UNTREATED LEPROSY: PROBABILITY FOR SHIFTS IN RIDLEY-JOPLING CLASSIFICATION. DEVELOPMENT OF "FLARES", OR DISAPPEARANCE OF CLINICALLY APPARENT DISEASE

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The material for this presentation is from a continuing study of leprosy which commenced in 1962 in the Karimui District of the Eastern Highlands of New Guinea. There are many contributors to this study and due acknowledgment must be made of the work of Douglas Russell, Charles Shepard, Denis Ridley, Clem Boughton and Don Vincin: my role is that of epidemiologist.

The Karimui study began as a controlled trial of BCG (Bacille Calmette-Guerin) then in 1968 expanded into a field trial of DADDS (Acedapsone). From its inception in 1962 this study has been population-based: in fact the total population has been examined on eleven occasions and complete demographic and epidemiological data is available.

From 1962 to 1967 the population remained untreated; there were simply no medical services available, and sequential observations during this five year period provided information on the natural evolution of untreated disease.

The classification used is that of Ridley and Jopling. Shifts may occur anywhere within the space bounded by Indeterminate, TT (pure tuberculoid) and LL (pure lepromatous) but the pure tuberculoid type, TT, is considered extremely stable, virtually an end point.

Early in the Karimui study we became very much aware of the phenomenon of spontaneous healing. A proportion of patients, with obvious clinical signs of disease and biopsy confirmation at initial diagnosis, just healed completely. The characteristic skin signs disappeared, and with minimal, or no evidence of any neurological abnormality or sequelae.

Over a period of five and a half years, and in the absence of any treatment, we were able to observe the progress of 362 cases: 88% with histopathologic confirmation. All clinical assessments were made by Dr. Russell and all histopathology by Dr. Ridley. We observed spontaneous healing in the Indeterminate, TT, TT/BT and BT forms, but no cases at the borderline to lepromatous end of the spectrum healed; these latter cases clinically remained stationary or slowly deteriorated.
During the period 1962 to 1967 we noted a phenomenon which we named a "flare". We described the "flare" as a sudden increase in the number and size of skin patches between one survey and the next. These multiple, large hypopigmented patches may have indeterminate or tuberculoid features, and in a proportion of cases, mixed features. At an earlier examination the patient may have had only one, perhaps two, relatively small patches, but at a later examination the skin lesions are so extensive that the comment "covered in patches" would provide the most apt description and many cases were recorded as such in the records.

A typical case history - 1962, a small hypopigmented macule on right buttock, biopsy - indeterminate: 1964, patch faded, resolving: 1966, multiple large hypopigmented well-defined tuberculoid patches, anhydrosis. The patches covered both thighs, right arm, left arm and shoulder, abdomen and portion of the back. 1967 - increase in patches, biopsy - early BT.

What we have described as a "flare" resembles the "low resistant tuberculoid leprosy" described by Leiker in the Journal (1964:32:359) but the "flare" is not the reactional tuberculoid mentioned in Cochrane and Davey but must the "flare" be confused with the same term used by Dr. Bullock to describe the minor reversal reactions seen in lepromatous patients treated with transfer factor. The Karimui "flare" does NOT progress toward the borderline/lepromatous type. We would agree, at least in part, with Ridley and Jopling (Int. J. Lep., (1966) 34:255) who state that "we consider the low resistant tuberculoid leprosy described by Leiker falls within our BT group".

For the moment let us avoid the difficulties of the semantics of clinical classification and simply define a "flare" as a sudden, unexpected appearance of multiple large hypopigmented patches with indeterminate and/or tuberculoid features.

Between 1962 and 1967 we had observed shifts from one type of disease to another. We had seen the phenomena of spontaneous healing and the "flare"; and by 1967 we became aware of the severe neurological damage which is almost always associated with the "flare".

By 1969 after two year's treatment with acedapsone (DADDS) and seven years observation of the effects of BCG vaccination, three clearly significant conclusions could be drawn -

1. The effect of BCG vaccination is type specific: there is a highly significant reduction in the incidence of the borderline tuberculoid, BT, form of the disease in the vaccinated group.

2. With the advent of acedapsone (a) the "flare" ceased to exist, and (b) the shifts in the type of disease we had noted during the untreated phase no longer occurred, particularly changes in type from BT or Indeterminate toward the borderline/lepromatous end of the spectrum.
All new cases detected in the Karimui population during this eleven year period (1964-1974) were confirmed by biopsy, except two. By December 1974 a total of 264 new cases had been detected (Table 1). The person-years denominator is practically identical hence the actual numbers of cases can be compared to illustrate the incidence of the disease in the two groups.

Although the incidence is lower in all types in the vaccinated group, only for those patients with the biopsy type BT (borderline-tuberculoid) does the difference reach statistical significance: 21 cases in the vaccinated compared to 68 cases in the unvaccinated.

There is a difference in the number of cases in the borderline/lepromatous groups (BB to LL), 8 vaccinated and 13 unvaccinated, but how much of this difference might be attributed to BCG vaccination if some proportion of BT cases can be shown to shift toward the lepromatous pole? I began to wonder about the measurement of the effectiveness of control measures in population groups rather than merely the efficacy. If BCG vaccination reduces the incidence of BT cases, and acedapsone prevents the "flare" and also changes in type toward the lepromatous pole, it is clear that these control measures may be acting directly or indirectly on particular phases of the natural evolution of leprosy, that is, on the transformations or shifts in type implied in the traditional diagram.

What is required is some measurement of the possible changes which may occur in the dynamics of the natural evolution of the disease, specific for each histopathological type. What proportion heal? What proportion "flare"? What proportion of indeterminate forms progress to other types? In particular, what proportion of cases progress toward the lepromatous pole? Briefly, what are the probabilities of each type of disease shifting, healing or "flaring"? If an estimate of these probabilities could be obtained it should be possible to construct epidemiometric models to assess in more detail the effectiveness of control measures and gain greater understanding of their modes of action, and the subtleties which underlie differences in the distributions and patterns of disease in various populations.

All the data collected between 1962 and 1967 were reviewed: a total of 362 cases, 87% had had at least one biopsy and 20% of these biopsied cases had had two or more biopsies. In 1962 we biopsied a large number of patients to provide a baseline for the trial of BCG. We resurveyed the population in March 1964, August 1966 and December 1967. New cases were detected and the clinical condition of the patients diagnosed in earlier years was recorded, and new cases and cases suspected of having progressive disease were biopsied. In 1967, just before acedapsone commenced, a large number were rebiopsied to provide a baseline for DADDS assessment, particularly the suspected bacilliferous cases, cases in which some change in type might have been expected on clinical evidence, or in which an earlier biopsy result was equivocal.
All the data had been coded for the computer and it was possible to produce a sorted, condensed, readable version of the events between 1962 and 1967, including the results of the neurological examination in 1967. I looked for those cases which had changed type, healed or "flared" and such events were confirmed by biopsy.

Might I emphasize that from this point I am referring to patients with at least one biopsy result: the 13% of cases without a biopsy have been excluded. In only nine instances has it been necessary to have recourse to the clinical notes to establish the initial type of disease. For example, the initial biopsy might have stated -- "section too hard to cut", "inadequate specimen", or "almost normal skin", but review of the clinical records clarified the situation. Hence with these nine exceptions we are dealing exclusively with the biopsy results provided by Dr. Ridley.

The results are imposed on a traditional chart of the transitions of Ridley-Jopling groups in Fig. 1. I did examine the data to detect possible differences in the sexes, but there was no significant difference in males and females with respect to the probabilities of healing, "flaring" or changing type, hence the diagram represents both sexes combined. The time period over which these events might be expected to occur is five years.

First the indeterminate cases -- the probability of healing is .2850, i.e. about 28% healed spontaneously during a five year period, but let me clarify what is meant by "healed."

In each of the surveys 1964 to 1967, Dr. Russell examined the cases "blind" in that the records of previous examinations were withheld until the case had been examined (the same method was also used for Dr. Boughton's neurological examination). For many healed cases, the only sign of a previous skin patch was a scar from an earlier biopsy, and "nil signs" on the records really meant just that: no hypopigmentation, no infiltration, no tubercles, just nothing except perhaps the scar from the earlier biopsy.
However "healed" also implies a virtually normal neurological examination. In 1967 Dr. Boughton used a structured and codable format in the examination and recording of the neurology of all cases; this examination was repeated in 1969, 1971 and 1974, but the results obtained in 1967 were used to obtain the proportion of healed cases shown in the diagram.

We did regard "minimal detectable weakness" in motor power as normal, because it is difficult to disregard "handedness". Similarly a "doubtful" nerve enlargement (after comparing the size of two symmetrical nerves) was regarded as normal, provided such nerve enlargement was not associated with the site of a skin lesion, an area of sensory loss, or motor weakness. Often the results of the examination in 1969 substantiated neurological normality, but any contracture/deformity or muscle wasting automatically excluded the patient from the "healed" group.

About 28% of indeterminate cases heal spontaneously, 12% may develop a "flare", 4% move toward TT, and 1% to TT/BT. But 11% shift toward BT and almost 9% move toward the borderline/lepromatous stage; this latter group may have progressed via a BT stage, but we did not detect it in the biopsy results. Note also that the borderline (BB) to lepromatous (LL) group have been considered as a single entity, the term "bacilliferous" would be an apt label for this group.

Only one patient contributed a "double shift"; a female patient, indeterminate in 1962, BT in 1964 and finally to lepromatous in 1966. With this exception, each transition from one biopsy type to another shown in this diagram is based upon the transition seen in one individual, so a small number of patients does not contribute excessively to the shifts noted.

For the TT or pure tuberculoid group no type changes were recorded at any time, but 10% healed and nearly 13% "flared". We noted no "flares" in the TT/BT group, they may well occur, but we did not see any; however 16% are observed as healing.

The BT (borderline tuberculoid) group appear the most unstable of all: in a five year period about 9% might be expected to shift toward the lepromatous pole, and a smaller proportion, about 5%, ascend toward TT, but the probability of a BT flaring is .4063, that is about 40% will "flare", and 18% demonstrate healing.

The interrupted line from BT to TT/BT indicates that such a shift is possible but we did not observe it.
Apologies for the mass of information presented, but someone would be sure to ask about frequencies. The indeterminate probabilities are based on a total of 143 indeterminate cases; that is, patients with a biopsy report of indeterminate at some time during the 5 1/2 year period. There was a total of 73 TT cases, and 72 borderline tuberculoid or BT cases.

Doubtless, some of the mathematically oriented will have noticed that if 14 indeterminate cases "flare" in a total of 143, the probability of "flaring" might be .10 or 10%, not .1247 as shown. Similarly, with the BT group -- of a total of 72 cases ever seen, 18 "flared", so the probability of a BT flaring should be .25 (25%), not .4063 as indicated.

The reason for this apparent discrepancy is the use of an actuarial method to calculate the probabilities, using a person-years approach which excludes, or includes, cases as they enter or leave the population at risk at the appropriate time according to change in type, healing, flaring or death.

Certainly for some shifts the numbers are small, only one from indeterminate to TT/BT and two only from BT to TT, but all shifts are confirmed by biopsy.

Does BCG vaccination have any effect on the probabilities for changes in type shown in this diagram? Remember that 277 of the 362 cases on which the diagram is based had the onset of disease before 1962 and thus prior to BCG vaccination, but there is no clear evidence that BCG influenced any changes in type. Of the ten cases progressing from indeterminate to lepromatous pole, 5 were vaccinated and 5 unvaccinated. Of the 12 progressing from indeterminate to BT, 4 had been vaccinated and 8 had not. It would be attractive to hope vaccination after onset of disease might prevent BT cases from shifting to the lepromatous pole, but of the four such cases -- two had been vaccinated, two had not. Neither sex nor age is clearly associated with changes in type but healing is more likely to be seen in the younger age groups.

Does BCG vaccination affect the probabilities of healing or "flaring"? There is nothing of significance in the data for the TT and BT groups: vaccination does not affect either healing or the "flare." However, for the indeterminate groups, when the proportion of healed cases in the vaccinated is compared to the proportion healed in the unvaccinated, there is a difference. For the statistically minded, the difference between 21/48 and 11/52 has a P value of less than .02, two chances in a hundred. However the allocation of cases to BCG and Saline groups was not done to test the efficacy of BCG for "healing."
In general we might conclude that BCG vaccination (or perhaps tuberculosis?) does not influence the onset of the flare or changes in type of disease, but may promote healing in the indeterminate form. However, BCG does affect the incidence of the BT form, and acedapsone does prevent the "flare" and prevent changes in type. As soon as acedapsone commenced, the "flare" no longer occurred; DADDS literally reduced the "flare" probabilities to zero; nor did we see any changes in type, particularly toward the lepromatous end of the spectrum.

I have mentioned earlier that the neurological examination was structured in such a way that results could be coded and scores allocated for varying types and degrees of damage or abnormality recorded. The results of the examination were subdivided into four sections:

Loss of Motor Power (Motor Loss), Contracture/Deformity, Sensory Loss and Nerve Enlargement: and a score could be given to each section indicating the degree of abnormality, the higher the score, the greater the abnormality, damage or disability.

Table 2 shows the average or mean scores for the TT and Indeterminate groups: for those cases with the "flare" -- and those without the "flare." Healed cases are considered in the last column. Let us look at the TT group -- 15 TT patients suffered a flare at some time between 1962 and 1967, and 30 TT patients had no "flare" at all during this period. In all cases the duration of untreated disease was at least 5 1/2 years.

It does not require any statistical methods to assess the difference in the scores: 14 of the 30 patients without the "flare" were absolutely normal neurologically. In fact, two patients, with no evidence of a "flare" over a 5 year period but with considerable neurological damage, contribute significantly to the totals from which the mean scores were calculated.

Similarly in the Indeterminate group; 20 of the 42 patients without the "flare" were absolutely normal.

However, the use of numerical methods may have little meaning to those unfamiliar with them, unless translated into clinical terms. The following two examples will serve to illustrate the clinical neurology of the hypothetical "average" TT (pure tuberculoid) case.

The first one, the average TT patient with NO flare: Loss of motor power, score of 2: slight weakness of finger abduction, right hand, plus slight weakness of right foot dorsiflexion. Contracture/Deformity, score of 1: slight wasting of small muscles of left hand. Sensory loss, score of 1: the ulnar region of the left hand. Nerve enlargement, score of 2: slight enlargement of left ulnar and right popliteal nerves.
The average TT patient, WITH a "flare": Loss of motor power, score of 12: severe weakness left wrist dorsiflexion, not quite a wrist drop, score of 3; severe weakness abduction and opposition of left hand, score of 4; and also a complete right foot drop, score of 5. Contracture/Deformity, total score of 7: contracture and loss of parts of 4th and 5th fingers of left hand accounts for 5 points; the loss of three toes on the right foot contributes 2 points. Sensory loss, total of 8 points: right leg, loss in the area supplied by the lateral popliteal and lateral cutaneous of thigh, 3 points; "glove" anaesthesia left hand, score 5; ulnar and radial loss on right hand, score of 2.

Patients classified as indeterminate and BT also show similar differences between those who have "flared" and those who have not and there is no need to use statistical methods to assess the significance of the differences in neurological damage -- it is obvious by inspection of the table. Flares were not observed in the BB to BL group.

Summarized briefly -- whether the biopsy type was TT, BT or Indeterminate, approximately 50% of such patients WITHOUT a "flare" have absolutely normal neurology after a duration of untreated disease of at least 5 1/2 years. The remainder without the "flare" generally exhibit only small amounts of damage. If a "flare" occurs, deformity and disability are extremely likely in the absence of treatment.

Is the "flare" an indication of a shift toward the lepromatous pole? The answer must be NO! Between 1962 and 1967 we saw a total of 60 patients considered to be "flares" and only two gave any indication of bacilliferous activity. Both patients were BT on biopsy, but smears were taken because clinical evidence in one case, and the presence of acid-fast bacilli in the biopsy in the other, suggested a borderline type. Both these patients could produce only one 1+ smear from a total of six sites. Were these two patients just a little further down the spectrum than a true BT, that is, could a "flare" and some bacilliferous activity coexist? Not impossible, in fact likely, because of the concept of a disease spectrum rather than a clear-cut categorization of disease types.

To return for a moment to the possible impact of BCG, tuberculosis, therapy, time or other influences on the natural evolution of leprosy. BCG significantly reduces the incidence of the BT form, hence vaccination, or possibly tuberculosis infection, will reduce the number of BT cases and also the number of BT cases available to shift toward the borderline/lepromatous end of the spectrum, and the number who may develop the "flare" Note in Fig 1, within a five year period about 40% of BT cases may be so affected, with all the neurological damage and potential disability which is associated with the "flare."

I emphasize that the probabilities shown in the diagram are based upon events which we observed over 5 1/2 years. It is of course quite possible for a patient to present as a "flare" or as a borderline/lepromatous case at the initial examination. Some did so, but such cases are excluded from
the probabilities shown in the diagram, for the diagram represents the dynamic changes occurring within a disease system.

In relation to disease control, the ideal is the prevention of the onset of disease. Fig. 1 illustrates that there are opportunities for control measures to operate within the dynamic situation depicted here. With a longer period of observation of untreated disease, a greater proportion of each type may have healed. Equally possible, more cases may have "flared" or shifted to the lepromatous end of the spectrum. We do not know just what would have happened, because the introduction of the depot sulfone, aceadapsone, put an end to a unique opportunity.

While I have specifically mentioned the influence of BCG vaccination (and I must mention that Karimui is free of tuberculosis), is it possible that over a period of about 500 years, the tuberculosis endemic may have modified the pattern of leprosy in Europe?

It is also possible that nonspecific factors may influence the probabilities in the diagram? What might be the effect of good nutritional status on spontaneous healing? Is it not possible that the age at onset of infection, or the age at onset of overt disease might influence the probabilities? There is a marked peak in the age distribution of "flares" in males at ages 15-19; in females, the distribution tends to be bimodal, the major rise at 25-29 years and a lesser rise at 10-14 years. Might not physiological factors during puberty and pregnancy influence the natural history? It is recognized that aceadapsone is effective against falciparum malaria, and malaria is endemic in Karimui. Might not the control of falciparum infection by aceadapsone or other means decrease the probabilities of a change in type toward lepromatous, or even the "flare."

How certain are we that the "flare" is associated with a definite biopsy-determined type of disease? There was a total of 60 flares observed between 1962 and 1967: in 20 such cases the biopsy coincided with the "flare" -- indeterminate 7, TT 7, and BT 6 cases. Eighteen of the patients were biopsied after the "flare," mostly about one year afterward: 5 proved indeterminate, 3 TT, and 9 BT. In 20 cases however, the biopsy preceded the "flare": 10 were regarded as indeterminate, 4 TT, and 3 proved to be BT. It is possible that a proportion of the latter cases, particularly the indeterminate, might have been regarded as TT or BT if the biopsy had been done at the time of the "flare," but there were certainly no borderline (BB) or lepromatous (LL) patients with a "flare."

There are at least two factors which may influence the particular biopsy type found in patients with a "flare." The site chosen for biopsy is usually that which shows the most active signs of disease, but it is reasonable to assume that the histopathology will be identical in every portion of the large lesions which constitute a flare? Secondly, the duration of the "flare." Generally there is a gradual decrease in the number and size of the patches, the lesions tend to flatten out, pigmentation returns, and in a proportion of cases, all skin signs disappear. (Is this the origin of the polynuritic?) If the "flare" is dying out, an indeterminate report seems quite likely.
Fig. 1 shows that "flares" may be indeterminate, TT or BT, but it would be a mistake to assume that the diagram illustrates a static situation, particularly with respect to the "flare." The evolution and course of this disease should be regarded as a fluid, dynamic process, and at Karimui we were able to take a "snapshot", albeit with 5 1/2 years exposure time, of an evolutionary process which may extend over decades. With more frequent biopsies, taken from many sites and over longer periods of time, we might well have noted changes from indeterminate to BT; then a "flare", with later gradual regression to indeterminate with some signs of the "flare" persisting; and finally the disappearance of all skin signs. Although the fire in the dermis has died out, the neurological ashes remain as evidence of the conflagration.

We are somewhat uncertain as to whether neurological damage may precede the "flare"; the first structured neurological examination was in 1967. What might have been found in 1962 if we had examined all those cases which "flared" later on, we do not know. Certainly those cases which "flared" just prior to the commencement of acedapsone therapy generally have little neurological damage.

It is also possible that neurological damage may occur in the absence of a "flare". Ten patients were noted to have suffered considerable disability and deformity by 1967, but we had not observed any "flare." Possibly the "flare" occurred before our first survey in 1962, or perhaps in a small proportion of cases, the damage can arise even though the "flare" phenomenon does not occur.

If the "flare" were associated with shifts to lepromatous, one might postulate some decrease in cellular immunity. The problem is that there is no association with lepromatous shifts. The epidemiological evidence suggests an "all or none" situation; if the "flare" occurs, damage and disability are almost certain in the absence of prompt treatment. But if the "flare" does not occur, there is a 50% chance that there will be no damage at all, and for the remainder of the non-flare cases, only minor neurological damage and disability.

Professor Newell in his paper entitled "An epidemiologist's view of leprosy" raises many questions concerning the distribution and natural history of this disease, and the answers to some of them at least may well lie in a clearer understanding of the natural evolutionary process and the factors which may modify the dynamics involved.
<table>
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<th>Year of diagnosis</th>
<th>BCG group (Cumulative no. of cases)</th>
<th>Saline group (Cumulative no. of cases)</th>
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Table 1. The incidence of leprosy in Karimui 1964 through 1974 by biopsy type.
Table 2. Results of neurological examination in 1976, according to disease category and presence or absence of flare in interval 1962-1967.

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<th>Indeterminate</th>
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<th>Without flare</th>
<th>TT</th>
<th>With flare</th>
<th>Without flare</th>
<th>BT</th>
<th>With flare</th>
<th>Without flare</th>
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<td>Patients diagnosed in 1962; not healed by 1967</td>
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<td>Mean neurological score at 1967 examination</td>
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<td>1.3</td>
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FIGURE 1
NATURAL EVOLUTION OF LEPROSY
TRANSITIONAL PROBABILITIES BASED ON 5 YEARS OBSERVATION OF UNTREATED CASES

"FLARE" .1247

INDETERMINATE .2850

HEALING

TT .0445

TT/BT .0089

BT .091

BB TO LL .093

"FLARE" .0452

HEALING .1053

HEALING .1263

HEALING .1613

HEALING .1806

HEALING .4063

HEALING NONE