4. Discussion

4.1. General background

Exposure to *M. leprae* seems to represent a generally accepted factor or agent, *necessary* to contract leprosy. However, it appears that only a minor proportion of exposed persons develop the disease (Leiker, 1977; Davey, 1978). Furthermore, immunological techniques have demonstrated that a large number of persons exposed, may even become infected, but without developing any signs or symptoms (Godal and Negassi, 1973).

In general, immunological studies during the last decade have brought a considerable amount of knowledge of the pathogenesis of leprosy, and in particular many details on the nature of the immunological deficiency in lepromatous leprosy are revealed (Godal *et al.*, 1974, Godal, 1978a). Protective immunity in leprosy, a disease with intracellular multiplication of bacteria, is considered to be due to cell mediated immune reactions, though the role played by humoral antibodies does not yet seem to be clear. In lepromatous leprosy there is a T-lymphocyte associated defect in responses to *M. leprae*; however, the precise *mechanism* behind the defect is still unknown.

Far less is known of the *cause* of this lack of protective immunity. Apparently, *M. leprae* is not a *sufficient* aetiological factor; *additional* factors are decisive as to whether an exposed person is to contract leprosy or not. The differentiation of the disease into separate types is also caused by such additional factors. On this basis a comprehensive discussion has evolved over several decades.

Put simply, additional factors of possible relevance may relate to the host or the agent (Doull, 1962). Factors relating to the *host* refer to terms like 'susceptibility' and 'resistance'; terms until now used mainly for theoretical discussions. From an epidemiological point of view, knowledge of the substance of these terms and their practical implications is still scarce. Nevertheless, the use of the term 'susceptibility' in the epidemiological discussion of additional factors may prove fruitful. Factors attached to the host may be of *environmental origin* like poverty, malnutrition and poor hygiene. Furthermore, factors attached to the host may be of *genetic* origin.

Factors attached to the *agent* may relate to *qualitative* aspects, like different strains of *M. leprae* with variations in pathogenicity; e.g. recently, primary dapsone-resistant strains appear to have been demonstrated (Meade, 1977). Or the factors may relate to *quantitative* aspects, i.e. dose and duration

of the exposure. Furthermore, quantitative aspects may even represent an environmental factor attached to the host; increasing evidence seems to suggest that dose and duration of exposure may influence the susceptibility of the host (Godal, 1978b).

In the strict sense of the word, *risk of exposure* represents no aetiological factor. Still, risk of exposure should be taken into account in epidemiological analyses of leprosy. However, to separate quantitative aspects related to the agent from risk of exposure is often difficult. Furthermore, factors which are often considered as environmental, may also be related to risk of exposure; e.g. sociological patterns of males and females.

Probably, most of the different types of factor mentioned may be relevant to the aetiology of leprosy. Accordingly, the task of the epidemiologist is not to pinpoint the one of all the possible factors that is effective and exclude all the others. Although perhaps impossible at the present stage, his task should be to assess the relative importance of the different factors in an attempt to form a basis for prevention of the disease.

4.2. Interpretations and inferences

4.2.1. GEOGRAPHICAL DISTRIBUTION

Striking geographical differences in morbidity rates were observed in Norway. In areas with approximately one half of the population, the disease was almost unknown, while in the rest of the country, leprosy represented a serious public health problem.

Communications

This finding might be related to different risks of exposure due to geographical differences in patterns of *communication*. During the observation period the majority of the traffic was by ship; water represented traffic arteries while inland and mountains represented barriers. Probably, passenger traffic was far more extensive in districts with high rates, i.e. in districts near the sea (Table 13). This was particularly important for the population occupied in the *fisheries* of West and North Norway. The finding of relatively numerous cases in health districts of the low frequency areas near the county with the highest rates, is consistent with a higher risk of exposure. The overland traffic occurring between high and low frequency areas, passed through these districts.

Yet, patterns of traffic cannot explain the difference in rates between rural districts and towns, nor the fact that leprosy was almost unknown in East Norway, even in districts close to the sea.

Mycobacteria in the environment and tuberculosis

However, a hypothesis based on the finding of cultivable and non-cultivable mycobacteria in *sphagnum bog vegetation* in West Norway today (Kazda *et al.*, 1979) seems to be consistent with the geographical distribution of leprosy in Norway. The non-cultivable mycobacteria have still not been identified, but the hypothesis suggests an influence of these micro-organisms on the occurrence of leprosy, either as a pathogen or, more likely, as an additional factor perhaps influencing susceptibility. Growth of these mycobacteria is, among other factors, dependent on humidity and temperature (Kazda, 1979).

A high relative humidity, important both to growth of sphagnum vegetation and mycobacteria, is related to *regional conditions*, such as rainfall. It appears that the area in Norway with a mean relative humidity in the air in July higher than 75%, coincides, to a striking extent, with the area of the high frequency regions (Figs. 1 and 12, Table 16). The lack of association in Naustdal, the health district with the highest morbidity rates, between a farm's distance from the sea and the occurrence of leprosy at the farm was also in favour of the concept that the sea, *per se*, was of minor importance.

A high temperature, most important for the growth of mycobacteria, is mostly influenced by *local conditions* and may, independent to some extent of air temperature, rise to optimal levels in localities where accumulation of solar energy is possible; e.g. in localities where orientation and slope of the ground are favourable. Accordingly, an association, at *country level*, between air temperature and morbidity rates might not be expected; neither was this found. On the other hand, at the *local level*, an association was demonstrated between the occurrence of leprosy and conditions favouring a sufficiently high temperature in the vegetation, documented by the sphagnum index and also by the finding of a higher rate on the northern bank of the fjord, which in general is more exposed to the sun than the southern bank.

If the geographical distribution of leprosy in Norway were related to the finding of mycobacteria in the environment, most probably the mechanism would be that these micro-organisms interfere with the induction of protective immunity induced by *M. leprae* itself. This would be consistent with a hypothesis introduced by Stanford and his colleagues (Shield and Stanford, 1977; Godal, 1978b) who suggest that slow-growing mycobacteria may possess such a property of interference.

Besides, the importance in the epidemiology of leprosy of viable *M. leprae* outside the human body has recently been stressed, in part since *M. leprae* appears to be able to survive more than 1 week after excretion through nose blows (Desikan and Sreevatsa, 1978) in part since leprosy may represent an indigenous disease in wild armadillos (Walsh *et al.*, 1975; Skinsnes, 1976b).

In the discussion of the geographical distribution, the occurrence of *tuberculosis* in Norway should be briefly mentioned. The first reliable mortality rates of tuberculosis in Norway refer to the period 1881–85 (Backer, 1961). Of

Table 52. Annual mortality rates of tuberculosis 1881–85 and incidence rates of leprosy 1881–90 per 100,000 in the counties of the high frequency areas. (Central Bureau of Statistics and The National Leprosy Registry of Norway)

County	Annual mortality rate of tuberculosis per 100,000 1881–85	Annual incidence rate of leprosy per 100,000 1881–90
Rogaland	510	0·9
Hordaland	300	4·9
Sogn & Fjordane	160	12·4
Møre & Romsdal	220	6·4
S. Trøndelag	330	6·7
N. Trøndelag	270	7·6
Nordland	220	10·8
Troms	210	3·3
Finnmark	270	3·3

all counties in Norway, Sogn & Fjordane, the county with the highest incidence rates of leprosy, had the lowest mortality rates of tuberculosis (Table 52). (It should be noted, however, that even in this county, mortality rates of tuberculosis were far higher than the highest incidence rates of leprosy registered in the county.) Furthermore, in the other counties where incidence rates of leprosy were high, mortality rates of tuberculosis were relatively low. If this association were involved in the aetiology of leprosy, the explanation might be that *M. tuberculosis* (as a fast-growing mycobacterium) induces protective immunity against leprosy, as BCG appears to do under special conditions (Godal, 1978b; Shield and Stanford, 1977). The hypothesis that leprosy and tuberculosis are inversely related, is not new and has been advocated by several authors (Chaussinand, 1948; Davey, 1975), though doubted by others due to lack of a clear negative correlation between rates of leprosy and tuberculosis in a number of countries studied (Newell, 1966). A discussion of the validity of these statistics is beyond the scope of this study. Yet, the hypothesis seems to be consistent with the epidemiological development of leprosy and tuberculosis in Norway, and also with the suggestion that mycobacteria, other than *M. leprae*, are relevant in the aetiology of leprosy.

The geographical distribution of leprosy in Norway differed considerably, not only from region to region, but also at county, health district-, village- and farm-level. Apparently, this represents a general feature of the epidemiology of the disease (Leiker, 1960; Doull, 1962; Newell, 1966; Bechelli and Martinez Dominguez, 1972; Lechat, 1973; Ratard and Bravo, 1978; among others). While the geographical distribution of leprosy in other parts of the world apparently exhibits the same gross features as in the present study, it is obviously impossible to say whether the distribution in these countries is influenced by the same

environmental variables. At this stage it should be stated that further research in the fields of immunology, bacteriology and epidemiology is necessary to enlarge upon the hypotheses on tuberculosis and other mycobacteria as additional factors, and to assess the relevance of these hypotheses to primary prevention.

Malnutrition

Apart from occurring particularly in localities at which conditions for growth in spagnum vegetation of mycobacteria were good, leprosy at the local level, was also associated with *production of food* at the farms. Lack of association with tax value seemed to indicate that nutritional aspects of the production were essential. On the other hand, a weaker association with production of potatoes than with production of milk and oats should not, without further consideration, be interpreted in favour of a specific protein-deficiency as a factor. The lack of association with production of potatoes may be due to a pattern of production in which potatoes apparently represented the basic product of much the same quantity per person at each farm, and oats represented the excess, particularly found at farms with a high production of food. On the other hand, the finding does not exclude the influence of a protein-deficiency, which has been advocated by several authors (Chandra, 1974; Skinsnes, 1976a).

Today, malnutrition in Norway may seem strange, and it may be doubted that this factor played any significant part in the aetiology of leprosy. However, nutritional conditions as well as living conditions in general were far from fair in Norway in the middle of the last century, particularly in parts of the country where leprosy was prevalent. This is stated not only by doctors travelling around the districts in search for aetiological clues (Hjort, 1871; Bidenkap, 1858; 1860; Hansen, 1874), but also by Eilert Sundt (e.g. 1869) in his pioneer sociological studies on living conditions in Norway.

Overcrowding

No association was demonstrated to exist between *overcrowding* and leprosy, even if the range of number of persons per house was considerable. This finding appears to be contrary to the associations found in Cordova (Doull *et al.*, 1936) and Talisay (Guinto and Rodriguez, 1941) in the Philippines, however, the associations reported were apprently not strong. (The results are not comparable).

Obviously, all persons living in a household together with an infectious patient, are exposed to *M. leprae*. However, it seems reasonable to assume that if close physical skin to skin contact, e.g. sharing a bed, is necessary for the transmission of the disease, overcrowding might represent an additional factor. On the other hand, if direct contact is not necessary, the disease may propagate to susceptible members in a family irrespective of overcrowding. Accordingly,

the findings agree with the hypothesis that nasal discharge with droplets represents a potent source of infection. Route of entry, however, cannot be clarified by the present material.

Genetic factors

In iteself the geographical distribution is compatible with a *genetic background*; high levels of inbreeding for instance, were frequent in Norway in the last century. However, genetic factors can certainly not be related to the extremely rapid decline of leprosy in Norway, occurring over 70 years.

4.2.2. DECLINE

The separate leprosy censuses of 1836 and 1845, together with time trends of morbidity and morality rates, appear to document that peak rates occurred at the middle of the century, though the disease had previously been endemic in the high frequency regions. Subsequently, a continuous and increasing decline was registered. This conspicuous decline has aroused justified attention in Norway and abroad (Lie, 1929; Doull, 1962; Davey, 1975; Skinsnes, 1975, among others); *justified* because this experience proves that leprosy, under certain conditions, may disappear from a population during a few generations, but also *challenging* because of evident implications for primary prevention.

Obviously, some of the possible additional factors already discussed, might have been relevant also to the rapid decline in morbidity rates.

Malnutrition

No doubt, the *nutritional* conditions in the high frequency regions greatly improved during the latter half of the 19th century, presumably rendering the population less susceptible to leprosy.

Mycobacteria in the environment and tuberculosis

The influence of possible *environmental mycobacteria* was probably reduced during the period because extensive new ground was cleared, increasing the distance from the farm houses to localities with favourable conditions for growth of mycobacteria. The risk of contact with such sources also diminished since the use of boots, even in summer, became more and more common, and since wells were used for provision of drinking water instead of brooks and bogs.

Morbidity rates of *tuberculosis* increased until beyond the turn of the century, and the increase was relatively high in the high frequency regions. Accordingly *M. tuberculosis* was more widespread in the population than previously, diminishing, according to the hypothesis, its susceptibility to leprosy.

Emigration

Emigration to the USA seemed to represent a special factor responsible for the rapid decline in morbidity rates. Emigration was particularly frequent in those counties, and in those age- and sex-groups, with particularly high incidence rates. In spite of this fact, and even though several patients with leprosy also emigrated, the disease never propagated in the USA (Aycock, 1940; Lie, 1938; Boeck, 1871; Holmboe, 1865; Washburn, 1950) presumably since new environmental conditions reduced the susceptibility of the emigrants.

Isolation

In the discussion of the effects of *isolation*, a concept relating to differences between *infection in the household* and *infection in the community* at large should be introduced. The concept, which has previously been applied in a most interesting and fruitful way by Doull and colleagues (1947), implies that the disease, both from an epidemiological and a preventive point of view, acts differently when it occurs in the household and in the community at large. The difference does not relate only to risk of exposure, but to the hypothesis that *dose and duration of exposure* represent an additional factor, influencing the susceptibility of the individual at risk. The hypothesis is supported by studies with the lymphocyte transformation test (Godal and Negassi, 1973) and with skin tests (Shield *et al.*, 1977).

Accordingly, it seems reasonable to infer that the removal from a household of all infectious patients, would greatly diminish the risk of the remaining persons, though infected, of contracting clinical disease. On the other hand, the removal of a patient from the community at large would, to a negligible extent, reduce the risk of the population, i.e. persons belonging to *other* households, of contracting clinical disease. As long as infectious patients remain in the community, susceptible individuals may be infected and contract the disease, even if the dose is low and the duration of exposure is short.

There is strong evidence which supports the assumption that leprosy may be transmitted in these two different ways; and relative attack rates have been calculated for groups consisting of persons in infected households and for groups without known exposure. (Guinto *et al.*, 1954; Rao *et al.*, 1975).

Thus, in an epidemiological situation characterized by a high relative importance of infection in the household, i.e. when a high number of households is affected and prevalence rates are high, isolation may cause a fall in subsequent incidence rates. However, when prevalence rates are low, and the relative importance of infection in the community is higher, due to a lower occurrence of infection in the household, the effects of isolation may be low. This is consistent with the results of the present study. Accordingly, physical isolation in Norway of infectious patients in special leprosy hospitals is considered an important cause of the initial decline in incidence rates during the observation period.

To state a level of prevalence, indicating in general under which conditions isolation may be effective, is not possible since prevalence should relate to infectious cases. Until now, doubt has been thrown on the assumption that all tuberculoid cases should be considered non-infectious (Godal *et al.*, 1974; Rao *et al.*, 1975) and for the Leprosy Registry it seems reasonable to believe that risk of infection applied also to other than type 1 cases (*vide* 4.2.4.). Furthermore, today only theoretical interest is attached to the question of such a prevalence level. As stated previously, there is no longer need for this measure in leprosy control.

However, the material may clarify a question of considerable practical importance for today. The present findings, as well as results of evaluation studies of 'chemical isolation' (Rasi *et al.*, 1975), are consistent with the concept that dose and duration of exposure play important parts in the aetiology of leprosy, by which a rationale for medical treatment as primary prevention is established. If a project of chemical isolation seems inefficient, the reason is probably not that the index cases have infected contacts before chemical isolation of the index cases is obtained; most likely they have. The reasons should be sought in problems relating to compliance or drug resistance, which today represent serious obstacles in leprosy control (Meade, 1977).

It is interesting to note that objections against the Norwegian control policy were already raised at an early stage, and not only based on humanitarian considerations. Hutchinson (1906), in defence of his fish-eating hypothesis, argued that the degree of isolation was too low (in fact underestimated by him) to influence incidence rates. If isolation was to affect transmission in the community at large, the argument might have been valid. However, it appeared that isolation was effective even when less than 50% of the cases were admitted to hospital.

Thus Skinsnes (1975) suggested, on the basis of experience from Hawaii, Taiwan and Hong Kong, that a similar effect may be expected when chemotherapeutic segregation is available, even to less than 50% of indigenous cases, in a community similar to the Norwegian, i.e. a community of rapidly rising standards of living.

On the basis of most elegant epidemiometric models, Lechat and colleagues (1977) doubted the efficiency of isolation. However, differences with respect to assumptions made on practice of isolation, and differences with respect to epidemiological conditions in Norway and India, where data for calculation of the parameters in the models were obtained, (Lechat, 1971, Lechat *et al.*, 1974) seem to impede further comparisons. Networks of contacts, for instance, are supposed to be more comprehensive and involving more persons in India than at remote farms in Norway, and this may influence the efficiency of isolation.

4.2.3. SEX, AGE AND TYPE

In the discussion of sex, age and type, further consequences of the concept of infection in the household and infection in the community will be outlined.

From a theoretical point of view *infection in the household* is associated with a low mean age at onset; the children are infected at an early age. The sex ratio is close to 100; risk of exposure is equal in males and females. Type index is high; dose and duration of exposure, probably important to host responses provoked and to the differentiation into types (Godal and Negassi, 1973; Shield and Stanford, 1977), are high. Infection in the household is relatively predominant when morbidity rates are high, as in the first part of the observation period in Norway and particularly in Naustdal.

Infection in the community is associated with a high age at onset due to a postponement of the time of infection. Sex ratio is dependent on sociological patterns. However, if males, due to work, have more extensive contacts outside the home than females, as in Norway in the last century, sex ratio will be high. Type index is low; dose and duration of exposure is low. Infection in the community is relatively predominant when morbidity rates are low, as in the last part of the observation period and particularly in the low frequency areas.

The present results indicated that mean age at onset, sex ratio and type index of new cases of leprosy in Norway, varied in accordance with the theoretical concept, as shown in the following.

Age-specific incidence rates

Apparently, the trend in age-specific incidence rates with a peak in young adults (Fig. 16), is in part due to varying lengths of the incubation period, e.g. age at onset is postponed in type 1 patients because the incubation period appears to be longer (Feldman, 1973; Godal *et al.*, 1974). Thus, only patients with a short incubation period will be registered in the youngest age group. Later, patients with both short and long incubation periods will be registered.

In part the trend is influenced by different risks of exposure in different age groups.

Accordingly, the low incidence rates in the age group 0–14 years represent (mostly benign) cases infected in their households, while the higher rates between 15 and 50 years of age represent in part (malignant) cases infected in their households, in part cases infected in the community. The lower rates in the age group over 50 years are most probably due to a lower risk of exposure, and particularly since the rate in the females is lower than the rate in males. However, in part the result may be caused by the relatively low frequency of patients with extraordinarily long incubation periods.

An interesting interpretation by Bechelli and colleagues (1973), who suggest that the lower prevalence rates in high age groups are due to the possibility that persons who may have had incubating infections, do not live long enough to present signs of the disease, is hardly tenable. Obviously, *number of cases* may be reduced due to this reason, but if the mortality rates during incubation are no higher than in the general population, the *incidence rates* are not influenced. However, provided mortality rates of leprosy patients increase more by

age than those of the total population, *prevalence* rates will be further diminished, as observed by Bechelli and colleagues.

Age-specific incidence rates and level of incidence

The trend in age-specific incidence rates and mean age at onset by average incidence rate (Table 38, Table 39, Fig. 33) with a low mean age at onset in high rate areas and vice versa, may, according to the concept, be related to increased exposure in young age groups when the incidence rates are high, i.e. in the household. The trend might have been even more marked if infection in the household was not associated with a high relative frequency of malignant cases with long incubation periods.

Age-specific incidence rates according to year of onset and year of birth

Different trends are found in age-specific incidence rates and mean age at onset by calendar year, dependent on whether tabulations are based on year of onset or year of birth (Figs. 19–24).

According to Sartwell (1950) the frequency curve of incubation time in general takes the form of a logarithmic normal curve. This appears to be equally true of diseases with very short and very long incubation periods. Thus, leprosy cases with extremely long incubation periods, e.g. 20–30 years, exist, but they are infrequent compared with total number of cases *infected* at the same time. However, towards the end of the observation period in Norway, when incidence rates were low, patients with a long incubation period, infected when the rates were far higher, were more frequent compared with the other patients *taken ill* at the same time, i.e. at the end of the observation period. Accordingly, mean age at onset increased by calendar year of onset. However, registered during a period with an increasing relative importance of infection in the community, the trend was most probably also due, to some extent, to the postponement of time of infection to a higher age group.

The opposite trend, registered in consecutive birth cohorts has also been demonstrated in other leprosy materials (Feldman and Sturdivant, 1975). The trend is attributable to the fact that the first period of life in each cohort, due to the rapid fall in morbidity rates, to an ever increasing extent, is the period with the highest risk of exposure. This finding implies that also adults may be infected and subsequently taken ill. Accordingly, trends in age-specific incidence rates are not only influenced by the lengths of incubation periods. However, postponement of infection to a higher age group towards the end of the observation period did not represent a characteristic feature. A decreasing age at onset in consecutive birth cohorts will always occur when aetiological factors are removed from a population, due to a younger age of infection. Analyses of mortality rates of tuberculosis in Norway have given similar results (Backer, 1961).

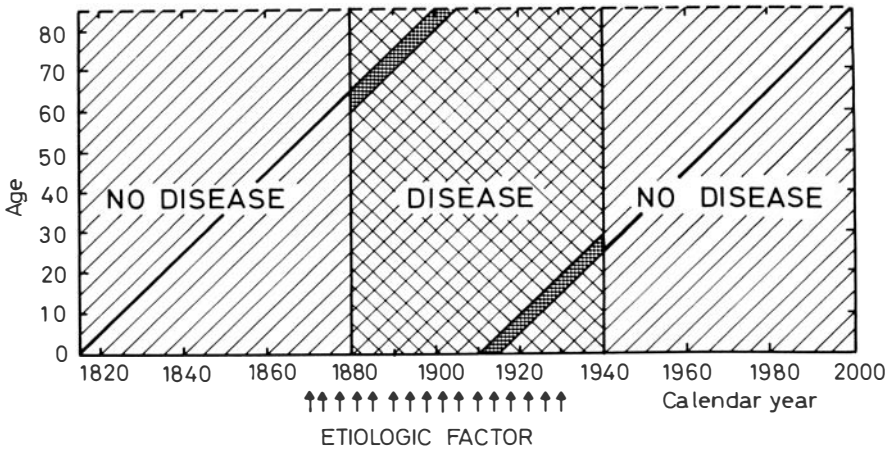

Figure 35. Lexis' table modified for illustration, in a simplified way, of the occurrence in consecutive birth cohorts of a disease by age, according to the time at which the cohorts were influenced by an aetiological factor.

On the other hand, when aetiological factors are introduced into a population, the first birth cohorts will inevitably consist of elderly patients (Fig. 35).[1]

Sex-specific incidence rates

The trend in sex ratio by age (Fig. 17), with a peak in the age group 30–49 years, may be related to increased risk of exposure in adult males. In addition to risk of exposure in the household, adult males bear a higher risk than females of being infected in the community due to work outside the household. The trend in sex ratio by time (Fig. 15), with an increase during the observation period, is consistent with a higher relative importance of infection in the community towards the end of the observation period. The trend in sex ratio by average incidence rate (Table 38, Table 39), with a low ratio in high-rate areas and vice versa, is also consistent with the concept.

Type index

The trend in type index by age and sex (Fig. 27), with a relatively low-type index in the age group 0–9 years and a higher index in the group 10–14 years, and with no difference between males and females, is apparently related to children infected during the first years after birth, indicating a longer incubation

[1] The figure shows courses of life, i.e. diagonals, between 0 and 85 years for cohorts born between 1815 and 1915. In this simplified example, aetiological factors influenced the population from 1870 to 1930. With a mean incubation period of 10 years, persons might be taken ill from before 1880 to after 1940. The oldest cohort, born 1816–20, would be affected only over the age of 60 years, while the cohort born 1911–15 would be affected only under the age of 30.

period in type 1 cases. A high-type index in males 20–39 years (and in females 20–24 years), and a lower-type index in females than in males in the age group 25–59 years, may be related to the fact that vocational contacts, primarily of males, outside the household were more close and prolonged than non-vocational contacts, in particular because of the fisheries during which many men, and especially men from the high frequency regions, lived together in small shanties for longer periods. These contacts might involve a dose of exposure even as high as in a common household. The lower index in the age group 50+ in both males and females, refers to the patients who, though relatively few, were after all taken ill at a late age, probably infected with a low dose and a short duration in the community, but not due to vocational contacts.

The *increase* in type index in all age groups towards the end of the observation period in males (Fig. 29) might be caused by the fact that when incidence rates are rapidly declining, patients with long incubation periods (and accordingly more malignant types of the disease), will be more and more frequent in all age groups. The increasing sex ratio in the age group 50+ towards the end of the observation period (Fig. 18) might be related to the increasing relative importance of vocational contacts. At the end of the observation period, males infected through such contacts would have a higher age at onset due to the longer incubation period.

However, the opposite trend, involving a *decrease* in type index towards the end of the observation period, caused by an increasing relative importance of infection in the community, might counteract the effect of prolonged incubation periods. This might relate to the trend in type index observed in females, with a decrease in type index towards the end of the observation period particularly in the age groups over 30 years (Fig. 29). However, why males and females were affected in different ways is not obvious. Apparently, there is no indication that female contacts with the community at large increased considerably towards the end of the observation period. The influence of other factors related to a decreasing susceptibility, cannot be excluded.

Bias in the registration

Possibilities of *bias* in the registration have been discussed previously (*vide* 2.3.4.). However, on the basis of the results, the problem may be further enlarged upon. It seems reasonable to suppose that in areas and periods in which the disease occurred infrequently, the risk of under-registration could not be neglected. Thus a high mean age at onset and a high sex ratio registered in areas where average incidence rates were low, and registered towards the end of the observation period, might be caused by under-registration, since women in general and men below the age of 20 were generally less known to the public and might hide away in the home. (A high age at onset might also be caused by delay in the registration work under the same conditions, though this possibility

has already been disproved). However, this was not consistent with the finding of a low-type index in areas with low average incidence rates; i.e. in these areas the less conspicuous type of leprosy was more frequent. Thus, there appears to be no reason to believe that the other trends are due to biased registration. Furthermore, the peculiar finding of a lower-type index in females towards the end of the observation period cannot be explained as due to such a bias in registration.

Predictions of incidence rates

The associations demonstrated to exist in the present material between the measures: sex ratio, mean age at onset and type index of patients registered in a period on the one hand, and incidence rates in the same period on the other, proved to be sufficiently strong to form a basis for prediction, with reasonable validity, of incidence rates and even time trend in incidence rates. The associations of mean age at onset with the dependent variables, were far higher than the associations of sex ratio and type index. A high association between an increasing mean age at onset and a decreasing incidence rate will most likely occur irrespective of time and place. A similar trend has been recognized in other countries (Kim, 1979; Saikawa, 1975; Kyaw Lwin and Zuiderhock, 1975), and also in other chronic infectious diseases such as tuberculosis (Backer, 1961). The trend is mainly due to the increasing relative predominance of long incubation periods; irrespective of other conditions.

However, for the other independent variables, different values of the coefficients will probably be found in other materials, possibly due to different epidemiological conditions; (Kinnear Brown, 1959) e.g. socio-economic or environmental patterns.

Features in other countries

To find, through the interpretation of epidemiological data, general patterns in the distribution of leprosy patients according to sex, age and type in other countries, represents a difficult task. In part, different methodological approaches make comparisons even of trends impossible (Meade, 1971), in part different epidemiological conditions overshadow common features.

In the Philippines, a country with most reliable epidemiological data on leprosy, Doull (1962) has reported trends which appear to be similar to those discussed in the present study. Attack rates were low in young and old age groups, however, highest rates being found at somewhat earlier age than in Norway, viz. 10–14 years against 15–29 years in Norway. Male and female prevalence rates (Doull *et al.*, 1936) by age depicted a trend similar to that found in Norway, with no male excess in the young age group, and a male excess particularly in the age group 30–49 years. In the Philippines, incidence rates of tuberculoid leprosy exceeded rates of lepromatous leprosy in all age

groups; accordingly, type index was far lower than in Norway. The lower-type index with shorter incubation periods, was probably one reason why mean age at onset was lower in the Philippines. Type index had a peak in the age group 15–29 years, as in Norway. Furthermore, it was demonstrated that patients of exposed households had a lower mean age at onset than patients of households which were not known to have been exposed.

Similar trends were found in studies in Burma (Bechelli *et al.*, 1973), and in the New Hebrides (Ratard and Bravo, 1978). In addition, prevalence data in Burma and incidence data in the New Hebrides, together with prevalence data (Rao *et al.*, 1972a) and clinical data (Sehgal *et al.*, 1977) in India, demonstrated that type index in adult males, to a varying extent, exceeded type index in adult females.

In Nigeria, Davey (1957) made an observation of particular interest. In a community where females did not lead secluded lives, a sex ratio near 100 was found, indicating a relationship between sociological features and risk of exposure. A similar finding was reported by Browne (1965).

Apparently, a statement by Newell (1966) has made a great impact on subsequent research. Prevalence rates of lepromatous leprosy, Newell asserted, are never observed to exceed 5–10 per 1,000. On this basis, the causation of lepromatous leprosy was related to a host determined characteristic possessed by a fixed proportion of all people everywhere. The basis of this inference is hardly compatible with the present findings. In several health districts in Norway with high morbidity rates, type-1 prevalence rates exceeded 10 per 1,000. Similar observations were made by Bechelli and Martinez Dominguez (1972).

As demonstrated by Godal (1978a), Newell's statement was based on a heterogeneous epidemiological situation in which differences in incubation period between lepromatous and non-lepromatous cases apparently were not taken into consideration. Obviously, susceptibility of the host, in addition to dose and duration of exposure, may influence the clinical course of the disease and the differentiation into type. However, that this host determined characteristic should be possessed by a fixed proportion of the population everywhere, seems unlikely. On the contrary, the distribution of possible additional factors influencing susceptibility, e.g. malnutrition, most probably involves considerable geographical differences, consistent with the great differences observed in the occurrence of leprosy between different regions.

Thus, most of the findings in Norway as elsewhere, seem to be consistent with the concept of differences relating to infection in the household and infection in the community, implying a higher total incidence and type index when dose and duration of exposure is high and a longer incubation period in lepromatous cases. Thus, most of the differences observed in the distribution of cases according to sex, age and type seem to be caused by different risks of exposure and not necessarily by inherent differences in susceptibility (see also Kinnear Brown, 1959; Doull, 1962; Davey, 1957; Newell, 1966; among others).

Compared with other countries, sex ratio was relatively low and type index was high in Norway. The proportion of type 1 cases (the lepromatous index conventionally calculated) registered in Norway during the observation period amounted to 53·8%, and number of male cases per 100 female cases was 139·4. This is supposed to be due to the assumption that the relative importance of infection in the household was greater in Norway than in most other countries, in part since traffic in Norway has always been hindered by a rugged landscape, in part since density of the population was low, and in part since the scattered population, even at the local level, did not live clustered in villages as in other parts of the world; the farm houses were separated by relatively long distances.

Movements in the diagnostic spectrum

Movements in the diagnostic spectrum were consistent with trends which are considered general principles of such movements (Godal, 1978a). Type 2 patients moved far more frequently than patients belonging to the two polar types. Furthermore, these type 2 patients tended to move towards the lepromatous end of the spectrum more than towards the tuberculoid end; 62·1% and 37·9% respectively. However, the trend in movements towards type 1 did not exceed the relative proportion of all type-1 cases compared with all type-3 cases. Movements from the polar types occurred almost as frequently in type 1 as in type 3; however, movements towards the intermediate type 2 were far more frequent than movements towards the other polar type.

A high frequency of movements from type 2 might, in accordance with the general principles, be due to a more unstable character of the intermediate type. However, the trend might also be caused by the instructions of the Chief Medical Officer to avoid the classification of a case as type 2 (*vide* 2.5.3.). However, such an interpretation seems less likely because of the extensive use of type 2 also in the description of movements in the diagnostic spectrum.

4.2.4. OCCURRENCE IN FAMILIES

Incidence rates of persons living in households together with an index case are higher than rates of persons not known to be so exposed. Without doubt this observation is due to differences in dose and duration of exposure. In addition, differences with respect to susceptibility may play an important part. Susceptibility may relate to environmental or genetic factors. However, people living together in a household usually share a common background of genetic and environmental factors, which has represented a major problem to the epidemiological approach of studying susceptibility in families. The avoidance of this problem was attempted in the present study.

Present findings

In all categories of families in the present study except marriages, the distribution of cases with respect to type differed from expected frequencies, and the distances between the members of each family were shorter than expected, implying concordance. Furthermore, type index increased with number of patients per family. However, these findings might be due to environmental or genetic additional factors.

On the other hand, in sibships in which age at onset of one or more patients exceeded 30 years, type index did not increase with number of patients per sibship; and more importantly, distribution of cases with respect to type did not differ from expected frequencies (Table 34). In general, it may be assumed that old sibships in many ways are mutually more different than young sibships, and possible differences present in old sibships, but not in young ones, are considered to be due to environmental rather than genetic factors. Thus, a high degree of concordance with respect to type, found in young sibships and not in old ones, indicates an effect of environmental factors. Obviously, however, it should be stated that this finding does not preclude other effects of possible genetic factors.

The finding of a higher type index in children of sick mothers than in children of sick fathers (Table 35) is consistent with a higher dose of exposure when mother was ill. In such cases it appeared that children contracted type 1 irrespective of the type of disease in the mother, implying a considerable infectiousness also of non-lepromatous cases. However, a father with type 1 apparently represented a dose of infection sufficient to produce type 1 cases.

Degree of concordance within sibships consisting of sick children and between sick children and their sick parent was higher in families where father was affected compared with families in which mother was affected. Presumably sick mothers, irrespective of their own type of leprosy and also of the relative susceptibility of their children, would tend to propagate type 1 to their children. The result would be that sibships with a high susceptibility would react homogeneously and develop type 1, while sibships with a low susceptibility would react heterogeneously, and degree of concordance, mutually and with mother, would be low if present at all. This interpretation is consistent with the concept that susceptibility is not *only* dependent on dose and duration of exposure.

Number of affected children per marriage was higher for affected mothers than for affected fathers, and in particular for parents affected with type 1. Without doubt, this might be caused by a higher dose of infection represented by sick mothers. However, probably total number of children (patients and non-patients) was dependent on whether father or mother had leprosy. Childless marriages in Norway were more frequent if the husband was affected and particularly with type 1, than if the wife was affected (Lie, 1911). Apparently, male fertility is severely impaired in untreated leprosy (Davey and Schenck,

1964). Thus, total number of children in families with a sick father might have been lower. This is also consistent with the finding that fathers with a higher dose of exposure, represented by fathers affected by type 1, did not have more sick children than fathers affected by type 2 and type 3.

In pairs of spouses, type index was higher in the second-cases than in the first-cases. Three causes seem obvious. First, if a person already affected with leprosy was to marry a healthy person, the patient most probably was affected with type 3, the most benign form. Secondly, if two spouses were infected at the same time, and one spouse was taken ill a considerable time before the other, the second-case would tend to be of type 1 and the first-case would tend to be of either type 2 or type 3. Thirdly, a spouse infected by the other spouse, would have a relatively high dose and long duration of exposure and would, accordingly, tend to develop type 1.

On the other hand, the finding of a low type index in the first-cases suggests that type-3 cases were also infectious. If not, type index in the first-cases would have been far higher than type index in the second-cases. Nothing beyond speculation may be offered to explain the peculiar high type index in spouses with contemporary onset of leprosy.

Thus it may be concluded that type index in families is influenced according to the hypothesis of dose and duration of exposure. Furthermore, dependence within families with respect to type of leprosy, i.e. concordance, seems to be related to susceptibility influenced by an environmental factor of uncertain duration, apparently not present in sibships with age at onset higher than 30 years and in spouses. Probably, individuals in the first group had lived apart from each other too long, and individuals in the latter had lived together too short a time to be influenced by this factor. Obviously, the hypothesis of an influence of genetic factors is not disproved by the present findings; however, such a hypothesis is not supported either.

Other studies

Major methodological problems are involved in the studies of the occurrence of leprosy in families (Lechat, 1965). Up to the present time the part played by genetic factors in the aetiology of leprosy appears obscure (Godal, 1978a; White *et al.*, 1978). Conclusions based on studies of the major histocompatibility complex seem inconsistent (Rea *et al.*, 1976; de Vries *et al.*, 1976; Fine *et al.*, 1978). The difference in degree of concordance observed between monozygous twins and dizygous twins (Chakravartti and Vogel, 1973) does not appear significant. Associations demonstrated to exist between chronic subclinical hepatitis and lepromatous leprosy have been supposed to be due to a genetic factor, since chronic subclinical hepatitis appears to be related to the socalled Au-gene. (Blumberg *et al.*, 1970). However, conclusive evidence to support the hypothesis is lacking. On the contrary, in a study in Uganda, comprising more than 20,000 children, no evidence was found that the incidence of

leprosy varied according to a child's genetic relationship to a leprosy patient, once allowance had been made for the degree of physical contact (White *et al.*, 1978).

Secondary attack rates among spouses are found to be under 10% in most studies (Mohammed Ali, 1965; Newell, 1966). Sand (1910) found a rate of 3·3% among patients at a leprosy hospital in North Norway, and Lie (1911) found a rate of 5% among hospital patients in West Norway. Observations of the occurrence of leprosy among spouses, claimed to be influenced by genetic factors (Mohammed Ali, 1965), may just as well be related to environmental factors.

Apparently no findings in the abundant literature preclude the suggestions that the occurrence of leprosy in families is influenced in part by the high dose and duration of exposure, and in part by a susceptibility related to environmental factors.

4.3. Concluding remarks

Risk of exposure, apparently, plays an important part in the distribution of leprosy. Higher incidence rates in adult males than in adult females, and higher incidence rates in young adults than in elderly people and children, are attributable to differences in risk of exposure. Accordingly, the supposition of an inherent susceptibility in special age- and sex-groups seems unnecessary to explain differences in age- and sex-specific incidence rates. It should be emphasized that not only children but also adults and elderly people may be infected and taken ill if exposed.

The geographical distribution of leprosy in Norway, at regional level, seemed to be related to *patterns of communication*. Moreover, differences between the regions in air humidity, an important condition for *growth of mycobacteria in the environment*, seemed to correspond with differences between regions in the occurrence of leprosy. Also at local farm level, the distribution appeared to be related to conditions for growth of mycobacteria. Several species of cultivable mycobacteria, but also unidentified non-cultivable mycobacteria, were found in local bogs in a formerly top-prevalence health district. Furthermore, the distribution of leprosy within this district was associated with local conditions for growth of mycobacteria in the sphagnum bog vegetation. However, it is most important to state that validation of this hypothesis, and clarification of its theoretical and practical implications, should be based on further studies in areas where leprosy is prevalent today.

At a local level, the distribution of leprosy was also associated with *malnutrition*, while overcrowding apparently represented no significant additional factor.

Also in families, the occurrence of leprosy seemed to be related to *dose and*

duration of exposure, causing a high-type index in families with several patients. Concordance with respect to type might be explained as being due to environmental factors influencing susceptibility. The findings did not imply the influence of genetic factors.

The rapid decline in incidence rates over 70 years seemed hardly attributable to genetic mechanisms. It appeared that *physical isolation* of infectious patients in leprosy hospitals in high prevalence situations represented an important cause of the decline. Probably isolation was particularly efficient when the relative importance of infection in the household was high; i.e. when prevalence rates were high. When the relative importance of infection in the community at large was high, i.e. when prevalence rates were low, isolation was probably less efficient. Improved *nutritional conditions* and *selective emigration* of high-risk groups represented other important causes of the decline.

Even though isolation obviously is not a relevant control measure today, the rapid decline together with the considerable geographical variation in incidence rates, also observed in other countries, form in part the basis of *future leprosy control*. In large areas it may be assumed that improved nutrition will most probably reduce susceptibility for a considerable proportion of the population. At the present stage, no more than speculations can be offered about practical implications of the finding of non-cultivable mycobacteria outside the human body. However, the importance of further research to assess the relevance of these findings to the epidemiology of leprosy and to leprosy control seems evident. The development of an efficient vaccine will, if feasible (Godal, 1978b), no doubt offer an important control measure (Lechat, 1978). However, in a comprehensive control programme, a possible vaccine should be applied, taking all relevant aspects of primary prevention into consideration.

Irrespective of the approach used in primary prevention, leprosy control should be based on reliable information as to level of morbidity rates and time trends, i.e. preferably incidence rates. However, in many areas, incidence rates are still difficult to obtain, and to the extent that associations in such areas exist between incidence rates and trends in incidence on one hand, and characteristics of the patients registered on the other, *indices*, used as substitutes for incidence rates, may be employed.