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ORIGINAL ARTICLES

DIAGNOSIS AND MANAGEMENT OF REACTIONS IN LEPROSY

By

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INTRODUCTION

The existence of the M. Leprae which propagated in security in the human for some seven thousand years is now, in the 20th century, seriously threatened by the challenge of the Sulphones.

The onslaught of the Sulphones on the M. Leprae, however, sometimes precipitates or enhances the disturbances which normally occur in the reluctant human host engaged in a death struggle with the M. Leprae. These disturbances are known as Reactions and as they are serious enough to necessitate a withdrawal of the Sulphones, the very basis of modern treatment is shaken to its foundations. Reactions in Leprosy have, therefore, to be considered with some circumspection and measures to deal with them have to be devised with care.

There seems to be some confusion in the literature with regard to some of the Reactions. Even the terms applied to them appear to be ambiguous. Cochrane (1959a) states that Erythema Nodosum Leprosum (ENL) has variously been described as 'Rose spot nodules', 'Panniculitis nodosa', 'Acute Lepra Reaction' (ALR), etc. and is of the opinion that ENL may co-exist with Progressive Lepra Reaction (PLR). Ridley (1960a) states that ENL has not always been distinguishad from ALR. Wolcott (1947a) as far back as 1947 considered ENL and Lepra Reaction (LR) distinct from each other but was of the opinion that they do not co-exist. With regard to their prognosis also there appears to be no unanimity of thought. Wolcott (1947b), Muir (1951), Erikson (1957), Rodriguez (1957), Souze Lima 1957) and Cochrane (1959b) consider ENL a favourable sign. Davison (1957), Yosshinobu (1957), Chaussinand (1957), Susman (1958) and Ridley (1960b), on the other hand, maintain that ENL is of bad prognostic significance.

Under these circumstances it becomes necessary to delve into the origin of Reactions. Reactions are, however, a part of the varied manifestations of Leprosy

lesions. Hence the prerequisite for the understanding of Reactions and their management is the understanding of the genesis of the varied manifestations of Leprosy lesions and their progression.

GENESIS OF THE VARIED MANIFESTATIONS OF LESIONS

The progression of Leprosy from the primary lesion to a large number of lesions with deformities extends over 20 years in some and 10 years in others. In others still it may be as short as 5 years. The progression of lesions is thus slow, moderate and fast. To explain this variation in progression of lesions a factor generally known as 'Resistance' has to be postulated.

This Resistance has not yet been defined. Antibodies till to-date have not been discovered (Khanolkar, 1961), and these especially serum gamma-globulins are increased in the least resistant variety viz. Lepromatous type, contrary to expectation (Cochrane, 1959c). Further, it is not yet possible to define the existence of resistance in any given individual. The Lepromin test, though considered to be an indicator of resistance by some, is believed to be merely a sensitization reaction by others (Figueredo & Martins, 1959).

Whatever this factor may be, it is logical to assume that it is highest in those patients in whom the disease progresses slowly, moderate in those in whom the disease is not so slow and lowest in those in whom the disease advances very fast. The Resistance is also correlated with the number of bacilli in inverse proportion. Thus Lepsosy divided into 3 main Groups :—

(1) Tuberculoid – the most resistant with few bacilli,

(2) Intermediate – the less resistant with moderate number of bacilli and

(3) Lepromatous – the least resistant with the largest number of bacilli.

One would expect dissimilarities in the lesions exhibited by the 3 groups in relation to resistance and this is so. But there are dissimilarities also in the lesions displayed by the patients within each group in correlation to the gradations of resistance of individuals within each of the three groups. These sub-variations within each group are termed 'Types'.

The Groups and Types are :—

(1) Tuberculoid Group :—

Tuberculoid Major (TM), Tuberculoid Minor (Tm), Maculo-anaesthetic (MA) & Primary Polyneuritic (PP).

(2) Intermediate Group :—
Indeterminate (I), Reactional Tuberculoid (RT) & Borderline (B) or Dimorphous.

(3) Lepromatous Group :—
Early (L1), Moderately Advanced (L2) & Advanced (L3).

PROGRESSION OF LESIONS

(a) *Slow Progression :* Lesions of all types whether flat (MA, I, L1) or raised (T, RT, B, L2) gradually increase in size and number and reach the last stage of deformities or disfigurement without any sudden systemic disturbances or sudden change in the characteristic appearance of the lesions.

(b) *Activation :* In some cases the slow progression may be marked by distinctive features. Flat lesions may become erythematous partly or wholly. Raised lesions may increase in height and become erythematous partly or wholly, or erythema, if present, may increase in intensity.

(a) *Transformation* : Activation may result in a 'change in type'. Thus the flat lesions of MA type may become raised and acquire the characteristics of TM. By a similar change flat lesions of the I type, may change to RT or B. As the transformation is a slow process it is not uncommon to observe flat and raised lesions in the same individual in various stages of transformation.

(d) *Reaction* : In some cases the activation is accelerated suddenly and may be accompanied by systemic disturbances like fever, joint and nerve pains, swelling of hands and feet, and development of new lesions in a few days. This type of activation is termed 'Reaction'.

Since the resistance varies in an individual from time to time, it is logical to assume that a gradual lowering of resistance will lead to slow progression, a sudden but slight lowering of Resistance will lead to Activation or Transformation, and a sudden and severe lowering of Resistance will lead to Reaction.

AETIOLOGY OF REACTIONS

Though the cause of reactions has not yet been defined, certain factors are known to precipitate Reactions probably by lowering the Resistance of the patient. They are :—

(a) *Diseases* :— Like Typhoid, Malaria, Dysentery, Ankylostomiasis, Influenza.

(b) *Conditions* :— Diet - deficient, excessive or unbalanced. Climatic changes - excessive heat or cold. Mental distress - caused by social stigma, Anxiety neurosis.

Small-pox Vaccination, Late months of pregnancy and child-birth.

(c) *Drugs* :—Sulphonamides, Sulpur derivatives and Iodides. Iodides in small doses, even when contained in expectorant mixtures and antidysenteric drugs can bring about a Reaction.

The exact mechanism of the lowering of the resistance by these factors is a moot point. Muir (1962a) has recently advanced the view that the General Adaptation Syndrome of Selye operates as the basic cause of Reactions.

In most cases the reaction subsides when the precipitating factor is removed. In others, however, it recurs a number of times despite the removal of the factor. Such persons have been observed to have or develop undue susceptibility to a number of precipitating factors and hence exist subsequently in a more or less 'Reactive state'. In these cases it is not unlikely that their Resistance is lowered to such a low level initially that recovery unaided is not possible. This has been described as the 'Stage of Exhaustion' by Muir (1962b).

CLINICAL DESCRIPTION

Reactions occur in all the three Groups.

I. *Reactions in the Tuberculoid group*:– Reactions in this group are infrequent and are limited to TM type, when the term 'Tuberculoid in Reaction' is applied to them to distinguish them from the Reactions in the RT. The Reaction consists of sudden increase in thickness and erythema of the existing lesions. New raised lesions which may simulate nodules appear in a short time. The bacteriological status remains unchanged even during the reaction. Systemic disturbances are slight. Low fever may be present and joint and nerve pains.

II. *Reactions in the Intermediate group*:– These are confined to RT. As the term implies, the individual is in a more or less Reactive state. The systemic disturbances are more marked than in Tuberculoid in Reaction. The bacilli increase in number with each successive reaction leading ultimately to Transformation through B to the L group.

III. *Reactions in the Lepromatous group*:– In this group three types of Reactions can be recognised: (a) ALR, (b) PLR & (c) ENL.

(a) *ALR*:– This consists of sudden exacerbation of existing lesions and formation of new ones, even nodules, accompanied by fever, which may be of the hectic type. Nerve and joint pains with swelling and oedema of hands and feet are common features. Iritis, iridocyclitis, lymphadenopathy and orchitis can occur. Paresis and contractures in hands and feet, and bony deformities occur after repeated and untreated attacks. A reaction, when untreated, has a tendency to recur at short intervals. It has a very steady course and may last from a week to a month. Repeated reactions may lead to PLR.

(b) *PLR* :– In PLR the reactions are very frequent. In fact new lesions and nodules appear when the previous reaction has only partially subsided. All the signs and symptoms of ALR are intensified and, in addition, subcutaneous nodules develop and may ulcerate. Oedema of glottis may occur at this stage sometimes requiring tracheotomy for acute respiratory distress. Chronic refractory diarrhoea may set in in the late stages and marked emaciation and exhaustion supervene. Death may occur from exhaustion, inanition, intercurrent infections like pneumonia or tuberculosis, and amyloid disease (though the last named condition is rare in Bombay – Khanolkar, 1959).

(c) *ENL* :—The term 'rose spot nodules' aptly describes this reaction. The lesions are few in number when subacute. They are discrete and become dark purple or brown on subsidence and then dessquamate.

While some of them are subsiding, a few, new bright red or pink lesions may appear and may undergo similar changes as the old ones. This particular feature is pathognomonic of ENL. Systemic changes like fever, malaise, joint and nerve pains are present in varying degrees but are not as severe as those found in ALR. Repeated attacks of ENL, if untreated, may give rise to ALR with which it can co-exist. Usually ENL is not associated with severe complications like iritis. neuritis and orchitis, unless ALR co-exists. With the introduction of the Sulphones ENL is frequently met with and is the most important complication that requires treatment. When ENL co-exists with ALR, the patient, in addittion to systemic disturbances and complications, exhibits a few rose spot nodules, which come and go.

MANAGEMENT OF REACTIONS

Since a variety of diseases act as precipitators of reactions, specific drugs for the precipitating diseases will control reactions in the majority of cases. This is the reason why a variety of 'specifics' for reactions ranging from Antimalarials on the one hand to antihistaminics on the other have and are being recommended. Obviously none of them can give unequivocal results in all cases. Antimalarials are recommended by Ramanujan, (1960), Merklen and Riou (1960), Ramu (1960) (Chloroquin); and by Casals (1958), Thangaraj (1959) (Camoquin). Antibiotics reported to produce good results are: Streptomycin (Sasnz, 1952; Cochrane, 1959d), and Chloremphenicol (Majumdar, 1961). Other drugs found useful are Colchicoside (Floch, 1954); Butazolidin and Irgapyrine (Melamed & Janquieres, 1956). This is reminiscent of the pre-antibiotic and pre-chemotherapeutic era when treatment of diseases like typhoid and pneumonia consisted of a similar array of drugs, apparently unrelated to one another, and used because of lack of specifics for the diseases.

As the sulphones are specific for leprosy, the precipitation of reactions by the specific seems to be an anomaly. This leads to the conclusion that either the the sulphones leave much to be desired or their induction into the human body has not been placed on a standardised basis.

Under these circumstances the treatment of reactions has perforce to be on the lines of the treatment of diseases and conditions current in the pre-antibiotic and pre-chemotherapeutic era.

The following management of reactions is that which has been found to be suitable after experience over a number of years at the Clinic of the Acworth Leprosy Home.

(a) *Discontinuation of DDS* :- DDS should be stopped and substituted by Diphenyl thiourea (DPT)* with a commencing daily dose of O. 5 G. for 6 days per week for 2 to 3 months and increasing cautiously to 1. O G. daily. This dose should be continued for 6 months to a year and then, as the patient's condition permits, DDS should be reintroduced though now in very small doses e. g. 10 mg. twice a week, and gradually increased. When a maximum of 600 mg. per week is reached, DPT can be withdrawn. DPT itself may cause reactions, usually mild, which subside in the majority of cases on continuation of the drug.

In case DPT is not available, DDS can be subsituted by less toxic sulphones like Promin or Sulphetrone.

Promin:- 1 G. I. V. twice a week for 2 months, 1 G. thrice a week for another 2 months increasing gradually till a maximum of 2 G. per day for 6 days per week is reached.

Sulphetrone:- $\frac{1}{2}$ ml. of 50% solution deep I. M. twice a week for 2 months, 1 ml. twice a week for another 2 to 3 months, increasing gradually till a maximum of 3 ml. twice a week is reached.

* S U 1906 was supplied by Ciba for trials.

In either case the maximum should be given for a period of 12 to 18 months, after which DDS in small doses should cautiously be reintroduced as in the case of DPT, and parenteral sulphones withdrawn.

(b) Usual treatment of the disease or condition precipitating the reaction, when known, should be undertaken concurrently with the treatment described in (c) and (e) below.

(c) Symptomatic treatment for systemic disturbances, when present:- This consists of rest in bed, saline purgatives, salicylates, diaphoretics etc.

(d) Good nourishing diet with vitamins and, when indicated, haematinics.

(e) Beneficial drugs whose use is emperical:-

(1) *Methylene Blue (MB)*:- MB 1% in distilled water with a pH of 7, with 10 ml. of 25% glucose I. V. twice a week; 1st dose 5 ml. MB, 2nd dose 8 ml. MB, 3rd and maximum dose 10 ml. MB thereafter, to be discontinued when the reaction subsides. In any case, the injections should not be given for more than a month. MB treatment results in a blue discolouration of the diseased skin areas which disappears after a varying period of 1 week to 1 month after cessation of the MB treatment. If, moreover, the pH is not adjusted to 7, fever will occur after each injection.

(2) *Antimony Compounds*:- (Potassium Antimony Tartarate - PAT, and Stibatin I. V.). PAT 2 ml. of a 2% solution (or Stibatin 5 ml.) with 10 ml. of 10% calcium gluconate I. V. thrice a week for not more than one month. Antimony

compounds should be used when MB fails to act or if the patient objects to the blue discolouration of the skin.

(3) *Adrenaline Chloride*:- 1 in 1000 solution subcutaneously twice or thrice a week when oedema, nerve and joint pains do not subside with MB or Antimony. Adrenaline can be given concurrently with MB or Antimony.

CORTICOSTEROIDS

At the Seventh International Congress of Leprology held at Tokyo (1958) Corticosteroids were recommended for reactions in all the Groups. Trials at the Clinic of the Acworth Leprosy Home, however, reveal that they are of doubtful value in reactions occuring in Non-lepromatous Leprosy (RT & Tuberculoid in reaction) which are better treated with MB or Antimony etc. Hence the following description is confined to their use in reactions in the Lepromatous Group only (ENL, ALR and PLR). The major portion of the literature deals with the results obtained in ENL and LR. Spectacular results were obtained with the use of corticosteroids in the early years. Later doubts began to creep in.

Roche et al (1951), Melsom (1952), Dharmendra (1953), Iglesia (1954), Jopling & Cochrane (1957) and Lechat (1958) reported very good immediate results with ACTH or Corticosteroids in ENL or LR. But at the same time they agreed that relapses, though less severe and less frequent than before, did occur on discontinuation of the drug. Casals (1957), on the other hand, reported intense and resistant relapses on suspeding corticosteroid therapy. Dharmendra (1953), Jopling & Cochrane (1957) maintain that there were no bad late results with corticosteroid therapy; whereas Lowe (1952) was of the opinion that the late results often led to aggravation of the underlying disease.

Cochrane (1959e) is of opinion that in ENL corticosteroids should be used if there is no response to PAT. He does not favour their use in PLR but states that they may be given and continued even for 2 years when the reactions are severe and prolonged. In conclusion he states that intermittent cortisone therapy is worse than no cortisone therapy at all and, therefore, the decision to use this drug must be taken with all seriousness.

In recent years an increasing number of cases in a Reactive state, the result of indiscreet corticosteroid therapy, have been seeking advice at the Clinic of the Acworth Leprosy Home. It was found by the treating physicians that increasing doses of corticosteroids were necessary to suppress the reactions leading to a point when an attempt at withdrawal of the drug, necesitated by the presence of their toxic effects, resulted in an increase in the intensity of the Reactions and the disease process.

A serious situation can thus be created by the use of corticosteroids – a situation which has its parallel in other diseases. Tegner (1962), for example,

points out the hazards in treating Rheumatoid arthritis with Corticosteroids. He concludes "steroids should not be administered prematurely or as the first line of treatment". This advice can be advocated also in Leprosy.

The treatment involving corticosteroids has to be considered from two points of view :—

(a) Withdrawal of the corticosteroids used indiscreetly and

(b) Use of Corticosteroids.

(a) *Withdrawal of the Corticosteroids* : The following procedures should be undertaken concurrently :—

(i) The Corticosteroids are withdrawn by reducing the dose very gradually and persistently.

(ii) Symptomatic treatment,

(iii) MB or Antimony etc.

When the reaction subsides or has very greatly decreased, DPT, to be followed later by the Sulphones, should be introduced in the manner decribed on page 8.

(b) *Use of Corticosteroids* : If symptomatic treatment, MB, etc. fail to control reactions the only alternative is to use the corticosteroids sparingly as follows :—

Prednisolone (5 mg. tablet) or its equvalent. I tablet 5 times a day for the first two days, 4 times a day for next two days, thrice a day for another 2 days, twice a day for another 2 days once a day for 2 days and ½ tablet for the last 2 days. A repetition of the above dosage is inadvisable, and any further reactions should be treated with MB or Antimony. It may be necessary in some cases of extreme debility to give only one or two injections of MB in 2 weeks, using Antimony in between whiles.

TREATMENT OF COMMON COMPLICATIONS

(I) *Acute Neuritis* : Physiotherapy (as described later) is indicated. Procaine, hyaluronidase or hydrocortisone injected perineurally, alone or in combination, are advocated by some workers (the Seventh Congress).

Orchitis : Complete rest to the part by scrotal bandage, locally counter-irritants in the form of belladona ointment, and aspirin for pain and fever.

Iridocyclitis : Atropine and ½ to 1% cortisone as an ointment or as subconjunctival injections.

PHYSIOTHERAPY

A short description of physiotherapeutic measures for complications of reactions is given below :—

(a) *Heat Therapy* : In the form of Infra-red radiations and Wax-baths to relieve pain and swelling in acute neuritis, to reduce oedema of hands & feet, and to prevent deforming changes in bones and joints.

(b) *Immobilisation* : In the form of Plaster of Paris casts in acute neuritis; and in the form of splints to prevent the changes in the bones and joints, e. g. Cockup splint to keep hand in functional position.

PREVENTION OF REACTIONS

It will be obvious that attention to complicating diseases and conditions, and the witholding of drugs which act as precipitators of reactions, will prevent the occurrence of reactions. Precipitating factors, however, may not be present when the treatment is commenced, but may be encountered during the course of treatment. As the Sulphones themselves can precipitate reactions, the addition of other precipitating factors will intensify the reactions. Hence a slow induction of the Sulphones is being advocated in recent years. Chaussinand and Bourcart (1960) recommend 25 mg. DDS daily for six days per week increased by 25 mg. till the maximum dose of 2 mg/kg. is reached after five months of treatment in Non-lepromatous cases, and after ten months of treatment in Lepromatous cases, with a weekly cessation of treatment every three weeks.

At the Clinic of the Acworth Leprosy Home statistically controlled trials are being conducted in various small dose schedules. Conclusions have not yet been reached as the trials are in their initial stages.

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