

*“Vertical Analysis” of  
Human African  
Trypanosomiasis*

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## *I Introduction*

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Sleeping sickness, as a clinical entity in humans, has been known to Europeans for centuries. It was described in medical terms as early as 1734 by John Atkins, a surgeon of the Royal Navy, under the name 'sleeping distemper'. For a long time it was thought that this disease was present only in the African coastal areas, the only ones that were known by Europeans, and it was regarded as something of a curiosity. Then began the penetration of the interior, and later the colonial drive, punctuated by happenings like the Brussels 'International Geographical Conference' in 1876, called by king Leopold II, and in a more formally geo-political way with the Berlin Conference of 1884-1885, called by Bismarck. The African continent south of Egypt and Sudan, and north of the Zambezi River was to be explored, civilised, mapped, protected, occupied; the slave trade was to be suppressed and other forms of trade were to be fostered. The European powers 'went in'.

Quickly sleeping sickness was to be regarded as a major problem. Africa was generally considered as an insalubrious place, but this disease was visibly something very special. The 'curiosity' was taking epidemic proportions and entire population groups were occasionally disappearing. In the Senegambia, an epidemic was observed from 1876 onward, in the Upper Volta region from 1880. A violent epidemic broke out in Nigeria in 1886, another one around Lake Chad in the same year. In the Congo Independent State, sleeping sickness flared up along the Congo river and the Lualaba in the course of the 1890s, quickly followed by the more northern territories and the Kasai region. In Angola, in 1870, sleeping sickness broke out in the Malanje focus, east of Luanda, and again in 1895 in the plantations along the Cuanza river in the same general area. In the French Congo the Niari region was suffering from the same problem in 1895. And so on.

But around 1900 it became a very hot issue indeed. Suddenly the 'sleepy distemper' had started to kill thousands and tens of thousands of

Africans in a few years' time in the area of the Busoga District, on the northern shores of Lake Victoria. This epidemic, the violence of which remains to this day an enigma, was described as, and felt to be, a scourge that was going to decimate the African populations, which for various reasons was considered intolerable. Intervention was deemed extremely urgent. And once interventions were selected and decided on, they were implemented with force - of course in the context of the spirit and prevailing values of these (early colonial) times.

How were these interventions selected? Evidently on the basis of the understanding, at the time, of the mechanisms of transmission, propagation and diffusion, and on the basis of what was known or thought to be known about the 'disease entity' and its 'natural history'. In other words, on the basis of available epidemiological and clinical understanding. Epidemiology and clinical investigation being 'scientific' disciplines does not mean, however, that they can be seen as entirely independent from the epoch (and its values) in which they are practised.

The accumulation of a systematic body of observations concerning sleeping sickness (a clinical entity not linked with the *Trypanosoma* parasite before 1902) in the first decades of the 20th century is a rather epic tale. At the origin of this huge effort must have lain an acute sense of urgency, induced by the conjunction of a rather spectacular epidemic, (colonial) political, economic and military considerations, and the emergence of 'tropical medicine' as a field that was establishing itself and cutting out its rightful place in the order of things medical.

Even present day, cool headed historians investigating this period do not escape the taste of drama and the feeling of awe inspired by what was happening then. Witness a sentence taken from M. Lyons' book *The colonial disease: 'In the five years between the close of 1900 and the end of 1905, sleeping sickness killed over a quarter of a million Africans in the British Protectorate of Uganda. This tragedy sparked off one of the most dramatic chapters in the history of medicine.'* (M. Lyons, 1992) Or, to take another sample, this time by a contemporary molecular biologist: *'Sleeping sickness was the AIDS of the turn of the century. This disease made AIDS look like nothing. Two thirds of the*

people on the north shore of Lake Victoria died and no one knew what was causing it. All the big colonial powers were there and they were worried that the disease would disseminate to enormous numbers of people.' (J. Boothroyd, quoted in G. Kolata, 1985).

Such was the stage at the time the Lake Victoria epidemic broke into its full force, by 1901. A lethal disease was threatening the promises held by Africa. This enemy had to be contained, defences had to be erected, the knights of (Western) medical science were called in. This, I think, is the metaphor that may allow us to make a beginning of sense of the early history of sleeping sickness control as practised by the European colonial powers. It has to do with political power, it has to do with economic power, it has to do with scientific ambition and prestige, it has to do with the drama of deadly epidemics and the basically humane willingness to do something about it, it is at the same time very practical and eminently romantic. But the social and political dimension should not be neglected if one wants to understand why sleeping sickness - which had been known for centuries - suddenly became a declared priority. *Declaring* an epidemic is always somehow a political decision. An epidemic is, among other things, a social event, not only an epidemiological one. And investigating a threatening epidemic 'in its full force' is another kind of epidemiology than studying the relationships between diabetes and high-density lipoproteins in the previous generation's diet. Of course.

A second element that is needed in order to understand how sleeping sickness control interventions were selected at the beginning of this century, relates to the roots of epidemiological 'doctrine' in the early years 1900. We should not forget that the old dispute between 'miasmatist' and 'contagionist' theories of epidemic disease had only recently been concluded in favour of the contagionists. The germ theory, providing an etiologic explanation for (infectious) disease, was 'confirmed' and gained wide acceptance from the 1860s and Pasteurian bacteriology onward. This new and highly successful etiologic explanation, however, tended to monopolise the attention in terms of 'causation' of disease. At the risk of caricaturing and simplifying things out of proportion, one could say that controlling the 'disease' tended to be reduced to controlling the *germ* and, if that could not

be envisaged, by controlling the germ-carrying host, some way or another. This was perfectly compatible, in terms of the epidemiological doctrines of the time, with the (implicit) assumption that *epidemics are caused essentially by germ-carriers arriving in an area where the germ was not (yet) present*. In order to avoid this, 'infected' and 'not infected' areas needed to be mapped, and non-infected areas cordoned off. In other words, *propagation* of the disease (carrying it from one geographical space to another) was the prime concern and needed to be avoided at all cost. This could only be done, of course, by limiting people's movements, essentially an administrative measure - and a very difficult one to implement.

When in 1903 king Leopold II of Belgium invited the Liverpool School of Tropical Medicine (founded in 1899) to investigate sleeping sickness in what was then still called the 'Congo Free State', the Liverpool School sent a team of three scientists, Cuthbert Christy, Joseph Everett Dutton and John Lancelot Todd to the Congo. Their expedition lasted one and a half year, at least for Todd (Christy, who joined as a volunteer, did not complete the expedition, and Dutton died of relapsing fever in February 1905 and was buried in Kasongo). It produced a wealth of observations, as well in the field of scientific understanding of the disease (the scientists' prime concern) as in terms of its 'mapping' in the Congo Free State territory. Their advice to the colonial administration centred largely on the notion of *protecting the uninfected regions* (mainly the important northern Uele region), thus reflecting quite clearly the doctrinal bias of that time (emphasis on containing the propagation by containing the germ-carriers). This advice was quickly and strictly acted upon by the colonial authorities and led to a body of control measures that pervaded almost every aspect of the native population's social life (Lyons, 1992).

Somewhat counterbalancing the emphasis on 'germ propagation', at least theoretically, was the then (and now) common belief that epidemics were made possible - or were enhanced - in a situation where a set of selected, observable, physical phenomena were produced together. This 'environmental' approach went some way in trying to understand the nature and causation of epidemic disease, but was and is somewhat less helpful for deciding on immediate, urgent control interventions aimed at reducing or

containing the problem with quick results. It tried to identify and, if possible, to understand the *host* factors in disease (resistance to infection or vulnerability) and certain (physical) *environmental* factors. The importance of these phenomena had been observed quite clearly in the European 19th century context (the effects of crowding, poverty, climate, working conditions, extreme nutritional status,...); however, in terms of possible ways to change them quickly, they often were too complex to tackle effectively and rapidly.

Applied to the West African sleeping sickness problem, it was soon clear that occurrence of the disease is a very *focal* phenomenon, linked to the environmental conditions necessary for the tsetse fly to exist and to play a sufficiently effective role in the transmission of the disease from man to man. Some environments (or environmental conditions) are clearly more dangerous than others. There are basically two ways to react to this: either change the (dangerous) environment, or separate the potential victims from this (dangerous) environment. The first approach has been extensively practised with the perspective of making life difficult for the tsetse flies (bush clearing, game extermination, fly catching or poisoning), mainly in East and South-East Africa, although it also formed one of the elements of the French and Belgian approach in West and Central Africa. The second one implies, if it is to be practised on a large scale, moving and resiting human population groups or changing settlement patterns. A combination of the two approaches was called, in the terminology of Jamot's doctrine 'agricultural prophylaxis' (*la prophylaxie agronomique*). It is not so hard to imagine what kind of resistances are to be expected if this kind of interventions are implemented consistently and on a large scale for 'beneficiaries' who do not really share the bio-medical paradigms on which they are based.

Apart from the socio-political (and geopolitical) considerations, and the prevailing epidemiological reference doctrines, a third element may be useful in trying to understand the logic in the choice of interventions, namely what could be called 'historically developed attitudes', themselves largely dependent on the difference between trypanosomiasis of the savannah and those of the forest.

The history of trypanosomiasis control is a complicated one. The fact that the name of a parasite species (*Trypanosoma*) is used to name a variety of distinct problems (human and animal, *gambiense* and *rhodesiense*) certainly contributes to the confusion, especially if in the name of (African) 'trypanosomiasis' far reaching generalisations are made.

In the East and South-East Africa (savannah) fly-belts, then mainly populated by tsetse of the *morsitans* variety, cattle could not survive because of *nagana* - a form of animal trypanosomiasis disease - known since a long time and by everybody to be 'caused' by tsetse flies, long before the etiologic agent was identified as a trypanosome by Bruce in 1894-1895. Especially the British - but before them already the Zulu - concentrated their efforts on getting pasture land free of flies, thought to 'poison' the cattle in some direct way. In 1890 the great rinder pest epidemic took care of both the game and cattle animals *and* the flies for a while, but once it was understood that the tsetse was only an intermediary, carrying the parasites from a trypanotolerant game reservoir to trypano-sensitive cattle, the logic of intervention in (animal) trypanosomiasis control was to a large extent directed towards environmental intervention. Human trypanosomiasis in East Africa - of the *rhodesiense* type - tended to be appended, as a problem, to the animal trypanosomiasis which were, historically, the first and prime concern. The first - isolated - case of human *rhodesiense* sleeping sickness was reported in 1910.

Two alternative camps developed: those who wanted to starve the tsetse by removing their source of food (the game, which at the same time constituted the animal reservoir of the trypanosomes) and those who wanted to remove the tsetse without killing wild animals. For various reasons the latter faction largely prevailed. The entomologists took a leading role, but this does not mean that the 'British tradition' excluded all flexibility. When and where it was judged necessary or indicated - and notably when they were confronted with *human* sleeping sickness - the main corpus of intervention or control programs was case finding and chemotherapy.

On the other hand, as John Ford puts it, '*The French and Belgians were not impressed by the entomological argument. The great Congo epidemics still raged. In the luxuriant West African forests, bush clearing was obviously impossible and elimination of wild animals pointless when the reservoir of the trypanosome was man himself. It was a problem for the doctors [...].*' (Ford, 1979). These 'great Congo epidemics' were indeed far from easy to control. Between 1920 and 1923 more than 62,000 new cases were detected in the Kwango basin population (Belgian Congo) where average detection rates were close to 10 %. Comparable figures were obtained in the Uele basin. Even in 1930, the medical teams detected more than 33,000 new cases by examining some 30 % of the population of the Belgian Congo (with the methods available at the time). The French teams in their Central and West African territories detected and treated hundreds of thousands of parasite carriers in the first half of this century. This was a major and for a long time urgent problem indeed, and obviously quite different from the East African one, both in its nature and in its perception, and consequently in the development of traditions to tackle it.

With the emergence of progressively more effective treatment, the West African sleeping sickness control strategies concentrated mainly on the notion of 'sterilising the human reservoir' while maintaining emphasis on the containment of infected populations. Jamot's doctrine (1916) is explicitly based on the starting point that *infected people should not move*; therefore medical teams should go out and find them (and treat them where they find them), which is the basic rationale for the mobile team (or the 'spatialist') approach as developed and operationalised by the French and the Belgians. The prime effort is on man, through administrative and medical measures; the environment is somewhat secondary, although not neglected (at least in theory). Later, after the second world war, this is even more accentuated when 'chemoprophylactic' treatment is instituted with six-monthly pentamidine injections. The bulk of the human trypanosomiasis control program was concentrated on the human reservoir.

In recent years a more comprehensive trend in the interpretation of the 'epidemisation' of sleeping sickness is more and more gaining attention. The basic question always was (and still is): what is at the origin of these

'epidemics'? Somewhat simplistically, one can discern two extreme epidemiological standpoints:

- (1) the 'single source' hypothesis, with an emphasis on (germ) propagation;
- (2) the premise of the 'multiple dormant sources', with an emphasis on epidemic activation by changes in the hosts' susceptibility, brought about by changes in the social and 'ecological' environment. This is somewhat comparable to the two-level epidemiology of (e.g.) tuberculosis, where *infection* and *illness* are quite distinct events for an individual, 'illness' being brought about by entirely different determinants than 'infection'.

In line with the theory of propagation (the 'migratory thesis'), the first standpoint tries to explain the onset of epidemics by identifying parasite carriers and establishing where they came from. Its basic working question would be: who introduced this parasite into this community? Application of this logic ultimately leads to the notion of a single 'mother focus' of sleeping sickness, comparable to the epidemiological understanding of other great epidemics like influenza, plague, cholera. The focus of interest in this approach is the *parasite*. An example is Morris' attempt to describe '*The movement of sleeping sickness across Central Africa*' (Morris, 1963), by which is meant, in fact, the movement of the parasite. Another example would be to trace the Busoga outbreak or the spread of the Congo epidemics to movements of groups of people, troops and caravan trains, during the (pre-)colonial penetration. Thus the famous (or rather infamous) Busoga epidemic has been 'traced back' by some to Stanley's rescue expedition to Emin Pasha in 1888.

The second standpoint would state that in most cases slow circulation of the parasite is maintained in 'endemic', 'slumbering' foci, and that from time to time epidemic flare-ups are produced (i.e. faster circulation of the parasite among the human population) under the influence of certain conditions, many of which are not really known. The focus of interest in this approach is not so much the parasite, but its interaction with the *host* and the *environment*, in the large sense of the word. This includes not only

the narrowly biological environment, but also the social, political and economic environments, intimately linked in a dynamic equilibrium. Thus the great epidemics which 'started' around the turn of the century would to a large extent be ascribed to the turmoil occasioned by the colonial conquest and occupation, producing radical changes in the human ecology. Examples of this approach are M. Lyons' analysis of the social history of sleeping sickness in the Belgian Congo (1992), P.G. Janssens' analysis of the epidemisation of trypanosomiasis (1992), and on a more micro-social scale Hervouët, Meda and Laveissière's analysis of the Vavoua focus in Ivory Coast (1991,1992). But it would be a mistake to think that this approach is only a recent one; it was already present in the minds of control authorities, as expressed through statements about the importance of '*improvement of the conditions of living among the native tribes*' at the Conference on Sleeping Sickness in Entebbe, 1933 (quoted in Duke, 1936).

Then of course there are the combinations and the intermediate positions, with their greater or lesser biases, 'biomedicalising' or 'socialising'. The (moderate) biomedical bias would lead to statements such as: '*Human African Trypanosomiasis is in essence a biological phenomenon with, possibly or admittedly, some serious social consequences or maybe even some social cofactors among its determinants*'. A radical social (or socio-political) bias might lead to statements such as: '*Human African Trypanosomiasis is a social phenomenon masquerading as a disease*'. In the case of sleeping sickness the latter statement is likely to meet with a complete mental block on the part of the medical professions. Still, it is a useful intellectual starting point for a better understanding of the problem. We may consider the parallelism with the concept of famine.

Looked at from a somewhat mechanical perspective, 'famine' equals 'too many people and too little food', or something like 'the demand for food is far greater than its supply'. The cause may be identified as 'drought'. The solution would then be to increase the supply (which is what a relief organisation would do) or, somewhat less acceptable, to reduce demand (which is what an enemy army might do). Looked at from a socio-political perspective, 'famine' may be said to be caused by a loss of compensatory mechanisms to deal with food shortages (which may be induced by drought)

because of disruptions of mainly social or political structures. The solution then is somewhat less clear-cut or less easily identified. Both perspectives do not necessarily lead to real fallacies, but the purely 'mechanical' perspective is bound to produce solutions that may very well create new socio-political problems which in turn may create or maintain further 'famine', as experience has shown.

In other words, the system of logic (the perspective) that is used to *understand* the problem can be expected to be a determinant of the kind of interventions that are selected in order to *solve* it (together with the formulation of their *objectives*), which will further have an impact on the kind of *structures* that will be set up in order to implement these interventions. What we are trying to say is that the system of logic - or the 'perspective' - is a prime determining factor; however, these systems of logic are not always made explicit, even if they have been so at some moment in time. What makes human trypanosomiasis such a difficult and at the same time such an intellectually challenging and fascinating problem is precisely the fact that different perspectives are needed in order to simply begin to understand it. The fact that trypanosomes, tsetse flies and human beings have to come together in order to produce the medically defined 'disease' *Human African Trypanosomiasis*, thus making it one of the '*diseases caused by protozoa*' (as it still used to be called in the 17th edition of Manson's *Tropical Diseases*, 1972), gives us one element of understanding: this is the necessary condition. But it is clearly not enough; we cannot say that it is also a sufficient condition.

This, of course, raises the question of how well we need to understand things in general, and a problem like trypanosomiasis in particular. Again, simplistically, we will discern two extreme positions.

The first one would state that we need to know as much as possible of what there is to know, in order to further our knowledge about the world. An illustrative phrase that fits in with this position would be 'to push back the frontiers of the unknown' (a phrase that actually can be found in recent calls for candidates for academic prizes; a certain romanticism has not yet disappeared from the face of the academic world).

The second one would state that we need to know only what is needed in order to decide on specific action, thus reducing the notion of 'relevance' to 'practical relevance'. Looked at from the first position, everything is potentially relevant or 'interesting'. Looked at from the second position, knowledge is relevant only if it gives us a sufficient basis (a sufficient 'theory') to decide on - and to implement - a course of action, or a control strategy.

Still taking illustrations from real life, the trypanosomiasis literature and oral tradition provides somewhat contradictory sentences like:

*"The epidemiology of human African trypanosomiasis is far from understood."*

and:

*"L'épidémiologie [de la trypanosomiase humaine africaine] est d'une simplicité cristalline."* (Lapeyssonie, 1992)

The second statement refers probably to the fact that the basically simple *Trypanosoma-Glossina* life cycle provides all the elements that are needed to *justify* a chosen control strategy: detection and treatment of as many parasite carriers as possible, or eliminating as many tsetse flies as possible, i.e. with the most effective techniques. The strategy can be made more effective by improving the techniques, but that would not change the stratagem in any essential way. Therefore, everything that complicates the simple life cycle model can be judged to be 'irrelevant' or 'academic'. This would fit in with the words of a frustrated trypanosomiasis control officer: *'I know what to do; just give me the necessary resources to do it'*. True, of course, except for the fact that the resources are always part of the problem. But again, both statements, although contradictory, cannot really be faulted for obvious fallacy, at first sight, that is.

At this point, it would seem appropriate to state *our* position. This is, in fact, to a large extent determined by our outlook on public health and on the way health care (services) can be organised.

It is not our position that any new element of understanding is 'relevant'. It may be 'potentially relevant', but that does not necessarily mean that it is relevant *now* or that its usefulness can be foreseen. On the other hand, it is not our position either that everything is known that needs to be known about sleeping sickness epidemiology; our understanding of the notion of relevance tends to place it in a somewhat wider perspective. It is still essentially of the kind '*what is useful for decision making*', but we start from the premise that the strategic decision *has not yet been made*. This rests mainly on two considerations:

- the simple (life cycle) model strategy, although it has unquestionably accomplished an enormous breakthrough in the past, also shows unquestionable shortcomings;

- the structural and organisational consequences of the choice of strategy, in terms of efficiency, resource allocation and health service organisation are very considerable, and are a determinant of relevance on their own.

Thus the tension between '(more) complete understanding' and 'usefulness for decision making' results in a dynamic and changing equilibrium that needs to be reassessed regularly, not only because of changing 'disease' conditions, but also because the disease problem cannot be analysed anymore outside the social and professional control systems in which it develops and with which it interacts. For someone who needs to formulate rational and rationally defensible action strategies, the human African trypanosomiasis problem cannot be adequately analysed without taking into account the environment, the population that is at risk of contracting and/or developing the disease, the health care delivery structures, and the interactions between them, all of which are elements of a 'system' within reality and all of which are of practical relevance. As these dynamics change (they always do), we may be confronted with new 'puzzles' (inadequacies of the model used so far, or more uncertainty), but we may also positively learn relevant things about a reality that may be or appear more complex than we thought. The trick then appears to be to render the increasingly complex understanding sufficiently simple to be able to *act* on

the problem on the basis of a coherent set of practically relevant elements. The latter could be used as a first working definition of a 'model' - in this case a descriptive or analytic one.

Pragmatically speaking, not much is gained by a mere increase in our awe before the wonders and complexity of the world, or by a mere increase in our humility when faced with the insufficiencies of our understanding however beneficial these feelings may be for the human soul. For public health practice, better (or more profound) understanding remains relevant only if it contributes to better decision making and implementation. 'Pushing back the frontiers of the unknown' therefore needs some steering, for some frontiers are clearly more of an obstacle than others.

We hope this will clarify to some extent the structure and methodology of the work presented here.

The first part, called *Vertical Analysis*, is an attempt to analyse the problem of human West-African trypanosomiasis (*Trypanosoma brucei gambiense*) without prejudice, and to find out what is known (and relevant to us) and what is not (but should, from our perspective). The second part, the condensed summary of the Kasongo study results, will attempt to show what we have been able to learn from this survey, and to what extent some of the gaps in our knowledge are filled, if any. The third part will be an attempt to draw the appropriate conclusions in terms of problem management, from the point of view of our public health perspective and health care organisation doctrines.

It will be clear that this may look like a somewhat presumptuous undertaking, especially because, in fact, it intends to approach the problem of West-African trypanosomiasis in a way that is as comprehensive as possible. We think, however, that this 'presumptuousness' is necessary; there is a need to establish the *common ground between the epidemiological, biomedical and health-systems-organisational* disciplines, because all of them have to be used in the interaction between communities, individuals and health care providers. In this kind of needed exercise a synthesis needs to be made which is possible only if a fundamentally *generalist* attitude is adopted and maintained. Although we certainly cannot claim to be the only ones

capable of formulating this synthesis, it is one of the specificities of our 'general public health' discipline, as we see it, to develop methods to do so in a systematic way.

The work presented here is mainly about an application of such methods. It attempts to bring together, and to make explicit, the ways in which decisions in health care need to be made. These ways are not restricted to the sleeping sickness problem. They are applicable (and, in our view, should be applied) to most if not all important health problems for which programmes are developed. In order to be individually and socially acceptable, the decisions must not only be based on validated knowledge and understanding but also be subjected to an accepted set of values expressing the ethical dimension of human health care delivery, in which *care* includes - but transcends - *cure*.

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## *II Vertical Analysis*

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### *The vertical analysis approach*

What we will call 'vertical analysis' is an intellectual exercise that consists in the identification, description and systematic analysis of a health problem in its various aspects, in order to make an inventory of all possible solutions or interventions, which is expected to permit us to select, as objectively as possible (i.e. without prejudices and without preconceived ideas), those activities that have to be implemented with some degree of priority in order to solve or reduce the problem.

By doing this, it is highly probable that one comes to identify areas of uncertainty - or gaps in the knowledge that is needed for rational decision making - which may direct our choice of research priorities.

This approach has been formulated and codified by P. Mercenier in 1972 and has been practised systematically in the Institute of Tropical Medicine's courses in tropical medicine and the International Course for Health Development for quite a number of years by now; one could say that it has matured in the process. It has proven to be a useful tool, in our experience, in order to formulate relevant questions on specific health problems and as a 'skeleton' around which our understanding of health problems can be 'draped', so to speak, in a comprehensive way.

Generally speaking, one could say that this approach tackles the following questions: - is there a problem, and what is it? - where is the problem? - what are the problem's determinants? - which elements of the problem do we want to influence or solve? - how can we influence or solve these elements of the problem?

In practice, the 'vertical analysis' encompasses 7 stages:

1. An evaluation of the importance of the problem
2. The description of the 'system'
3. The listing of possible activities or interventions
4. The identification of the type of services necessary in order to implement these activities
5. The identification of the type of personnel that is needed
6. The formulation of operational intervention strategies
7. The formulation of how these interventions are to be evaluated

Although unquestionably useful, this strictly systematic approach also has its limitations, which it is appropriate to point out right from the start. Probably the most important one is that this approach tends to force one to isolate the health problem from its wider context. This is somehow linked to our 'medical bias' to label a (health) problem with the name of a disease. The latter is a nosological entity, closely linked to the medical concept of diagnosis, a logical fiction invented by the medical profession that is necessary, within the system of knowledge that is at the basis of modern medicine, in order to put some order in the observed universe. It is a bio-medical abstraction.

On the other hand, a problem, even if it is restricted to be a 'health' problem, is a much broader and comprehensive concept than what can be implied or covered by the name of a disease, and it is quite possible that there exist better ways to name it or to circumscribe it than through this rather narrow abstraction that a 'disease' is condemned to be - even if for the moment we can do no better.

However, we think that, as long as we remain conscious of our bias, it is possible to maintain an attitude that is as objective as possible, keeping in mind that we are concentrating on one aspect of a much more complex reality.

In this context, it may be of interest to note that even diagnostic entities are not always as semantically and conceptually precise as they may

give the impression to be. In fact, concerning the topic at hand, the term Human African Trypanosomiasis, as a disease entity, is an etiologic description, referring to a parasite-host relationship, whereas the term sleeping sickness is a clinical description. Although the two terms are often used interchangeably, they do not really mean the same thing. In common parlance, an asymptomatic parasite carrier can rightly be said to be a case of 'trypanosomiasis', but it would be somewhat premature to say that he is suffering from 'sleeping sickness' as long as he is neither 'sick' nor 'sleeping'.

## *Preliminary assumption*

When describing the problem of Human African Trypanosomiasis (HAT) of the *gambiense* variety, we will start from a basic working hypothesis - which is basically an option we think it is necessary to take, in order to be and remain consistent in our approach. This option is *to treat the disease as a homogeneous entity (i.e. it is considered to be one disease); it is assumed that variations in the expression of the disease are attributable to 'epidemiological' factors related to the level of endemicity, the history and dynamics of the endemic (in other words, observed variability can be 'explained')*.

In this vertical analysis we will formally take the exercise first through steps 1, 2 and 3: the problem, the 'system' and the possible interventions. Issues directly or indirectly related to the selection of types of services, personnel and operational interventions (steps 4, 5 and 6) will already be touched upon in this process.

## *The importance of the problem*

### 1. DEFINITION OF THE PROBLEM OF HAT

In the context of the vertical analysis approach, the 'health problem' is neither the parasite, nor the transmission, nor the infection, but the *individual and collective suffering caused by the disease, including its economic and social cost* (World Health Organization, 1964).

In order to facilitate reflection, the 'overall' problem of HAT can usefully be split in two:

- the 'actual' or 'present' problem: the suffering of symptomatic patients, caused by their illness, and the repercussions of this on other people;

- the 'potential' health problem: the suffering that can be expected by asymptomatic infected patients, if and when they will become symptomatic, on the one hand, and the suffering that can be foreseen for the uninfected if and when they become infected and can evolve toward the stage of symptomatic patients, on the other.

## 2. ELEMENTS OF THE IMPORTANCE OF THE PROBLEM

The *importance* of a health problem (in public health terms) is a combination of different factors: its impact on individual health and well-being (what is called here 'severity'), its frequency, its cost in the broad sense of the word. Analysis of this 'importance' serves two main purposes. First, deciding whether the health problem can be called a *priority* or not, which is essentially a question of willingness to use - or find- resources. Second, helping to decide *what precisely is most important* in a given situation, so that choices can be made and specific objectives formulated.

For the first purpose (priority yes or no), not only the 'importance' is taken into consideration, but also what we will call '*the vulnerability*', i.e. the possibility to do something about it, (to which should be added the *perception* of the problem by the communities if we are talking about health service development in a context where rationally responding to existing 'demand' is the first obligation, independently of the tackling of 'objective needs').

For the second purpose also (deciding on what precisely will be the objectives), decisions are not reached merely on the basis of analysis of 'importance'. Again, 'perception' of the problem will need to be considered and, of course, available resources; but also elements of the problem's system description (cf. *infra*).

Finally, if the variables of 'importance' can be quantified, they may constitute the elements of interest for the evaluation of programme impact, in case this is judged to be necessary.

### *2.1. 'Severity' of the individual problem*

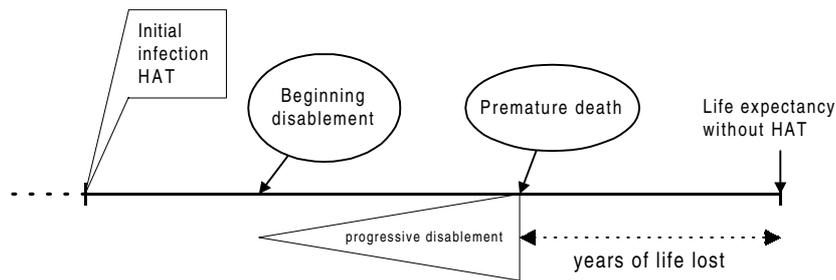
How can this 'severity' be defined? In order to be able to describe this aspect, we will use a gross simplification of the natural history model of HAT in its worst course. According to this simplified version we can divide the evolution after initial infection into two periods: the first one, generally asymptomatic, or, at least, usually without too many serious reasons for complaint; and the second one, quite symptomatic, with progressive evolution in the severity of complaints and progressive disablement, ending in death.

We will accept the hypothesis that this evolution (the worst one) will not occur in all cases. In other words, the evolution toward the symptomatic phase (of real suffering and invalidity) is not considered to be inevitable or absolute (even in the absence of intervention) and we do not preclude beforehand the possibility of 'spontaneous cure' or (a series of) systematic 'remissions'.

#### *2.1.1. Disablement and chronic health deficit*

If and to the extent that infected individuals, even before the stage of Central Nervous System (CNS) involvement, are more vulnerable to other diseases, one could consider even the early (asymptomatic) stage to be disabling. However, it can be accepted that the major progressive disablement is to be found toward the end of the evolution, in the cerebral stage of the disease. The duration of this major disablement can be expressed in terms of months rather than years, its severity ends up in a (close to) total incapacity to take an active part in social life. We will develop this suffering and symptomatology in more detail later on.

The following diagram summarises the simplified evolution of the disease:



Of course, the subjective value of premature mortality (years of life lost) is not always accurately assessed by mere numbers of years. Dying at the age of 20 years instead of 30 is not usually felt to be the same thing as dying at the age of 75 years instead of 85, both individually and socially - although in both cases there would be 10 years of life lost. These 'years' would possibly need to be adjusted for *quality*, but one could also say that they need to be adjusted for *time preference* (which leads to the notion of 'discounting'): when offered a choice, most people would prefer to live (and enjoy life) *now* (or young) than to live *later* (or old). Adjusting for *quality of life* leads to the notion of QALYs (quality adjusted life years) lost or gained. Going one step further and taking into account *time preference* would lead to the notion of 'discounted QALYs' lost or gained.

Our purpose here is not to really try and quantify all this. But these additional adjustments and refinements may give an extra dimension to the relative importance of the problem we call HAT; in many micro-epidemiological settings the disease is contracted especially by the young and active rather than by the old (and usually less active...), even when one adjusts for the demographic bias that the young(er) are more numerous than the old(er) in African society. If time preference is valued, this adds to the importance of HAT as a problem

### 2.1.2. Case fatality

The 'natural' case fatality of HAT is estimated to be close to 100 % from the moment the CNS is demonstrably affected. Before this stage, the probability to die of the disease (which is, grossly speaking, the complement of the probability of spontaneous cure and/or arrest in the asymptomatic

phase) is uncertain and may vary according to certain variables that are linked to the history of the parasite-host relationship in the community, and to the individual and collective level of resistance potential to pathogens in general.

A problem is, of course, the fact that with the (usually) long evolution of a disease like HAT, affected patients have plenty of opportunity to die of other things like intercurrent bacterial, viral or parasitic infections. If these deaths are to be counted among the case fatality of HAT, this implies acceptance of the hypothesis that the trypanosomes are at the basis of (much) increased vulnerability to other pathogens. The evidence for this is rather scanty, except in the truly terminal phase of the clinical evolution.

### 2.1.3. Premature mortality

This is determined essentially by the case fatality, by the mean 'natural' duration of the possible evolution toward death and by the age of infection.

If we accept that the average duration of the (worst) evolution is of the order of 2 to 3 years, that the case fatality is important (at least from a certain stage onward) and that it is possible and probable to get infected at all ages, the potential for premature decease can be considered to be quite high.

## 2.2. Frequency

### 2.2.1. The disease and the health problem, infection and morbidity, infection and suffering

As this chapter is about the importance of the *problem*, we should now be investigating the importance of *suffering* from HAT, since that is how we have defined the concept of 'problem'. In fact, this is what we should call 'morbidity'. In actual fact, the available information about the frequency of HAT 'morbidity' always uses the variable *infection* as a proxy for morbidity.

There is, right from the start, a considerable semantic and conceptual problem here. The finding of parasites (a positive parasitologic test result)

does not really define *morbidity* (which is linked to the notion of *suffering*) but rather *contagiousness* (if this is defined as such!), or, more realistically, the ultimate proof of *infection*. This confusion is of the same order as the one caused by the indiscriminate use of the terms 'sleeping sickness' and 'human African trypanosomiasis', and is difficult to resolve as long as the logic of disease control (concentrating on *cure* of an *infection*) and the logic of clinical curative care (concentrating on *care* for an *illness*) are implicitly intertwined. Thus, to the extent that *infection* is not necessarily linked to *suffering*, the frequency of infection is not an accurate description of the frequency of the problem. It is one of its *determinants* and as such, it belongs conceptually to the second part of this analysis: the description of the disease system.

Another ambiguity resides in the different interpretations that are given to *direct* and *indirect* evidence of the presence of parasites. Direct evidence, the visual discovery of parasites (what we will call parasitological positivity) is usually considered as sufficient proof of *infection* to justify the need for treatment. These individuals thus become 'patients' (the French 'malade' is even more suggestive), suffering from an *infectious disease*, independent of how they have been detected and independent of subjective suffering. In this case the basis for these implications (infected = need for treatment = patient = diseased) has nothing to do with suffering. It has to do with parasites in people. On the other hand, indirect evidence of past or present infection (like the detection of specific antibodies) leads for most people to the category of *suspects*, for whom treatment is not always or not necessarily justified. The presence of antibodies is interpreted as a marker of infection and the probability that these individuals will be pronounced *diseased* is much lower. Still, in both cases (direct or indirect evidence) the question is about the same concept: infection.

Apart from this conceptual ambiguity, there also is a very practical problem with parasitologic tests; they are known to have low sensitivity with respect to the real presence of parasites, especially when done once, and there is not really a practicable reference test that can be accepted to be sufficiently 'perfect' to serve as a 'gold standard'. Therefore,

misclassification is important particularly among those classified as not infected.

In spite of all these caveats, we will discuss the frequencies of infection within the context of discussion of the *problem*. The main reason is that the available information (on frequencies) does not permit us to make the distinction between evidence of infection and suffering (i.e. the problem).

### 2.2.2. Frequency of infection and disease

#### *Prevalence of infection*

For practical purposes we can define *infection* here as the presence of *T.b.gambiense*, in whatever quantities (i.e. visually detectable or not). In terms of present day technology the phenomenon most closely linked to this presence of parasites is the detectable presence of specific antibodies.

Infection prevalence rates can in principle be measured - or estimated - by *serologic prevalence* rates among those who are not old cases of trypanosomiasis (an important proportion of the latter remain serologically positive for a long time after treatment - Pépin et al., 1986). If we accept the existence of the phenomenon of spontaneous sterilisation, the notion of 'old cases' is impossible to define with precision, in practice. In that case one could restrict their definition to 'known old cases'.

Single cross-sectional serological prevalence rates may be difficult to interpret or to compare. In field conditions there may be quite a bit of cross-reactivity (false positives) and for purposes of comparison the threshold (or cut-off point) for serologic positivity needs to be defined in a uniform way (although the results of serologic tests, in the case of prevalence estimates, are interpreted in a dichotomous way - positive/negative - these tests are always essentially quantitative, involving a decision on positivity thresholds). Also, in order to be comparable, serologic prevalence rates should be measured on comparable populations in terms of age distribution.

Serologic prevalence rates of up to 30 % have recently been observed in some foci in Northwest Uganda, using the CATT technique on whole

blood (Paquet et al., 1992). Prevalence rates of this order of magnitude certainly denote a big problem, by any standards, and will only be found in places where sleeping sickness is (already) acknowledged as a major problem.

On the other hand, the question needs to be asked from what level of measured (serological) prevalence one can speak of prevalence of (real) infection. Using the same CATT technique on whole blood, Bafort et al. found a *false positive rate* of 3.9 % (excluding doubtful reactions), in a sample of clinic and hospital patients, in a HAT-free population in South Africa (Bafort et al., 1986). As a measure of specificity, this may be interpreted as 'good', but it also means that in areas where HAT is (or used to be) endemic, a serological prevalence rate of about 4 %, with this technique, can hardly be interpreted as conclusive evidence of the presence - or of the absence, for that matter - of *Trypanosoma* infection in this human population.

#### *Incidence of infection*

Infection incidence rates could theoretically be estimated by *serologic conversion* rates per unit of time (sero-conversion is only applicable to individuals who were formerly known to be negative, by definition). In optimal circumstances such an incidence rate can give an idea about the intensity or speed with which the parasite circulates in the 'men-flies system' in a given population and in a given location.

The same technical difficulties apply as were mentioned for the measurement of infection prevalence. Moreover, in order to be significant, observed *conversion* rates need to be greater than what would be observed on the sole basis of lack of reproducibility ('within laboratory' or 'within observer') of the test that is being used.

To our knowledge, real serologic conversion rates have rarely if ever been estimated. The difficulty inherent to the calculation of this kind of rates is that one needs to follow up strictly defined and entire cohorts, which is rarely feasible in a context of control programs (in practice the main source of information on frequencies).

### *Prevalence of parasitic disease*

If 'parasitic disease' is defined as '(visually) detectable presence of parasites' (a positive parasitologic test), it could be measured by the prevalence rate of individuals who are parasitologically positive (possibly making the distinction between those with and those without symptoms). Recently, in 1992, parasitologic prevalence rates in the neighbourhood of 25 % have been observed in NW Zaire (Arbyn, personal communication) in some foci.

### *Incidence of parasitic disease*

Again, if parasitic disease is defined by a positive parasitological test result, this incidence could theoretically be measured by the rate of parasitologically positives among (all!) the formerly negatives, per unit of time (which is, of course, rather a detection rate than a real incidence rate). Because of the need for strictly defined cohorts if one wants to measure this kind of rates, they are rarely available.

In practice some rough approximations are used like the 'Index of New Contagiousness' (ICN, 'Indice de contagiosité nouvelle'), for which the denominator includes all the individuals who are examined, and in which the time dimension is only indirectly involved (dependent on information about the periodicity of mass examinations).

With the presently usual parasitological techniques the measurable incidence may sometimes attain values estimated to be of the order of 25-30 per thousand inhabitants per year, in well-defined at risk populations. Measured on large populations (not all of which are at the same risk) ICN figures of 5 to 10 per thousand are on record (Burke, 1992).

An indirect measure of the incidence of the disease in a stably endemic focus is the probability for each exposed individual to have contracted the 'disease' in a life span. In foci where diagnostic and treatment facilities have been available for a long time, this can be approximately measured by calculating the proportions of formerly treated individuals in the higher age groups of the population.

In the Kasongo survey population, which we will be reporting on further, this proportion is of the order of 1 out of 3 individuals in the age group of 45 years and older (the Kasongo HAT control mobile unit's report on the year 1986 calculates an ICN of 7.8 per thousand - Unité Mobile B.C.T.-Kasongo, 1990). To the extent that the majority of these formerly treated individuals have been diagnosed by passive case detection, this proportion also gives some information on true (although past) morbidity, not only on the presence of infection. Of course, the fact that they have been identified and treated in this given area does not necessarily mean that this is also where they have been infected.

### 2.2.3. The problem of denominators, endemic disease and epidemics.

All these prevalence and incidence rates and indices have a problem in common: how to define the denominator? HAT is said and known to be a *focal* disease, but what is a 'focus'? Where does it end? In other words, when do these rates and indices become irrelevant, because the denominators are inadequately chosen?

How to define a 'focus'? It may be considered to be an essentially spatial concept, which contains an 'epicentre', but also a 'functional space' (Hervouët, 1992), roughly defined as *'the physical and social space normally occupied by the populations who are touched by the disease, to which should be added the space occupied by the populations who habitually have contact with the epicentre'*. Such a functional space is ecologically and geographically determined but also socially, to the extent that in the pathogenic system of HAT, land use (the use of space, the management of space) and social organisation play an important role in the diffusion of the parasite.

Looked at in this way, a 'focus' becomes something conceptually more defined but also practically more difficult to determine, because in the absence of quantitative criteria of some sort this extends the notion of 'focus' to the entire geographical zone where transmission is theoretically possible, i.e., ultimately, the entire fly belt. This is very close to the initial concept of 'infected' and 'uninfected' areas (to be mapped and cordoned off) as it was used by the early European sleeping sickness investigators in the first decade(s) of the 20th century. In order to be practical, the definition should

include some criteria to decide where the perimeter of a 'focus' can be located. In practice, such decisions are made in an empirical way, and retrospectively, based on numbers of identified disease.

In HAT, related to the concept of 'focus' is the concept of 'epidemic'. One definition is given by Hervouët, with Laveissière, in 1992:

*'Pour ne pas compliquer les choses (sic), nous considérerons ici les phases endémiques de la maladie comme celles où elle est socialement inapparente ou peu s'en faut. Au contraire dans une phase épidémique les individus touchés sont nombreux, la maladie est identifiée par les populations, et la survie de la société peut être mise en cause.*

*Le passage d'une situation endémique à une situation épidémique traduit aussi l'établissement d'un état d'inadéquation entre les potentialités du milieu et les systèmes d'utilisation du milieu mis en place par les sociétés humaines.' [...] 'Il ne peut y avoir d'épidémisation que s'il y a, après transmission du parasite, diffusion de celui-ci à l'intérieur d'un espace, que ce dernier soit physique ou social. La transmission originelle peut être conséquence de propagation de la maladie, de l'importation du parasite d'une manière circonstancielle par un quelconque "passant", qu'il soit ou non lié aux populations résidentes. La transmission peut aussi être le résultat de la présence dans l'espace considéré, d'une manière aisément perceptible ou non, du parasite.*

*Au contraire de la propagation, circonstancielle, la diffusion de la maladie à l'intérieur d'une société est un phénomène stochastique, structurel et conjuncturel lié à la transmission qui est ponctuelle, que ce soit dans le temps ou dans l'espace, et relève des lois de probabilité en relation avec les structurations physiques et sociales données au milieu par l'homme.*

*Le passage d'une phase endémique -sans diffusion ou presque- à une phase épidémique doit être considérée comme étant la traduction de l'accélération de la circulation du parasite entre les hommes par l'intermédiaire de la glossine vectrice, c'est à dire que la diffusion est alors importante.'*

We have quoted here rather extensively and in the original language because this description is the most precise and at the same time synthetic one we have met. The authors conclude:

*'La trypanosomiase humaine est un réel système écologique qui existe et change par le jeu de divers processus interactifs dont chacun s'inscrit dans un réseau de déterminations, en grande partie stochastiques, qui s'enracinent parfois loins dans le temps et souvent très au delà des limites spatiales des foyers.'*

But maybe the phenomenon of epidemics (as defined here: a socially identified disease problem) is even more complex. In the above description the basic emphasis is on the speed with which the parasite circulates in the human population, in other words on the incidence of infection. This is undoubtedly plausible and legitimate. However, it takes into account only the 'outside' mechanics of transmission and diffusion, even though these are explained to be co-determined to a large extent by social events and practices. Another way to look at the determinants of 'epidemics' is to investigate the 'inside' dynamics of the parasite-host relationship, how the individuals constituting human populations react to infection, and why. This would also be determined to a large extent by outside factors, but the determinant of 'epidemisation' would be a *change in relative virulence* of the parasite vis-à-vis its host or host population (or conversely, a change in 'receptiveness' of the hosts for the development of the parasite), resulting in an acceleration of the natural evolution of the infection and/or the 'awakening' of dormant infections. In the words of John Ford (1979):

*'It is a complex subject, involving not only change in human ecology, [...] but also the associated changes in composition and behaviour of vegetation and soils, of the wild fauna and of the tsetse which live upon them and, throughout the animal components of this ecosystem, change in their immunological interrelationships.'*

Another conceptual problem with respect to the notion of 'epidemics' is the possibility that high numbers of 'cases' are simply the result of a lack of suitable intervention. Thus, observed high prevalence rates would simply be the accumulated result of 'normal' transmission and diffusion patterns. The implicit hypothesis here is that, if nothing is done about it, high prevalence

rates for HAT are unavoidable (at least in some places), and have not necessarily anything to do with accelerated circulation of the parasite or with an altered response of the human host population. In that case it would be less confusing to use the term 'pseudo-epidemics', or simply 'high prevalences', the latter always being the observation that is at the basis of action oriented reflection.

So, to return to the problem of the denominators, their choice should, obviously, be based on *relevance*. It is clear to everyone that the total population of Zaire is not appropriate as a denominator if one wants to quantify some sort of incidence density of HAT in that country. For that purpose, the numerator alone (absolute number of newly identified cases) would be much more appropriate - if correctly interpreted. At the other extreme end of the range, a family size denominator (say, 30 individuals), even though a (high) rate calculated on such a denominator can be highly informative about some local aspect of reality, is not necessarily very relevant for planning purposes.

If the distribution of HAT is focal, the relevance of the chosen denominator, for *practical* purposes, lies in its usefulness for calculating a rate that is *informative* for what one wants to know for operative decision making: first, where is the 'epicentre', second, where does this 'focus' end, or, conversely, which populations are included in it, third, how does the frequency of disease evolve in time and space. If we accept this, all social units inside which HAT is non-existent (for reasons that are understood), should ideally be excluded from the denominator.

On the other hand, if the purpose is to decide on *priorities*, in a given administrative or political context, the denominator should be relevant for this particular context. In such a context, numerators are probably more decisive than denominators anyway.

#### 2.2.4. Specific mortality due to HAT

Specific mortality due to HAT is defined here as the proportion of deaths, in specific age groups, that can be attributed to HAT.

Again, there is a conceptual problem here, well known in mortality statistics, which centres on the distinction between *cause of death* and *last illness*. If and to the extent that HAT renders individuals more susceptible to other diseases, or is synergistic in their lethality, specific mortality becomes difficult to define. Two extreme 'case' definitions are practicable (a case here is the event '*death attributable to HAT*')

- (1) all deaths among known parasite carriers, excluding accidental or traumatic death;
- (2) only those deaths, among known parasite carriers, that have gone through the terminal clinical stage of HAT.

In both cases, precise and accurate measurement of the occurrence of these events will be very difficult. It may rather have to be expressed in terms like 'unnoticeable', 'important', 'very important', 'dramatic' and the like.

It can be accepted that in situations of high endemicity, in the absence of specific interventions, HAT is responsible for an important part of surplus mortality in the age groups that are exposed to the risk of infection - generally speaking, from young adult age onward, although this is not necessarily so. Some epidemic situations have been described in which one could speak of 'more than dramatic' mortality. Probably the best known one is the much cited Busoga - or Nyanza - epidemic on the northern shores of Lake Victoria, which is said to have 'killed' 200,000 individuals out of a population of 300,000 between 1901 and 1906 and which provided the most important impetus for the colonial powers to put 'sleeping sickness' on top of their priority problems' list.

Strictly speaking, the mortality that is 'induced' by the toxicity of treatment is not really part of the 'health problem' that is HAT, but is part of the intervention, of which it is a 'cost'. The consequences of this treatment lethality are to be taken into consideration for the assessment of the *acceptability* of possible interventions.

### 2.3. Economic cost

It is useful here to make the distinction between *direct* cost and *indirect* cost.

Although technically economists may not agree on these definitions, we will define *direct cost* as the sum of all the expenses caused by attempts to do something about the (existing) problem of HAT, as well by the households or individuals as by the health services or other authorities, public or private. *Indirect costs* will be defined here as the loss of productivity or economic activity caused by the health problem.

Defined this way, it is clear that if nothing is done about the problem of HAT, there will only be indirect costs and almost no direct costs. This would mean that there is no programme or specific intervention to tackle the HAT problem and that the patients do nothing at all to seek care (be it in the modern or in the traditional sector) or to avoid infection.

It is equally clear that, with these definitions, lowering indirect costs, if possible, will have to be done at the expense of high(er) direct costs. The latter will, of course, vary with the kind of intervention that is selected.

This cost must be interpreted also in terms of the *opportunity cost* it represents, i.e. what could have been done with these resources, if they had not been used as they have, in order to meet other needs (Drummond et al., 1987). This is essentially a matter of deciding on priorities among different needs, and therefore essentially a political decision in the larger sense of the word. The notion of opportunity cost will equally intervene in the choices to be made between different possibilities of action, when cost-effectiveness techniques will have to be used in order to compare different approaches.

The *indirect cost* corresponds to the loss of economic activity (production of goods and services) that can be attributed to the existence of the health problem. In subsistence economies and in situations of near universal unemployment, this indirect cost is difficult to measure. It can be accepted that this indirect cost of HAT is not the most important one,

except in extreme situations. Again, the classical example of one such extreme situation has been the Busoga epidemic, mentioned before, which, with the help of some hindsight, elicits present day comments like 'sleeping sickness was the AIDS of the turn of the century' (Boothroyd, quoted in Kolata, 1985). The same event induced, according to some interpretations, a profound fear among the colonial powers that the African population, an important colonial resource in terms of labour force, would be decimated (Lyons, 1992). Apart from rather qualitative descriptions of this kind, the literature in this field is not very illuminating.

#### *2.4. Social cost*

Social cost here means those more or less intangible - but very real - consequences of the health problem which cannot, or at least not easily, be expressed in economic terms, and which go further than the context of individual suffering. There is, of course, also a 'social' cost to the interventions, programmes or actions undertaken in order to do something about the problem.

Among the social costs of the problem of HAT are the many problems that are linked to the reduced quality of life for the suffering individual (pain, incapacity, anxiety, fear...) and the repercussions of these problems on the other members of his/her family and the larger community of which he/she is a part. Premature deaths create orphans, widows and widowers, and almost always impose a serious burden on community and individuals. Partial or total incapacity implies that the tasks and duties of the diseased have to be taken over by other persons. If important numbers of HAT patients need to be admitted to hospitals, this may influence the quality of hospital care that can be given to other people. And so on.

Depending on the severity and frequency of the HAT problem in epidemiological terms, its social cost may be or become very important and may be the principal source of motivation for patients (or potential patients) to partake actively in the search for solutions. On condition, of course, that the social cost of the 'solution' is not greater than the social cost of the 'problem'.

### 3. CONCLUSIONS WITH RESPECT TO THE IMPORTANCE OF THE HAT PROBLEM

HAT is a potentially very important problem in many areas, mostly well defined.

Describing its importance is not a simple matter. There is, first, the conceptual ambiguity about the difference between infection (determinant of disease) and suffering or morbidity (the real problem). Second, the frequency variables that are used (prevalence, incidence) vary over time and are not always comparable, given the range of techniques and criteria that are being - or can be - used.

Moreover, within these frequency variables, the choice of the denominators is far from simple and depends on the use one wants to make of them. For ordinary planning and management purposes, one could say that the numerators are the more important element anyway, but for research purposes (and these may be relevant also in the routine planning and management process), correct denominators are essential. In the case of a focal disease like HAT, the choice of the denominator is then essentially a problem of correctly stratifying the population, but this is possible only if the risk factors or determinants are known sufficiently well. As to the latter, we will try and find out what is known about them in the following sections: the system and the possible interventions.

#### *The 'system'*

In this kind of analysis we define the *system* as a structure of constituting elements and the dynamic relationships that link these elements together. These elements are selected with relation to their relevance for describing the system in a public health perspective.

The *model* of the system is presented in the form of a diagram in which each 'box' represents a well defined group of the population (if only theoretically, but preferably also in a very practical way), according to their status of 'ill' or 'not ill', 'infected' or not, 'contagious' or not, and possibly

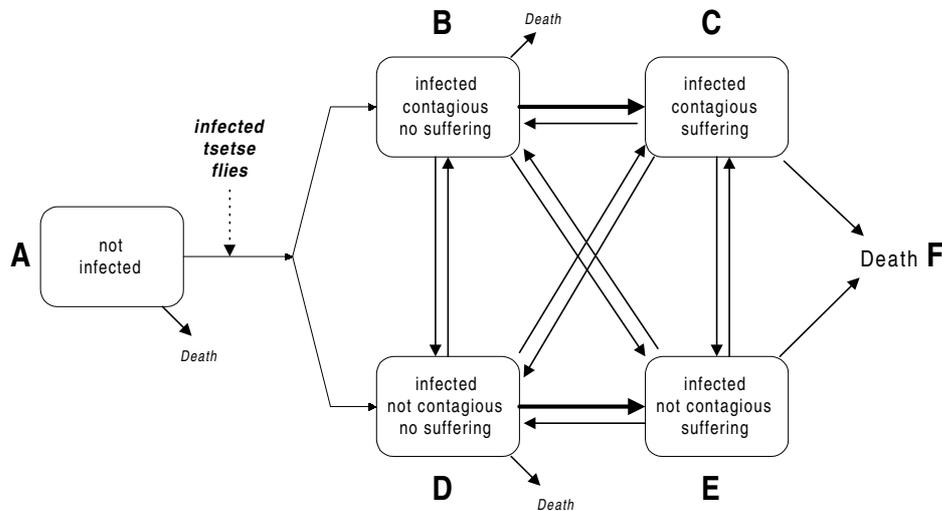
according to other criteria if these are relevant. The boxes are linked to each other by the probabilities to pass from one to another (arrows), which have the dimension of 'risks' (even if the direction of the arrow is toward a more 'advantageous' status). As much as possible, these risks are expressed in their time dimension (per unit of time).

Part of this model represents the natural history of the disease. To this is added the transmission part. In order to complete it, one adds the factors that may influence the probabilities of transitions between the boxes and, if possible, the 'weight' of this influence. The complexity of the model is determined by the relevance or usefulness of the distinctions that need to be made: the model needs to be as complex (or detailed) as necessary for a good understanding of the system and for the consequent selection of interventions or activities.

In the case of HAT, which is a transmittable disease, and from the public health point of view, one could start from the principle that there are three important and relevant characteristics that may help one to define distinct human population groups in the model:

- *infection*: the fact of having been infected with the parasite, and therefore the *possibility to evolve or progress through the natural history* of the disease;
- *contagiousness*: the capacity to participate, as a source, in the transmission between man and fly;
- *suffering*: the human condition that is at the origin of a call for help, in other words, of the demand for curative care (which a health service is supposed to meet).

The simplest theoretical model would then be the following.



The implicit hypothesis with this presentation is that the animal reservoir, if it exists, is of marginal or negligible importance - from a public health point of view.

The condition for departure from box **A** is *transmission*.

The condition for transmission is the existence of boxes **B** and **C** (combined with the presence of flies that are susceptible to infection).

The return to box **A** can be termed '*sterilisation*'.

Between boxes **B**, **C**, **D**, **E** all sorts of circuits can be followed which describe (or are variations of) the natural history of HAT, it being understood that the probabilities of certain circuits are much stronger than others...

The fact that these boxes seem to be simply defined does not mean that in reality all individuals can easily be 'classified' according to these 3 criteria. To the extent that these criteria are relevant and necessary, the practical difficulties in classification would be relevant areas of research. Moreover, the probabilities to go from one box to another (in 'natural'

circumstances) are far from well defined. Again, to the extent that it is important and relevant to know these probabilities, they also would be relevant research questions. From the public health point of view, 'important to know' means, in essence, 'useful - or necessary - for rational decision making'.

We may very well be compelled to make this first model more complex, by dividing certain boxes in two or more categories. For instance, in the boxes containing the element 'suffering', knowing that there is a potentially important progression in this suffering, it will probably be necessary to distinguish patients whose CNS is affected, or those who show a serious handicap or incapacity. But as a first step, this simple model allows us to identify the different *types* of interventions that are theoretically possible.

## *The interventions*

According to the rules of the method we are following, the first list of possible interventions should be exhaustive and include every theoretical possibility. The reason for this is that by doing so a maximum objectivity is guaranteed: elimination of certain interventions will have to be *argued* on rational grounds and based on specified criteria. All the same, certain theoretical possibilities are, almost inevitably, eliminated from the beginning (like, e.g. 'treatment of infected tsetse flies', which really sounds too much like science-fiction, at least for the moment).

This illustrates how this analytical method can and needs to be adapted to the purpose of the exercise. If this purpose is to reduce the problem by acting on the system *now* or in a foreseeable future, the list of interventions should contain only those possibilities for which at present technical possibilities exist. On the other hand, examining (or inventing) possibilities for which no technical means are presently available may be a creative exercise for the purpose of directing or generating relevant research activities.

Selection of interventions will have to be done in a second step, on the basis of well defined criteria.

We propose to order a first list of possible interventions according to a 'rough-but-robust' classification based on the different types of 'prevention':

- *Primary prevention*: prevent the non-infected from getting infected:
  - avoid the contact between 'non-infected man' and 'contagious fly'
    - ✓ by acting on the contact with contagious flies (1)
    - ✓ by acting on the contagious flies (elimination) (2)
  - avoid the contact between 'contagious man' and 'non-infected fly'
    - ✓ by acting on the contact with non-infected flies (3)
    - ✓ by acting on the contagiousness of man (treatment) (4)
  - protect non-infected man against infection
    - ✓ by acting on his active immunity (immunisation) (5)
    - ✓ by protecting him (chemoprophylaxis) (6)
  - protect non-infected flies against infection (7)
- *Secondary prevention*: stop the evolution toward suffering:
  - identify non-suffering infected man and treat (8)
- *Tertiary prevention*: stop the evolution of the suffering toward invalidity and death (i.e., strictly speaking, curative care):
  - identify infected man suffering from HAT and treat (9)

From the public health point of view, the **criteria for selection** of an intervention would be summarised mainly by the words *feasibility* and *desirability*. These two notions are determined by a number of characteristics of the intervention, some of which they have in common:

- its *technical efficacy* (which is what one could expect of it theoretically, as measured or observed in highly controlled circumstances), but, more important,

- its *operational efficacy* (or 'effectiveness'). The latter depends on how effective a technically efficacious intervention is, or can be, in routine or real-life settings (where a lot of elements in the overall environment are not controlled), and is therefore also defined by characteristics of (i) the health

service (when relevant): existence, accessibility, functioning; (ii) the community: perception of the problem and 'compliance' with the intervention; (iii) the environment;

- its *cost*, and derived from that, its *efficiency* (effectiveness as compared to resources that are available or need to be found);

- its *acceptability* and, consequently, its acceptance by the community

The comparative 'desirability' of an intervention will have to be assessed in terms of how it can influence the disease *system* as a whole and, possibly, other disease systems. This 'desirability' will depend on the effectiveness, of course, but also on the epidemiological context. It is not necessarily a criterion of the 'all or nothing' type; some activities may be more 'desirable' than others. Moreover, solving the health problem in terms of individual suffering is always considered desirable and relevant, even if it does not affect the system.

The way the listed interventions have been formulated so far, they clearly are not offering sufficient information to make this kind of selection. It will be necessary to examine in some more detail how they can be implemented.

#### (1) ACT ON THE CONTACT BETWEEN 'NON-INFECTED MAN' AND 'CONTAGIOUS FLIES'

This is essentially a question of the use and management of space by man. It is, in principle, possible for man to avoid encounters with contagious tsetse flies. Since he cannot know *if* a tsetse fly is contagious or not (except in areas where there is no HAT), this means, in practice, avoiding encounters with all tsetse flies.

In order to do this systematically and consciously, it would be necessary

- that man recognises tsetse flies;
- that man knows that the tsetse are the vectors of HAT;

- that the flies live and stay exclusively in well identifiable areas;
- that man is capable of defining and recognising such areas;
- that these areas are not of vital interest to man.

This is a matter of human behaviour. If the nuisance caused by the flies' attacks and bites is not by itself a sufficiently motivating factor for adapting this behaviour, the fear of the risk to get infected with trypanosomes will be (potentially) motivating only if the illness is a sufficiently recognisable phenomenon and sufficiently frequent for individuals and communities to pay attention to it. In this context it may be useful to point out that the link between the presence of tsetse flies and the occurrence of HAT is by no means obvious for someone who has not read the textbooks. Many areas are heavily infested with the flies without producing any case of *human* trypanosomiasis for long periods; in others, just a 'handful' of flies appears to be capable of maintaining high prevalence of the disease. In other words, in West African trypanosomiasis it is not (so much) the number of flies that is correlated to the occurrence of infection, but rather (among other things) the 'closeness' of the man-fly contact, resulting in a higher probability for each single fly to bite different men. In terms of 'closeness', one of the more effective transmission modes is exemplified by the 'peri-domestic' transmission as described by Frézil and his team in the Niari focus in Congo (Frézil et al., 1980; Gouteux, 1991). Another type of possibly very close contact is produced in an environment where the tsetse's ecological requirements force it to live and hunt in highly restricted areas (like rare water holes) which also happen to be vital to man (cf. Dutertre, 1968; Snow et al., 1991).

A KAP survey in the Vavoua focus in Ivory Coast (Laveissière and Meda, 1992) revealed that only 11 % of interviewed individuals knew that HAT was transmitted by tsetse flies. Moreover, only about 37 % really knew how to recognise the flies. (It is true that many of these people were not indigenous from the area but that situation is not uncommon anywhere, nowadays).

The effectiveness of an adapted behaviour in 'using and managing space' (i.e. its effectiveness on the level of endemicity of the disease) may be

quite high (cf. the differences between ethnic groups living together in certain foci of Ivory Coast, as analysed by Hervouët and Laveissière - 1987), even if it is not necessarily legitimate to state that this behaviour is consciously adopted with the objective of reducing or avoiding the HAT problem. They show that different ethnic groups, living within the same geographical 'focus' show quite different incidences of trypanosomiasis and that this difference can be attributed to the way their 'social space' is conceived and organised.

If we are talking in terms of *interventions* this would mean actively trying to change people's behaviour, a notoriously difficult thing to do. If we are talking in terms of *research* (trying to understand), the theoretical potential of investigations into the space using behaviour of population groups would be the possibility of identifying sub-groups in a focus' population that would be more at risk (or the only ones at risk) of being infected, thus better circumscribing the 'focus population'.

On the basis of almost all past experience one can say that the real effectiveness of trying to *induce a 'conscious' change* in people's behaviour is very low as long as the problem is not perceived to be grave, the risk to be high, and the change in behaviour understood to be effective. In early 20th century colonial times, a different use of space was often *imposed* on the local population. This involved measures such as destroying villages, moving and resiting populations, trying to change the settlement patterns of entire ethnic groups (like the Azande in Central Africa), controlling the movement of individuals ('medical passports') and communities; these interventions went under the name of '*administrative*' or '*agricultural prophylaxis*' and proved to be extremely difficult to implement (as can easily be imagined).

Another type of intervention that can theoretically be considered consists in *modifying the ecosystem*. An example of such an intervention (from the pre-colonial era, even) is described<sup>1</sup> by G. Prins (1989): '*Shoshangane of*

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<sup>1</sup> A more detailed account of this story, or at least of a remarkably similar one - the names are either spelled differently or really are different - is given by Swynnerton,

the Gaza ordered his people to congregate around him in the tsetse bush of the Mzilizwe valley. The bush was cleared, the new land cultivated (and thus kept clear), but several large areas were deliberately left uncleared. Wild game was confined to them and outside them the game was hunted. Game guards controlled their movement. The tsetse vanished.' [...] 'Shoshangane was succeeded by his son in 1885.'

Of course, the perceived problem in this area (Southeast Africa) and at that time, was not really human trypanosomiasis, but *nagana*, the animal form of sleeping sickness, for which the correlation with (and the role of) tsetse flies had been well perceived since a long time (i.a., see Bado, 1993), and which made it impossible to keep cattle or horses in large areas of land. Thus the problem was rather well understood and its existence felt everyday (although Shoshangane's rather drastic solution was implemented in the spirit of an 'experiment' or an empirical test which proved to be successful). Nevertheless, it remains a clear example of how modified land use *can* be effective in avoiding contact with the tsetse. It is also clear that the type of societal organisation plays an important part in the feasibility of this kind of intervention.

Still another theoretical solution, if one wants to avoid man-fly contact would be to offer other targets for the flies to feed on. This rests heavily, of course, on the hypothesis that, in practice, there is no other than a human reservoir.

There is evidence that for *G. palpalis*, to have a real chance to become infected with metacyclic forms of *T. brucei gambiense*, a number of rather restrictive conditions need to be fulfilled (Wijers, 1958):

- the fly's first blood meal must be taken within the first 24 hours after emergence of the fly;
- the first host must be human (and sufficiently contagious);

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1921.

- the fly must then survive for at least 18 days in order to become contagious for man.

If there is a choice of other likely animals to feed on, the probability that this first blood meal is taken on a contagious human is, of course, reduced (Sékétéli, 1989).

Other remaining possibilities to reduce man-fly contact are physical barriers (?) and repellents (?)

After reviewing this possibility of intervention, what can we conclude so far?

- In terms of *theoretical efficacy* we can say that, depending on a number of conditions, man can avoid contact with tsetse flies through his use of geographical space and by influencing the ecosystem. It has been done and it is being done, although usually only to a certain extent. Its theoretical efficacy is quite high.

- In terms of *operational efficacy*, the effectiveness in routine situations of this kind of intervention is dependent on many conditions, not the least of which is the willingness to change one's behaviour and the fact that tsetse infested territory must not be vital to man.

- In terms of *cost*, the intervention's cost is mainly determined by the opportunity cost of alteration of land use and/or of behaviour.

- In terms of *acceptability*: this will depend on the 'cost', but also on the perception of the problem and the risk involved in contacts with infested flies, but also to a high extent on the understanding of the effectiveness of a change in behaviour.

In conclusion: this is probably not very realistic as a main intervention, but can possibly be useful as a secondary measure, in selected areas and environments.

## (2) ELIMINATING CONTAGIOUS FLIES

The objective here is to reduce, as much as possible, the number of infecting bites.

In practice this amounts to eliminating all *Glossina* flies without distinction, infective or not, i.e. 'vector control'. Various methods have been tried and are available:

- trapping and killing;
- poisoning with insecticides (by spraying or by using impregnated screens);
- reducing fertility in the fly population (sterile males).

Making life hard for the tsetse flies by modifying the environment, which may also 'eliminate' the fly population very effectively, has been covered under (1).

At present, the most popular trends in vector control appear to be the use of traps (several sub-species specific versions of which are named after their different inventors or after the focus where they have been developed) and impregnated screens.

Another effective means of reducing tsetse fly populations appears to be ground spraying of the vegetation in and around villages, with remanent insecticides like the pyrethrinoids. Possibly available atomisers used for agricultural pest control can be used for this method (Sékétéli et al., 1985; Sékétéli and Kuzoe, 1986).

A reduction of the apparent density of the vector population by more than 90 % is said to be satisfactory if it can be maintained for the duration

of the pupal stage of the insect (Sékétéli and Kuzoe, 1986) , which is about 1 month at a temperature of 25 °C. <sup>2</sup>

- The *technical feasibility* of vector control by trapping and spraying appears to be good, if and as long as the necessary resources are available. The 'social' feasibility of maintaining the necessary effort, on a large scale, for a long time, poses an important problem of organisation and motivation of the community.

- The *impact of vector control on the level of endemicity* (in the human population) depends on a number of factors.

a) If vector control is practised as an isolated measure: one would not expect much initial impact on the *prevalence* of HAT. If and when the number of infecting bites can be reduced to almost zero, one can expect an im-

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<sup>2</sup> Normally tsetse populations have a relatively slow rate of increase, although at low fly densities the fly populations will tend to grow faster, due to the absence of normal density-dependent constraints (Rogers and Randolph, 1984).

Because of the relatively slow rate of increase, sustaining an additional fly mortality of 3 % per day can eradicate an (isolated) fly population within one year (Dransfield et al., 1991).

Savannah flies (generally of the *morsitans* group) are highly mobile (flights of up to 2-5 km a day). For trapping and killing interventions this means that these flies will readily find their way to traps and targets. In these circumstances for vector control interventions (by trapping) to be effective, large control areas (> 100 km<sup>2</sup>) are needed, but relatively few traps are needed per km<sup>2</sup>.

On the other hand, riverine and forest flies (generally of the *palpalis* group) are less mobile (flights of 200-500 m). Therefore the number of traps/km<sup>2</sup> offered to the flies needs to be much higher, but more local control (e.g. at village level) is possible (Dransfield et al., 1991).

Female tsetse flies copulate only once and are larviviviparous; they live for about 3-4 months and bear <10 larvae in this lifetime (Janssens and Burke, 1992). This opens up the theoretical possibility to effectively decrease reproduction by introducing (sufficiently competitive) sterile males. In terms of operational feasibility, however, this approach has never been sufficiently simple to break through as a large scale intervention.

portant and rapid reduction of the *incidence of infection* (but this is difficult to measure directly) <sup>3</sup>.

b) If vector control is practised jointly with case-finding and treatment of contagious men: the 'marginal return' of the vector control activities seems to be related to the effectiveness of the case-finding and treatment. If the latter is high, resulting in a reduction of HAT endemicity to very low levels, the marginal return of vector control appears to be lower (Simarro et al., 1991).

c) The level of endemicity is a co-determinant of the potential impact of vector control activities: possibly a well implemented vector control programme may be the decisive input that is necessary in order to *extinguish* a 'focus' that has been 'activated', in other words, to entirely stop the

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<sup>3</sup> Remarks:

- tsetse fly populations re-establish quickly to their previous levels once vector control activities are stopped. In order to have a significant impact on the level of endemicity of HAT, vector control as an isolated intervention can have a more or less lasting effect only if it is maintained over a longer period than the survival of contagious men;

- the flies' infection rates with *Trypanosoma brucei* are consistently very low (less than 0.5%, even in situations that are termed 'epidemic' - Mooloo et al., 1971). Reduction of the flies' numbers as a 'blanket measure' (which is the kind of vector control we are talking about here) can be expected to reduce the number of infective bites on condition that these low (fly) infection rates can be attributed only (or mainly) to purely probabilistic factors. If this is not the case (in other words, if a subgroup of especially effective vectors exists that may have different habits), vector control would have to be more selective in order to be effective.

It has been shown that tsetse susceptibility to *Trypanosoma* infection is strongly associated with (maternally inherited) midgut infection with 'Rickettsia-like Organisms' (RLOs) (Maudlin and Ellis, 1985; Maudlin and Welburn, 1988). To what extent this is associated with different fly behaviour is not known. More aggressive probing behaviour has been observed with infected tsetse flies of the *morsitans* group (Jenni et al., 1980), but to what extent this would be true for flies of the *palpalis* group (the most important one in West African HAT) we do not know.

parasite's circulation in a given area for a sufficiently long time. It is not something to be done in order to 'prevent the apparition of cases of HAT', at least not in a tropical forest environment (Laveissière and Meda, 1992). This may be different in the case of HAT of the *rhodesiense* variety, where new cases are recognised easily and quickly, given the natural history of this (different) disease. In the latter case, even vector control as an isolated measure may offer visible 'protection' to important populations (Lancien, 1991).

d) The 'stability' of transmission also plays a role: vector control programmes are much more cost-effective in zones where the transmission is 'unstable', i.e. where the flies are living in a less favourable biotope than would be ideal (for them) (Lancien, 1992). In such a case, 'tipping the balance' to the detriment of the tsetse is easier and quicker to achieve.

e) The fly species: some fly species have more of a predilection for human beings than others. In HAT, not so much the size of the tsetse vector population is important, but rather the intensity of man-fly contact. The degree of anthropophilic feeding behaviour of the different fly species can be examined by identifying the host species of the blood in captured tsetses' stomachs. If some fly species were not anthropophilic at all, reducing their numbers would evidently not result in reducing the number of man-infecting bites (which would always be close to zero). However, within the *G. palpalis* group, the main vectors of West-African *gambiense* trypanosomiasis, this is not very likely. The species specific behaviour is mainly of interest for the effectiveness of the traps and screens that are being used to control the fly population.

- *Cost of vector control activities.*

There is no uniform way of expressing cost for this kind of intervention. This is explained by the different types of environments in which it is practised (savannah, forest, 'pre-forest',...), resulting in quite different approaches in terms of surface to be covered and, therefore, widely varying numbers of traps and screens needed. Thus, cost per surface unit covered is not necessarily useful for comparison purposes. Because of varying population densities and different exposure distributions, cost per protected

individual is not very enlightening either. The cost of a trap appears to vary between US\$ 3 and 10, depending on the type. In South East Uganda (*rhodesiense* territory nowadays, transmitted by *G. fuscipes*) total annual program cost for vector control (using traps) was calculated to be US\$ 95 per km<sup>2</sup> (Lancien, 1991), of which US\$ 45 are needed for the traps alone.

In forest conditions (Ivory Coast) annual cost was calculated at US\$ 125 per km<sup>2</sup> or 7.25 per inhabitant, for the first year. After that, it would drop to US\$ 18 per km<sup>2</sup> - or US\$ 1 per inhabitant (Laveissière et al.1990).

Dransfield et al. (1991) calculate the cost of 1 'NGU' trap at US\$ 15 per year to make and operate, excluding labour and transport costs for servicing.

What can we conclude for an intervention aimed at eliminating contagious flies?

In terms of *theoretical efficacy*, what needs to be done is a drastic reduction of the number of flies in order to reduce transmission or stop it altogether. This reduction needs to be maintained for a sufficiently long time. The theoretical efficacy is quite high.

In terms of *operational efficacy*, the effectiveness of vector control in routine situations will depend very much on the input of expertise and on the motivation of the communities to continue implementing or supporting these activities.

The *cost* of vector control interventions is quite high in situations where an extensive fly belt needs to be tackled. It is possibly much lower if transmission sites are restricted to a small number of identifiable places. Exact figures may be available to us, but are not easy to interpret. However, vector control is never cheap and cost is likely to be the major constraint for this type of intervention if it is to be practised on an important scale.

The *acceptability* can be assessed to be high in principle and initially. The social and economic cost for the community may easily become too high in the long run, depending on motivation. This motivation may

depend, among other things, on the nuisance felt to be caused by the flies (i.e. mainly on their numbers), which is not necessarily related to the problem of HAT. However, motivation can be influenced, although this cannot be expected to be easy.

Conclusion: in principle a feasible and desirable intervention, but its feasibility depends very much on cost and consequently on the motivation to bear that cost. Results in terms of reducing human suffering will not be quick in the case of *gambiense* HAT.

In terms of needed knowledge, it appears that a lot of issues in the transmission dynamics through the tsetse vector population remain largely mysterious and/or unexplainedly variable. The finding that tsetse susceptibility to trypanosome infection is highly associated with another fly infection could open up important perspectives for a better understanding of HAT epidemiology and, thus, for a more rationally founded approach to tackle the problem.

### (3) ACT ON THE CONTACT BETWEEN 'CONTAGIOUS MAN' AND 'UNINFECTED FLY'

In practice this means identifying 'contagious men' as soon as possible and removing them (physically) from the transmission cycle. Another way to obtain this would be to act on the man-fly contact in general, but this has been covered in (1) and (2).

In the early history of sleeping sickness control this (removing infected people from the transmission cycle) was practised or attempted on a large scale, (identification and isolation of sleeping sickness patients in lazarets), among other reasons because there was not much of an alternative... We will not belabour the lack of acceptability of this kind of intervention in the present context, given the available alternatives.

If it is assumed that this exclusion from the transmission cycle is theoretically possible or feasible, the potential impact of this type of intervention

will in the first place depend on the technical possibility to *identify contagious men*, all or most of them, sufficiently early.

Identifying contagious men

Theoretically, '*contagious man*' is defined as '*an infected person capable of transmitting Trypanosoma parasites to the vector flies*' .

In practice, on the basis of a consensus firmly rooted in tradition and rarely challenged, are considered contagious all persons who can be shown to be carriers of parasites

- a) visually (i.e. on the basis of morphologic criteria), and/or
- b) on the basis of biochemical criteria (antigen serology), and/or
- c) more indirectly, through the parasites' effects:
  - presence of specific antibodies (Ab): Ab serology
  - pathognomonic clinical signs (if they exist).
  - alterations in bio-chemical characteristics of body fluids

The choice of a), b) and/or c) implies a series of **underlying hypotheses**.

In all three cases, it is admitted that '*demonstrable infection*' equals '*contagiousness*'. To what extent this is true is not really known. Clearly contagiousness is not possible without infection, but it is far from clear that infection is a sufficient condition for contagiousness.

There is a theory that only recently infected man would be contagious (Dutertre, 1968). This would be derived from Duke's observation that a strain of parasites residing in the same vertebrate host loses its aptitude for transmission. Furthermore, the quality rather than the quantity of parasites would play an important role, the 'stumpy forms' of the parasite being the most infective for the fly, and these stumpy forms would be most frequent in the course of the initial multiplication processes of the parasite (in man),

when different antigenic expressions of its coat are succeeding each other, but would disappear again afterwards (Dutertre offers no supporting references for this, in this otherwise consistently coherent and rich description). If this is true, the human reservoir of trypanosomiasis would be really functional as a source of transmission for a limited time only in each infected individual.

The hypotheses involving the parasite's life cycle and the infectivity of 'stumpy' and/or other forms have been a matter of much controversy, and the question does not seem to be resolved. The 'stumpy form hypothesis' was first formulated and thought to be confirmed by Muriel Robertson (1913), and went for a long time unchallenged. Duke (1933) provided some indirect (and rather weak) supporting evidence, and remarked that 'non-transmissible strains' are more likely to be found in slowly progressive disease than in the early stages. In 1960, Wijers and Willett, using monkeys, observed no relation between the level of parasitaemia and infectivity for the flies, but a good relation between proportions and absolute numbers of stumpy forms and infectivity. After 12 hours in the fly gut, only stumpy forms appeared to remain (Wijers and Willett, 1960). In 1964, Walker challenged Robertson's conclusions in these terms: '[...] based on one monkey, too few trypanosomes, no accurate counting method and only demonstrated in two of the three cycles given.' (Walker, 1964) It is true that Robertson's way of presenting and interpreting quantitative data looks rather artistic when assessed with present day critical methods... In 1971, Ormerod affirms that stumpy forms are not necessary as the sole infective stage for the fly (and also reintroduces the existence of amastigote extravascular forms in sleeping sickness trypanosomes - Ormerod and Venkatesan, 1971). He reaffirms in 1979 that stumpy forms are not known to be infective or not (he regards them as a degenerating form), but that other forms are known to be infective, and presents an alternative life cycle which is reproduced in the latest edition of Manson's *Tropical Diseases*, including tissue stages during which the trypanosomes change from one antigenic variant to another (Ormerod, 1979), a phenomenon also observed by Van Marck et al., who observe that the choroid plexus matrix could serve as a shelter for trypanosomes - and that invasion of cerebral parenchyma by parasites leads to a dead end - at least in rodents (Van

Marck et al., 1981). The infectivity of the stumpy forms is, however, brought back on the scene by the entomologists when Turner et al. report that in the tsetse midgut, slender forms were killed more rapidly than stumpy forms, suggesting that 'stumpy forms are primarily responsible for transformation to procyclics' (Turner et al., 1988). As we stated before, the question does not seem to be resolved. The existence of extravascular forms, however, appears as a possibly quite relevant parallel product of life cycle research, in spite of the enigmatic '*elimination of most information about tissue stages of this parasite in the English literature between 1912 and 1969*' (Ormerod, 1979).

Let us go back to the possible methods for identifying 'contagious man'.

- ad a): visual demonstration of parasites: the use of presently available visual (morphological) techniques as a criterion for decision on contagiousness implies that this contagiousness is directly related to the level of parasitemia. If parasites can be seen, the person would certainly be contagious; if one cannot see parasites, this would not necessarily mean that there are none, but the contagiousness would be considered to be less.

Even if, at first sight, this seems 'logical', on the basis of what has been said before and of what is known about some animal models there is reason to be somewhat less than positive in this assertion. The 'acute mouse' model fails to infect tsetse flies; the 'chronic rabbit' model appears to be much more contagious for the flies (Le Ray, 1989). Nevertheless, within one host species, the relation between contagiousness ('infectivity' for the tsetse fly) and level of parasitemia seems to be an easily accepted hypothesis, although nobody knows if this is really true.

- ad b): demonstration of parasite matter (Ag or DNA): if the method gives no information on the quantity of Ag or DNA - e.g. the extremely sensitive polymerase chain reaction techniques (PCR) - it would be admitted that there is no relationship between this quantity and contagiousness.

- ad c): presence of specific Ab: this assumes that, if there are parasites, there are Ab (which is not always true); it would equally be assumed that, if

there are Ab, there are Ag and therefore parasites (which is not always true either);

An alternative to the laboratory is to depend on clinical signs. This assumes that sufficiently pathognomonic signs exist, and it would be assumed that, if these signs are produced, the person is (still) contagious.

All these methods present a number of problems. All the techniques that are used have insufficiencies in terms of sensitivity and specificity, to variable degrees. These problems are partly attributable to the techniques themselves, partly to fluctuations (in time) of parasite densities (particularly in the case of visual morphological techniques). The most specific techniques have problems of *operational feasibility*, because of their technical complexity, the work load they imply when used on a large scale, and their cost. Therefore there is a need to '*concentrate*' contagious people first with a *screening* test, based on the presence of a 'screening sign'.

### Screening

The choice of the screening sign is based, implicitly or explicitly, on a series of hypotheses with respect to the natural history of the disease. Ideally, for a chronic or slowly evolving disease:

- the screening sign occurs **early** in the evolution of the disease;
- **all the affected individuals** present the sign at some time in the evolution of the disease (potential for sensitivity of the sign);
- the sign is present **for a sufficiently long time**, so that it is not missed by periodic (repeated) examinations, if this is the strategy that is used;
- the sign is present **with a higher probability** among the 'diseased' than among the 'non diseased' (if this is not the case, the 'screening sign' would not concentrate the target population, but would only reduce it in a random way). Such a higher probability is expressed by a *likelihood ratio* (LR) that is  $\gg 1.0$ , but, indirectly, one can

obtain a comparable information through figures of *relative risks or odds ratios* (RR,OR), which are then also  $\gg 1.0$ ;

- the sign is **easy to identify** and its identification is **not costly**.

Apart from this last criterion, which results only from the need for efficiency, all these criteria are determined by the *natural history* of the disease (place of the sign in the evolution of the disease, duration of the sign, frequency of the sign) or by the *epidemiological situation* of the environment where the disease develops (LR, RR).

Generally used screening signs are

- the presence of 'typical' neck glands (in practice usually 'puncturable' glands)
- the presence of specific antibodies
- the presence of suggestive complaints or symptoms.

**Gland palpation** has the important advantage not to be very costly and not to involve sophisticated technology. However, as an isolated practice and in mass examinations, the *likelihood ratio* of this sign (presence of glands) is very variable and may not even be significantly different from 1.0. This was recently quantified in *Kwamouth* - on a point prevalence basis using 1981 data - (Mentens H., 1992, personal communication) and in *Kasongo* - on a longitudinal basis (see further in this work), thus resulting in a random (or almost random) reduction of the target population, without any real contribution to effective concentration for case finding. Apparently this is not always so. Using data published by Todd in 1910, the sign 'enlarged glands' can be calculated to have a (significant) likelihood ratio of 2.37 and a sensitivity of 0.45; both these values point in the direction of a very useful screening sign. Generally speaking, the LR of this sign tends to be higher and gland palpation more useful when the disease is highly prevalent (or 'epidemic') as was recently observed once more in Northwest Zaire in 1992; once the prevalence has been brought down, or has fallen by itself, the 'concentrating power' of this screening sign tends to be much reduced. This may happen rather quickly: anticipating on the results of the

Kasongo survey that will be reported on further, in a multiple round study resulting in the finding of 40 parasitologically positive cases, 11 cases were identified by gland puncture, but 10 out of these 11 were identified in the course of the first of a total of 4 rounds.

This conclusion is far from new; it has been suggested decades ago, but often the differences in usefulness of gland palpation were attributed to geographical variations of the disease or differences in parasite 'strains'. Like most generalisations in the field of trypanosomiasis, it should be regarded with appropriate suspicion.

A second problem concerning the value of gland palpation as a screening test is the question if this sign occurs early in the disease, and how long it lasts (a few months?). In Winterbottom's original description (1803) of the sign that was given his name, it is mentioned as a feature that is soon followed by the clinical cerebral stage (in: Ormerod, 1991) and it was considered as such by the slave traders of that time and before. Also in the Kasongo study, out of 11 parasitologically positive cases identified through gland puncture, 9 were in the second stage of the disease as determined by cell counts in cerebrospinal fluid (CSF). Again, this may depend, at least to a certain extent, on the level of endemicity.

Clearly, as a screening sign, the 'presence of typical glands' has serious drawbacks. The least that can be said is that it can not always be relied on.

The **presence of specific antibodies**, detectable by mass screening techniques, is an early sign (2 to 3 weeks after the initial infection) and is expected to stay more or less constant during the entire evolution of the disease. Its LR in relation to the visual detection of parasites is very high, as well as its Positive Predictive Value (PPV) in situations of perceived endemicity. Its sensitivity, very high and far superior to that of the typical glands, varies between 80 and 95 % (Noireau et al., 1988), depending on the technique and probably on the parasite strains' variations.

A problem with serological screening techniques that is not very well documented is the lack of stability of individual test results over time. 'Spontaneous' sero-inversion rates have been observed that are surprisingly

high (reaching almost 50 % between two rounds in the Kasongo study, using indirect immunofluorescence; similar observations with the card agglutination test - CATT - on whole blood have been made in Ivory Coast and in Zaire - Laveissière et al., 1990; Pépin et al., 1986). Part of this lack of stability may be attributed to a biological reality (lowering of antibody concentrations below the positivity threshold), but another part reflects the lack of reproducibility that is inherent to the techniques itself. In order to obtain the full potential of these serological tests, this latter aspect needs to be controlled as carefully as possible and these tests need to be handled in a highly standardised way and with effective quality control measures. A positive serological screening result is without any doubt a very useful screening sign, but it also has its limitations.

The **presence of suggestive symptoms or complaints** (different from 'signs' such as the presence of glands or biochemical characteristics) is generally considered to be a screening sign of limited effectiveness if the objective is to identify contagious men early in the evolution of the disease. Logically speaking, the potential of this sign would depend on:

- the *existence* of early symptoms and their *frequency*;
- the '*perception*' of these symptoms by the individual or his social surrounding (are these symptoms perceived as 'problems' and can they be expressed as such?);
- the *motivation* they induce to express these 'problems' to someone whose function it is to 'find cases';
- the capacity of the 'case finder' to *recognise* these symptoms or complaints as a screening sign;
- the *discriminating quality* of this sign with respect to HAT.

Collective experience seems to indicate that, even if and when the verbal expression of complaints is highly facilitated and actively sought, complaints are concentrated in the group of patients who are generally qualified as 'second stage' (with altered CSF). However, the perception and the motivation to express complaints (in a context of HAT case finding) rest on individual psychological, cultural and social considerations that are

much more complex than what could be expected on the basis of purely and narrowly rational logic...

Still, in spite of their relative insufficiencies, the *simultaneous* use of the three screening signs that have been mentioned (glands, antibodies, complaints) will improve the effectiveness of the case finding, because the lack of sensitivity of any one of them will be partly compensated by the sensitivity of the others. The most sensitive sign (presence of antibodies) will always let go a number of 'contagious' individuals who will be partly recuperated by the much less sensitive sign (typical glands) or the sign (symptoms-complaints). The sensitivities are *unequal* but also *partly overlapping*. Moreover, their relative values appear to change with the epidemiological dynamics of the disease.

The possibility of *alterations in biochemical characteristics* offers a curious case of the 'blind spot' phenomenon in medicine, and we propose to develop this in some detail.

From the earliest years of parasitological trypanosomiasis research, around the turn of the century, it had been noted that the blood of sleeping sickness patients produced an immediate '**auto-agglutination**' when whole blood was put on a slide and covered with a cover slip. Whenever investigators at that time saw this phenomenon, they reacted by examining the blood in an extra careful way (as John L. Todd wrote in 1904: [...] "*bloods which 'agglutinate' in this manner are looked upon with the greatest suspicion*" (Dutton et al., 1904). However, it was considered that 'this appearance was by no means an infallible test for the presence of trypanosomes', and they left it at that. Six years later (1910) the issue was raised again and Todd, who had not considered it necessary to publish the observations before, apparently dived back in his field notes and produced a remarkable table, which we think worthwhile to reproduce here in a format that looks somewhat more contemporary (Todd, 1910).

auto- agglutin.	Apparently healthy individuals			Cervical gland enlargement			Symptoms of sleeping sickness		
	parasit			paras.			paras.		
	+	-		+	-		+	-	
+	51	145	196	81	48	129	51	19	70
-	5	806	811	12	179	191	7	2	9
	56	951	1007	93	227	320	58	21	79
	sensitivity: 0.91 specificity: 0.85 Overall sensitivity: 183/207 = <b>0.884</b> Overall specificity: 987/1199 = <b>0.823</b>			sensitivity: 0.87 specificity: 0.79			sensitivity: 0.88 (specificity: 0.10)		

In 1911, Warrington Yorke published a long article, mainly reporting on investigations into 'agglutinins', in different species of mammals including man (Warrington Yorke, 1911). Todd's 1910 article is given quite a bit of attention here, in the concluding pages. Yorke ends by writing "[...] *In conclusion it may be stated that in the light of the information obtainable a well-marked degree of auto-agglutination of the red blood cells is an extremely rare occurrence, apart from infection with trypanosomes*".

In 1912, A. Dubois published another 'note', confirming in fact Todd's sensitivity figure on a series of 38 untreated cases (parasitologically confirmed): 34 out of the 38 (89.5 %) presented 'marked' ("*nette*") auto-agglutination (excluding 'weak' agglutination - Dubois, 1912). His purpose is to draw attention to the fact that this auto-agglutination also occurs in people without trypanosomiasis (34 'healthy' individuals, 19 with agglutination; 22 'variously diseased' patients - '*malades divers*' -, 20 with agglutination). Dubois concludes: "[...] (la présence de l'auto-agglutination) *n'entraîne aucune conclusion diagnostique chez le noir du Congo*". However, his 'healthy' patients are described as 'no trypanosomes were found or they were not looked for because the person had no signs to suggest such a search', which suggests rather strongly that they may not be so innocently healthy as

would be needed for a relevant specificity calculation on a general population. As for the 'variously diseased' patients, Todd had already gone out of his way to show that auto-agglutination also occurred (though less markedly) in cases of relapsing fever, syphilis and beriberi. It is striking how fervently this 'lack of specificity' is stressed by the investigators of that time.

Nevertheless, the auto-agglutination phenomenon remains (quietly) on the scene. In 1927 Ledentu and Vaucel (Institut Pasteur de Brazzaville) write: "[...] *L'auto-agglutination des hématies est jusqu'à présent le seul signe objectif classique de probabilité de la trypanosomiase, probabilité assez vague d'ailleurs, comme l'ont montré L. Todd et A. Dubois*" (Ledentu and Vaucel, 1927). Using the same scoring system for agglutination as Dubois, they present findings on a group of 74 parasitologically confirmed cases of trypanosomiasis, resulting in a sensitivity (excluding 'weak' agglutination) of 60/74 or 81 %. They also examined a group of 96 individuals (controls) in whom no parasites were found, the majority of which were 'suspect' because of enlarged cervical glands. Using the same 'cut-off point' as used for sensitivity (i.e. 'weak' agglutination is counted as absence of the sign), auto-agglutination would be absent in this group ('specificity') in 62/96, or 65 %. Again, this is not a group of patients in which trypanosomiasis can be firmly excluded, as these authors are well aware: *'En réalité, il est bien probable que bon nombre de ces suspects étaient des malades [...]'*. Their main purpose was to compare the performance of the 'formol-gelification' test (Gaté-Papacostas) with the auto-agglutination, the latter appearing to have some 'normative' status. Incidentally, this formol-gelification test appeared to have had a sensitivity of 100 % in the group of 'cases' and a 'specificity' of 73 % in the group of 'controls' as defined here. Its main obvious drawback is that it takes 30 minutes before the result can be interpreted as 'negative'. Although the crude auto-agglutination has not been forgotten entirely, more sophisticated tests are being developed, hoped and expected to provide more insight. One of these is the 'red-cell adhesion', a variant of the 'Rieckenberg reaction', i.e. adhesion of red cells on trypanosomes from laboratory animals - not to be confused with auto-agglutination (Brussin and Beletzky, 1925; Davis and Brown, 1927; Duke and Wallace, 1930) ). Apparently, as the sophistication of laboratory techniques grows, the far too simple auto-agglutination (which produces itself) recedes from the

investigators' interest, to the point of being forgotten. While everybody starts looking in other directions, the auto-agglutination phenomenon appears to disappear in some long lasting collective amnesia.

The concepts of quantified sensitivity, specificity, positive and negative predictive values were not yet as fashionable at that time as they are now (except for sensitivity, which was sometimes calculated in the form of percentages), but all the data were there. The curious thing is that these findings have never been acted upon on a large scale, until Noireau and colleagues had the idea to repeat the experiment and published their findings (Noireau et al., 1991). Their experiment is conducted on 100 parasitologically confirmed patients and 166 controls (immunological non-cases) and auto-agglutination is assessed under the microscope with a power of x 20 (Todd stated that auto-agglutination can be 'recognised, very easily, by the naked eye', but it is not entirely clear whether that is how he assessed the phenomenon in his series). They come up with a sensitivity of 91 % and a specificity of 90 %, values that are basically very similar to the ones Todd provided the data for. The fact that their specificity figure is higher can be attributed to a more sensitive parasitological technique, which eliminates more false positives (agglutination + / parasit. -) than in Todd's series. Their main conclusions are that this technique could be very useful for 'health workers in deprived areas' (in general first line health care structures), especially because of the high *predictive value of a negative result* (99 % in a situation where the prevalence of the disease would be 3 %). Of course, in such a situation, the prior probability of *not* having the disease is already very high ( $100\% - 3\% = 97\%$ ; a negative auto-agglutination result would only add 2 % more certainty, but that kind of reasoning is applicable to all kinds of screening tests). We have no idea to what extent their findings are being acted upon in the practical organisation of case identification in the field.

At any rate, looked at with the presently prevailing, 'probabilistic', attitudes (of what some of us would call the *Homo economicus bayesiensis*), and if these data are confirmed in other epidemiological settings, this auto-agglutination phenomenon appears to have the potential of a remarkable screening test. It would compare very well with present serological

screening tests applied on general populations, which would make it especially useful for *active* case-finding (where 'active' refers to the fact that the initiative for the contact is on the side of the health service). To what extent its specificity remains reasonably high in a population of sick patients (like the ones presenting at some curative clinic, be it in a health centre or in a referral hospital), thus making it a useful screening test for *passive case identification* without increasing too much the work load involved in confirmation, is less clear. It is also quite possible that, in order to be of value for *excluding* trypanosomiasis in such a setting (in other words, for the predictive value of a negative result to remain very high), even 'weak' auto-agglutination should be considered as a positive result. Investigations of this type would surely be of great practical importance.

Since in the present context the intervention which would consist in identifying 'contagious men' and removing them (physically) from the transmission cycle, is not acceptable anymore, given the available alternatives, we will not discuss its (lack of) merits here. We will only keep in mind the discussion of the problems of identifying contagious men when discussing the next intervention.

#### (4) ACT ON THE CONTAGIOUSNESS OF MEN THROUGH TREATMENT

Practically speaking, this amounts to identifying contagious men and treating them effectively. In this context, an 'effective' treatment is one that '*eliminates contagiousness*'. Again, in practice, the hypothesis will be that 'contagious' equals 'infected', not necessarily on conceptual grounds, but in terms of identification criteria. Effective treatment will thus be expected to guide people back to box A, the 'not infected' (i.e. 'sterilisation'). If this equation ('contagiousness' = 'infection') is not accepted, one could ask the question if there does not exist a 'treatment' that eliminates - or reduces - contagiousness (the capacity to infect tsetse flies) without eliminating infection in man (the presence of parasites). Although at first sight this may seem unusual, it is not to be excluded *a priori*. There are parallels in medicine: tuberculosis patients, treated with isoniazid alone, which prove to be infected with isoniazid resistant strains, appear less contagious than before treatment (Riley et al., 1962). Another example is the treatment of

pertussis patients with antibiotics, which is done solely in the hope that contagiousness may be reduced.

To what extent therapy-resistant HAT patients remain contagious for tsetse flies is, to our knowledge, unknown.

The question of the identification of contagious men has been treated above (3).

The *effectiveness of the chosen treatment* (on the contagiousness of man) will depend theoretically:

- on the level of contagiousness before and after treatment implemented according to the state of the art (the hypotheses concerning the degree of contagiousness, in practice and according to the screening techniques used, have been expressed above);

- on the feasibility of (correct) execution of the treatment.

How can one measure the degree of contagiousness of men? One can submit that contagiousness is reduced to zero when there is 'sterilisation' (absence of parasites). However, this is impossible to observe directly, given the relatively poor sensitivity of the techniques that are used in order to demonstrate parasites, and given the sometimes prolonged presence of positive antibody test results among individuals who were correctly treated (Paquet et al., 1992; Kegels et al., 1992; Pépin et al., 1986).

In a more indirect way, and in the long(er) run, one can deduce a reduction of the *contagiousness* through the observation of an appreciable and sustained reduction of the *prevalence* (of infection) after treatment of all the 'infected' individuals in a community that is more or less stable and sedentary, in the absence of vector control activities. According to the observations of *Van Nieuwenhoven* in the Sudan, this is exactly what happens (Van Nieuwenhove, 1992a). A similar observation is reported by Bruneel et al. in Zaire (1994). The observations in Kasongo go in the same direction: reduction of serologic prevalence rates after one year of intensive case finding, even if in the latter case only those 'infected' individuals were

treated who ended up being confirmed cases according to visual, morphological criteria (parasites observed in gland fluid, blood or CSF).

A question that, to our knowledge, is not resolved is, whether treatment of an infected individual (supposedly contagious) in the second stage of the disease, with a treatment that does not attack parasites in the CNS, has a (lasting) impact on the contagiousness of this individual; and, if any, for how long? In the early Atoxyl treatment days, every detected parasite carrier was treated with this drug in the hope of 'sterilising' the peripheral blood, although it was known that the drug could not *cure* patients with irreversible central nervous system involvement; but to what extent this had any impact on transmission is not known.

Generally speaking, the intervention (4) has been one of the mainstays of systematic trypanosomiasis control ever since some sort of sterilising treatment has been available. Its objective is the reduction of the human parasite reservoir. The interpretation of its success in reducing the prevalence of parasite carriers needs to take into account the screening method used for identification of infected individuals. Since it appears that the value of a screening sign like 'gland palpation' depends on the epidemiological dynamics and history of the endemic (being much less useful in 'late epidemic' or 'low endemicity' situations: less sensitive and less discriminating), it is somewhat understandable that maintained trypanosomiasis control campaigns, entirely or mainly based on this screening sign, end up being less and less effective. This could be one of the reasons why the HAT problem reappeared on the Zairian scene so unexpectedly soon after the loosening of the (very intensive!) control measures, which were yielding progressively less and less 'cases' in the late fifties: it is possible that the human reservoir had not been cleaned up as thoroughly as was thought because, among other things, the screening technique (neck gland palpation) was not effective anymore in identifying parasite carriers.

What can we conclude from this analysis of interventions (3) and (4)? In this context one aims for a depletion of the 'human reservoir'. While we know that the reservoir *is* located in infected human beings, we do not

really know in which groups of this infected population contagiousness for tsetse flies is significant (i.e. relevant for transmission). Depletion of the human reservoir would be highly effective in reducing transmission if treated populations are highly sedentary with little demographic exchanges between foci.

Thus, in terms of our criteria:

- *theoretical efficacy*: potentially quite high;
- *operational efficacy*: the effectiveness of these interventions will depend on
  - the effectiveness (sensitivity) of the identification procedure;
  - the coverage (with these interventions) of the exposed population;
  - the effectiveness of treatment in terms of reducing contagiousness.

Especially the first two elements represent important problems, but these are to a certain extent vulnerable;

- *cost*: always (very) high, but variable according to the technology used for identification and treatment. Cost-effectiveness (in the medium and long run) with presently available identification techniques is probably better, in spite of higher initial investment, because of longer lasting effect;
- *acceptability*: if these interventions are implemented on a massive scale, their acceptability will depend to a large extent on the perception of the problem that is being tackled (HAT). Participation (or 'compliance?') with this kind of interventions seems to have been rather low in recent decennia.

The more important areas of the unknown seem to be the following.

*Which* infected individuals are contagious for tsetse? All or some? If some, when? What is the most important group? This question emerges as a fundamental one in terms of efficiency in routine conditions.

In the hypothesis that all infected individuals are to be considered contagious, what is the effectiveness of identification procedures? An answer to this question is needed in order to be able to predict the possible impact of these interventions and, therefore, for planning purposes.

Keeping in mind that we are in the discussion context of reducing or stopping man-to-fly *transmission*, we are compelled to conclude that the rational basis for this kind of control intervention, in *ordinary circumstances* of low or stable endemicity, is not very firm. The same or similar methods may be used with another purpose (prevent the future suffering of infected human beings), which will be analysed later.

#### (5) PROTECTING UNINFECTED MAN THROUGH (ACTIVE) IMMUNISATION

Although it would, of course, be very nice if an effective and non-toxic vaccine against this disease could be developed and used, up till now all attempts to develop an effective human vaccine have failed, for various reasons, mainly related to the antigenic wizardry of the parasite.

#### (6) PROTECTING UNINFECTED MAN THROUGH CHEMOPROPHYLAXIS

In order to have good impact, chemoprophylaxis implemented as an isolated measure, must: be effective (good protective effect); be non-toxic; and be maintained for a sufficiently long time and with sufficient coverage.

When given to (or taken by) the *uninfected only*, effective chemoprophylaxis would protect them as long as the substance is present in protective concentrations.

When given *indiscriminately* to all individuals of a community where HAT is endemic, and to the extent that the substance is also curative

('sterilising') for the non-identified infected individuals, one could theoretically expect a spectacular drop in the transmission, since the *contagiousness* of man for the flies is tackled at the same time as his *receptivity* for infection by contagious flies. If chemoprophylaxis were maintained for a sufficiently long time, the human population would be 'sterilised' and new generations of flies could not get infected. Ideal.

This optimistic scenario assumes: that the protective effect of the substance is (close to) 100 %; that the 'curative' or 'sterilising' effect (elimination of man's contagiousness) is (close to) 100 %; and that man is the only reservoir.

Let us accept that, for all practical purposes and as a general rule, the third assumption is confirmed for HAT of the *gambiense* variety.

In the history of trypanosomiasis control, especially in the former French and Belgian colonies, *suramin* first, but later especially *pentamidine* was thought to meet the conditions of 'protection' and of 'elimination of contagiousness' sufficiently well in order to be operationalised in the form of mass chemoprophylaxis ('pentamidinisation'). Moreover, pentamidine had the advantage of being eliminated very slowly from the organism; the protective effect of one injection was thought to last up to 6 months, which corresponded, at that time, to the interval between the rounds of the HAT control teams. Knowing that this substance does not pass the blood-brain barrier sufficiently well, and therefore does not penetrate the CNS, it was known from the start that this operation could not be sufficient to 'eradicate' the disease (in the hypothesis that a person, receiving pentamidine while being at the stage of CNS involvement, will remain contagious or become contagious again as long as he survives). However, it is often admitted that the practice of mass pentamidinisation has been useful, in the former Belgian and French colonies, to "reduce the HAT problem to manageable proportions" (as expressed in the 17th edition of Manson's 'Tropical Diseases'). This is not quite correct; in the Belgian Congo the first pentamidinisation campaigns were started after 1945, while the 'Index of New Contagiousness' (Indice de Contagiosité Nouvelle) had dropped already to 0.24 % in 1940, which is a quite 'manageable' situation

already (cf. Burke, 1971). At any rate, during the years of systematic mass treatment with pentamidine in the Belgian Congo, from 1947 onward, the numbers of new detected cases of trypanosomiasis declined steadily, in spite of increasing detection efforts, and in contrast with the 1941-1948 period during which these numbers remained rather stable (Janssens and Burke, 1992). The effort made for these campaigns is difficult to imagine these days; around 1950 some 2,000,000 people in the Belgian Congo received a pentamidine injection every 6 months (Burke, 1971).

It may be illuminating to re-examine the (published) evidence on which the "long lasting protection" of pentamidine was based. One such publication appeared in 1944 (Van Hoof et al., 1944). If one only reads the conclusion, one would find: "*Evidence is adduced of the prophylactic value of pentamidine. Guinea-pigs [...] were free from infection for at least 120 days. Volunteers injected with a single dose of 0.002 or 0.003 grammes per kg resisted for 10 to 12 months repeated bites of infective tsetse flies.*" One has to read the rest of the article to find out that the total number of volunteers was *two* and that no control volunteers (without pentamidine prophylaxis) were used in the experiment. Dissection of the flies resulted in the conclusion that Boukumu, the first volunteer, had been bitten, over a 12 month period, by 60 infective flies (infected salivary glands) and Moya, the second volunteer by 32 infective flies over a period of 9 months. The underlying assumption appears to be that no one can sustain such a challenge without becoming detectably infected (it is true that in nature, assuming a fly infection rate of 0.2 % in an endemic focus, 60 infective stings over 12 months correspond to a daily number of more than 80 tsetse stings, which is quite a bit). But even if we accept for the moment that in these circumstances no controls were necessary (which is quite debatable), it would be hard to imagine, nowadays, how an entire pentamidinisation programme could be justified on the basis of the results of experiments involving a sample of 2 individuals. A second experiment (Van Hoof et al., 1946) appeared to clinch it: guinea-pigs receiving a total of 6 mg/kg were 'protected' for 60 days; 3 human volunteers, this time receiving 4.5 mg/kg, did not become demonstrably infected for *up to* 184 days. Conclusion: "*la pentamidine peut prévenir l'infection naturelle de la maladie du sommeil chez l'homme pendant 6 mois.*" Prophylactic pentamidine campaigns were started in the Eastern

French territories in 1946, in the Belgian Congo in 1947. One can only hope that there was a lot more indirect supportive evidence to justify this move.

Investigation of the prophylactic action of trypanocidal drugs had been started before, notably by Lyndhurst Duke on suramin (Duke, 1936), who used, first, 7 'protected' volunteers (and 7 'clean', unprotected volunteers as controls) and later another group of 9, and then again 9 volunteers. All those having received suramin resisted experimental infection for at least 3 months. (Duke's published experiments were conducted mainly for *T. rhodesiense* infection, presumably with a view to controlling outbreaks; suramin could provide a more humane strategy than the "*dreaded old-time consequences of detection as a sufferer: removal to a distant hospital, wholesale evacuation of the homeland, and all the well-remembered restrictions and dislocations imposed in the days of our comparative ignorance and inexperience...*")

The low toxicity (or, at least, the low lethality: 1 death per 300,000 injections) of pentamidine was confirmed after some years of prophylactic mass campaigns (Gall, 1954; Jonchère, 1951). Injection sites are very tender and sterile gluteal abscesses are reported in 5 % of cases, using the intramuscular route (Pépin and Milord, 1994).

The argument that is often put forward against the practice of chemoprophylaxis is that it would 'hide' the infection and that afterward one would only see cases with CNS involvement, who are more difficult to treat. This is rather obvious, given the properties of pentamidine, but it is hardly an argument. In the logic of *protecting the uninfected*, it would suffice to discover the optimal periodicity of injection for concentrations not to fall below the ones needed for effective protection, while making sure that infected (and supposedly contagious) men are identified and treated adequately. We now know that for many people this period of effectiveness is much shorter than 6 months. Recently reported elimination half-lives, after one dose, vary from 9.4 hours (Conte et al., 1986) to 29 hours (Conte, 1991), and after 10 daily doses a median elimination half life of 47 hours was observed in trypanosomiasis patients (Bronner et al., 1991). The latter

also report that pentamidine was detected in all examined CSF samples, at a concentration of 0.5 to 0.8 % of the plasma concentration (an observation not reported before). Interestingly, a recent investigation put the elimination half-life of *suramin*, after a 6 g (therapeutic) dose, at more than 44 days (Cheson et al., 1987).

In view of all this recently emerged information on elimination half-lives, the effectiveness of the systematic pentamidinisation as practised in the forties and fifties, may have to be attributed more to an "early therapy" effect (of newly infected individuals) than to a real "chemoprophylactic" effect (for not yet infected individuals). Of course, these concepts are difficult to separate in practice.

Probably the most important argument against this 'chemoprophylactic' practice is its cost, if it is to be implemented correctly, and how this cost compares with that of other interventions. Moreover, the question should be asked if the drug is sufficiently innocuous and from which moment (or from which low level of endemicity or transmission) its massive use should be stopped in order to avoid creating more problems than are solved.

Conclusion:

Theoretically this is a desirable kind of intervention if the tools are adequate. Feasibility is severely limited by cost and limited duration of protection. If an effective intervention is carried out to identify and treat infected individuals, administering prophylaxis to still exposed but not infected individuals in selected circumstances may be effective - and feasible - in helping to reduce the prevalence of infection significantly; but the perfect *prophylactic* drug still needs to be invented.

#### (7) PROTECT THE TSETSE FLIES AGAINST INFECTION

Although at first sight this looks like science fiction, let us not forget that a conceptually comparable approach has been highly successful in rabies control in Europe: the principal 'vectors' of rabies, wild foxes, were successfully immunised with an oral vaccine, incorporated in judiciously

distributed bait (strictly speaking, in the case of rabies, foxes can also be considered to be the 'reservoir' rather than the 'vector'...). Of course, this is not quite the same thing as 'immunising' flies, although the idea is rather alluring.

Science fiction or not, it appears that some gene sequence regulating the tsetse fly's susceptibility to infection with trypanosomes has been identified and that a modified gene sequence can be incorporated in the fly's genome ('genetically engineered immunisation'? P. Elsen, pers. comm.) To what extent this approach is feasible on a large scale as a control activity is, of course, another matter.

Although we may not (yet) be able to *act* on the susceptibility of the tsetse flies to trypanosome infection, a better understanding of this issue is certainly of interest for a better understanding of HAT epidemiology. If we knew what determines the flies' susceptibility to trypanosome infection, we may have learned something crucial for understanding HAT transmission.

There is not only the finding of genetically 'regulated' susceptibility; another finding is the high association between (previously established) RLO midgut infection in the flies and susceptibility to trypanosome infection, mentioned before, through lectin regulating mechanisms (Maudlin and Ellis, 1985; Maudlin and Welburn, 1988), which throws a remarkable light on the dynamics of transmission. If this finding is widely valid, there would appear to be a subgroup among the fly population, independent of taxonomic criteria and maybe also of feeding behaviour, that may be responsible for transmission. One can therefore formulate the hypothesis that if the flies do not have this 'RLO disease', they will not get the '*Trypanosoma* disease'. In that case it would of course be relevant to know what determines the occurrence of this 'RLO disease', and how we can possibly act on this.

It may sound far-fetched, but if it were possible to 'protect' the tsetse from RLO infection, to prevent them from getting it, there might not be a problem of HAT.

(8) IDENTIFY INFECTED INDIVIDUALS BEFORE THEY START SUFFERING AND PREVENT THE SUFFERING THROUGH TREATMENT

This kind of intervention is in the area of what is called 'secondary prevention' (halt the evolution toward suffering).

We are not talking here about the notion of 'contagiousness' (i.e. acting as a source for transmission, and thus conceptually linked to the transmission process), but rather about the notion of 'infection' (i.e. to be a parasite carrier, conceptually linked to the probability to *evolve in the natural history of the disease*). In practice, the tendency is to use these two notions indiscriminately, because we do not know whether it is technically possible to make the distinction.

However, in a context of secondary prevention, the benefit of treatment is dependent on the '*value of treating*' as compared to the '*value of not treating*'.

The decision to *treat non-suffering infected man* implies, in practice, two levels of uncertainty: is the person really infected or not; and is the infected person really going to evolve toward suffering or not?

Let us accept that it is possible to determine with certainty whether a person is infected or not. In this case it would be necessary to know what is the 'predictive value' (the term 'prognosis' would be more apt) of this sign for the phenomenon '*ulterior suffering caused by trypanosomiasis*'.

This question can be represented by a contingency table:

		Suffering in future	
		yes	no
Infected	yes	a (TPs)	b (FPs)
	no	c (FNs)	d (TNs)

Since we start from the principle that, by definition, a not-infected individual cannot progress in the natural history of HAT, 'c' equals zero (there are no 'false negatives' for this sign -FNs) and among the not-infected there are nothing but 'True Negatives' (TNs).

The 'positive predictive value' of the sign 'infected' equals  $a/(a+b)$  (i.e. the prognosis, in probability terms, of future suffering). This value would be one of the elements of description of the natural history of the disease. It is unknown with any accuracy. Moreover, it is suspected to vary according to elements that determine human 'resistance' to the parasite's effects, like nutritional status (Dutertre, 1968) and some sort of acquired immunity of the premunition type (Burke, 1971; Burke, 1992) which may be limited to locally prevalent strains of trypanosomes.

Let us suppose, all the same, that we know this value with sufficient accuracy. We would then be left with the second level of uncertainty, that of the characteristics of the test that is used to decide whether someone is infected or not: to what extent does the test result correspond with reality?

A second contingency table could represent this question:

		Really infected	
		yes	no
Test result	positive	a' (TPt)	b' (FPt)
	negative	c' (FNt)	d' (TNt)

This time, none of the values (a',b',c',d') is expected to be zero.

The '*value of treating*' would then be composed of the advantages of treating the TPs (the number of whom depends partly on the predictive value of the test) minus the disadvantages of treating the FPs (the number of whom is also partly depending on the predictive value of the test).

The '*value of not treating*' is composed of the advantages of not treating those who are not going to suffer, minus the disadvantages of not treating those who would suffer.

Of course, all these 'advantages' and 'disadvantages' are partly subjective and the way they are expressed needs to be made explicit. However, as long as the basic probabilities are not known, even approximately, one can hardly speak of a very 'rational' decision (in this precise context which is 'secondary prevention': stop an infected person to evolve toward suffering).

In practice, the question is probably still more complex. In fact, the concept of *infection* carries with it a *time* dimension. A person who received an 'infective' bite (from a contagious fly) can, in all probability, go through a relatively short episode resulting in getting rid of the infection ('abortive infection') The phenomenon of transient serologic positivity on screening (or spontaneous serologic inversion) supports this hypothesis (which refers, by the way, to a rather general phenomenon in human medicine). On the other hand, this 'infective bite' may also result in long time presence of

parasites ('sustained infection'). The question is then to find out, with a sufficient level of certainty, on the basis of a test result, whether the person belongs to the first or to the second category. This question is superfluous only to the extent that, in the composition of the *value of treating*, the element 'disadvantages of treating false positives' (in terms of ulterior suffering) can be considered to be non-existent or negligible.

Can we conclude anything at this point?

As for the *theoretical efficacy* of preventing future suffering in infected individuals, by treating them, we can be confident that adequate treatment is effective, but we do not really know how effective it is, because we do not know as much as we would like about the natural evolution of the infection. In other words, we are confident, all things considered, that the value of treating is higher than the value of not treating, but we cannot say by how much.

In terms of *operational efficacy*, the effectiveness of such an intervention would also depend on our ability to identify infection in individuals, in other words on the operational characteristics of tests to diagnose *Trypanosoma* infection, and on the number of people reached with the intervention. With presently available tests, the *technical feasibility* of such an operation is probably quite high, but the *social feasibility* is likely to depend on the perception of the HAT problem in the community.

The *cost* of an operation of this kind is high when high numbers of people are to be reached, and is furthermore variable according to the techniques used.

The *acceptability* will depend to a high extent on the perception of the HAT problem in the community and on the relation between health services and communities. This perception is, of course, different in a low endemicity situation from what can be expected in a high endemicity or epidemic situation.

The natural evolution of the infection (to illness and suffering) and its possible determinants remain imperfectly understood, although clinical and

pathological descriptions of clear cases of disease are quite documented and rich.

Conclusion: this kind of intervention is certainly desirable in situations of high endemicity or in the case of epidemics. In such situations it is also likely to be feasible because the community can be expected to participate actively (having made its own cost-effectiveness assessment, consciously or not). If we accept this, the decision to be made is rather on *when* this kind of intervention would have to be started - and when it would have to be stopped - and *how* it would have to be organised (which kind of service, which kind of personnel, which target groups, etc.)

#### (9) IDENTIFY INFECTED INDIVIDUALS SUFFERING FROM HAT AND TREAT THEM

This amounts to stopping or reducing (individual) suffering attributable to HAT and to stop and reverse the evolution towards (permanent) incapacity or death.

The need to distinguish, among the suffering, the patients with (massive?) CNS involvement is based on the difference in necessary or sufficient treatment. This distinction is made on the basis of the sign *altered cerebrospinal fluid* (CSF). The test used to decide on this sign is, in practice, the counting of cellular elements per unit of volume of CSF, or its albumin content, or the finding of parasites in the CSF on the basis of visual, morphologic criteria; more sophisticated, but less often used is the finding of a sufficiently high concentration of specific IgM antibodies (Mattern, 1968; Dutertre, 1968; Van Meirvenne, 1992).

It is generally accepted that without effective treatment, the probability for a patient with CNS involvement to evolve towards permanent incapacity and death, in a relatively short time, is close to 100 %. How long this generally takes is not very clear (or is very variable), just as it is not very clear how to define - or describe - this CNS involvement: it has been argued more than once that this CNS involvement occurs quite early in the natural history of the disease (Dutertre, 1968; Boa et al., 1988). Part of this

uncertainty is probably due to the fact that the decision on CNS involvement (yes or no, stage I or II, stage II treatment or not) is taken on the basis of biochemical and biological examination of the CSF (laboratory results as 'objective signs') whereas the presence of clinical (neurological) signs and symptoms of cerebral involvement would result in quite different conclusions. Clinical evidence and biological (laboratory) criteria only partly overlap.

A possible confusion is the one between *invasion* of the CNS by the parasite and *CNS involvement*. The latter is an essentially *clinical* phenomenon, the signs of which are structural (evidence of inflammatory reaction: cells, protein) or functional (clinical signs and symptoms that can be traced to CNS malfunctioning). These clinical phenomena are then attributed to the lasting presence of *Trypanosoma* parasites in the CNS (who have 'settled' there, so to speak). The former, 'invasion' of the CNS by the parasite, is a description of parasite behaviour, with no explicit time dimension; it could be a transient phenomenon with or without functional consequences.

One could say that the likely sequence of events, pathology wise, would look like this:

- from early in the evolution of the infection, parasites are carried with the blood stream to the cerebral blood vessels, at first intra-vascularly;

- at some moment in time, parasites penetrate into the *peri-vascular* tissues, where they produce some peri-vascular reaction and meningeal irritation, resulting in what Manson terms a 'chronic lepto-meningitis'. The clinical translation of this would be composed of signs of meningeal irritation: increased numbers of cells in the CSF, etc., possibly already some *Trypanosoma* parasites in the CSF.

The question now is whether we can say that this is a sign of cerebral *involvement*? Has the blood-brain barrier been successfully overcome (from the point of view of the parasite), or is this only an inconclusive temporary 'skirmish' with transient results;

- finally (and possibly) there is invasion of the *brain tissue*, in advanced stages, i.e. presence of parasites in brain centre tissue without relation to blood vessel structure: the brain centres are affected, the blood-brain barrier has definitely been overcome and the parasites are there to stay. An alternative interpretation is that in this stage the role of the parasites is not so important anymore in terms of infective agents, but that the immune systems and mechanisms are out of control and are at the basis of progressive demyelination and destruction of brain centres, without affecting the cortex directly (Dutertre, 1968).

To what extent this latter description is accurate is, however, debatable. After having carried out a post-mortem on 24 natives and 2 Europeans, Mott reports lesions as 'primarily interstitial' with 'some secondary parenchymatous atrophy' and wonders why so few trypanosomes are found in sections (Mott, 1906). The quasi absence of parenchymatous lesions is supported by the finding that - at least in rodents - 'invasion of the cerebral parenchyma by parasites leads to a dead end' (Van Marck et al., 1981), whereas, in chronically infected rodents, trypanosomes were found to concentrate extravascularly in the choroid plexus in mice, the matrix of which could serve as a shelter for the parasites; trypomastigotes have been observed dividing within ependymal cells in the choroid plexus (Abolarin et al., 1986). The 'destruction' of brain centres seems to be *functional* rather than structural, and may be dependent on perivascular processes.

Frézil and Coulm find a reversed correlation between the numbers of WBC in CSF (essentially a sign of meningeal inflammation) and the concentration of antibodies in blood, but a straight correlation between numbers of WBC in CSF and antibody concentrations in the spinal fluid (Frézil and Coulm, 1977), which supports the formulation of a 'cerebral polarisation' hypothesis<sup>4</sup>.

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<sup>4</sup> It is said that the difference between 'meningeal irritation without invasion of the brain centres' and 'invasion of the brain centres' cannot be established clearly on the basis of cell counts in the CSF; the transition would be progressive and there would not be a clear cut-off point (Neujean, 1951a); moreover, meningeal

A better criterion than inflammatory signs like CSF cell counts and albumin is certainly desirable if one wants to continue making the distinction between stage I and stage II, in view of different treatment methods. According to some, the distinction between stage I and II has no scientific interest at all (Dutertre, 1968).

The confounding effect of other diseases (like, e.g. syphilis) on the number of cells in the CSF is probably negligible <sup>5</sup>.

inflammatory processes would be found very early in the evolution of the disease. These conclusions have been reached on the basis of the phenomenon of 'relapse' (with cerebral involvement) after treatment with suramin or pentamidine. If we examine Neujean's own published data, however, this 'progressive transition' is far from evident, and the figures are certainly not convincing statistically. Moreover, if we present the distribution of cell counts in his series of 716 patients, with his cell count classes, we come up with a *bimodal* distribution, separated by a trough at 20-29 WBC/ $\mu$ l:

0 - 9	36 %	(0-3: 10 %	4-9: 26 %)
10 - 19	12		
20 - 29	2		
30 - 99	13		
100 - 499	26		
500 +	9		

Although the essential arbitrariness of the choice of cell count classes makes it difficult to interpret this kind of data, this type of distribution suggests the existence of 2 distinct groups. This is further supported by the observations on the high efficacy of pentamidine treatment for patients with up to 20 WBC/ $\mu$ l (Neujean, 1951b) and even with up to 40 cells (Duggan and Hutchinson, 1951) or more (Lourie, 1942), but it must be noted that in this latter report the follow-up period is only one year. The upper limit of 'normality' of CSF was put at 3 cells/ $\mu$ l in 1942 at the Meeting of the Scientific Committee on Trypanosomiasis Research in Lourenço-Marques (Neujean and Evens, 1958), but it is difficult to find out on the basis of what criteria this decision was made.

<sup>5</sup> It may be useful to mention that for the intervention we are developing here the question is not so much anymore to compare the *value of treating* to the *value of not treating*. Whenever there is (individual) suffering, the question of treatment or no treatment is not relevant anymore; some help needs to be given, and preferably an

The more relevant question here is *which is the most appropriate* treatment. The probability of error in attributing observed suffering to HAT is not zero, but is variable in time, because of the fact that 'individual suffering' due to HAT is also variable in time.

In this context, the two principal questions to be resolved appear to be:

(a) how to identify people *suffering* from HAT

(b) how to select the best method of helping them (choice of treatment)?

(a) *Identification of people suffering from HAT disease*

The first question can be subdivided in other sub-questions:

- how to establish or facilitate contact between suffering individuals and health care providers

- how to establish the link between the suffering and HAT?

The answer to the first 'sub-question' (facilitate contact) lies essentially in the field of the organisation and availability of health services (accessibility in time and space, acceptability). The answer to the second one, the question of (correct) diagnosis, lies essentially in the field of the operationalisation of services (strategies and technical means of diagnosis) for the specific problem that is HAT. Conceptually and epistemologically this requires first an answer to the question: "to what extent can one be sure that the observed suffering is caused by the disease HAT, and to what extent can one be sure that adequate treatment of the *disease* (in the case of HAT this can be summarised by the presence of parasites) will also be adequate treatment of the *illness* (the suffering of the individual patient).

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effective form of help. The only conceivable 'value of not treating' in this case would be based on the probability of being wrong when attributing the suffering to HAT.

This is basically a question of semiotics: is the relation between sign and event causal or not.

Although in the precise context of this intervention (reducing the individual suffering) a number of relevant questions can be formulated concerning these semiotic links, we will propose to simply accept their existence.

However, a less theoretical question is the one about the nature of this suffering.

What is this suffering caused by HAT? To what extent is it linked to the 'staging' of the disease? Is there some specific kind of suffering when the CNS is not (yet) involved (or invaded)? Is this possible (early) suffering of a kind to motivate the patient to seek care in some 'modern' health care delivery structure? Do all the patients with CNS involvement have problems, and possibly starting when?

The importance of answers to these questions lies in the consequences in terms of detection strategies if and when 'multi-functional' services are available and functioning. If there exist signs and symptoms that are sufficiently motivating for a patient before the stage of CNS involvement, it would be possible to make use of them in a strategy of early detection - with a better prognosis in terms of treatment.

What do we know about it? Are there any hard facts? Several attempts have been made to systematise signs and symptoms of trypanosomiasis. Three useful approaches can be distinguished:

- comparing frequencies of signs/symptoms in a population of known cases with those in a population of controls (non-cases)
- describing frequencies of signs/symptoms in a population of known cases;
- comparing frequencies of signs/symptoms in a population of stage I cases with those in a population of stage II cases.

For the comparison of populations of cases and controls, the concept of odds ratios can be applied. This has been done in Kwamouth, Zaire (De Muyck, Mentens, Henry; data of 1981, analysed in 1992; personal communication). By using a 'risk score' composed of odds ratios of clinical data and certain risk factors, they end up identifying about 2/3 of detected parasite carriers, positive at direct parasitological examination. This is, of course, a sensitivity figure only; it tells us nothing about specificity (which is rather low). In this analysis, no distinction has been made between stage I and stage II patients.

As compared to the control group, clinical signs with significant odds ratios appear to be:

- *poor general condition* (OR 5.9, observed in 30 % of cases),
- *itching* (OR 2.2, 10 % of cases),
- *head aches* (OR 6.3, 17 % of cases),
- *inversion of sleeping rhythm* (OR 4.4, but rare),
- *apathy* (OR 5.4, but rare),
- *pain in the feet* (OR 8.0, 9% of cases),
- *personality changes* (OR 7.6, but rare).

The situation in which this study has been carried out is one of (very) high prevalence: 118 parasitologically confirmed cases against 1990 controls, parasitologically and serologically (IFI) negative (i.e. a prevalence of about 6 %). In this population the presence of cervical lymphadenopathy of all sorts (very frequent, about 2/3 of the population) does not contribute to distinguish 'cases' from 'non-cases' (OR not significantly different from 1.0). At any rate, lymphadenopathy is rather a *sign* than a *complaint* (which is an expression of suffering), and in this context we are mainly interested in 'suffering'. However, if we consider the clinical elements mentioned above, we find a number of 'sufferings' (or potential complaints, since 'suffering' becomes a 'complaint' only through its formulation) that qualify as 'discriminating signs' and which could be helpful in identifying patients suffering from HAT (even if we have to put them all in the same category, with or without CNS involvement; it can be suspected that in this population of 'cases', the majority would be classified as stage II).

In the longitudinal *Kasongo study* (data of 1989-90; see further), where the prevalence is much lower (40 parasite carriers identified in the course of 4 rounds with intervals of about 4 months, in a population of some 3000 people), 30 cases out of 40 present with an 'altered' CSF (cell count  $\geq 5/\mu\text{l}$ ). Of these 30 'stage II' cases, 20 have expressed no complaint that could be considered 'suggestive' for HAT (in answer to an open question). None of the cases with normal CSF expressed any 'suggestive' complaint, except one (if 'generalised itching' is considered to be such a suggestive sign).

All the same, among the 40 cases that were identified (with parasitological confirmation) 15 have been diagnosed by passive case-finding, and one can reasonably assume that they have contacted a curative service point for some reason. All 15 had an 'altered CSF'.

Frézil has attempted to put some order in data on symptomatology, while trying to place them in a framework of the natural history (or the natural evolution) of HAT, and while adding elements of 'kinetics' of the endemic and 'level of immunity of the populations' as explanatory elements (Frézil, 1983). In other words, his approach tries to take into account the natural history of the disease in terms of its evolution in individuals as well as in terms of its historical evolution in population groups.

He analyses clinical signs ('objective signs' as well as 'potential complaints') in a population of 317 cases actively identified in two foci of the Congo Republic (Loudima and Ngabé). Some of his observations:

- '*... nous avons été frappés par la pauvreté de la symptomatologie...*'

- '*... La symptomatologie varie en fonction du degré d'endémicité du foyer: dans le foyer épidémique de Loudima, les signes sont rares et le pourcentage des ganglions positifs important. Tandis que dans le foyer de Ngabé, en récession, les ganglions sont rares, et les signes cliniques souvent plus marqués.*'

- '*... il semble y avoir un décalage entre l'évolution clinique et l'évolution biologique: on note des malades en 2ème période paraissant moins gravement atteints que d'autres en première période.*'

- '... à souligner: - la précocité des signes nerveux qui souvent se manifestent chez des malades à LCR non encore perturbés. [...] Et Dutertre (1968) affirmait: "le système nerveux est atteint dès le début et c'est une des raisons qui font que les périodes ont peu de signification"! (note: there seems to be a change in paradigm here...)

- '... Seuls, les troubles du sommeil, les ganglions chez les sujets de plus de 30 ans et les oedèmes de la face chez les sujets de moins de 20 ans constituent des signes intéressants, mais ne concernent qu'une proportion trop modeste de malades.' (??)

In other words, it is complicated. And this complexity is, without doubt, very real. Yet, one of the important advantages of Frézil's type of analysis, it seems to us, is that he does not try to get rid of the problem by saying that HAT is different everywhere and that there is no 'common denominator', but that he maintains the starting point that there exists something (more or less) homogeneous (or at least recognisable) *within which differences could be explained* if one knew the mechanisms that produce these differences. And he suggests some of these mechanisms that are not based only on 'diversity of strains' or on 'geographical' criteria: the level of endemicity and the level of immunity of the population, in other words, two aspects of the 'historical' dynamics of the parasite-host relations. This may not be a big *scoop* in the HAT literature (suggestions in that direction have been formulated tens of years ago), but at least it provides an interesting and somewhat more systematic lead, provided it can be followed...

An attempt to classify signs and symptoms according to the staging (I or II) has been made in the (forest) focus of Daloa, Ivory Coast (Boa et al., 1988). Their data are not presented in the form of odds ratios, but these can be calculated from the data as published. They analysed 300 cases, only 39 of which were 'stage I'. Almost half of these 300 cases (48 %) were detected through spontaneous consultation.

'Stage II' in this study was defined by positivity of one or more of the following signs:

- more than 4 cell elements per mm<sup>3</sup> in the CSF (249/261 ; 83 %)

- and/or more than 40 mg protein per 100 ml in the CSF (165/261 ; 55 %)
- and/or visible presence of parasites in the CSF (169/261 ; 56 %)

The contingency table for calculation of the odds ratios would take the following format:

		Stage	
		II	I
Sign	Present	a	b
	Absent	c	d

Odds ratio = a/b divided by c/d = ad/bc

On the basis of the odds ratios, signs and symptoms that appear to be *not useful* for distinction *between stage I and II* (i.e. OR not significantly different from 1.0) include:

- lymphadenopathy (interpreted very broadly; present in 87 % of all cases)
- head aches (present in 73 % of all cases)
- itching (present in 43 % of all cases)
- temperature  $\geq 37.5^\circ$  (present in 30 % of all cases)
- splenomegaly (present in 15 % of all cases)
- 'endocrine disorders' (libido disorders in man, amenorrhea, ravenous appetite, facial oedema..(?)) (present in 16 % of all cases)

More useful signs for distinction between stage I and II would include:

- 'more than mild' disorders in waking and sleeping (present in 19 % of all cases):
  - OR for stage II: 4.01 (statistically significant)
  - Positive predictive value (PPV) for stage II: 0.953
  - Negative predictive value (NPV) for stage II: 0.164
- - 'more than mild' peri-oral reflexes (present in 25 % of all cases)
  - OR for stage II: 2.44 (not significant)
  - PPV for stage II: 0.932
  - NPV for stage II: 0.150
- 'more than mild' cheiro-oral reflexes (present in 34 % of all cases)
  - OR for stage II: 5.347 (significant)
  - PPV for stage II: 0.961
  - NPV for stage II: 0.178
- 'abnormal movements' (a very widely interpreted notion, including 'trembling'; 34 % of all cases)
  - OR for stage II: 3.2 (significant)
  - PPV for stage II: 0.941
  - NPV for stage II: 0.167

All these more useful signs are rather clear clinical evidence of some disorder of the CNS brain centres (contrary to the signs that appear not useful) which is not very surprising. Their positive predictive value (for deciding if the patients are to be classified as stage II, as defined here) is very high (more than 90 %), but the absence of these signs does not mean much in terms of staging: the negative predictive value is very low (less than 20 %).

It should be remembered that all these patients are parasitologically confirmed parasite carriers and that the predictive values are to be understood only in terms of belonging to stage II as defined here. It should also be remembered that this sample contains not more than 39 stage I patients (13 % of the sample population), therefore the prevalence of stage II patients is extremely high (87 %). Knowing this means that the PPV of

the simple visually confirmed presence of parasites , for belonging to stage II, is already as high as 0.87 (before looking at anything but parasites in blood or lymph gland fluid). Thus the high PPV values found for the 'more useful' clinical signs is not surprising; in order to mean anything at all, in terms of additional information, they should at any rate be significantly higher than 0.87 (and even 'itching', one of the 'not so useful signs' has a PPV for belonging to stage II of 0.90).

These authors comment that if the vast majority of their patients are classified as stage II, most of them are in what they call the stage of *acute early CNS involvement* ('atteinte précoce aiguë du SNC'), which they argue on the following grounds:

- high frequency of 'initial' signs and symptoms among stage II patients (essentially archaic brain-stem reflexes ?);
- weakness of expression of neurological symptoms for most of these patients;
- high frequency of presence of parasites in CSF.

Their implicit question (although it is formulated as sympathy with the difficult choices a practising physician is faced with) is whether these patients with 'acute early CNS involvement' should be subjected to the dangers of treatment with melarsoprol (Arsobal®). The answer to this question, it seems to us, lies in the comparison of the (lack of) effectiveness of treatment with less toxic first stage drugs and the toxicity of melarsoprol treatments for these patients.

This comment about 'early CNS involvement' reveals elements of an underlying model of the 'natural (clinical and pathological) history' of the disease HAT, and more specifically about the staging. First, it is implied that there exists such a thing as 'initial' (presumably 'early') signs and symptoms of CNS involvement (be it on the basis of the nature of these signs, or on the basis of the strength of expression). Second, it is implied that the presence of parasites in CSF is something that occurs *early* in the process of CNS involvement.

This latter assumption may sound somewhat unusual in the light of previously conducted studies; in a series of 716 cases, 139 of whom had trypanosomes in their CSF, Neujean found a very clear correlation between the *number of cells* in the CSF and the *frequency of the presence of parasites* in the CSF (Neujean, 1951a, p.1174). The same author concludes, independently from this observation, that CNS involvement is a progressive process, translated in CSF terms by the appearance, *first*, of lymphocytes, *then* of raised albumin concentrations, *last* of pathological cells and trypanosomes (ibid., p. 1230). Finally, the appearance of cells other than lymphocytes appears to be correlated to the total number of cells in the CSF (ibid., p. 1178). Thus, there would be a correlation between the progressive CNS evolution of the disease, the number of cells in the CSF and the appearance of trypanosomes in that fluid, the latter being a sign of more advanced CNS involvement. However, this reasoning still rests on the assumption that the event 'evolution to advanced stages of the disease' (i.e. progressively more thorough functional destruction of the nerve centres) is correlated with the sign 'increasing abnormality of the CSF'. A definite confirmation of this assumption (is the relation between sign and event accurate and constant) can only be given by the results of clinical trials, which are formally very difficult to conduct, if only for ethical reasons. The available evidence is largely drawn from control programme data, treated by retrospective case-control methods, or based on 'experience', individual or collective. As Burke (1971) remarks concerning the late interbellum period - even if his comment applies to the epidemiology of HAT rather than to the study of clinical and pathological sequences - '[...] *Malheureusement, encore une fois, les tâches sont nombreuses et le personnel restreint. Il faut à tout prix dépister et traiter les malades. On se borne à observer sans avoir le temps d'étudier à fond.*' (Burke, 1971) Studies like the one Neujean conducted in Kinshasa (then Leopoldville) around 1950 tried to fill some of the important lacunae in systematically acquired knowledge.

Curiously enough, Neujean concluded from his experiments that there is no way of knowing, on the basis of the usual CSF examination, whether a patient's CNS is attacked or not. Since the process of CNS involvement is a 'progressive' one, it may occur early in the course of the disease, and for him *all* trypanosome carriers should receive a treatment that reaches the

parasites in the nerve centres, at least in the case of standardised treatments in a context of mass programs where no more sophisticated investigations can be carried out. Unfortunately there is no argumentation involving the comparison of 'costs' and 'benefits' (in the broad sense of the word) other than 'indubitably reduced chances of healing for those who have continued their CNS invasion *à bas bruit*'. In other words, ordinary CSF examination, using standardised criteria for cells, protein and parasites, would yield too many *false negatives*. In this approach, somewhat surprisingly, there is no question about the hazards of false positivity, which makes it a rather typical example of the 'medical maximising bias' as described by Scheff: the decision rule generally used in medicine is primarily based on the reluctance *to miss a case*; the treatment of 'false positives' is easily accepted as a justified price to pay (Scheff, 1963).

The question then seems to be: is the staging of the disease HAT, on the basis of CSF examination with the usual criteria (cells, protein, parasites), a useful 'fiction' or would it better be abandoned altogether? If it is an anatomical and/or pathological 'fiction', its only usefulness can reside in the possibility of reducing toxic sequels of stage II treatment, and maybe in better financial feasibility through partly cheaper treatment.

In this context, the 'value of treatment' approach can usefully be applied, not on the question of 'treatment vs. no treatment', but on the question 'advanced stage treatment vs. early stage treatment'. The main theoretical - but also very practical - question here seems to be: *are advanced stage treatments (melarsoprol, DFMO, nifurtimox, all of which carry with them important immediate post-treatment mortality) as dangerous for early stage patients as they appear to be for advanced stage patients?* To our knowledge, the answer to this question is not entirely clear. Haller and colleagues state that reactive arsenical encephalopathy (RAE) with melarsoprol treatment according to 'Neujean's protocol' (Neujean, 1952; Neujean and Evens, 1958) occurs both in patients with and without CNS involvement, but show a series in which RAE occurs 6 times as often in stage II patients (12/165 vs. 2/165; chi-square=7.44; p=0.006) (Haller et al., 1986). Pépin and Milord report that RAE occurs twice as often (12 %) among patients with more than 100 cells/ $\mu$ l in the spinal fluid than among

those with 6-99 cells/ $\mu$ l in the CSF (6 %), but their entire series (556 cases) is composed of patients classified as 'stage II' (Pépin and Milord, 1991). Most other authors do not separate patients on the basis of cell counts in CSF.

Another hypothesis (Ginoux et al., 1984) is that encephalopathy observed with melarsoprol treatment is related to the number of *series* of injections (melarsoprol is administered in one or several series of 3 injections, the series being separated by 2 weeks).

Recent statements express an (implicitly) different attitude, focusing more on the problem of false positivity;

- '[...] Current CSF-parameters [parasites, leukocyte count, protein content], used to distinguish between disease stages, are unsatisfactory. Those criteria are arbitrary. Recent concentration techniques allow to demonstrate trypanosomes in some otherwise normal CSF-samples, although those patients may still get cured with early-stage drugs. CSF leukocyte count and CSF protein content are not specific at all.' (Van Nieuwenhoven, 1992b, referring to Cattand et al., 1988)

- '[...] The mere finding of a few trypanosomes in the CSF is no conclusive indication for involvement of the CNS. More reliable parameters are the increase of white blood cells, total protein, albumin and particularly the presence of IgM and anti-trypanosome antibodies.' (Van Meirvenne, 1992; no supporting references, but based on Mattern, 1968). Mattern does not say, however, how he identifies patients with CNS involvement.

When reviewing all this, one may come to the conclusion that there are those who fear to do too little, wanting to avoid false negatives; and there are those who (also) fear to do too much, wanting to avoid false positives;

The problem of uncertainty is not present in all cases; it becomes most prominent (as usually with measurements of continuous variables involving the notion of a cut-off point), in the 'area of uncertainty', where false positives and false negatives overlap. It is not unlikely that this area of uncertainty will be of variable importance according to epidemiological factors

(level of endemicity, history of the disease in the population), but we do not seem to know much about these - at present.

Going back to where we started from (identification of individuals suffering from HAT), and putting aside for the moment the uncertainties that surround the staging of the disease, we feel that it is admissible to say that, at least theoretically, the potential for identification of HAT sufferers on the basis of complaints (if expressed) is not negligible. A more systematic strategy of identification on the basis of certain discriminating signs could certainly be worthwhile, as long as one does not expect to find all parasite carriers this way.

*b) Choice of the most adequate treatment*

The *selection of the treatment* depends on the following criteria:

- effectiveness (not only in terms of 'sterilisation' but also, and in the first place, in terms of reducing suffering);
- ease of execution (possibility to standardise, acceptable duration, technically easy to administer);
- absence of untoward effects;
- efficiency (acceptable economic cost)
- acceptability for the patients (linked to the first three criteria, but also linked to socio-cultural factors; in case the patient has to finance the treatment himself, the economic cost will also interfere).

The *effectiveness* of different alternatives of treatment seems to change according to a number of variables. If efficacy is defined in terms of sterilisation and absence of relapse among survivors, it appears to be linked to variables like *successful previous treatment*, *the clinical stage of the disease* (even before the stage of altered CSF (?)), *age of the patient* (?), and maybe some others.

The one that is probably the most relevant is the *failure of previous treatment*; as a matter of fact, it appears that retreating relapsed cases with the same therapeutic regimen (or with the same drug) results in far lower prob-

ability of success in the medium term (important 're-relapse' rate - Ngampo, 1992; Pépin and Milord, 1994; Neujean and Evens, 1958). The chances for success are strongly and progressively reduced with the number of successive relapses. Of course, this is not really surprising and suggests rather clearly that the problem resides in the parasites' resistance to the drug.

Of course, measuring or interpreting data on effectiveness is a whole problem area all by itself. These problems include: theoretical and practical definitions of 'cure' and 'relapse' (involving the theoretical and practical definition of the necessary duration of follow-up and the criteria used for decision making), lack of standardisation of patient groups (especially for the newer treatments), which denominators are being used for 'cure rates', lack of rigour in the carrying out of the treatments, and all those other practical problems that are associated with difficult working conditions and the need for long follow-up periods.

At present, drugs accepted as effective - and available so far - are:

- in stage I treatment only:

- *suramin* (Bayer 205)
- *pentamidine* (Lomidine®; Pentacarinat®)
- *diminazene aceturate* (Berenyl®; for veterinary use; not officially registered for human treatment)

- in stage II treatment:

- - trivalent arsenicals: *melarsoprol* (Mel B, Arsobal®): introduced in 1948 (the pentavalent arsenicals tryparsamide and atoxyl are less effective and less toxic);
- nitrofurans: *nitrofurazone* (Furacin®); not used anymore (high toxicity); *nifurtimox* (Lampit®): recently introduced (1977 first, again in 1981);
- *eflornitine* or *DFMO*: recently introduced (1981).

Resistance to some of these drugs has been an important feature, especially in the case of tryparsamide. Around the time of the introduction of

melarsoprol, resistance to tryparsamide in the Belgian Congo was said to be as high as 80 % (Friedheim, 1949; Van Hoof, 1947), although, for example, in Sierra Leone the situation was far less dramatic, apparently (Duggan and Hutchinson, 1951). At any rate, melarsoprol got an enthusiastic reception as the new miracle cure; Friedheim's first reports state a cure rate of 100 % (50/50) and 'no untoward effects', among mostly tryparsamide resistant patients (Friedheim, 1949), and a relapse rate of only 3.3 % in a much larger series of tryparsamide resistant patients in Cameroon (Friedheim, 1951).

Still, generally speaking, remarkably little additional resistance to the first line drugs (suramin, pentamidine, melarsoprol) appears to have developed over the decades (Apted, 1980; Pépin and Milord, 1994).

The *ease of execution* is not really a value by itself, but will determine to a large extent the accessibility and acceptability of the treatment or treatment regimen.

If the treatment can be standardised (as well in terms of its administration as in terms of the necessary follow-up), it is possible to delegate it to non-specialists, which opens up wider possibilities for accessibility and continuity of treatment. In order to be 'standardisable', a task needs to be relatively *simple* and all contingencies (or at least the great majority of them) need to be foreseeable and foreseen, and formulated in the form of intelligible instructions. Concerning the delegation to non-specialists, our main rule is that this delegation does not depend on the severity of the (health) problem nor on the importance (or even the cost) of its solution (or the response to the health problem), but in the first place on the *possibility to standardise* the activity or the task, and, consequently, on the technical *possibility to supervise* it adequately. Moreover there should be sufficiently *frequent occasions to execute* the activity or the task.

If we agree on these criteria, this standardisation-delegation-supervision complex is not so simple as would be apparent at first sight. We only have to consider all the problems that appear to be connected with the correct (i.e. rigorously according to the rules) carrying out of screening and diagnostic tests, which are seemingly simple and theoretically standardised, in order to understand that in practice variations are more numerous than

would be imagined. See the variants of the CATT test used in the Congo Republic (Penchenier et al., 1991; reproducibility of IFAT test between Kasongo and Antwerp laboratories, briefly reported further in this work).

If treatment (or some of it) is delegated to polyvalent health care structures, its accessibility and acceptability may, generally speaking, be increased. But on the other side of the scale are increased difficulties of logistics, training, supplies and supervision, all of which are not negligible. This kind of decision thus has to be made according to local realities. However, this tension between 'accessibility' (directly linked with delegation and decentralisation) and problems of, broadly speaking, 'logistics', is rather universal and should be considered systematically.

We may take as an example the case of DFMO treatment (even without taking into account its economic cost). Let us accept that there are, grossly speaking, two major modes of administration: one intravenously, the other orally. Let us accept also that, in cases with evidence of CNS involvement, the (immediate) effectiveness of the intravenous treatment is between 90 and 95 % and that the effectiveness of oral treatment is less: some 80 % (summarised from Milord et al., 1992). Let us also accept that oral treatment can be decentralised in non-specialised health care structures - with acceptable problems of 'logistics' - and that this would not be the case with the IV treatment mode.

In that case, the 'accessibility' of the 'better' treatment mode (IV) is conditioned by the willingness to pay the 'logistic price' not only of supplying DFMO but also of supplying IV fluids (far from negligible) and of more complex training (not to speak of greater needs for hospital admission and intensity of hospital care), which puts limits to the possibility of decentralising the treatment. Thus it is conceivable that the oral treatment, although technically less effective, may produce a net result that is more interesting in terms of influencing the 'disease system' (because it can be made more accessible through decentralisation), if there is willingness and commitment to pay the other kind of 'logistic price' (supplying oral DFMO to a greater number of health care structures, instructing them on its use

and providing supervisory support). Essentially this kind of choices depends therefore on the existing health care structure and its organisation.

The *absence of untoward effects* is a criterion that appears to be a subject of non-resolved debate, in the case of HAT.

One gets the impression that this debate is centred around two axes. The first one seems to oppose, in terms of the *origin* of the existing toxic effects, the *pharmaceuticals* themselves to the *state of the patient* (staging). The problem here seems to be that nobody really seems to know the discriminating criterion (or sign) for the prediction of severe toxic reactions (which can be summarised by the term 'encephalopathy'), once the patient has been classified as 'HAT with CNS involvement'. For the moment, and to our knowledge, there is no clearly convincing evidence that there would be a relevant difference between patients with and without CNS involvement, at least as far as melarsoprol is concerned. It seems reasonable to state that reactive encephalopathy can be expected more often, statistically, among patients with higher cell counts in the CSF, but it does occur also in patients with 'normal' CSF.

The second line of thought, for explaining the severe toxic reactions, centres on the subject of *how the treatment is carried out* (more or less 'aggressively') and how quickly or how completely the parasites are 'massacred' (*cf.* Hunter et al., 1992; for the opposed view: Milord and Pépin, 1992).

A newer, third line of investigation is into the possible role of cytokines and other immune mediators.

The question is important, given the fact that stage II treatment is closely followed by death in proportions that vary between 2 and 10 %, depending on the series, as well with melarsoprol as with DFMO, maybe less with nifurtimox (Pépin et al., 1987; Milord et al., 1992; Van Nieuwenhove, 1992b).

Melarsoprol treatment, apart and independent from the risk for encephalitis, also carries an appreciable risk (10 %) for potentially severe polyneuropathy (Nkanga et al., 1988; Pépin et al., 1989).

Severe toxicity with the use of stage I drugs (suramin, pentamidine) is very rare in terms of immediate mortality; for pentamidine it is estimated at 1 death per 10,000 treatments (Organisation Mondiale de la Santé, 1986).

When comparing the toxicity of different treatments, the practical problem that has to be resolved is, of course, to what extent observed deaths (or other severely dangerous phenomena) can be attributed to the treatment, apart from the problem of homogeneity of the patient populations for the purpose of comparison. Probably the most reliable indicator of lethal complications is the proportion of *all* deaths observed during or immediately after treatment, even if it is not possible to establish with certainty the causal link between the two events (treatment and death), which means that this indicator will almost certainly overestimate real treatment toxicity.

The *efficiency* of different treatments is expressed in their relative cost-effectiveness. This 'effectiveness' needs, of course, to be defined: which outcome is it that will be measured: 'sterilisation', remission or clinical improvement, lack of relapse, years of life gained (possibly adjusted for quality, and even discounted...), combinations...

Also the cost needs to be defined. Which elements are taken into account? In this area, the literature is not always very enlightening. When one wants to compare different treatments, a rather obvious problem is that it is very difficult to separate the treatments and the overall strategy in which they are used. Thus, it is not always very relevant to limit oneself to the sole cost of the drugs (cf. the choice between the two modes of administering DFMO with their respective 'logistic prices'). Nevertheless the cost of the necessary pharmaceuticals for an (average) treatment is already an important indicator and can be interesting in its own right. Some of these prices are given below. They are of necessity somewhat approximate figures.

Drug	Treatment dose	Cost in BEF	Cost in US\$
Pentamidine	10 vials	385	11 (*)
Suramin	6 vials	1500	43 (*)
Diminazene	1.5 g	50	1.5 (*)
Melarsoprol			
- for stage I treatment	4 vials	850	25 (*)
- for stage II treatment	12 vials	2560	73 (*)
DFMO			
- orally	??		
- I.V.			500 (**)
Nifurtimox			10 (?)
	15 mg/day		
	21 days	555	16 (*)

(\*) Early 1990 prices, FOB + 20 %, syringes etc. not included. 1 US\$ = 35 BEF. (Van Nieuwenhoven - Lunda, Rapport d'évaluation BCT, 1990, annex 9). (\*\*) Another source mentions US\$ 140, for the active substance only.

Due to the relatively recent interest in pentamidine for the treatment of *Pneumocystis carinii* pneumonia (PCP) in HIV patients, the sales price of this drug has been multiplied by a factor 30 in 1994, but the producing company has agreed to deliver the drug free of charge for the treatment of African trypanosomiasis, under the trade name Pentacarnate® (Pépin and Milord, 1994).

Most of these treatments are quite expensive (in a context of African developing countries) nowadays, and the development of new drugs, rendered necessary by the progressive (and inevitable) increase in the frequency of resistance, is seriously hampered by the economic considerations of (lack of) profitability, given the poverty of potential customers in this particular market. The company that developed eflornitin (DFMO) as a trypanocidal drug, out of what originally was meant to be a cytostatic drug (at one point in time, DFMO was a '*drug desperately in search of a disease*', as S. Van Nieuwenhoven puts it - 1992b) has offered all rights (and production procedures) to WHO, but these negotiations do not appear to have resulted in any firm bilateral commitment up to this day,

and production by Marion-Merrell-Dow was said to be discontinued after 1993. At any rate, DFMO treatment is likely to remain very expensive.

However, there appear to be major differences in the cost of these treatments, the cheapest one (for stage II patients, at least) being nifurtimox. The drawback of the latter drug is its oral administration mode extended over a period of 3 weeks, which needs to be strictly supervised (especially in view of the fact that many cerebral stage trypanosomiasis patients are likely to be confused and cannot be depended upon to carry out pharmaceutical treatment instructions correctly). Apart from this consideration, melarsoprol has been associated for so long with (effective) trypanosomiasis control (more than 40 years by now), that for many people it must have become synonymous with treatment. This may help to explain why it remains the (almost) unchallenged mainstay drug for HAT control programs.

## *Conclusions at this point*

Having come this far in our 'vertical analysis' it may have become possible to identify and list some of the more important *gaps in available knowledge* which it would be relevant to try and fill in, if we want to formulate rational decisions for a more efficient and feasible way to tackle the HAT problem.

Necessary knowledge (or insights) can be structured in two main fields:

- *insight in - or understanding of - the disease problem's system*: this can be subdivided in areas that we could roughly designate as clinical epidemiology (natural history, 'epidemiology of the *illness*'), and the epidemiology of the endemic/epidemic (the system's model, 'epidemiology of the *disease*');

- *the operational characteristics of the tools we (can) use to do something about this health problem, and how we can refine or improve them*. By 'tools' we understand here the wide range of techniques and applications that are used and combined in different strategies, i.e. 'tools' in a rather wide sense.

A list of questions concerning these fields would be, inevitably, somewhat coloured by our interest in questions related to validity, relevance and cost-effectiveness of strategies to control HAT in basic health services, and by our level of knowledge and understanding of the problem at hand. The following is, therefore, not meant to be complete.

Questions regarding the *natural history of the illness*:

- What is the most likely sequence (and probability) of events in the trypanosomiasis illness, and more specifically the place of serological changes, presence of 'typical glands' and symptoms in the natural history of the illness? This includes the question of the probability for 'infected' individuals to evolve toward 'suffering'.
- How to define 'stage II' (what is it, if it exists), or, translated in practical terms, how to distinguish patients with (irreversible) cerebral involvement?
- Is the danger of treating patients with 'stage II' drugs (like melarso-prol) comparable for everyone, irrespective of the real staging status (if this notion is relevant)?

Questions in the area of *epidemiology of the endemic/epidemic*

- What determines the evolution towards an 'epidemic' situation and how can we (better) predict such an event?
- What determines contagiousness in man (for flies)?
- What determines man's susceptibility for infection?

Questions in the area of *operational characteristics of tools (s.l.)*

- How to decide on the most adequate (and safe) drug treatment for individual patients in rural Africa? This would include better ways to identify *which patients* to subject to which type of treatment, as

well as finding *optimal treatment mixes* (effective, efficient and less toxic) using available drugs.

- What are the operational characteristics (essentially sensitivity and specificity) of different screening and diagnostic tools (signs and techniques)?
- What is the effectiveness and efficiency of different screening criteria or signs? An important practical point in this category, it seems to us, would be the possible confirmation of the operational usefulness of the auto-agglutination phenomenon.
- What is the marginal effectiveness (or usefulness) of an active case finding approach as compared to an approach where the initiative for contacting (permanently accessible) health care providers is on the side of the individual (or community)?

To our knowledge, partial or hypothetical answers to these questions have been formulated, but a lot of inconsistencies remain. One of the reasons (though certainly not the only one) why a more precise knowledge is needed is the fact that, in the present context, a potentially quite important problem like HAT needs to be tackled with possibly quite restricted resources and at the lowest possible cost. For decision making purposes, we need elements that can guide us in answering the question: given the present situation, and given the available resources, how can we best control the problem? - or how one needs to know more when one is poor.

In the following part, which reports on a longitudinal research effort that has been carried out in Kasongo (Maniema region, Zaire), we will try to develop an answer to *some* of these questions. We will describe the research project and the information it has produced, but we will also develop the questions it has generated, at least for us, in terms of the validity and reliability of the results. In a sense, sometimes we may end up with more uncertainty than we started from. Fortunately, this will not always be the case.

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## III The Kasongo Study

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### *Origin and basic research questions*

In 1977 Mercenier published a paper in which he analysed detection mode and presenting symptoms of a series of 384 trypanosomiasis cases in the Kasongo health zone (Maniema, then Zaire), where a number of functioning general health care structures were available, and where a specialised (mobile) trypanosomiasis control team was also active (Mercenier, 1977). This analysis showed that in the examined series 292 (76 %) of detected cases were diagnosed after a spontaneous consultation, and that of the 68 who had not yet consulted and for whom the information was available, only 3 were symptom-free (as determined *a posteriori*). Thus the potential of passive case detection through permanent, decentralised general service points, in this series, appeared to be very important.

As this ran contrary to the prevailing (though mostly implicit) trypanosomiasis control doctrines, this statement was sufficiently controversial to make the idea grow to set up a carefully designed population based prospective study into early signs and symptoms that could be used to detect the disease. The Kasongo district provided a good setting for such a study, since it contained old and more or less “stable” trypanosomiasis foci. In one of these, in the area of the Kongolo health centre, a cluster of villages was selected, containing some 2500 people. Based on the experience of active and passive case detection in the past, the annual detection rate in this population was about 10 to 12 new cases per 1000 inhabitants. A prospective multi-round survey over two years was thus expected to yield some 50 cases of trypanosomiasis.

The study was designed around the following questions:

- *What is the predictive power of indicators of risk, detectable in a rural setting with a permanent and accessible first line health service, and to what*

*extent can they contribute to early detection of trypanosomiasis with T. b. gambiense ?*

*- What would be the marginal effectiveness of an active case finding strategy as compared to passive case finding in an adequately functioning basic health service?*

“Indicators of risk” (more accurately, maybe, “risk markers”) were understood as, on one hand, a number of variables about which no prior hypotheses are formulated, but for which the individual information would be available in the study (like sex, age, area of residence, etc.). On the other hand there are a number of variables about which prior hypotheses are formulated and tested. Examples are cervical gland status, serological status, history of previous treatment for trypanosomiasis, and declared symptoms or health related complaints, expected to possess (some) significant or relevant predictive or prognostic power. The choice of these variables is justified by the feasibility of their identification in a first line health service setting. With the hindsight we now have, we must add that the autoagglutination phenomenon was not, at the time of the study design, within our field of vision - regrettably.

In each of the survey rounds the entire study population was to be screened for four signs:

- a positive serological test result, as determined by the Indirect Fluorescence Antibody Test (IFAT), carried out on dried blood, collected on Whatman 4 paper, in the laboratories of Kasongo and of the Institute of Tropical Medicine in Antwerp. Results of this IFAT test were expressed in terms of a semi-quantitative scale with four possibilities (“negative”, “weakly positive”, “clearly positive”, “strongly positive”);
- the presence of “typical” neck glands (i.e., in practice, which can be punctured with a needle);
- declaration of one or more “suggestive” symptoms, according to a preestablished list, with a duration of at least 30 days;
- being an infant (less than 2 years of age) born to a mother who was detected as a parasite carrier.

Every individual who screened positive for one of these criteria was eligible for further parasitological investigation, in the same and possibly following rounds until found positive, with a combination of tests including gland puncture (if “typical” glands were present), microscopic examination of fresh blood, microscopic examination of a Giemsa coloured thick smear and of the “buffy coat” after centrifugation in heparinised 100  $\mu$ l capillary tubes. If any of these were positive, cerebrospinal fluid was tapped and examined (white cell count and microscopic search for parasites).

Three months after a thorough census of the study population, the first round was started in January 1989.

According to the protocol, 4 rounds were foreseen in 1989 and 4 in 1990, covering a period of 24 months. In practice, only four rounds could be done, over a period of 18 months. Part of this can be explained by important problems of logistics; the second part of the explanation is the culmination of the political tensions between Zaire and Belgium in June 1990, resulting in a stop of all official technical co-operation and reducing the duration of the survey by 6 months.

## *Findings*

A detailed account of the analysis and results has been provided elsewhere (Kegels, 1995). Here we will restrict the presentation of findings to a summary of the main results, divided over 4 areas of interest.

### VALIDITY - RELIABILITY OF TEST RESULTS

In terms of reliability of the IFAT screening results, quite a bit of *random error* misclassification occurs. Comparing two laboratories, they appear to disagree on the other lab's *positive* results in about 1 out of 3 cases, independently of the fluorescence threshold chosen (i.e. including “weakly positives” or not). Within one laboratory, in a blinded reproducibility study, this proportion is reduced to somewhere between 10 and 15 %. However,

comparison of the two laboratories does not reveal any *systematic bias*, since they arrive at the same overall serological prevalence.

When formerly or presently treated cases are eliminated from the cohort, observed sero-conversion rates between the rounds of the survey are not meaningfully different from what can be expected on the basis of the test's inherent lack of precision (at this level of transmission).

Lack of IFAT reproducibility is concentrated in a relatively small group of individuals. Changes in IFAT results (conversion or inversion) are far less meaningful in previously treated cases.

Over time, individual IFAT screening test results appear to fluctuate a lot under and over the positivity threshold, also among those who were never treated before. The majority of recent "conversions" end up negative again, without treatment.

The reliability of the declaration of symptoms in answer to open questions (in a population based study setting) is questionable. Possible explanations may be linked to the interview situation itself and to perception and motivation of the interviewees to declare health problems.

#### ASSOCIATIONS BETWEEN POSSIBLE INDICATORS OF RISK

In this area and this population, the presence of "typical" neck glands, or of any type of neck glands, is not associated with serological IFAT positivity. However, the (rare) individuals who produce both signs (typical glands *and* IFAT positivity) are very likely to be detected as parasite carriers.

The prevalence of IFAT positivity appears to increase progressively and continuously with age, also among those who have never before been treated for trypanosomiasis. If we include "weak positivity", this serological prevalence (among those never treated before) increases gradually from 1.4 % below the age of 10 years to more than 12 % above the age of 50. Excluding "weak positivity", this gradient goes from 0.6 % to some 5 %.

The prevalence of “typical glands” (or any kind of neck glands) decreases gradually with age, from more than 25 % with “typical glands” below the age of 20 years to some 5 % above the age of 60.

IFAT positivity among previously treated individuals is much more frequent than among never treated individuals. The frequency of this serological positivity decreases with time elapsed since the last treatment, but this evolution is a matter of years rather than months.

#### CHARACTERISTICS OF PARASITOLOGICALLY CONFIRMED CASES

Among the parasitologically confirmed patients, the distribution of cell counts in cerebrospinal fluid appears to be bimodal. Two sub-populations are separated by an empty “dip” between 40 and 80 cells/ $\mu$ l.

Parasitologically confirmed infection occurs at all ages, but is most frequent in the age group between 10 and 50 years in this population.

In this study setting, 15 out of 40 parasitologically positive individuals have been identified in a “passive” mode. Among these patients almost all (14/15) have cerebrospinal fluid cell counts of more than 80 cells/ $\mu$ l.

#### OPERATIONAL TEST CHARACTERISTICS

A positive IFAT screening test result is no conclusive evidence of patent infection.

As measured against parasitological confirmation, the IFAT screening test’s sensitivity in this situation is of the order of 83 %, for cases confirmed in the same round. Sensitivity increases to some 88 % when parasitological positivity in the same *or following rounds* is accepted as definition of disease. These figures are independent of the IFAT positivity threshold used (“weakly” or “clearly” positive). Therefore, the higher positivity threshold appears to be as effective for screening purposes as the lower one, and much more efficient.

As measured against parasitological negativity in the same round, and using the higher positivity threshold for the IFAT test, the latter's specificity per round is between 97.4 and 98.6 %. The highest specificity figure is reached when "absence of disease" is defined as parasitological negativity during the whole survey as well as before the survey (never treated), and would be 98.5 % for the population of the first round.

The sensitivity of the sign *presence of "typical neck glands"*, as measured against parasitologically confirmed cases of the same round, is some 41 % in this situation. Sensitivity increases to 49 % if calculated on the group of parasitological positives in the same or following rounds. The specificity of the sign *"typical neck glands"*, as measured against parasitological negativity in the same round, ranges between 79.4 and 90 %. If "absence of disease" is defined as parasitological negativity throughout the 4 rounds of the survey, the specificity of the sign in the first round would be 79.4 %.

The odds ratio (OR) of the single sign *"typical neck glands"* (as measured against parasitological confirmation) is consistently very low, as well as its positive predictive value (PPV). However, when combined with IFAT positivity, this very rare combination has a very high OR as well as PPV, but unacceptably low sensitivity from the point of view of disease control effectiveness. Moreover, the majority of parasitologically confirmed infections with this combination of signs have high cell counts in the cerebrospinal fluid (the latter is true, for that matter, for all the screening signs).

The presence of the single screening sign *"any kind of declared symptom of at least 7 days' duration"* identifies a group in the first round population in which two thirds of its eventually parasitologically confirmed cases will be found.

If parasitological confirmation is maintained as the necessary condition for treatment, and if parasitological investigations, when negative, are continued after screening, the best combination of sensitivity and specificity (effectiveness and efficiency) is obtained with the single screening criterion "IFAT at least clearly positive".

Within an unchanging cohort population (in this epidemiological situation) the marginal effectiveness of repeated IFAT screening (at intervals of 5 to 6 months) is negligible as compared with pursued parasitological follow-up of the initial IFAT positives.



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## *IV Consequences for managing the West African HAT problem*

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### *Consequences with respect to the disease system's model*

The Kasongo study set out to examine the 'predictive value of indicators of risk and to what extent they could contribute to early detection of trypanosomiasis with *T.b. gambiense*'. This means, in other words, an examination of the operational 'qualities' of tools used to identify infection, be they 'concentrating' screening tools or diagnostic ones.

The findings of the Kasongo survey are not very revealing as far as early or late symptoms are concerned, as we have observed. But they shed a somewhat unsettling light on what we have considered as reliability and validity of other techniques used for identification of infected individuals. The presence of 'typical glands' turns out, or is confirmed to be almost unrelated to the detection of parasites, be it directly (parasitological confirmation) or indirectly (serological positivity), at least in this situation. Even the serologic screening technique, though unquestionably more effective than gland palpation for the detection of infection, has important problems of 'reliability' which are far from negligible: between-laboratory agreement is far from perfect; within-laboratory agreement is much better, but again not quite perfect; and individual test results change a lot over time, mainly in the direction of sero-inversion, without any specific treatment. Less pronounced, but quite intriguing is the change in predictive value of the IFAT test with age.

It could be argued that this IFAT screening technique is not the best serological test available at the moment. This may be true. However, on the basis of available evidence and on the basis of theoretical considerations we have every reason to believe that the presently available and possibly better

tests - like the CATT - would produce comparable results in terms of reproducibility, when used on a large scale and in routine settings. The question then comes up: is it *only* a matter of reliability?

We could also try to explain these findings by looking from another angle. Up till now we have always organised our reflection on the basis of the hypothesis that West African HAT disease is a predominantly *linear* process, based on the simple initial model used - and implied - for the vertical analysis exercise. After having analysed the possibilities for intervention that were formulated on the basis of the simple initial system's model (the vertical analysis) and what we can learn from the Kasongo experience, we can ask the question if it would not be useful to adapt the first model (which is largely theoretical and utilitarian for the purposes of the analysis) into something possibly more relevant.

What is the problem with the simple model?

A first problem with HAT epidemiological models is the real difficulty that is caused by the difference between what we could call *conceptual* classes and what we could call *semiotic* classes. What we have used in the initial model are 'conceptual' classes, i.e. more or less homogeneous groups defined by the presence or absence of some conceptual criteria, like 'contagiousness', 'infection' and 'suffering'. This has been, we think, very useful for purposes of analysis: it creates the opportunity to analyse in some depth the concepts and the tools that we are using in tackling disease related problems. However, it is less adapted to practical decision making: decisions are made on the basis of concrete factual observations, i.e. on the basis of the *expression* of these concepts (if these are the concepts that we wish to maintain as the most relevant). Grouping people in model classes according to combinations of concretely expressed, observable phenomena, is what we could call a *semiotic* classification, in which, e.g. 'contagiousness' is expressed by some test result or systematically observable phenomenon, as well as 'infection' and 'suffering'. The problem now resides in the fact that there is a lot of uncertainty about the congruence of (relevant) concepts and their alleged expression. As an example, the semiotic class [parasitological test negative *and* serological test negative] is not (entirely)

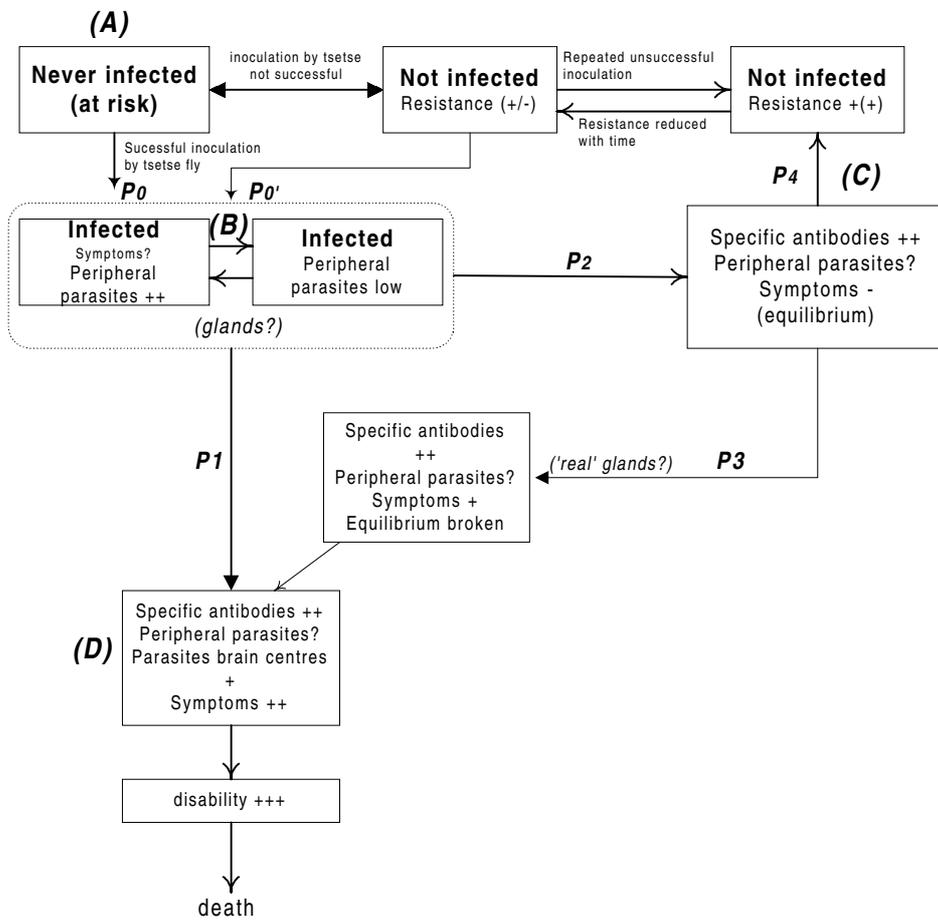
congruent with the conceptual class [not contagious *and* not infected], nor does the combination [parasitological negative *and* serological positive] indicate with certainty [not contagious *and* certainly infected]. In other words, each 'conceptual' class would have to be split up in a number of 'semiotic' classes in order to get all the possibilities together, which would make the model very complicated, not only structurally (the number of boxes) but also in terms of quantifying the transitions (between boxes).

Although, to some extent, this kind of problem is common to virtually all disease systems if they are examined in some depth, it appears to be very pronounced in HAT. This has to do with the imperfections of available tools (tests and signs) and of our capacity to interpret them. It also has to do with the apparently great variability in the expression of the 'natural history' of this disease, of which the determinants are clearly far from understood. But it is certainly related equally to the constantly recurring ambiguity between the logic of *disease control* and the logic of *care for illness*, between the concept of *parasite carrier* and the concept of *patient*, between the attitude of considering a parasite carrier as a *danger for society* and considering him/her as a *suffering* (or potentially suffering) *individual*, in need of care. Because of this ambiguity, which consists mainly in the implicitly made assumption that what is good for society also happens to be good for the individual (treating a 'contagious' individual will eliminate a source of transmission but will also 'save' the infected patient - thus blending disease control with caring for the individual), the implicit model that has always been used is a very simple one, based on the life cycles of the parasite in the vector and in the host. In order to support the decision 'kill as many parasites as possible', no complicated conceptual classification models are needed and it is not even very relevant to look for detailed knowledge about the spontaneous evolution of this infection. Thus the preferential decision to *act* (treat) whenever a person is a parasite carrier (within some reasonable margin of certainty) makes a conceptual classification largely superfluous: all that is needed is a practical criterion that switches the light to green: treat. The conceptual classification is then subordinated to and equalised with the semiotic one, and any doubt is felt to be counterproductive. The concepts (infection, contagiousness, suffering) tend to be fitted to the signs (antibodies, parasites, glands,

symptoms); not the other way around. This is, of course, nothing unusual, and a very frequent practice in medical decision making. But it tends to limit development of our understanding of the disease system to what is useful for *doing* something (or more), not to what could lead to *not doing* (or doing less).

On the other hand, a very practical, biological phenomenon, very typical of human African trypanosomiasis, complicates modelling: the parasite's quite amazing capacity to keep the host's immunity mechanisms busy by unpredictably altering its phenotype to a new 'disguise'. The practical consequence of this is, that the concept of 'immunity' (or maybe 'resistance') does not coincide with the presence of 'specific' antibodies (as would be the case in most of the 'ordinary' infectious diseases). In trypanosomiasis, immunity (or resistance) appears to be a very relative concept, and probably would have to be replaced by something biologically far less 'satisfying' (and much more difficult) like '*parasite-host equilibrium*' - or lack of it. This equilibrium is likely to be subject to change over time, determined or co-determined by a number of largely unknown influences, themselves changing with time. If this is true, the system's model cannot be adequately represented by simple flow diagrams with (more or less) constant probabilities of transition from one status to another. It will need to be made much more 'dynamic looking', by complicating the diagrams or by adding a profusion of question marks, or by adding lots of footnotes. Finally, a helpful or handsome way out of the problem could be to make a sort of hybrid model that includes conceptual as well as semiotic criteria.

A possible example of the latter solution could be the following system model, unquantified and restricted to the developments in the vertebrate human host.



In this representation, the probability  $P_0$  is the probability for a non-infected individual to have an infective inoculation 'catch on', in such a way that the parasites start multiplying in the human host (transition from (A) to (B)). This may involve a series of consecutive waves of high parasitemia as the parasite population develops new antigenic disguises, reacted upon by the production of adapted immune substances. This may happen several or many times (oscillating between the two boxes in sub-system (B)).

$P_1$  would then be the probability that the evolution of the illness is more or less instantaneous (transition from (B) to (D)). The immune mechanisms of the host are unable to control the development of the infection and a (most likely) irreversible process is started in which brain centre involvement becomes progressively more important, ending in severe disability and death: 'sleeping sickness'. Serological evidence of antibodies is present, but these are either not specific enough or the immune defence system is insufficiently effective for some other reason.

An alternative path would be represented by the probability  $P_2$ . In this case, an equilibrium is reached within the host, and the infection is 'put to sleep', so to speak, for a variably long period of time and there are no symptoms (suffering), but serological evidence of specific antibodies remains (box (C)). When for some reason the equilibrium is broken, and the parasites 'wake up', the evolution would be along the line of  $P_3$ : symptoms develop and sleeping sickness follows. If the parasites cannot survive, the human host would follow the path  $P_4$ , which is one of spontaneous 'sterilisation'; a new infective sting by a tsetse fly would be necessary to start up a new episode of infection.

So far, a model like this one can hardly be faulted for 'truth content'. The categories' existence is plausible, and so are the theoretical flows - although some may have been omitted. But the *relevance* of the model depends on the relative values of, for example, probabilities  $P_1$  and  $P_2$ , and the absolute and relative values of  $P_3$  and  $P_4$ .

The existence of a status that could be described more or less accurately by box (C) has certainly been documented, but rather as an anecdotal phenomenon. Instances of development of sleeping sickness symptoms more

than 10 years after leaving endemic areas have been described, and if one includes the phenomenon of *trypanotolerance* (asymptomatic, healthy status in the presence of prolonged, proven parasitemia) in this category, this has been described as well - again, as a rather anecdotal phenomenon (e.g. Ginoux and Frézil, 1981). To what extent this type of evolution could be a widespread occurrence, is unknown. But if it were, what could be the arguments in favour of it and what could be the possible relevance for decision making?

Arguments in favour of the existence of a possibly important group of 'latent' (asymptomatic) infections, which may also be self-limiting, may include the following.

Many serologically positive individuals keep feeling perfectly 'normal' - or would make statements to that effect - for long periods of time (taking into account the fact that trypanosomiasis generally occurs in areas where many other tropical and cosmopolitan diseases are endemic: malaria, filariases, schistosomiasis, iron and folic acid deficiency,...which may add a lot of 'static' to 'feeling normal'). They may never develop sleeping sickness symptoms. This 'stating to feel normal' is, of course, a relative argument given the fact that subjective statements can hardly be verified.

Serological positivity, as an isolated sign, has a PPV for the visual confirmation of presence of parasites, of close to 1/3 in the Kasongo survey (repeated and multiple parasitological examinations). However, the combination of serological positivity *and* presence of 'typical' neck glands (a *sign*, although not necessarily a *complaint*) has a PPV that is much higher (2/3) and is, moreover, strongly associated with altered CSF and probably brain centre involvement.

This could be interpreted by saying that an important proportion of serological positives are stably living with parasitemias that are low or virtually negative, whereas identifiable subgroups have (more easily) detectable parasitemia levels and are in a phase of 'evolving' disease. Again, this is not necessarily very convincing as an argument; other interpretations can easily be invented.

Serologically positive individuals are observed to revert to negativity without treatment. This has been observed in the Kasongo survey, but has been mentioned elsewhere (De Raadt, 1989) and it has been reported *en passant* in other situations (Laveissière et al.1990; Pépin et al.1986). There is no fundamental reason why this observation should be attributed *exclusively* to test imprecision.

'Epidemics' of sleeping sickness have been noted to coincide with 'hard times' (socio-political turmoil, famine,...), which could be interpreted as contributing to generally lowered resistance of the human population (Ford, 1979; Janssens and Burke, 1992). If a relatively important subgroup of the population is living in some 'stable' equilibrium with its parasites, and a more or less collective lowering of resistance occurs, the  $P3$  of the model would increase first, symptomatic sleeping sickness would rise, the problem would be socially recognised and an epidemic 'declared'. Thus increased incidence of the *illness* could, in a first phase, be explained without necessarily having to invoke an increased speed of circulation of the parasite (higher transmission-diffusion). If this is true, measures solely aimed at reducing transmission (like vector control) can be expected to be rather ineffective (on a short term basis) in such a situation <sup>6</sup>.

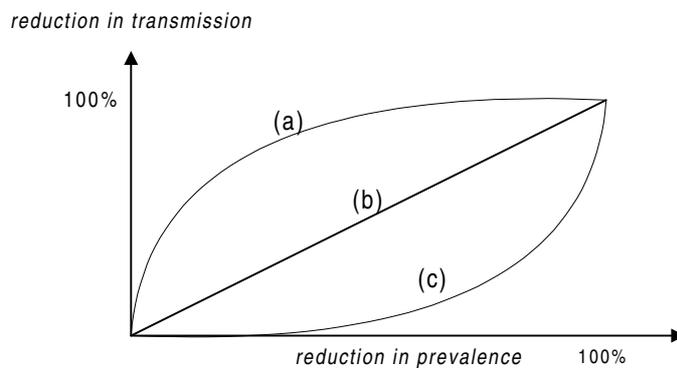
If it is true that changes in illness incidence are (at least for a significant part) provoked by changes in the probabilities  $P1$ ,  $P2$ ,  $P3$ , themselves varying under the influence of factors that are difficult to identify and maybe impossible to quantify, this is of course bad news for epidemiometric modellers. It would confirm the old reputation of *gambiense* sleeping sickness as a mysterious and often totally unpredictable disease. It would also be consistent with the success story (from the point of view of disease

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<sup>6</sup> Maybe it is useful to stress that we are talking here of human African trypanosomiasis of the *gambiense* variety. A possible way of explaining the difference with the *rhodesiense* type could be that in the latter the 'stable equilibrium status' is far less frequent (if not virtually non-existent), and the predominant pathway is an evolution along the vertical lines of the diagram, without any detour or return. If this is true, *rhodesiense* 'epidemics' can be tackled effectively and immediately at the transmission level and effective vector control can be expected to reduce the incidence of illness. Which seems to be the case (cf. Lancien, 1991), although this also seems to be questioned (Williams et al. 1993).

control) of the strategy that consists in systematically treating *all* serologically positive individuals (using a '*diagnostic*' test) - where and if such a strategy is feasible (Van Nieuwenhove, 1992) or the comparable approach reported by Bruneel et al. (1994): even if the individuals with 'stable' equilibrium status were *not* contagious for the tsetse flies and thus not important as a reservoir for *transmission*, they would constitute a pool for potential illness and therefore be a human 'reservoir' for *illness*. Eliminating infection in this latter 'reservoir', through adequate 'sterilising' treatment, could make the illness disappear for quite some time in a community. Which it seems to do.

This does not mean, of course, that the intensity or speed of transmission through the vector would be unimportant in the genesis of epidemics or in the maintenance of endemicity. The frequency of the event 'transmission' (the probabilities  $P_0$  in the model's diagram) should logically depend on the numbers of contagious individuals in a given population and on the 'closeness' of the man-fly contact. If the latter factor is constant, the relation between the prevalence of (contagious) infection and the incidence of new infection (transmission) is unknown, but could theoretically be of several more likely types (Mentens, 1992). Graphically the more obvious ones could be suggested as follows:



If the relation is of the type (a), this would mean that a relatively small decrease in the prevalence of (contagious) infection would result in a

disproportionately important reduction of the transmission. On the other hand, if the relation is of the type (c), a very important reduction of the prevalence of (contagious) infection would be needed in order to obtain a significant decrease of the incidence of new infection. Type (b) would, of course, be a simple linear relationship.

As said before, it is not known which type of relation prevails, nor whether the type is unique or not. It could be that it changes with the situation or environment, or with fly species, behaviour or other characteristics. A general argument in favour of type (a) is that control activities in the past (e.g. before the African states' independence), although using screening techniques that were not always very sensitive (as we now know), still succeeded somehow in almost eradicating the disease, which would be compatible with the existence of some threshold of prevalence below which transmission becomes very difficult, and that this threshold may be higher than expected a priori. But the same observation could be used in support of type (c): maybe the final 'success' of these control activities should be attributed to their sheer volume and the obstinacy with which they were continued for decades without interruption, until in the end (and with the help of massive pentamidine administration!) the disease appeared to 'die out'. We do not know. And, of course, there is no good reason to exclude the possibility that the curve could be S-shaped or even more complex.

Still, the general impression is that, in ordinary circumstances, transmission of human trypanosomiasis is, because of its complexity, a rather 'fragile' process, and that (again, in ordinary circumstances) not much would seem to be needed in order to reduce it significantly.

With our 'hybrid' conceptual epidemiological model, the most violent or explosive epidemics would be those where  $P_0$  and  $P_1$  and  $P_3$  are all more or less simultaneously raised. This could happen for various reasons, related to hosts, parasites or environment, and it is quite possible that these probabilities exert a 'vicious circle effect' on each other. All this is speculative, but plausible.

If such a model remains - or has to remain - extremely vague in quantitative terms, what could possibly be its usefulness or relevance?

We think that the explanatory power of such a model is potentially higher, in theoretical terms. The extent to which it also has a higher potential for correctly *predicting* what is going to happen in a given situation will to a large extent depend on reduction of the uncertainty about the transition rates P1, P2, P3, P4, but also on the comparative 'contagiousness' of each of the various 'infected' groups. In particular, if the category 'stable equilibrium' is an important one (*quantitatively*) and *if* at the same time this group is highly contagious, these people would probably represent the most important reservoir for *transmission* as well as for *illness*, and their identification and treatment would be expected to be very effective in terms of control of the endemic/epidemic. On the other hand, as these people would not be *ill*, the acceptability of treatment would represent quite a problem (not necessarily insuperable, but certainly not easy to solve in a non-epidemic or not clearly epidemic situation). One way out of this problem could be to identify this group (e.g. serologically) and to consider them, operationally, to be a group at *high risk*, to be followed up closely. In practice, this can only be done if, where and when a reasonably accessible and preferably permanent service is available, in which this kind of follow-up activity can be integrated. If it so happens that the contagiousness of these people is not a big problem, this follow-up strategy would still remain highly relevant, given the fact that the *reservoir for illness* remains and can be circumscribed.

Theoretically, all this opens up areas of relevant but difficult research.

From our (public health) point of view, what will determine relevance of (further) research? A first criterion is that it needs to support decision making in some foreseeable way. However, another important criterion has to do with the decisions themselves and how they are related to *needs*, *demand* and *supply* of health care provision and health related interventions.

We will define *need* as the professionally and objectively defined health needs of a population, *demand* as the subjectively defined set of problems as identified and expressed by the population, and *supply* as the set of health care activities a given health service is capable of offering.

In our hierarchy of values, the first thing a health service must do is to respond to *felt needs*, i.e. to the area where demand and need overlap. This is essentially and mainly the domain of curative care and the initiative for contact is predominantly on the side of the 'patients', expressing their demand. To the extent that a health service wants to tackle *unfelt needs*, the initiative changes sides and the responsibility for the action and its consequences is entirely on the side of the health care providers: they must be able to foresee what will be the effect and what will be the cost of *their* action, especially if their action is an 'aggressive' one. In the field of responding to felt needs (demand), it may be acceptable to provide 'care' without 'cure'. When tackling *unfelt needs*, this is not permissible: the proposed action (be it in the form of curative, preventive or promotional activities) *must* be effective (Cochrane and Holland, 1971; Holland, 1993; McCormick, 1994). And since the proposed action always carries a cost that is ultimately born by the community, this kind of activity *must* be efficient also (i.e. as cost-effective as possible). Thus, the more health service action is addressing unfelt needs, and the more it is aggressive in nature and/or scope, the more this action needs a sound scientific basis. Therefore, the relevance of research activities does not only depend on their mere technical 'usefulness' for decision making, but also on the ethical, responsibility related implications of the decisions they are going to support. If we want to do better than what people ask us to do, we'd better be quite certain that we are really going to do better, *and* at an acceptable cost. In other words, we need to understand the disease system sufficiently well to be able to adequately predict what will be the effect and cost of our action.

How can we apply this to the problem and the disease system of West African sleeping sickness?

In essence, the questions seem to be: what do we need to know, and is what we know sufficient, in order to decide whether or not we are going

- (1) to treat ill (suffering) parasite carriers (a felt need)?
- (2) to identify and treat not yet suffering parasite carriers (an unfelt, potentially a felt need)?

- (3) to develop a programme to reduce the human reservoir (target: transmission)?
- (4) to develop vector control activities(target: transmission and 'pest' nuisance)?

The answer to the *first* question is yes, without any reasonable doubt. We may be justified in having theoretical doubts about ascribing the illness (the suffering) of individuals to the presence of *Trypanosoma* parasites, but we have little justification not to treat such people as cases of what we call the disease HAT. The decision here is not whether or not to treat, but *how* to treat *which patients*. There are important areas of uncertainty left as to the last question.

The answer to the *second* question (shall we go and identify not yet suffering parasite carriers, in order, of course, to do something with them for their benefit) depends on how sure we are that they are going to evolve towards illness (suffering). To our knowledge, the answer to this question is far from precise, although it is reasonable to accept that very many will develop illness. To the extent that this kind of decision involves important initiatives on the side of the health service, possibly not corresponding with a need felt by the potential patients or the population, this question would in principle need to be resolved *before* we can decide on this kind of action. It may be useful, for clarity's sake, to note here that in an 'epidemic' situation formerly 'unfelt' needs may very well turn into 'demand', and even to demand for 'aggressive' action. It is also clear that if the identification of and action taken with not-yet-suffering parasite carriers had little or no consequences in terms of induced suffering and of cost, the need for more thorough understanding would be reduced. However, this is really not the case.

If we accept that infection is a necessary but not sufficient condition for developing illness, what do we need to know? First, what are the respective *probabilities* of developing disease, of staying infected without illness and of 'sterilising'? Second, are there *determinants* for these different evolutions and what are they?

The answer to the *third* question (shall we try to interrupt transmission by systematically acting on the human parasite reservoir) depends on how sure we are of our ability to identify sources of transmission, in other words contagiousness. Up till now, the general practical consensus seems to be that the concept of 'contagiousness' is to be synonymous with the concept of 'infection' (i.e. being a parasite carrier). In fact, the truth is that we do not know how to distinguish these two states, although they are conceptually and practically fundamentally different.

As far as we can understand, the basis for the decision to act on the human reservoir in an active way is that tsetse flies cannot get infected if there are no vertebrate (say, human) parasite carriers. In the light of our position stated above, this can hardly be considered as a sufficiently illuminating and justifying insight (always *when we are talking of non-epidemic or low endemicity situations*).

If we accept that the tsetse flies' susceptibility for *T. brucei* infection is consistently and highly associated with Rickettsia like organisms (RLO) infection in the flies - this feature has been observed and reported (Maudlin and Ellis, 1985; Maudlin and Welburn, 1988), but may not be universal - then the logical conclusion would be that the transmission of *T. brucei* is to a large extent determined and conditioned by identifiable and variable *characteristics of the tsetse population* (other than their taxonomic characteristics and feeding and breeding behaviour). This is already a remarkable finding. But what is possible for the vector may also be true on the side of the vertebrate host. Why would there not be identifiable characteristics of the human population, other than parasitemia, that determine or condition receptivity for infection, contagiousness and transmission? A clear parallel is to be found in the HIV story, when it has been demonstrated that the presence of sexually transmitted diseases (other than HIV infection) plays a highly determining role in the probability of sexual HIV transmission (Kreiss et al.1988; Laga et al.1991; Cameron et al.1989; Plummer et al.1989 and many others).

The answer to the *fourth* question (do we know enough to decide on trying to control the fly population) is, in our opinion, a 'probable yes', depending on the circumstances.

If the flies are a great nuisance, which depends mostly on their sheer numbers or density, there may be a demand for adequate technology to reduce these numbers. However, in that case it may also be very difficult to control the vector and the effort needed may be felt to be too high. Moreover, we know that the fly density is not *per se* the most important determinant of transmission.

On the other hand, it may also be that the flies are not felt to be a great nuisance, but that there is a serious felt problem of HAT. In that case, it may be that small fly populations, often living in a biotope that is unfavourable to them, can be effectively controlled without too much effort, in a geographically targeted way, an action in which the community and health professionals can develop a fruitful interaction.

If the flies are felt to be a great nuisance *and* at the same time there is a serious felt problem of HAT (a typical situation might be the 'peridomestic' mode of transmission), selective vector control activities in addition to treating patients may be feasible and effective if continued for a sufficiently long time. The technology for this is available: correctly positioned fly traps and/or screens and/or sixmonthly ground spraying (the bush clearing alternative appears too cumbersome to be widely 'acceptable', especially in a forest environment).

If further research activities are needed in this field of tackling the tsetse link in the transmission chain, they are, we think, of two types:

- fundamentally epidemiological research into the determinants of the tsetse populations' capacity to transmit the infection. If these determinants are (better) known, direct or indirect surveillance of the tsetse populations might provide useful information to predict changes in the speed of transmission and thus possibly 'epidemisation' of the HAT problem;

- action oriented research, aimed at better understanding under which conditions and how vector control activities can optimally be implemented in real life and routine situations

## *Consequences for the practical management of the HAT problem*

For the rational formulation of operational strategies with respect to the handling of the HAT problem, we need not only an adequate model -or insight- into the *disease* system, but also an adequate understanding of the *health* system (or the health care delivery system): what are its functions, its responsibilities, how does it relate to the community, what is its optimal organisational model, on what basis are decisions made concerning its activities, how do different structures and levels relate to each other, how are they developed, how are they managed?

In the following pages we will first develop our premises on how health services should be organised and then how the handling of the HAT problem can fit in these structures.

### 1. THEORETICAL CONSIDERATIONS ON HEALTH SERVICE ORGANISATION

#### *1.1. Concepts in the area of health service organisation*

The definitions proposed here reflect the conceptual tradition of the Public Health Unit of the Institute of Tropical Medicine in Antwerp. They are the result of an effort to put together, in a coherent set of concepts, a model through which health service organisation and functioning can be analysed.

These definitions are not universal in a semantic way. They are to be seen as working definitions intended to make communication possible; semantically, they are a set of less-than-universal conventions.

- *Three areas of the 'vertical'*

We use the adjective 'vertical' principally with three different nouns: a vertical *approach* (or vertical 'analysis'), a vertical *programme* and a vertical *structure*.

We will define a '*vertical approach*' (or vertical analysis) as the intellectual exercise that consists in analysing the importance and 'vulnerability' of a health problem (such as, for example, the one resulting from Human African Trypanosomiasis) in a systematic way (i.e. step by step) and without prejudice (if such an attitude is conceivable...), according to a rigorous methodology. Part of this is what we have tried to do in part II.

A '*vertical programme*' is defined as a set of activities, (preferably) useful and necessary, aimed at reducing the importance of a health problem or of a limited number of health problems, but without taking position on the structure or the service that is going to implement these activities. An example of a vertical programme is the 'Extended Programme of Immunisation' (E.P.I.)

A '*vertical structure*' is a structure - or a service - that is in essence *specialised*, tackling one health problem or a limited number of health problems. The fundamental objective of a vertical structure, when it implements a (vertical) programme, is usually formulated in *epidemiological* terms, and a vertical structure will be judged or evaluated according to the criteria of effectiveness and efficiency, resulting from the optimisation of its operational technicity (unless it is evaluated on more emotional grounds).

- *Horizontal structures and integrated systems.*

Conversely, a '*horizontal service*', in the area of health care delivery, is an essentially multi-functional ('polyvalent') service, with the purpose of responding to all the problems of suffering (actual or potential) as they are

present in a community. It delivers health care that is said to be 'integrated' and 'continuous', through a package of activities that is large enough to be able to respond to the community's demand. Its organisational structure rests on the principle of accessibility, in the temporal and spatial dimensions of the word. Thus its first line functional units will be *permanent* and *decentralised*.

Such an organisational structure is also built on the principle of complementarity between different tiers of the health care delivery system - what we call an *integrated system*. In such an integrated system the different tiers (first line structures, referral level structure) have functions that are *not overlapping* (i.e. the functions of one level are not the ones of the other), there are *no gaps* in the delivery of care (i.e. the system is able to respond to all demand, even if it is accepted that some problems have a higher level of priority than others), and there is an *optimal movement of individuals and information* between the different levels (no useless barriers for referral or counter-referral, transfer of the necessary information in the two directions).

The principal place of interaction between the community and a horizontal service is the *first line health service*. In Africa this is most often materialised in the form of a Health Centre or a 'dispensary'. The quality of the health care at this level is to a large extent defined by criteria pertaining to the social quality of *human relations*: taking into account the total person, accepting shared responsibilities on both sides, empathic attitude of the health personnel, involving individuals and communities in decision making, etc. 'Health' in this context is conceived as a value among others, one of the conditions that have to be met for people to realise their potential, not only as an epidemiological dimension. Therefore, such a (horizontal) service will be judged or evaluated not only in terms of effectiveness and efficiency, but also in terms of its *acceptability* to the community it serves. This acceptability is essentially determined by a relationship of *confidence*, which is in turn conditioned by a level of technical quality perceived to be good (or sufficiently good) and by the quality of interpersonal relationships in the interactions between service staff and the community. In order to be *good*, such a service must first have *credibility*.

- *Different meanings of the notion of 'integration'*

The words *integration* and *integrated* have already been used: 'integrated' care, 'integrated systems'. There are still other uses of this term, which deserve to be made explicit. We will try and put everything together.

When we use the term *integrated care*, we mean that as well curative as preventive as 'promotive' care is given to a given community by the same (small) team, which accepts to take the responsibility for making such a package of care available, and which must, therefore, be multi-functional ('polyvalent').

By the term *integrated system* we mean a body composed of complementary elements which have a common objective, organised in such a way that within this system functions are not overlapping, that there are no 'gaps' and that there are no useless internal barriers (cf. *supra*). A good 'horizontal' service is organised as an integrated system.

One can also *integrate a (vertical) programme (or its activities)* in the activity package of a horizontal service. The decision whether or not to proceed with this 'integration' must take into account the requirements of the (vertical) programme as well as those of a horizontal service. Among the latter, the *credibility* criterion is among the most important ones. We will come back to this further on.

1.2. *Conditions for the integration of 'vertical' programme activities in 'horizontal' services*

From the point of view of someone in charge of multi-functional ('polyvalent') services (a 'horizontalist'), and within the terminology that we have just described, *one does not integrate (polyvalent) services - or their resources - in the implementation of a programme, but one can integrate programme activities in the package of activities of a (multi-functional) service.*

The decision to do this (or not to do it) is made, in principle, according to rational and explicit criteria, not because one is *for* or *against* integration.

This having been said, it is true that a 'horizontalist' will tend to have a certain bias in favour of integration, but only to the extent that a widening of the capacities of a basic health service may add to its value and credibility, thus possibly contributing to a better interaction with the community. However, this is not necessarily always the case. A quite typical example is the Immunisation Programme.

It is, of course, for a Health Centre team, of great importance to be able to offer its population the possibility to have their children immunised. This is a useful and important activity, which has become quite essential these days, contributing to the liberation of individuals and communities from a number of important health problems. Thus, integration of vaccination activities in the Health Centre's package of activities is almost certainly an excellent thing, from the point of view of a horizontalist. But the situation is quite different when it is the 'National Extended Programme for Immunisation' (a 'vertical' programme with certain vertical structures) which decides *'to integrate'* the existing multi-functional services in order to implement its programme, formulated in operational terms of maximum coverage. In this case a possible hazard would consist in a 'drain' of multi-functional personnel toward intensive and prolonged vaccination activities, possibly with financial 'incentives' and the whole range of sticks and carrots (the objective is maximum coverage), so that the other essential activities of a multi-functional team end up being abandoned. In such a case, the multi-functional ('polyvalent') structure cannot live up to its role anymore, and this 'integration' will have been disastrous. Examples of such situations are not really difficult to find.

That is why we propose the following (simplified) method as an element of decision making concerning the possible integration of (vertical) programme activities in the package of a multi-functional structure.

For this decision methodology, the questions are the following:

(a) *What* would need to be done in order to reduce the health problem (e.g. HAT, but this applies to any health problem for which a programme is being developed) in a given environment, once it has been decided that the problem is sufficiently important and 'vulnerable'?

The answer to this question should be the outcome of a 'vertical analysis' and will probably consist in a 'programme'.

(b) *How* can we operationalise this programme, taking into account this environment's realities?

The elements to be considered now are:

- the *existing structures*: geographical distribution, competence, existing or potential technical level, range of activities, work load, motivation, etc.; in short, an inventory;

- is it *useful* (for the effectiveness or success of the programme) to integrate some or all of the tasks included in the programme in the package of activities of existing structures?

- is it *feasible* (practicable) to integrate these tasks or activities in the package of basic multi-functional structures, given their level of technicity and competence (possibly selecting an adapted technology)? In this context it is important to remember that the possibility to delegate important responsibilities to non-specialised personnel with a limited theoretical competence, does *not* depend on the severity of the health problem, but on the extent to which it is possible to *standardise* and *supervise* the activities;

- is it *opportune* (for the existing structures and for their functioning) to integrate these tasks in their package of activities? As a rule, adding a relevant activity, and one that is perceived as such by the community (and thus acceptable and accepted), can be considered to be an enrichment for a basic health care structure (say a Health Centre), but *not at any price*. If the new activity can only be implemented at the cost of abandoning or neglecting other relevant activities, the balance may be negative.

(c) If it is *potentially effective, feasible and opportune* to integrate these activities, and if they are implemented correctly, what will be their *impact* on the health problem? If this impact can be assessed to be good or acceptable, one will have gained something valuable by integrating. If in spite of the adopted strategy the health problem remains too important (or

even unchanged), supplementary or different interventions will have to be considered.

If it is not useful or opportune to integrate an activity, it is better to forget about integration.

One special element that somewhat hides behind all these criteria is the *required speed of response* to existing health problems. Integrating new activities in existing multi-functional structures takes time, if only because inevitably a number of resistances, internal and/or external, need to be overcome. Therefore, if the health problem needs a quick or urgent response, it is often not useful, *nor* feasible, *nor* opportune to integrate such an activity in a basic health service unit, at least not to begin with. Typical examples could be the control of a cholera epidemic, or responding to high demand for contraceptive services in (typically) urban situations in developing countries.

### *1.3. Complementarity and levels of decision making*

One can be (or position oneself as) a 'verticalist' or a 'horizontalist', by training, by conviction, by ideology, by doctrine, by habit, even by character or by nature. The difference between the two approaches can result in a debate, a conflict even - latent or open - but this is not necessarily useful or even opportune. These approaches are essentially complementary; however, they can only really be so if there is some mutual understanding.

In the (theoretical) field of definitions, one can try to side-step the problems that are situated at the level where the horizontal and vertical systems of logic meet, in a relatively easy way by using neutral and dispassionate words like 'complementarity'. But in everyday practice this is a lot less easy... Horizontal and vertical systems use different quality criteria (since they have different objectives), and historically their relations have often been strained because of power conflicts and competition for (by definition limited) resources. Looked at this way, this relation is rather comparable with the sometimes tumultuous relations that can be observed to develop between general practitioners and specialists. Only from the

moment when the former and the latter's specificity is mutually recognised and accepted can dialogue and co-operation really begin.

If and when a 'horizontal' system is organised as an 'integrated system', administrative and technical responsibilities are unified (just avoiding the word 'integrated') within the same team. These days, the level that is considered to be the most adequate for operational decision making, where the top-down planning/programming and the bottom-up decision logic meet, is the 'health district'. If we accept this, *all* the health care inside this well-defined territory (and its population) that is called the district, is delivered under the administrative and technical responsibility of the district leading team, in which the medical doctors must find and take their responsibility. The task of a district leading team can be described as the 'translation' of a country's health policy (and its priorities) into an operational practice that is adapted to the local reality.

Within this doctrine (using the word without the negative connotations it sometimes carries with it), interventions of vertical, specialised *structures* (like, e.g., the ones of specialised trypanosomiasis control teams) are implemented *in support* of horizontal structures' activities (and not the other way around). The support of competent and trained medical specialists consists essentially in establishing quality *norms*, in *training* of operational personnel, in technical *quality control, evaluation and research and (technical) development*. To the extent that the specific health problem is sufficiently frequent, the operational personnel (to be trained) will preferably (as a rule) be of the multi-functional ('polyvalent') type. If the problem is too rare (but still judged to be important enough), the operational personnel will logically be of a (more) specialised type.

Still within this doctrine, a dominant role is given to the district leading team (which represents and guides the 'horizontal' integrated system). This option rests on several considerations:

First, the necessity to have an overall view on all (health) problems and to master at the same time the technical, social, operational and administrative systems of logic, in order to be able to set relative priorities

(which is essentially a matter of resource allocation and management, human as well as material and financial resources);

Second, the 'fragility' of horizontal systems, whose functionality depends to a large extent on the dynamics that are developed with the populations. The relations of a 'horizontal' service with its population (especially at the level of first line structures like health centres) are relations of dialogue and participation, in a social and 'political' relationship of shared responsibility. A vertical, specialised structure or service, with an epidemiological objective ('disease control'), functions in a necessarily somewhat different relationship that cannot always avoid a 'coercive' approach (even if the latter is disguised in the form of 'social marketing', and even if this might possibly be justified or acceptable);

Third, the absurd situations that result from a systematic negation of this doctrine, where, for a given population, an autonomous service 'takes care' of maternal health, another of immunisations, a third of diarrhoea problems, a fourth of malaria, another one of trypanosomiasis, one of family planning, of sexually transmitted diseases, etc., etc....., all with their logistic systems, their information systems, research programmes and seminars. It would appear self-evident that such a mosaic is highly inefficient, and, moreover, perfectly opaque for the patients. If there is no one who can operate some kind of *synthesis*, the patient is reduced (and will feel reduced) to an 'epidemiological object', instead of being at the centre of the caring effort. But this synthesis function does not lead anywhere if it is not accompanied by a co-ordination or steering function. Which means that the principal decision centre should be where the synthesis is made.

Of course, if and when horizontal, multi-functional services do not exist (for reasons of health service coverage problems) or do not function at all, the potential relational problems between horizontalists and verticalists do not really exist either. However, it would not be an irrelevant question to ask what could be the sense of an isolated vertical intervention in a context where there is no (reasonably permanent) multi-functional basic service. Such an intervention can only be justified (in terms of effectiveness) to the extent that the specific problem that it tackles constitutes, all by itself and

even in isolation, such a severe and frequent health problem that its solution will be perceived as an improvement of the population's well-being. In practice this means we are talking about severe catastrophic or epidemic phenomena (in the large sense of the word) or about severe morbid phenomena with a clearly limited geographical distribution. Otherwise, there is a high risk that an isolated vertical intervention will do nothing but displace the sources of suffering, without resulting in an overall positive balance.

## 2. OPTIMISING THE HANDLING OF THE PROBLEM OF HUMAN AFRICAN TRYPANOSOMIASIS

### 2.1. *Relevant variables to take into account*

The objective of disease control is, or should be, to reduce the *problem*, as we have defined this word before: the sum of suffering and cost (broadly defined) occasioned by a health problem.

Since HAT is, in medical terms, an 'infectious disease', the possible control targets can be identified as the *transmission process(es)*, the people who are identifiably *at risk* of developing illness, and the people who *are ill*. Consequently, action would be directed mainly at:

- correctly diagnosing ill people and treating them effectively.
- identifying infected people at risk of developing illness and preventing their evolution towards illness;
- reducing or stopping transmission;
- identifying present or potential problems ('surveillance' s.s.)

When it comes to selecting the activities in a particular situation, a number of 'relevant' variables have to be taken into account, which can be usefully ordered according to several '*contextual*' dimensions... One can look at it

- along the dimension of the context of the *HAT problem*, as an isolated problem (which is what we have done in the 'vertical analysis' part);
- as a problem that is embedded in the wider dimension of the *sum of all the health* problems a community or society is confronted with;
- as a health problem that is embedded in the still wider dimension of the context of general or *overall 'development'*.

It will probably not come as a surprise if, by widening the dimensions, we will be confronted with conflicting variables, and that the selection of activities will be the result of a balancing act, inherent to most if not all 'dynamic' situations.

Within the first (and simplest) dimension of considering HAT as an isolated health problem, selection of activities or interventions will most readily be guided by knowledge of the variables *effectiveness*, *efficiency* and *acceptability*, within a context of accessible services.

Whereas the first two of these variables are predominantly technical in nature, the latter one (acceptability) already involves a number of environmental, social and circumstantial variables. The acceptability of an intervention (for a given community) can be said to be determined by the *perception of the problem* (by the community) and by the *cost of the intervention* (for the community). 'Perception of the problem' can be determined by the *weight of the (present) suffering* in the community (frequency and severity of illness) but also by the *memory of (past) suffering* as a social historical phenomenon: the latter depends on the 'collective memory' within a given community (and on the time that has elapsed since, say, the latest 'epidemic') and on the cultural explanation that is given to the health problem by the community. On the other hand, 'cost of the intervention' for the community can be determined by its *economic cost*, but also by its *social or subjective cost* (e.g. in terms of effort and time needed for participation in control activities, not to mention the effort of possibly having to change usual behaviour) and the expected or observed *iatrogenic effects* of the intervention - to be balanced against the observed objective

and subjective positive effects. That all these determinants of 'acceptability' form a complex but highly determining system, is maybe most dramatically exemplified by the difficulties AIDS control programs run into, even in communities where the problem is clearly and openly dramatic, and even if the proposed intervention (say, condom use) is so 'rational' and seemingly evident. Likewise, in trypanosomiasis control, acceptability is in part determined by people's conclusions from past experience and from their personal and collective 'cost-effectiveness analysis', and this is likely to be different when we are dealing with the population of an historical focus' epicentre or with a refugee population arriving in an endemic area.

Still staying within our first 'dimension' we could roughly summarise the variables that may be relevant for selecting activities:

- effectiveness;
- efficiency;
- acceptability;
- perception of the problem (by the community): collective memory (history of the focus); felt weight of suffering (frequency of recognised illness);
- cost of the intervention (for the community and individuals): economic cost (money); social and subjective cost (time, effort, change in behaviour expected); expected or observed iatrogenesis.

When we start widening the horizon to the dimension of all health problems within a given community or society, more variables will come up.

First and most evident seem to be the availability and use of resources (financial, material and human), and the opportunity cost that all choices entail. In the economic and political context of the countries where HAT occurs, these resources (especially the financial ones) are predominantly of the public or semi-public type (as opposed to 'private') and their use is therefore to a large extent dependent on political - or policy - decision making (which should not be surprising). But even if the decisions are made within the (technical) management of health service organisation, the question will always crop up what will be the order of the HAT problem in the priority list. HAT never occurs in areas that are free of

other major priority problems. Its order on the priority list will, therefore, not only depend on its own (variable) importance as a problem, but also on the importance (also possibly variable) of the others. In order to manage that kind of necessary flexibility, one would need, of course, adequate information, which is not necessarily synonymous with 'very precisely quantified' information. But it should be at least reasonably continuous and dependable, and the quality of this information will depend to a large extent on the quality of the interactions between the community and the health service, and on the interactions between different elements of the health service. The presence of well functioning polyvalent services within an 'integrated system' is in this context an asset, the more so if the interaction between community and health service results in a positive two way communication. If this is the case, understanding 'acceptability' issues and possibly influencing them becomes much more feasible, and matching professionally defined 'needs' with 'demand' as expressed by the community becomes (somewhat more) possible.

Another aspect of a specific disease problem, looked at in the context of the sum total of all health problems, is the possible 'displacement' effect it may have on the occurrence of other specific health problems. We are not talking of the possibly iatrogenic effects of interventions here, but of the possibility that diseases may 'hide' one another, in such a way that when one goes down, another one ('automatically') goes up. A rather typical example of this kind of 'see-saw' effect is the observation that the risk to develop cerebral malaria is higher in 'well nourished' children: malnutrition seems to 'hide' cerebral malaria (McGregor, 1988). In the case of HAT, the relation with other diseases may rather be the other way around, trypanosomiasis enhancing rather than hiding other health problems (which would be an argument to move it up on the priority list). P. Richet observed a long time ago that in many cases present foci of river blindness (*Onchocerca volvulus*) are located in places that were formerly important foci of sleeping sickness (Hervouët, 1990), but this can probably be 'explained' through population densities dynamics (flies/man ratios) rather than through any 'protective' or hiding effect.

When we start looking at disease control activities in the ultimate dimension of 'overall development', the questions and variables may become very numerous and complex indeed. In this dimension, the question is not only if a specific problem like HAT should be higher or lower in the health sector's priority list, but also what would be the priority rating of *health care activities* in general, given the needs and demand in other areas of 'development'. In the early 20th century, sleeping sickness got an extremely high priority rating by the authorities, and it is probably safe to say that this was the case because the then colonial powers considered the solution of this problem to be an absolutely necessary condition for everything else they had in mind. It is probably safe also to say that in the present context this attitude does not really prevail anymore. In recent years even international funding or research institutions appear to be reducing budgets earmarked for (human) trypanosomiasis research.

Although this 'overall development dimension' (be it in a socio-political context of purely economic trade development or in a broader social development context) is quite important and often quite determining in terms of resource allocation, it is somewhat outside the control of health care professionals and managers. Even if for the moment HAT is not the most fashionable or favourite resource wagon to jump on, we should at least be able to formulate rational strategies, either to be prepared when resources are made available, or in order to make them available, or to decide what to do in the meantime.

## *2.2. Operationalising: selection and organisation of activities related to the parasite and the human host*

If we accept the existence of 'relevant' variables for optimising management of the HAT problem, it follows that the selection and organisation of specific activities will also vary. We will now try to formulate realistic and feasible alternatives for different real-life situations, with a first level modulation around one of the variables: the availability of functioning, permanent polyvalent services.

For this development we will concentrate on the parasite and the human host, without considering the vector. This is not to say that interventions on the vector should not be considered, but because of their specific technicalities they are outside the scope of this discussion.

2.2.1. When functioning polyvalent services are available on a permanent basis.

A preliminary hypothesis that we can reasonably accept is that the foci of sleeping sickness endemicity are known.

Generally speaking, with respect to the problem of HAT, the functions that would be expected from a health service can be summarised as follows:

- (i) detection of ill patients, and provision of effective care to ill patients;
- (ii) identification of the at risk groups and diagnostic follow-up of at risk groups, and provision of effective cure for confirmed infection;
- (iii) surveillance (s.s.)

'*Detection of ill patients*' amounts to correctly diagnosing symptomatic patients as cases of trypanosomiasis, in need of specific and effective treatment. This logically includes a decision strategy on the kind of treatment to be selected, and on the choice of the personnel and the kind of health care structure that will have the responsibility for this treatment.

The term '*at risk*' can be used in different senses: first, at risk of being *infected* (contact with vector tsetse flies, behaviour linked elements); second, at risk of developing the *illness* in a more or less near future. The latter notion rests on the acceptance of a (long) period of stable equilibrium host-parasite, and would be translated in practice by a combination like [*serology positive* | *asymptomatic* | *no detectable parasitemia*]. These individuals can be considered to carry a higher risk of developing symptomatic illness than the others and are, therefore, an '*at risk group*'. Their identification rests mainly on the presence of the (screening) sign '*serology positive*' - or any valid equivalent. As a general rule, we will accept that in HAT the first '*at risk*' groups (exposed to infection) are usually known from past experience if and

when their distinction is useful (i.e. if almost all cases are concentrated in these easily identifiable groups within a geographically defined community). Thus 'identifying the group of individuals at risk' will be a more continuous function if we define 'at risk' in the second sense of 'at higher risk of developing symptomatic disease', and this will be the meaning of the term in this section.

We use the term 'surveillance' here in the narrow sense of the word, i.e. *not* (necessarily) including active control measures. In this sense, its main purpose is to be kept informed about the level of endemicity or the magnitude of the sleeping sickness problem. To the extent that it is possible to predict a change in frequency of the HAT problem on the basis of observations other than on *human beings* (e.g. changes in the ecological systems, changing land use patterns, changes in the fly population, etc.), such information may originate from elsewhere, outside the interaction between community and health service. However, in practice this 'surveillance' will inevitably involve case detection and/or screening activities, thus approaching and overlapping with the other functions (identification and follow-up of at risk groups, detection of ill trypanosomiasis patients).

*(a) Detecting ill patients and providing effective care*

A permanent multi-functional service is always expected to respond to felt need: in terms of the items on our list this means *detecting ill patients as cases of HAT* and *providing effective care*. To what extent these functions can be fulfilled effectively either at the first line level or at referral level (health centres or hospital) depends on the degree to which the activities they imply can be decentralised, standardised and supervised. This is essentially a matter of logistics, selecting techniques, formulation of instructions, training and supervision. There is little doubt that diagnosing an illness as a case of HAT *can* be done effectively at first line level, without insuperable investment. Techniques are available and sufficiently specific with respect to the detection of parasites. They may not be as sensitive as would be desirable, but they can be repeated and more than one technique

can be used in order to improve sensitivity. Decentralised and permanent health centre staff would normally be in a better position to carry out an individual 'parasitological diagnosis programme' involving repeated contacts and appointments.

Deciding on the place where treatment should be carried out may be more delicate. Treatment can, in principle, be sufficiently standardised for use at first line level. However, two aspects have to be considered: the frequency of the diagnosed disease and the risks inherent to the treatment. Very low frequency is an argument against decentralising treatment, as the necessary skills cannot be maintained sufficiently through practice. On the other hand, a high frequency may entail a very high workload, also because, according to presently available treatment regimens, treated patients need to be followed up with sixmonthly lumbar punctures for 24 months after termination of treatment. Stage II melarsoprol treatment itself comprises 12 IV injections spread over 30 days and patients need to be closely supervised for adverse reactions. Diagnosis, treatment and follow-up work for a patient with altered CSF adds up to a minimum of some 5 hours, not counting administrative and retrieval activities and not counting nursing, communication and time 'lost' between patients. If a health centre would treat some 50 patients a year, or on average one each week, this would add up to a very considerable proportion of personnel time. In such a situation, one can also expect, statistically, between 1 and 4 lethal encephalopathies in the course of one year. This would not necessarily be a worse outcome than in a hospital environment, but it may be psychologically very difficult or unacceptable for health centre staff, living in the same social environment as the community they serve, and the staff's credibility may be at stake. If these considerations would weigh heavily, alternative options could be to refer to a hospital environment for treatments with the (dangerous) 'stage II' drugs and/or 'relapses', or to strengthen the health centre with trained staff and equipment. This kind of decision would have to take into account the problems inherent to referral (which may not be accepted, for a variety of reasons: too difficult, too costly), balanced against the problems inherent to decentralised treatment.

(b) *Identification and diagnostic follow-up of the group 'at risk of illness', followed by appropriate action*

The activities this function implies consist in (1) identifying individuals who are at higher risk of developing symptomatic illness on the basis of signs of increased probability of infection, and (2) detection of proof of *infection* through some form of organised diagnostic follow-up. In contrast with the former function, these activities are performed on a population of individuals who do not suggest a symptomatic case of HAT.

As these activities may or may not be a response to a felt need, their integration in the package of activities of multi-functional basic health care structures is a decision that may have to be argued. In a situation of *high prevalence*, there may be a demand for this more preventive approach, and the question then would be *how* to organise it in the most effective and efficient way. If there is no demand, and if *prevalence* of the disease is *low*, organising these activities in polyvalent health services (or any other) would have to be based on the argument that it is demonstrably useful. At the collective level, this implies the existence of a (lower) 'threshold' prevalence of infection below which further 'epidemisation' of sleeping sickness is more unlikely (for a long time), and that there exists a practicable method to achieve this. At the individual level this implies that actively curing asymptomatic infection will significantly improve the individual's future prospects in terms of health. Both implications are likely to be true but difficult to quantify and probably the quantities involved will be variable according to the situation.

If it is decided to start *screening* populations or population groups for *likely infection*, i.e. identifying individuals who are at risk of developing symptomatic illness, this can be done in several ways.

#### SCREENING AND FOLLOW-UP IN THE PASSIVE MODE

In the 'passive' mode the initiative for contact lies with the patient. In this 'passive mode' the attitude of the health centre staff (with respect to the problem of HAT) can vary in 'aggressiveness': the most 'aggressive' attitude would be to screen *all* patients for HAT, no matter what their

reason for contact is; the least aggressive one would be to 'check' for a trypanosomiasis screening sign only when the reason for contact is somehow loosely suggestive of this disease (in other words, a more sensitive clinical combination than 'suggestive signs' calling for diagnostic confirmation).

- *Indiscriminate screening in the passive mode*

The *effectiveness* of such aggressive screening for identification purposes (still in the 'passive mode'), would always depend on the sensitivity of the screening test, whether the objective is to correctly identify individuals at risk, or ultimately to reduce the prevalence of trypanosomiasis infection in the community. However, for the latter objective, such passive mode screening can only be effective if a high proportion of the exposed population contacts the permanent service within a reasonable time period, which depends on the service's accessibility and acceptability, and its credibility. To the extent that identification of 'at risk' individuals would have to lead to further action, the speed with which the test result can be obtained is likely to influence the effectiveness of such a strategy: if some sort of retrieval needs to be organised (re-contacting patients when the test result is available), this will of course reduce practicability (by increasing work load) but also reduce effectiveness (retrieval is virtually never 100 % complete). Moreover, if retrieval is necessary this will be possible only if a well-organised filing system exists and if there is a good relationship of confidence and trust between the community and health service staff. This quality of relationship is to be considered as a continuous rather than as a yes-or-no type of variable and it is quite possible that retrieval activities actually contribute to an improvement of this relationship. But the least one can say is that they complicate life, and a screening test that involves retrieval should have serious advantages of another type (like much lower cost) to justify its selection.

The *efficiency* of this screening option, in terms of identification of 'at risk' individuals, will depend on the cost (broadly defined) *per correctly identified individual*, and thus not only on the cost of the screening procedure but also on the prevalence of the 'at risk' condition in the population to be

examined. If this prevalence is low or drops to very low values, the cost of this systematic screening, even in the passive mode, will become unacceptable when compared with the returns - if only in terms of psychological acceptability by the staff. Another criterion of efficiency would be measured by the work load that ensues from identification of at risk individuals (their follow-up). In this sense, efficiency will depend heavily on the screening procedure's specificity and positive predictive value as measured against the follow-up results.

Thus, for this systematic 'passive mode, indiscriminate screening' option in polyvalent health care structures, the *conditions* appear to be:

- high proportion of the population using the service (if the objective is to reduce the prevalence of infection);
- perceptible prevalence of the condition the screening is supposed to detect;
- a sensitive screening test, which should moreover
  - be of reasonable technicality (at least with regard to what should be done at health centre level) and highly standardised
  - be cheap
  - be sufficiently specific in terms of ulterior evolution towards illness
  - preferably allow immediate interpretation

These ideal qualities of the screening test are somewhat mutually exclusive in practice. At present the IFAT serologic test (screening version, on filter paper) is a cheaper test (at health service level about BEF 2) than the CATT, but requires centralised interpretation, which eliminates 'immediate decentralised interpretation' at the time of contact. The CATT screening test performs very well in the field and is capable of yielding immediately available test results, but is more expensive (delivered at health service level, about BEF 10) and its interpretation also needs to be correctly standardised and supervised. The cheapest screening test of all, neck gland palpation, in spite of its long history, cannot be relied upon to be sensitive or specific in many situations.

The *feasibility* (or practicability), of screening all contacts with some reliable screening test would depend on its cost (in financial terms and in terms of work load) and on its acceptability. As this acceptability is not very likely to be a problem with presently available screening tests, cost is likely to be the determining factor here.

In a setting like the one studied in the Kasongo survey, the prevalence of a screening sign like [*IFAT at least clearly positive*] would be some 3 % of the general population. It is not unlikely that a higher prevalence will be obtained when this screening is applied to health centre *curative contacts* (in the Kasongo survey population the prevalence of IFAT positivity among those who declared *any* kind or symptom of at least a week's duration was about 6 %, which is more than twice the prevalence found among people who did not declare such symptoms: 2.4 %). If all screening sign positives are subjected to an immediate follow-up action (parasitological examination), this can lead to immediate identification of parasitologically confirmed infection in some 15 % of this group. If only those are followed up who also have typical glands, the number of people to examine is much lower (7 to 8 times), and parasites may be found at the first examination in more than half of these individuals. If all people with typical glands would have to be followed up (independently of their IFAT status), some 20 % of the contacts may have to be examined, and the first examination would be positive very rarely: slightly more than 1 out of 100.

If the promising operational characteristics of the *auto-agglutination* test are confirmed, this test could well be the most appropriate one for this kind of screening strategy. It would have it all: minimal supply logistics, cheap, low technicality, high sensitivity and specificity, immediate interpretation. Moreover, if the high negative predictive value is confirmed, it would also be of use at the other end of the 'aggressiveness spectrum' in the passive mode (only examining contacts with reasons that are suggestive for the disease).

The last question to be decided upon is the *periodicity* of repeating the screening test on those individuals for whom it is negative. Again in a Kasongo-like endemicity situation, yearly infection rates (incidence of

infection) can be estimated to be very low. Serologic screening as a systematic *routine* measure (in the passive mode!) can certainly be separated by more than one year. It could be argued that this observation is valid only because the screening sign positives were followed up intensively and treated as soon as parasites were detected, thus quickly reducing the 'contagiousness' of the human reservoir and transmission. We do not know to what extent this is true; but at any rate there is not much of a point in screening aggressively and then *not* following up those who have been identified as at higher risk of infection. The results of the Kasongo study clearly show that repeated parasitologic examination is far more effective in identifying parasite carriers than repeated serologic examination of the same population.

Of course, if the screening sign is extremely simple and cheap to perform, the periodicity of the individual screening is a less important issue (always in the passive mode). This goes to show once again how interesting the auto-agglutination phenomenon could be as a screening sign or test.

- *Diagnostic follow-up*

Diagnostic follow-up of those identified as at higher risk can also be done in a more or less intensive (or 'aggressive') way.

One way of modulating follow-up intensity is by restricting follow-up to more selective screening criteria: e.g. only those who present the screening combination with the highest positive predictive value, like mentioned above. This will result in much reduced sensitivity, if the objective is to find as many parasitological infections as possible, but may be expected to be very efficient. The lowest type of follow-up intensity would probably be to consider the presence of the risk screening sign as a piece of information, and to use it only as an extra incentive to search more quickly and/or more intensively for parasites when suggestive signs or symptoms are presented, or to go and search more actively for possibly unexpressed health problems (with more directive questioning).

Another way to modulate follow-up aggressiveness is to increase or decrease the number of parasitological examinations. We have seen in the Ka-

songo study that within the identified group at risk repetition of the parasitological examinations, spread over a period of about one year after the initial (negative) examination added an appreciable number of parasitological positives to the first 'harvest': 13 parasitologically confirmed infections were added to the 10 confirmed in the first round, and it is reasonable to assume that the majority of these are not newly infected individuals.

Since we are still analysing a *passive* mode identification strategy, this means that we are dealing with health centre *contacts*. Organising this kind of individual follow-up examination 'programme' on the basis of screening of contacts will involve quite an effort, but such a programme can be expected to be followed more smoothly than if the contact for risk identification is made at the initiative of health personnel. However, in populations with relatively high prevalence of infection, it may result in an important work load. In Kasongo-like endemicity situations, and limiting the number of parasitological examinations to a maximum of 4 occasions, a health centre with a homogeneously exposed population of 10,000 may have to carry out some 20 parasitological examinations per week, only on the basis of follow-up of the identified group at risk (if some 40 % of the population passed by the health centre at one time or another in the course of one year - we are still analysing the passive mode). This may be a contributing argument for strengthening a health centre with extra (trained) staff.

- *More selective screening in the passive mode*

Still remaining in the passive mode (the initiative for contact remains with the individual as a patient), and still maintaining a screening strategy for higher risk groups as relevant, this could also be limited to *certain groups*, known to be more 'exposed' to the infection, or who are new in the area.

The possibility to stratify a population on the basis of exposure depends, of course, on the local transmission epidemiology. In the Kasongo study population, the probability of infection is homogeneously distributed over the entire group with respect to variables like area of residence, sex and occupation. Only age could be regarded as a possibly useful stratifying

variable, but not in any absolute way. In other situations, however, this can be quite different and risk stratification can be pertinent.

If the prevalence of infection is or becomes very low, systematic screening is impracticable in a multi-functional permanent health care delivery structure. If aggressive screening of all contacts (in the passive mode) is judged to be justified at a certain level of endemicity, it will have to be abandoned when and if the prevalence of infection and disease is reduced. An intermediate attitude could then be more selective screening.

The progression (in the passive mode) could be the following:

- aggressive screening *all* contacts (curative and preventive) with a one year periodicity
- aggressive screening all contacts at lower periodicity
- screening all curative contacts only
- screening curative contacts with complaints of a certain minimum duration (e.g. one week)
- screening only curative contacts from defined exposure groups and immigrants
- screening only curative contacts with suggestive signs or symptoms (combined with parasitologic examination).

In very low prevalence situations, it is less likely that motivation for intensive parasitological follow-up of screening sign positives will be high, and the case detection strategy will evolve towards purely passive case finding on the basis of clinical signs and expressed symptoms.

#### SCREENING AND FOLLOW-UP IN THE **ACTIVE** MODE.

In the 'active' **mode** the initiative for contact lies with the health service. Again, this can be done to varying degrees.

##### *Indiscriminate screening of a selected and identifiable exposure group*

If it is known that HAT is concentrated in more or less easily identifiable subgroups of the population (for whom it is a significant health

problem), the screening effort can be concentrated also and thereby reduced in volume. This depends of course on the local epidemiology of the focus. In the study area of the Kasongo river focus, no such subgroups could be identified to an extent that would justify 'active' selective screening. But in other foci, HAT can be considered to be an 'occupational hazard', be it of fishermen or of plantation workers (like in the Ivory Coast forest foci) and the efficiency of screening activities could be enhanced by an *active*, but selective approach.

Screening in the active mode can also be considered, as a complement to passive mode screening, for exposed population groups whose access to curative care is severely limited (e.g. for reasons of distance). Such active mode screening can possibly be combined with other outreach activities that need to be organised for such groups (like preventive activities in the area of mother and child health).

*Indiscriminate screening of the entire population of a HAT focus*

This would be a drastic, expensive (especially in terms of work load) and unusual adventure for ordinary polyvalent health centre staff and should not be decided upon lightly, if ever.

If in spite of reasonable 'passive' screening activities by permanent health centre staff the HAT problem is out of control (i.e. an epidemic or high prevalence situation), systematic active screening of the unscreened rest of the exposed population will be necessary. If the polyvalent staff is to keep carrying out its other (equally important) duties, *such systematic screening will best be carried out by specialised and of necessity mobile teams*. The question then is who will do the diagnostic follow-up and who will take the responsibility of treatment and post-treatment follow-up.

In terms of *diagnostic follow-up* (after screening), one of two fundamental options can be taken: to base the decision of treatment on the visual confirmation of the presence of parasites, or not (necessarily). In the latter case, a serologic technique that is more specific than the screening technique needs to be used, i.e. 'serological *diagnosis*' (like with the CATT test on diluted serum). The level of technicality of this latter method (and

the need for rigorously standardised interpretation of the test results) must be considered too high for delegation to other than specialised, well trained, disciplined, experienced and supervised technicians. If correctly carried out, and in situations of *high prevalence*, it probably has enough specificity for a positive result to be sufficient evidence to institute lumbar puncture and treatment, (especially) in situations where no alternative case finding modes are available and the situation is 'urgent'. Its great advantage is that no time consuming repeated (microscopic) parasitological follow-up examinations are needed.

In such situations of '*high prevalence, urgent response required*', liberal use of pentamidine (or any valid equivalent) for individuals without altered CSF must be considered a useful strategy, although the evidence to support this is only indirect (though rather convincing). The more important argument in favour of this strategy is these drugs' (relative) lack of toxicity, and the cost of such a strategy can be reduced by using it as a 'prophylactic' measure in a selective way: pentamidine (or some equivalent drug) only for the group of serologic *screening* sign positives, but serologic '*diagnosis*' criterion negatives (in practice, e.g. CATT positive on whole blood, but negative on diluted serum).

However, if this sero-*diagnostic* technique is not available or cannot be used, and classical microscopic examinations have to be used for confirming infection, it can be predicted that one time examination will probably miss (more than) half the patients who would eventually be found infected if the examinations were repeated several times.

To the extent that at risk patients have been identified and this information is transferred to permanent health service structures (health centres), a diagnostic follow-up programme could be organised with these structures, but this is by no means self-evident. Again, this may be an indication for strengthening the health centre structure, possibly on a temporary basis. And again, liberal use of pentamidine for those with unaltered CSF may be the more pragmatic solution in such a situation.

The desired *periodicity* of this kind of active screening activities will in the first place be determined, in practice, by the screening coverage and the

demographic changes (mobility!), and probably to a lesser degree by the incidence rates of infection (speed of transmission/diffusion). If screening coverage is of the order of 50 % (as is quite often the case in present large scale active case finding efforts), even very sensitive screening techniques may miss important numbers of infected individuals. To what extent a repetition of the active screening effort will recuperate an important proportion of the uncovered population is, of course, dependent on the reason behind the low coverage. If observed lack of participation with active screening activities is based on *refusal*, simply repeating the same thing will probably not increase coverage. If there are reasons of a more probabilistic kind, coverage may be raised significantly by simple repetition. In order to have an idea about these reasons, the quality of *communication* is, obviously, an essential factor.

The selection of where to locate treatment and post-treatment follow-up activities will have to be made according to the criteria developed before.

According to this type of analysis, it appears that the contribution of basic, permanent and polyvalent health services to the *screening* and *follow-up* of 'at risk' individuals is potentially quite important, but that, if it is possible and feasible to integrate this activity in the HC staff's package of activities, a number of choices still would have to be made. To make these choices in a rational - or at least reasoned - way, the relevant variables need to be taken into account. There is not just one good way to do it, and if one approach has been selected, it may well have to be changed or adapted after some time, given a changing disease environment.

### (c) *Surveillance*

As we have defined 'surveillance', in the narrow sense, it is in essence a matter of gathering the necessary intelligence, as efficiently as possible, to decide on the kind of action that would best be taken in a given health system environment, and how this action will need to be adapted to a changing environment. If the epidemiological characteristics of the transmission are sufficiently understood, surveillance will rest essentially on information about the numbers of HAT illness and/or infection present in

the community. To the extent that permanent case finding structures are available, information on HAT infection will be available for the populations who are effectively covered by this kind of services. If *additional* information on these populations is needed, this will be outside the functions of such multi-functional services and such information will have to be gathered by *specialised* services.

For purposes of planning and resource management, the available information will have to be aggregated according to the needed planning level.

In all cases, and especially if the prevalence is very low, all health workers in endemic areas should remain constantly alerted to the existence of HAT as a cause of illness.

### 2.2.2. When functioning polyvalent services are not available on a permanent basis

In such a situation the question can be asked if there is any sense in trying to do something about an isolated problem like HAT. We have already formulated the position that, in order to be of any use at all, isolated interventions aimed at isolated problems need to address a problem that is *all by itself* sufficiently severe for its solution to be perceived as a meaningful improvement in health status; in other words: severe epidemic phenomena (which HAT can be or become) or localised phenomena without 'epidemic' character, but with high prevalence for locally determined reasons (like the iodine deficiency - endemic goitre - cretinism complex, or the yaws problem - Meheus, 1985).

If HAT disease is a socially recognised and identified problem in a situation where there are no functioning permanent services available, there is obviously a felt need. This is, or may be, the situation that is covered by the analogy of the 'house on fire', which implies calling in the fire brigade - if there is one, and if it is not judged to be too 'expensive'. From the point of view of the professional, the fire may be a blazing one or may be just a smouldering one, but the decision to intervene, in the present context, should preferably be based on a felt need, shared by a large proportion of the community, if only because the kind of intervention that is needed implies a high level of participation on the part of the people. Direct coercion is not of this age and, moreover, it quickly becomes counterproductive.

Of course, 'felt needs' are not something dependent on 'fixed thresholds'. HAT is a highly focal problem, and the communities in the historical foci also have their collective memories. To the extent that HAT control activities have become more efficient in the course of history, the threshold for 'felt need' can be expected to go down, since these communities also make their own cost-effectiveness analysis.

If it is accepted, in accordance with what has gone before, that the approach to the HAT problem needs to be modulated according to the circumstances, and that this modulation can be structured along a basic set

of variables (like prevalence, felt needs, degree of emergency, level of technicality of the required response, feasibility, effectiveness, efficiency, credibility of general health services), then one can also see the need for a *flexible decision making structure* at the operational level. The main characteristics of such an operational management structure would be that it needs to be

- *decentralised*, i.e. responsible for and located in a manageable territory and population;
- in *close and permanent contact* with this population, in such a way that it can observe correctly and communicate adequately with the communities and individuals;
- *sufficiently supported* by specialised structures (including specialised personnel) where needed, in terms of logistics, know-how, training, technical quality assurance, and complementary interventions.

If a functioning district system exists, and if it is adequately supported by specialised structures, it would be the appropriate management structure as we have just described it. Such a formulation is subtly - or not so subtly - different from admitting that basic (general) health services also have a part to play in tackling the HAT problem; our formulation states, in fact, that it is the vertical HAT control structures who *also* have their part to play, a necessary and indispensable one, but complementary or subsidiary to the role of those who take the overall responsibility for the health of a community.

*With this kind of reasoning, the focus of interest for the decision making process is not so much controlling the parasite (anymore); it turns more towards assisting the community and the individuals in managing their own problems. Epidemiological and health care provision doctrines do change. The initial, almost century-old 'mechanical' doctrine of the germ and germ carrier who should be contained, has been adapted, or rather 'amended', since then. We think it has been also enriched, even if we may feel more insecure because of many as yet unanswered questions, and even if we may have the feeling that our present understanding of the HAT problem is more 'fuzzy' than before. The health care provision attitude of doing something for the communities, has evolved to the ideal*

*of doing what is necessary with the communities. We think the latter is a more realistic and at the same time more humanely acceptable kind of health care delivery, but it has never been simple or easy, and it will never be*

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## *Appendix : A chronology of West African trypanosomiasis*

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The following is a chronological list of events that have a bearing on this work. It is, of course, far from exhaustive and we are well aware that many important events have been omitted. On the other hand, it may contain events that are relevant only to Kasongo and the Maniema region, the site of the study that is reported on in chapter III.

Its purpose is to enable the reader to follow the chronology of the events that have punctuated the history of West African Trypanosomiasis as we look at it now, and to provide some historical markers that have not necessarily clear links with trypanosomiasis but add some wider perspective. It has no historical pretensions and the sources are all secondary ones. We have drawn heavily (and gratefully) on P.G. Janssens' impressive chapter on the African Trypanosomiasis in *Médecine et Hygiène en Afrique Centrale de 1885 à nos jours* (P.G. Janssens, M. Kivits and J. Vuylsteke; 1992) and on Maryinez Lyons' book *The Colonial Disease* (M. Lyons; 1992), both of which can without any doubt be considered as authoritative in the field. Another important source is Mulligan's (ed.) *The African Trypanosomiasis* (1970), and more especially the chapters by Duggan (*An Historical Perspective*) and by Williamson (*Review of Chemotherapeutic and Chemoprophylactic Agents*). Of course, the responsibility for possible errors and mistakes remains ours.

- 1734            *John Atkins* (a surgeon of the Royal Navy) provides a medical description of what he calls 'the sleeping distemper'.
- 1803            *Winterbottom* describes the enlarged cervical glands in sleeping sickness that will be called 'Winterbottom's sign' later on. This sign was already being used by the slave traders as a sign of poor prognosis.

- 1849-1855 *Livingstone's* first expedition explores the continent from the Cape over the Zambesi region to St Paul of Luanda.
- 1855 *Livingstone's* second expedition goes from Luanda back to the Zambesi region, over Victoria Falls to the Indian Ocean.
- 1858 *Burton and Speke* reach Lake Tanganyika and Lake Victoria (Nyanza).
- 1858-1863 *Livingstone's* third expedition explores the lower Zambesi basin.
- 1866-1873 With *Livingstone's* fourth and last expedition, he reaches Nyangwe on the banks of the Lualaba (not far from Kasongo) and ends up in Ujiji, east of Lake Tanganyika.
- 1870- Sleeping sickness breaks out in the *Malanje focus* (Angola)
- 1871 *Stanley's* undertakes his first expedition, in search of *Livingstone*. They meet in Ujiji.
- 1873-1875 *Cameron's* expedition meets the caravan carrying *Livingstone's* embalmed corpse in Tabora. *Cameron* continues west, through Kasongo and Nyangwe, and reaches Benguela on the Atlantic coast.
- 1875 *Tippo Tip* (alias Hamed ben Mohammed el-Murjebi), a powerful Afro-Arab trader, establishes a trading post in Kasongo. Nyangwe had also been established by the Arabs, who controlled the Lualaba river downstream from there.
- 1874-1877 *Stanley's* embarks on his second expedition, starting from the East Coast. *Stanley* meets *Tippo Tip* in Nyangwe, where he buys permission to descend the Lualaba, and travels down to the Atlantic coast.

- 1876 The '*International Geographical Conference*' is held in Brussels, called by Leopold II, king of Belgium.  
A sleeping sickness epidemic is observed in the *Senegambia*
- 1878 Stanley and Leopold II meet for the first time.
- 1879-1884 *Stanley's* third expedition takes him on the Congo-Lualaba upstream to Kasongo.
- 1880- A sleeping sickness outbreak is observed in the *Black Volta* region (Upper Volta)
- 1884-1885 The '*Berlin Conference*' is called by Bismarck, the German Chancellor.
- 1884 *Khartoum* falls as a result of the Mahdist revolt. General Gordon's lieutenant, surnamed Emin Pasha, retreats to the south.
- 1886- Sleeping sickness foci are detected in *Nigeria* and the *Lake Chad* region.
- 1887-1890 *Stanley's* fourth expedition is set up, to rescue Emin Pasha.
- 1890 The *Brussels Conference* for the abolition of the slave trade in Africa is held.  
Sleeping sickness outbreaks are observed along the Congo and *Lualaba* rivers.  
Tippo Tip retires to Zanzibar, leaving behind '30,000 guns' to protect Arab trading interests.  
Work starts on the Matadi-Leopoldville railroad, in the Congo Free State (finished in 1898).
- The catastrophic *rinder pest* epidemic sweeps away an alleged 95% of the (East-?) African livestock (and a comparable proportion of the wild game) between 1890 and

- 1896, at the same time drastically wiping out the tsetse fly populations on the eastern side of the continent. At the time, human sleeping sickness of the (East-African) *rhodesiense* variety had not yet been observed or described by Europeans.
- 1892-1893** *Dhanis'* heads the *Arab campaign* in the Maniema region. Sergeant Lippens and De Bruyne die in Kasongo, in 1892, killed by Tippu Tip's son, Sefou. *Dhanis* takes Nyangwe and Kasongo from the Afro-Arab traders in 1893.
- 1895** Sleeping sickness becomes a serious problem along the *Cuanza* river (Angola). *Bruce* identifies '*Trypanosoma brucei*' as the aetiological agent of animal trypanosomiasis ('*nagana*') and calls attention to the role of the tsetse flies in the transmission of the disease (the flies were already widely known by the indigenous peoples to be associated with the animal disease).
- 1896** The first cases of sleeping sickness are reported in the *Busoga* region (Uganda), the beginning of the famous *Busoga* epidemic.
- 1899** The *London* and *Liverpool Schools of Tropical Medicine* are founded.
- 1901** The *Hamburg Institut für Schiffs- und Tropenkrankheiten* is founded. The *Liverpool School* sends an expedition to the *Gambia*. *Dutton* identifies *Trypanosoma* parasites in human blood (of a patient suffering from what would be called '*trypanosoma fever*').
- 1902** *Castellani*, *Christy* and *Low* are sent to the *Busoga* area (Uganda), as a team of the *Royal Society*. *Castellani* spots a

'fish-like parasite darting about' in sleeping sickness cases; *Baker* finds *Trypanosoma* parasites in a patient's blood. *Castellani* finds a trypanosoma parasite in the cerebro-spinal fluid of a sleeping sickness patient. *Dutton's*, *Baker's* and *Castellani's* findings establish the link between human sleeping sickness and the *Trypanosoma* parasite.

1903 Leopold II invites the Liverpool School of Tropical Medicine to investigate sleeping sickness in the Congo Free State. *Christy*, *J.E. Dutton* and *J.L. Todd* start on an expedition that lasts till 1905. *Christy* leaves in 1904. *Dutton* dies of relapsing fever (the aetiological agent of which he had identified) and is buried in Kasongo in February 1905. The only one to complete the expedition is *Todd*. At the start of the expedition, *Dutton* is 28 years old, *Todd* is 27. *Bruce* and *Nabarro* demonstrate the role of *Glossina palpalis* in the transmission of *Trypanosoma gambiense*.

1904 The notorious *Casement Report* (named after the British Consul to the Congo Free State) is published, in which abuses inflicted on the indigenous population are highlighted. In Britain, the 'Congo Reform Association' is created.

1906 The *Brussels School of Tropical Medicine* is opened. In 1933 it will be transferred to Antwerp, where it will be renamed '*Prince Leopold Institute of Tropical Medicine*'. A Congo Free State administrative circular (*G.G. Wahis*) forbids all Africans with sleeping sickness to travel in uninfected areas. Three lazarets are created. Drug treatment is instituted: available drugs are Atoxyl, Trypanrot, strychnine sulphate, tatar emetic (none of which passes the blood-brain barrier effectively). The trypanocidal activity of Atoxyl had been demonstrated in Liverpool, 1905, by *Wolferton*

Thomas.

Probably the most prominent figure in the development and testing of antimicrobial compounds (arsenicals and dyes) around the turn of the century is *Paul Ehrlich* (1854-1915), who developed, among other things, the 'magic bullet' *Salvarsan* (and to whom also the Atoxyl compound is attributed by some). According to Williamson "*most of the important principles and requirements on which all synthetic antimicrobial drug developments still rely, were laid down before the First World War, in a context primarily of experimental trypanosomiasis.*"

- 1908 A Congo Free State administrative circular forbids Africans not employed by the state to travel without medical papers.
- 1909 *Kleine and Taute* unravel the complete biological *glossina-trypanosoma* life cycle.
- 1909-1910 The first case of *Trypanosoma brucei rhodesiense* (an isolated one) is identified.
- 1910 A Belgian Congo administrative circular institutes obligatory *medical passports*, valid 18 months and visaed every 3 months by a doctor.  
A '*cordon sanitaire*' is established around the north-eastern Congo triangle, believed to be uninfected with *T. b. gambiense*.
- 1914 The Belgian Congo administration gives doctors the powers of territorial administrators in regard to sleeping sickness.
- 1916 *Emile Jamot* (a French trypanosomiasis control officer) formulates his famous '*Doctrine de Jamot*' (mobile medical teams should go and find infected people, and treat them where they find them).

- 1917 Peirce, Brown, Jacobs and Heidelberger synthesize *tryparsamide*, which can pass the blood-brain barrier. Dressel and Kothe synthesize *suramin* (Bayer 205).
- 1920 The first 'Sleeping Sickness Missions' (surveys) are organised in the Belgian Congo (Uele and Kwango regions).
- 1926 The first chemoprophylactic trials, using *suramin*, in the Belgian Congo are set up.
- 1932 A mobile sleeping sickness control team starts operating in the Maniema region (where Kasongo is located).
- 1939-1943 A second outbreak of human sleeping sickness takes place in the Busoga area, this time of the East African variety (*T. b. rhodesiense*) and transmitted by the vector *G. pallidipes*, whereas the first and more famous epidemic (1900) was of the *gambiense* variety and transmitted by *G. fuscipes*, then still called *G. (palpalis) fuscipes*. The change in vector species is attributed to the modified ecology of the region (development of sugar cane plantations). According to Lancien, the more recent outbreaks of *rhodesiense* sleeping sickness in the Busoga area (from 1960 onward) are again transmitted by *G. fuscipes*, which is capable of transmitting *T. b. gambiense* as well as *T. b. rhodesiense*
- 1947 Friedheim synthesises *melarsoprol* (Arsobal<sup>®</sup>), a trivalent arsenical that can pass the blood-brain barrier and is to this day one of the mainstay drugs in (human) trypanosomiasis control.  
Around the same time *pentamidine* (Lomidine<sup>®</sup>), a long acting diamidine derivative, becomes available. It had been identified as a trypanocidal drug in 1939 by *Lourie and Yorke*. From the late 1940s mass chemoprophylaxis with pentamidine is being practiced in the Belgian Congo and

other areas of Central Africa.

- 1959** Examination of about 70 % of the population of the Belgian Congo yields some 1,100 new cases for a population of some 13 million. Systematic mass examination is discontinued immediately after the Central and West African countries gain independence.
- 1977** *Nifurtimox* (Lampit<sup>®</sup>), another stage II drug, is introduced. It is withdrawn shortly afterward, then re-introduced in 1981.
- 1981** *Eflornitine* (or DFMO), still another stage II drug, is introduced.
- 1986** The Central Bureau for Trypanosomiasis Control (BCT, Bureau Central de la lutte contre la Trypanosomiase) in Zaire reports 10,514 newly diagnosed cases for an examined population of 1,559,064 individuals. The New Contagion Index (*Indice de Contamination Nouvelle*, the proportion of newly detected parasite carriers in the examined population) is again close to 1.0 % by the early 1990s.
- 1994** Trypanosomiasis specialist P. Cattand estimates the case load in Zaire at 150,000 cases, "*with some villages reaching 'unheard of prevalence levels of 70 % infected'*" (*TDR news* No. 46, November 1994, published by the UNDP/WB/WHO Special Programme for Research and Training in Tropical Diseases - TDR).





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# Table of contents

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<b>I INTRODUCTION .....</b>	<b>1</b>
<b>II VERTICAL ANALYSIS.....</b>	<b>15</b>
THE VERTICAL ANALYSIS APPROACH.....	15
PRELIMINARY ASSUMPTION .....	17
THE IMPORTANCE OF THE PROBLEM.....	17
1. <i>Definition of the problem of HAT</i> .....	17
2. <i>Elements of the importance of the problem</i> .....	18
2.1. 'Severity' of the individual problem.....	19
2.2. Frequency .....	21
2.3. Economic cost .....	31
2.4. Social cost .....	32
3. <i>Conclusions with respect to the importance of the HAT problem</i> .....	33
THE 'SYSTEM' .....	33
THE INTERVENTIONS.....	36
(1) <i>Act on the contact between 'non-infected man' and 'contagious flies'</i> .....	38
(2) <i>Eliminating contagious flies</i> .....	43
(3) <i>act on the contact between 'contagious man' and 'uninfected fly'</i> .....	48
(4) <i>Act on the contagiousness of men through treatment</i> .....	60
(5) <i>Protecting uninfected man through (active) immunisation</i> .....	64
(6) <i>Protecting uninfected man through chemoprophylaxis</i> .....	64
(7) <i>Protect the tsetse flies against infection</i> .....	68
(8) <i>Identify infected individuals before they start suffering and prevent the suffering through treatment</i> .....	70
(9) <i>Identify infected individuals suffering from HAT and treat them</i> .....	74
CONCLUSIONS AT THIS POINT.....	96
<b>III THE KASONGO STUDY .....</b>	<b>99</b>
ORIGIN AND BASIC RESEARCH QUESTIONS .....	99
FINDINGS .....	101
<i>Validity - reliability of test results</i> .....	101
<i>Associations between possible indicators of risk</i> .....	102
<i>Characteristics of parasitologically confirmed cases</i> .....	103
<i>Operational test characteristics</i> .....	103
<b>IV CONSEQUENCES FOR MANAGING THE WEST AFRICAN HAT PROBLEM.....</b>	<b>107</b>
CONSEQUENCES WITH RESPECT TO THE DISEASE SYSTEM'S MODEL.....	107

CONSEQUENCES FOR THE PRACTICAL MANAGEMENT OF THE HAT PROBLEM ...	122
1. <i>Theoretical considerations on health service organisation</i> .....	122
1.1. Concepts in the area of health service organisation.....	122
1.2. Conditions for the integration of 'vertical' programme activities in 'horizontal' services.....	125
1.3. Complementarity and levels of decision making.....	128
2. <i>Optimising the handling of the problem of Human African Trypanosomiasis</i> .....	131
2.1. Relevant variables to take into account .....	131
2.2. Operationalising: selection and organisation of activities related to the parasite and the human host .....	135
<b>APPENDIX : A CHRONOLOGY OF WEST AFRICAN TRYPANOSOMIASIS.....</b>	<b>153</b>
<b>REFERENCES .....</b>	<b>163</b>