CONSIDERATIONS ON HAM/TSP

REDISCOVERING TUMACO

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SUMMARY — Considerations are made on the role of HTLV-I in the etiopathogeny of HAM/TSP. Neuroepidemiologic data reported in the literature are revisited for this purpose. Among results of this evaluation it is pointed-out that the Okinawan Community of Brazil presents ethnographic and demographic characteristics which are ideal for designining new studies. For instance, analyses on HTLV-I and on HAM/TSP in face of the cohort of such community classified according to time and direction of the migration (Japan-Brazil and vice-versa), will ensure promising results for the understanding of etiopathogeny of HAM/TSP. They can also be paths towards clarifying the simultaneous generating, of geographical foci of the disease distant one the other, as that of Tumaco and that of south Japan.

KEY WORDS: HTLV-I, myelopathy, neuroepidemiology, geographical distribution.

Reflexões sobre HAM/TSP: redescobrindo Tumaco.

RESUMO — São feitas considerações acerca do papel etiopatogênico do HTLV-I na paraplegia espástica tropical (TSP), a mielopatia associada ao HTLV-I (HAM). Aspectos neuroepidemiológicos registrados na literatura são reavaliados com essa finalidade. Da avaliação resultam perspectivas para novos estudos. Para estes, é salientado que a Comunidade de Okinawa no Brasil apresenta características étnicas e demográficas ideais. Análises sobre o HTLV-I e a HAM/TSP em confronto a coorte populacional dessa comunidade classificada de acordo com o tempo e o sentido da corrente migratória (Japão-Brasil e vice-versa) poderão, por exemplo, garantir resultados promissores para a compreensão da etiopatogenia da HAM/TSP. Poderão constituir-se também em caminho para esclarecer a origem simultânea de focos geográficos da doença tão distantes entre si como o de Tumaco e o do sul do Japão.

PALAVRAS-CHAVE: HTLV-I, mielopatia, neuroepidemiologia, distribuição geográfica.

«Does the flap of a butterfly's wings in Brazil set off a tornado in Texas?» — Edward Lorenz, 1979.

The chance discovery of an agent has given rise to an etiopathogenic discussion revolving around a nosological entity in some instances, in Medicine. This was the case in 1984 concerning tropical spastic paraparesis (TSP). The finding in two patients with TSP of seropositivity for HTLV-I [2], a retrovirus originally associated to acute T-cell leukemia (ATL)[7]. Since then, it is considered to have the «status» of the putative causal agent of this myelopathy. Seroepidemiological studies followed this event in TSP geographical foci previously defined that proved the significant association between TSP and HTLV-I [5,10,21,28,32,38]. And, as from the identity verified between this myelopathy and those associated to HTLV-I (HAM) from Japan, both condtions began to be known together as HAM/TSP [30]. The perspective opened by the possibility of the etiopathogenic

definition of TSP was confused at certain moments with the definition itself. This has triggered off frantic research, above all in the area of Molecular Biology, with regard to knowledge of the characteristics and biological proper-ties of HTLV-I. In vitro, however, the task of clarifying the pathomechanisms involved in HAM/TSP has not been at all easy. The discovery in the patients of cells similar to those of ATL, the demonstration of anti-HTLV-I antibodies in the serum and in the cerebrospinal fluid and of their local synthesis in the nervous system [25], the discovery of cells infected by HTLV-I [11], considered toge ther as being strong evidence of the causal relation of HTLV-I — are included only in the indirect category of proof. To the same connotation belong the isolated records of cases with the concomitance of HAM/TSP and ATL[9], of cases of familial occurrence [16-18,22], of cases «caused» by blood transfusion [19,23]. At the core of determinism, some precipitations have been committed such as: changing the diagnosis of chronic spinal forms of multiple sclerosis to that of HAM/TSP by the mere finding of positivity of reactions for HTLV-I [34]; mutatis mutandis, HTLV-I and related retroviruses have been prematurely regarded as possible causal agents of multiple sclerosis [13]. These facts have attracted the attention of researchers who made them the reason for a critical review of the criteria of differential diagnosis between the two entities [26].

Difficulties in the production of an appropriate experimental model prevent the definitive naming of HTLV-I as the etiological agent for HAM/TSP. Diffi-culties are here represented by the fact that today it is impossible to create «ideal» conditions that must obviously reflect, in an accurate fashion, the in natura conditions. In other words, these conditions will be ideal only if they are the result of perception followed by understanding of the epidemiological phenomenon. Therefore, the moment is right to reevaluate the subject from an epidemiological point of view that might, on the one hand, present us with the real extent of the question of myeloneuropathies associated to HTLV-I and, on the other hand, will afford us the outline and direction of new studies with a view to understanding the significance of this association.

The greatest controversies stem precisely from the epidemiological field: in the unusual record of 710 cases of HAM in Japan up to 1991 [20], owing to the use of a stricto sensu diagnostic criterion, that is, positivity of the reaction to HTLV-I, a bias is apparent that prevents us from perceiving the true signi-ficance of HTLV-I within the context of myelopathies whose clinical presen-tation is similar to that of HAM/TSP in the areas with a high prevalence of this virus. The incidence of a considerable contingent of clinical pictures similar to HAM/TSP in seronegatives and of their counterpart, the absence of cases clinically manifest in communities of Melanesia with a high prevalence of HTLV-I as, for example, the Hagahai natives of Papua New Guinea [37], offer a serious challenge to neuroepidemiological thought. At the present time, the validity of the supposed etiological relationship is sustained solely on the dimensions and on the intensity of the association between HTLV-I and such myelopathies obser-ved in those geographical foci. On the other hand, the decline in the incidence of HAM observed as from the suspension of transfusion of infected blood is considered the most important epidemiological argument in favor of HTLV-I as the causal agent. This is a relevant contribution of the Kagoshima School which is the nucleus of the work of Osame and his colleagues [24]. The comments which follow are centered on this and on other studies of the Kagoshima School.

Considerations on the thesis of the Kagoshima School. According to Osame et al.[24], approximately 17% of the cases of HAM in the city of Kagoshima are attributable to blood transfusion. A drop of 16% in the incidence of HAM on a national scale was also observed in the period 1982 to 1988, after the control of donors for HTLV-I was implemented in 1986. The authors are of the opinion that the decrease observed is strong evidence that infected blood trans-fusion caused the disease in some patients. To strengthen this idea, they main-tain that the constant incidence of patients with HAM/TSP not associated to transfusion, before and after November, 1986, suggests that this finding is not the result of record. However, certain details apparently insignificant of the results obtained in the study show controversial aspects of the theory, even if they are considered under the same line of argument as that of the authors.

The calculated rate of 17% of HAM/TSP cases attributable to transfusion in the city of Kagoshima when confronted with the rate of 20% of patients with an antecedent of blood transfusion in this same city indicates that 85% of the patients previously transfused acquired the disease by this means of transmission. In favor of the theory, blood transfusion when infected clearly shows its pathogenic force. Obviously, for this to occur it must at least be admitted that: 85% of the patients in this class is a recipient of contaminated blood; the blood transfused to these necessarily contains the appropriate amount of viral inoculum; 85% of these patients coincidentally has immunological reactivity or specific susceptibility (HLA haplotype) favorable to the development of the disease [35]. It seems little probable to us that, for a disease where the calculated risk of clinical manifestation is of the order of 1/1500 seropositives, there should occur the confluence or coincidence, at random, of such factors in so many instances under normal conditions. It is possible, therefore, that the blood transfusion factors still remain as a merely random occurrence. Consequently, the decline observed in the incidence of HAM/TSP as from 1986 could depend on factors other than the implementing of control for HTLV-I in the blood banks.

As to the «relative constancy in the frequency of HAM before and after November 1986, when the contingent resulting from transfusion is excluded» [24], the statement seems to be the result of the use of a temporal scale of inappropriate observation that affords only a partial view of the curve of incidence. For this purpose, compare Figures 1 and 4 of this article [24]. The study in question encompassed the period from 1982 to 1988 which, if conveyed relative to the general curve of incidence of HAM, corresponds only to 7 of its 57 years and, precisely, to the narrow bracket of the peak of incidence, after which a decline begins. Under these conditions of observation, broadening the bracket and at the same time isolating it from the whole of the curve of incidence, it is only natural that one will have a view of the «relative constancy in frequency» or even of a plateau preceding the decline. The constancy in frequency might thus correspond to an unreal view, resulting from the artifice of the choice of an inadequate scale. So much so that the curve of incidence shows unquestionably a tendency to rapid decline from 1986 to 1988. It would be, however, premature to attribute responsability for the decline to the control of transfusion. Because, if this control were in fact a determinant of the decline one must necessarily admit that the increase in incidence up to the 1982-1988 level, above that of the «constant frequency of patients with HAM/TSP not associated to transfusion» observed in the years prior to 1982, is also attributed to the noncontrol of contaminated blood transfusion. And, by using the same argument as the authors, in a country of slow demographic growth (4.6% from 1982 to 1988) it would be difficult to imagine such an occurrence, unless for reasons unknown Japanese society, particularly that of Kagoshima, had suddenly been submitted to an unexplainable increase in the indication of blood transfusion in the period prior to 1982. In the same article, Figure 1 patently shows the enormous growth in incidence of HAM/TSP, above all as from the seventies until 1982. To Osame and coauthors, the lower number of registered patients with a clinical picture from before 1982, as compared to yearly records after 1982, reflects «most probably, the less frequent recognition of the disease and the probable death of many of these patients». This line of thought contains a justification allusive to the constant frequency of patients with HAM/TSP not associated to transfusion, and an implicit negation of the temporal clustering clearly outlined in the curve of incidence. Certainly, the action of these factors on the inclination of the curve of incidence cannot be denied. The question, however, resides precisely in the intensity with which these factors do or do not act. The inclination of the curve, as from 1970, is visibly geometric. In the line of argument of the authors, it would be necessary to admit that there was in the population studied a sudden and rapid increase in life expectancy, including that of the patients, as from 1970. Besides, the island of Kyushu, of which Kagoshima is in the extreme south, is traditionally characterized by a subsistence agriculture activity. Within this socioeconomic context, it is improbable that crural paraparesis occurring at a constant frequency had not attracted the attention of the public health services.

As a result of what was discussed, it could be established that: blood transfusions exerted little influence on the inclination of the curve of incidence;

in the epidemiological sense, it would fit within the category of a random event; the curve of incidence of HAM/TSP in Japan would obey fundamentally the determining effect of other risk factors subjacent to the cases of HAM/TSP, not associated to transfusion; the apparent relevance of the transfusion effect in the period 1982-1988, would be the result of the artifice produced by applying an inadequate scale of temporal observation, the existence of temporal clustering, therefore, being real.

The example of the Island of Guam. From the Island of Guam comes an analogy by means of two studies on amyotrophic lateral sclerosis (ALS) and the parkinsonism-dementia-complex (PDC) with respect to deviations produced by applying an inadequate time scale.

These two studies reach diverging results by portraying among other aspects the controversial subject of the disappearance of the ALS-PDC. Zhang et al.[39] studied the period 1944 to 1985 and showed that the incidence of ALS-PDC is, in fact, declining. In Table 4, concerning the incidence, the authors clearly show the tendency towards a decline in two instances: the first from 1965 to 1967 and the second, more continuous and progressive, as from 1979. A diverging conclusion, that ALS-PDC is not on the way towards disappearing was presented by Lavine et al.[15] in the study on the prevalence of ALS-PDC between 1987 and 1988. According to these authors, not only ALS-PDC but also other neurodegenerative
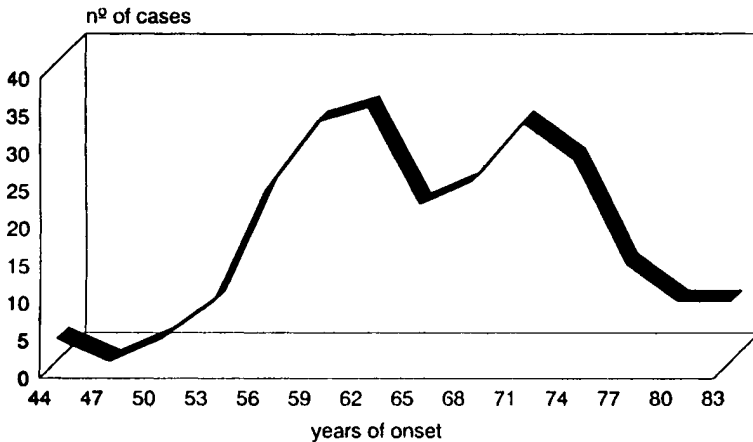

Fig. 1. ALS/PDC in Guam: graphic transcription of the Table 4 of Zhang et al. (1990).

diseases continue to be prevalent in Guam, as compared to the respective rates found in Rochester. The apparent decline reported in previous studies [4,29] is attributed by the authors to the insufficient record of cases observed as from 1982, the year in which the NIH ended its activities at its research center in Guam.

Some exceptions should be noted here before this result can be definitely accepted namely the measures used: the prevalence in the study of Lavine et al. and the incidence in that of Zhang and colleagues. The fact that they differ between themselves as to their scope and lend themselves to different ends, limit a comparison of the conclusions. Because both the cases remaining from previous periods and possible new cases are admitted in the rate, the prevalence relative to such a limited period as that of 1987-1988 cannot be used to reveal trends, whether in terms of growth or decline. Besides, as stated by Kurland, one of the cosignatories of the article by Lavine et al., in the discussion following the presentation of the work, in the course of a prevalence study or cross-sectional study cases of long duration are chosen in excess, for the cases of short duration may be dead before they are included. Obviously in this situation, the results obtained by Lavine and coauthors do not have the necessary force to invalidate the table of Zhang et al. of yearly incidence of PDC that reflects the encompassing period of 1944-1985, through the constant application of the same NIH protocol. Thus, contesting the decline in this case would have the same origin as the erroneous printing of a straight line in relation to the segment of a circle,

when this segment is examined through a powerful magnifying glass. In other words, the artifice of enlarging a fragment of the total event, by adopting an inadequate scale, obscures the importance of certain details.

The conclusion, however, that there is no indication that the rates of prevalence for ALS-PDC are lower in three villages in the south of Guam than they have been in the past (Lavine et al.), if its has not got the force to definitely deny the oscillations in the curve of incidence observed by Zhang and colleagues, could be reflecting a new growth in the incidence of ALS-PDC According to the survey by Zhang et al., in all of Guam, on December 31, 1985, there were 23 live patients with PDC. From 1987 to 1988, Lavine et al. found 33 cases of ALS-PDC in the survey that includes only three districts in Guam (Umatac, Inarajan, and Merizo). Even assuming that the 23 patients of Zhang et al. were still alive in 1987-88 and that they lived in those districts, an incidence is obtained of 10 new cases from 1987 to 1988. Dully corrected, this amount would be even greater if the calculation were projected for all districts.

In this way, we conclude that an event (that of the incidence of new cases) isolated from the whole does not eliminate the event of the preceding moment (that of decline) and, inversely, the tendency verified at a given moment cannot foresee that of the next moment (increase in incidence), except when there is a perfect identification of the risk factors and of the mode and time of action of these throughout the natural history of the disease.

The natural evolution of ALS-PDC in Guam is clear and transparent on the curve of its incidence with an apparently disordered succession of ups and dows. It is, however, impossible not to observe a certain pattern built into the succession of two humps and, possibly, of yet a third in the process of formation (Fig. 1). The descending slope of the first was recognized as a decline by Reed et al.[27] and that of the second by Garruto et al.[4] and by Rodgers-Johnson et al.[29]. In the epidemiological sense, the humps might signify the irrefutable revelation of temporal clusterings, just as valleys between humps would represent points of parcial overlap between temporal clusterings. For a condition that is provenly acquired such as ALS-PDC, the existence of a temporal cluster presupposes a critical period of exposure to a causal factor or factors.

Furthermore, each temporal cluster antecedes a period of specific exposure. Therefore, in face of the identification of at least two temporal clusterings, the occurrence of two distinct periods of exposure must be admitted. It is possible that the nonrecognition of the detail of two temporal foci led Zhang et al. to calculate only one period from 1949 to 1954 as the most recent and perhaps the last period of high risk and, to admit the variablity in the latency in a greater extension than it would be in reality. The idea, however, of critical exposure occurring at two or more times poses a question that places at serious risk the validity of the hypothesis in vogue for ALS-PDC: the etiological hypothesis of the toxins derived from Cycadaceae. For a single critical period of exposure, from 1949 to 1954, the justification is sufficient of the uncommon increase in consumption of Cycadaceae seeds by the Chamorros in that period as a result of the rise in prices of food resulting from World War II. Once such a rise in prices was curbed by the end of the conflict and by the progressive Americanization of customs, it is difficult to accept the cyclic recrudescence of the increase in consumption of Cycadaceae.

Both an examination of the curve of incidence in itself and a discussion of the elements built isto it also allow an explanation of the existence of a temporal clustering in the incidence of new cases of HAM/TSP, analogously to what was verified in relation to the ALS/PDC in Guam. The epidemiological phenomenon is there to be perceived and understood and, because of its condition as a phenomenon in natura, it always rearises irreducible, bothers the artifices that deny its existence, even if implicitly.

This seems also to have been the historical background to HAM/TSP.

Rediscovering Tumaco. A confirmation of an HAM/TSP temporal clustering comes from the other end of the Pacific.

In a neuroepidemiological descriptive study carried out in Tumaco, Román et al.[31] had already discovered the incidence of a local temporal clustering of TSP These authors emphasize the importance of new cases between 1975 and 1979 and the apparent decline in the occurrence of the disease in the last few years. This conclusion reflects the authenticity and the importance of the phenomenon observed, mainly taking into consideration that the study was carried out at a time when the diagnostic criteria of TSP were purely clinical, therefore

free of contamination by the fever of determinism. All the possible and putative causal agents were discussed at the same level of pathogenic potential. Contrary to what it might seem, this fact definitely does not mean that the purely clinical diagnostic criteria are insufficient, even going so far as to suggest in theory a causal agent for a given disease. They merely warn against adventures in this field. In a subsequent article by Román et al.[33], relating to the revision of endemic tropical myeloneuropathies, these criteria reaffirm their potential including the identification and definition of the geographical foci of TSP of unknown etiology in India, Africa, the Seychelles, the Caribbean Islands, Jamaica, and Colombia where, only later was there found an association between TSP and HTLV-I.

There is an unquestionable similarity between the Tumaco curves of incidence (Román et al.[31] Figure 3) and those of Japan (Osame et al.[24] Figure 1). In both there is clear evidence of temporal clustering and also of a decline. Considerations on various aspects, but above all, that of a condition of equivalence between the two regions as endemic foci associated to HTLV-I and defined at different periods, exclude the fortuitous nature of this similarity. As it is not mere chance and occurring in the epidemiological picture of one same nosological entity, this similarity leads us to consider that, in Japan, temporal clustering appears as a result of the action of common agents and subjacent to those of Tumaco. Therefore, in spite of the analysis by Osame and coauthors, the decline in incidence observed in Japan could arise independent of blood transfusion, since in Tumaco no significant environmental, nutritional, or genetic factor was found. In both foci, the similarity extends also to the period, the fifties, in which an ever-growing annual incidence of new cases can be observed. In this way, the curves of incidence in their overall general slope are superposable in these foci.

One difference can be observed, however. The descending slope of the curve of incidence for Tumaco began as from 1977 until 1982, while for Japan, as from 1986 until 1988. The apparent time discrepancy dissappears when the two figures are compared in the following way: in order to permit a more compact view Figure 3 by Román et al. is reduced to the time scale of Figure 1 by Osame et al.; then we proceed with a comparison of the figures making them coincide with the period. The procedure makes it clear that the temporal clustering in Tumaco between 1975 and 1979 is also built-in, in a similar way, into the curve of incidence of Osame et al. The apparent decline observed in Tumaco, as from 1979, is present also in Japan, around 1980, when an evident increase in the annual incidence begins towards 1986. In the study of Osame et al.[24] this datum could mean, as it did in relation to ALS-PDS in Guam, a succession of a new temporal clustering. The study of Román et al.[31] encompasses the period of 1952 through 1982. Within this context, the continuity of the work in Tumaco focussing on annual incidence deserves greater expectation.

Osame, in a revision on HAM/TSP [20] presents a picture according to which about 100 cases of HAM/TSP were recorded in Colombia up to 1991. To judge from this datum, even assuming that all 50 cases gathered by Román et al. are included among the 100, there was an extraordinary increase in incidence (50 new cases) in the period from 1982 to 1991 that, if transported to Figure 3 of Román et al.[31], would allow us to trace the curve of incidence with an inclination similar to that observed in Figure 1 of Osame et al.[24] between 1982 and 1988.

Proportionately, the two geographical foci are equivalent also in growth rate of incidence in this period of approximately 10 years. A panoramic view of this kind reveals at least a succession of two temporal clusterings that partially superpose each other around 1980. Once again, and analogously to what occurs in Guam, a pattern of succession of temporal clusterings can be perceived by means of an adequate scale. It is also possible that in both figures, the oscillations in the bars of incidence, apparently disarranged, observed in other periods, have other humps built in. The curves are real. They did not originate from artifices of geometric exercise. They include in themselves real numbers, rates, and measures of incidence. Therefore, they allow the perception of the dimension of an epidemiological phenomenon. Thus, the temporal clusterings in Japan appear pari-passu with those of Tumaco.

Each temporal clustering is preceded by a critical period of exposure and, in the same way as Guam, a succession of critical exposures in various periods therefore engenders a succession of temporal clusterings that partially overlap each other, and give rise to an inclination resulting in apparent geometric progression as from the 1950s. The phenomenon thus perceived would, by means of repeated exposures, determine high levels of anti HTLV-I antibodies according to the advancing age of patients, as was observed in seroepidemiological studies carried out in endemic foci [1,3,6,37].

As a corollary of this observation, it is necessary to make a correction to the period of latency admitted between infection and clinical manifestation. The succession of temporal clusterings, presupposing the existence of critical periods and antecedents of exposure, would admit a period of natural latency neither so variable nor so long, 15.6 years, as might be supposed [24]. It might perhaps be of the same order as that calculated for blood transfusion of 3.3 years [24].

The most intriguing aspect of this sequence, however, is represented by simultaneous occurrence, in Tumaco and in Japan. Assuming that HTVL-I is in fact the causal agent of HAM/TSP, this simultaneousness leads us obligatorily to admit that there was a cyclic recrudescence in phase of the pathogenetic potential of the HTLV-I in both the geographical foci. Although the cyclic phenomenon is recognized in so many other endemias or epidemics, especially those of an infectious nature, it would be uncommon that the HTLV-I would have manifested such a property in phase, involving closed communities, ethnically distinct and geographically distant. At the present time, therefore, the etiopathogenetic relation of HTLV-I would be to HAM/TSP as the Cycadaceae toxin is to ALS-PDC of Guam.

The mutual attraction, however, observed between HTLV-I and HAM/TSP is undeniable. If the association were to restrict itself to a region with a high prevalence of HTLV-I, there would always be difficulties and controversies in the interpretation of its significance. However, the picture of geographical distribution of HAM/TSP in Japan arouses relevant considerations in favor of the etiological relationship.

The occurrence of HAM/TSP in Japan is centered fundamentally in its extreme south (Kyushu and Okinawa) and north (Hokkaido), separated from each other by a significant hiatus represented by Honshu (Osame et al. 1987, apud Kubota and Osame [14]). This is an evident proof that the prevalence of HAM/TSP does not depend only on a geographical factor such as latitude but rather of a conjuncture. This leap is verified, from Kyushu to Hokkaido. The migratory current of peoples appeared as the most plausible of justifications, if not the only one for the metastasis. It is well known in Japan that the Island of Hokkaido, whose only native is the Ainu people was the common destination for important migratory flows observed at the time of the modernization of the country and after the end of World War II. The newcomers were mainly the peoples of the north of Honshu (with a low prevalence of HTLV-I) and those of Kyushu (of high HTLV-I prevalence) which together formed a mixed community, although integrated. Add to tis the fact that this newly-formed community and that of Okinawa maintain narrow and traditional bonds of excellent trade partners between themselves. In this context, it is admissible that this focus of HAM be constituted both of bearers originating from the South and also from the North that headed south who were submitted to critical exposure of southern environmental factors in the period prior to the migration or to the return, respectively. The lesser prevalence of HAM in Hokkaido, when compared to that of the extreme south, would reflect the result concerning the dilution of the southern prevalence in this community of heterogeneous origin.

Outlook for the designing of new studies. Considering what was discussed and paraphrasing Román and collaborators, it can be established that the cyclic recrudescence of the pathogenic potential of HTLV-I and its simultaneous occurrence in distinct endemic foci are keys of unknown significance.

By means of what mechanisms does HTLV-I, a retrotransposon of existence as remote as the antiquity of infected beings, acquire its pathogenic virulence simultaneously in distant foci and, at the same time, leave other commu-

nities equally infected such as those of Melanesia, practically intact? It seems obvious that, for this drastic transformation in the well-consolidated and apparently inoffensive virus-host relationship, the action of factors up to now unprecedented should be admitted. Furthermore, that the genesis of these factors was not natural and/or spontaneous, through its simultaneous and not random nature. In this way, it is suggestive that it was a transformation provoked in the ecological relations. Perhaps, only in this form can we understand how Tumaco and the south of Japan, so distant one from the other, could have been a target of action in phase of these factors.

In both foci, the curves of incidence suggest that the beginning of the formation of temporal clusterings took place around 1950. Under these circumstances, the immediate post-war period appears, inevitably and analogously to the Island of Guam as one of the principal, if not the first critical period of exposure of the communities to those factors. World War II, with its universality and simultaneousness with which it promoted cultural-socio-economic changes, would have indirectly and, in a lasting and/or cyclic manner, acted on the ecological systems involved. The environmental factors, thus modified, would have had traditional balanced systems as a favorite target. Peoples such as the Hagahai of Papua New Guinea remained free of the modifying factors, and were spared owing to the special circumstances of isolation. In the Southwest Pacific, with a high prevalence of HTLV-I in contrast to the virtual absence of clinical cases, the serological reactivity to HTLV-I is done against gag p 19, p 24, p 28, p 53, whereas the reactivity to gag p 24, tax p 36 and gp 46 was found only in a single patient with TSP recorded in the Solomon Islands [36].

The hypothesis of the participation of different lineages or variants of HTLV-I leads us to a very attractive line of etiopathogenic thought. Would it be possible that the HTLV-I prototype, prevalent in endemic foci would be chronically in a state of inoffensive coexistence with the host and that the HTLV-I variant would originate from the exposure of the prototype or of the virus-host combination to those modified environmental factors? In this respect, the finding of similar serological reactivity recently verified, in relation to cases of HAM/TSP in Japan is significant [8].

As an essential condition, the planning of new studies must include the possibility of answering to these questions stemming from selecting the community, from organizing the sampling and the classification of this sampling, according to the time and direction of migration. In this aspect, the outline of the study of Zhang et al.[39], referring to ALS-PDS in Guam, is ideal because it objectively establishes the classification of the Chamorro community into a group of natives fixed in Guam and another involving those who migrated to Continental America. This plan of cleavage was the key that allowed the authors to define the last critical period of exposure between 1949 and 1954.

As regards HAM/TSP, the Okinawan Community of Brazil presents itself to the study with the ideal ethnographic and demographic characteristics. Among these, especially outstanding is that of being a community that has been ethnically stable for generations and that is clearly divided as to the period of immigration into pre- and post-war generations. The migratory current that was observed in the opposite sense, from Brazil to Japan, with both isseis (first generation of immigrants) and niseis (second generation of immigrants) and whose return to Brazil often occurred only a few years after the end of the war, also provides us with an unparalleled opportunity for study.

Previous studies of seroprevalence of HTLV-I involving the Okinawan Community of Hawaii [1] and of Campo Grande, Brazil [12], showed a drop in the rate from the issei to the nisei. In these studies, however, one has the impression that the incomplete classification of the cohort according to the time of migration, both in one and in the other sense, rendered impossible a greater scope in the results obtained.

The analysis of the seroprevalence, of the prevalence and of the incidence of HAM/TSP, of the significance of seroconversion, of the types of reactivity to viral constituents, in face of the cohort classified according to time and the direction of the migratory current, will ensure promising results for the unders-

tanding of the etiopathogeny of the HAM/TSP in the south of Japan. It can also be the path towards clarifying the simultaneous generating of geographical foci as distant as that of Tumaco, just as the flap of Lorenz' butterfly's wings, in Brazil, might set off a tornado in Texas.

The objective to follow is clear: identify the butterfly.

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