeme has evolved under the influence of natural selection. The diagnosis of syphilis in a person indicates that the treponemes in that person have been passed down by venereal transmission (with only a rare exception) through twenty or fifty generations. In women, this means that in all established strains, the treponeme must have access to the mucous membrane of the vagina. This could be achieved either by a solitary sore in the vagina or by infection of the uterus. To the treponeme, infection of the uterus has a strong survival value since it ensures a constant stream of organisms to the vagina, where transmission takes place. In other words, in syphilis a strain of treponeme has evolved through natural selection whose main characteristic is that it infects the sex organs; all those that do not do this become extinct. It follows as a natural result that the foetus inside the infected uterus would also be invaded.

It is suggested here that the invasion of the internal organs so characteristic of syphilis is a result of this congenital infection, by development of organotropic strains through passage of the treponemes