

REPRINTED ARTICLES

Articles published elsewhere, considered by the Editorial Board to be of special interest, reprinted in full, or condensed form, or in free translation.

REGRESSIVE CHANGES IN LEPROSY UNDER PROMIN THERAPY*

By G. L. FITE, M.D.,†

and

F. GEMAR,‡

Carville, Louisiana

INTRODUCTION

During the past four years continuous intensive treatment with promin has been carried out in a considerable number of patients at the National Leprosarium, as reported by Faget and others.¹ These patients have been receiving daily intravenous doses, usually 5.0 grams, with rest intervals of one week for each three of treatment, in some cases for more than four years. It has been the continued experience of all connected with this work that the treatment is beneficial in most cases. Although clinical improvement is slow, and bacterioscopic improvement even more slow, relapses have been extremely rare, and the progress of improvement has been steady in most instances.

The purpose of this paper is to report biopsy findings in 32 patients who have been receiving the drug during periods of 18 months to 4 years, in order to determine the tissue changes associated with remission of the active disease process. In all cases the lesions which were selected for biopsy were those which were most prominent over the trunk and extremities, lesions of the face being avoided. In about half the cases these represent persistent small lesions in individuals in whom most original lesions were no longer clinically apparent. In all cases the biopsied lesions had undergone varied degrees of clinical regression. In four cases in which the biopsied lesions were still frank elevated lepromatous nodules, rich in organisms, there had been marked improvement in these lesions

Reprinted with permission from South. M. J. 39 (1946) 277-282.

*Read in Section on Pathology, Southern Medical Association, Thirty-Ninth Annual Meeting, Cincinnati, Ohio, November 12-15, 1945.

*From the U. S. Marine Hospital, Carville, Louisiana, and the National Institute of Health, Bethesda, Maryland.

†Surgeon, United States Public Health Service.

‡Assistant Bacteriologist, United States Public Health Service.

clinically, consisting of disappearance of signs of inflammation, and 50 per cent or more decrease in size of the lesions themselves. The lesions studied can thus be considered representative or the more severe, or more active, existent in the individual patients.

In 14 cases biopsies made two to three years prior to the present study were available for comparison. In eight of these the same area was subjected to the second biopsy, and in three cases the same lesion.

Paraffin sections were stained with hematoxylin and eosin, and frozen sections with Sudan IV. Frozen sections were also used for acid-fast stains, to insure total staining of organisms present, and several such sections were studied in each case.

RESULTS

Bacterioscopic Findings.—All the cases had been bacterioscopically positive at the beginning of treatment, but 10, or 31 per cent, of the lesions biopsied after treatment are free of demonstrable organisms. Five of the positive cases had had occasional negative smears from the skin of other parts of the body. In one case in which the biopsied lesion is free of organisms, other lesions in the body are positive by smear.

From comparison with previous biopsies it is clear that there is not only decrease in size of the lesions, but also decrease in average numbers of bacilli per cell. In only three cases are the vacuolated cells heavily laden with bacilli. For the most part, in the treated lesions the number of bacilli per cell is small; the bacilli are often feeble in their staining propensities. The degree to which large infiltrations may atrophy, leaving little behind, is astonishing in several of the cases.

In six cases the presence of large masses of bacilli in globi is an outstanding feature of the lesion. In five of these the large numbers of bacilli in globi stand in moderate contrast to the small numbers of poorly staining organisms in adjacent vacuolated cells. In these cases there is an obvious persistence, or even increase, of bacilli in the globi, in contrast to simultaneous decrease in vacuolated cells. It is also noted that small globi, and bundles of bacilli in typical cigar-packs, commonly associated with progress of lesions, are extremely rare in the treated cases.

However there are changes in several of these cases, as well as in some other lesions, which indicate clearly loss of bacilli from globi, so that the phenomenon of persistence of bacilli in globi is not uniform. Cowdry² showed that the investing "membranes" of giant globi consist for the most part of thinned out giant cells. The correctness of this is well seen in several of the present cases

in which giant cells enclose old global vacuolated masses which have shrunk greatly in size and lost most of the organisms, but still retain the global matrix of the globus, with perfect preservation of the giant cells themselves.

The bacterioscopic results of examination of skin smears in 100 cases after promin treatment for 2 to 4 years are presented in *Fig. 1*. The data are condensed from the results of examination of more than 2,000 smears made according to the commonly used technic of examination of small amounts of material, mostly tissue juices, obtained from a minute incision into the cutaneous lesions.

It is observed that the most significant drop in numbers of bacilli found in the lesions occurs in the fourth year of treatment. In a group of 42 patients who have finished nearly four years of treatment, 21, or 50 per cent, have shown persistently negative smears during the fourth year, whereas none of these patients had wholly negative monthly smears during the third year of treatment.

The group of twenty-six patients on promin treatment for the

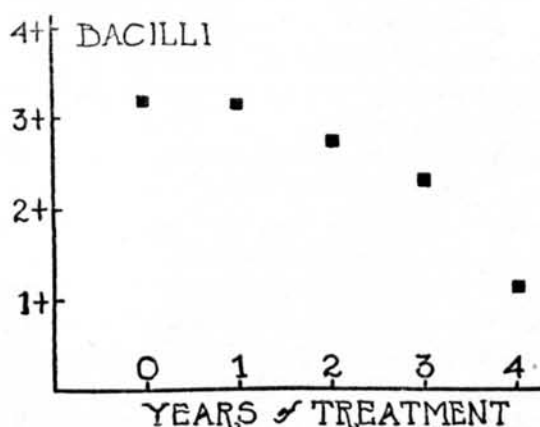


FIG. 1. Bacterioscopy of leprosy lesions after prolonged promin therapy.

past two years only shows a comparatively greater degree of improvement in two years, which may be partly accounted for by larger doses and more continuous treatment than were used at the beginning of the work.

Atrophic Changes.—With a single exception, all the lesions show extensive evidences of atrophy: atrophy of the epidermis, of sweat glands, of nerves, hair follicles, and so on, and most interestingly, of the vacuolated cells themselves.

The single exception deserves comment. This is the case of a white woman 40 years old, with leprosy of 11 years duration, consisting largely of numerous small discrete nodules scattered over most of the skin of the body. Under promin treatment for three years, only a few of the smallest

nodules have completely disappeared, but all have decreased greatly in size, including that taken for biopsy. The lesion, however, shows most numerous organisms in the superficial parts of the lepromatous areas, as is often the case in chronically active leprous lesions, and much fewer in slightly deeper areas, there being no bundles of bacilli, or globi.

This case is the exception. In all the others there is much decrease in size of the focal infiltrations about the various structures and appendages of the skin which make up the common lepromatous infiltration. One of the features, which readily demonstrates shrinkage from a previous much greater size, consists of the persistence of many small blood vessels in the lesion, even after most of the adventitious cells have disappeared. This is a constant feature seen in varying degrees in nearly all cases, sometimes only in the more superficial foci, sometimes throughout the lesion.

The atrophy of the lesion also appears frequently as simple loss of cells from the foci, leaving the remaining cells much more distinct. In the ordinary chronically active lepromatous infiltration, distinction of individual vacuolated cells is difficult. In the atrophic foci the single cells are often plainly seen, separated from one another by a little edema fluid, or by infiltrating lymphocytes. It is found that under these conditions a majority of the vacuolated cells have more than one nucleus.

Another feature associated with atrophy is a greatly increased number of lymphocytes in certain foci. It is never certain, of course, whether these are increased numbers, or residual lymphocytes made more prominent by loss of vacuolated cells. In the case of plasma cells, which in small numbers are a routine feature of lepromatous infiltrations, the latter seems definitely to be the case.

Atrophy of the Epidermis.—The epidermis covering lepromatous lesions is regularly thinned out, and the papillae are flattened. Following regression of the lesion, this change is often permanent, as has been noted of maculo-anaesthetic lesions in the past, and as is evident in the permanent alteration in the character of the epidermis clinically in many cases. In other cases various degrees of formation of new rete pegs occur, sometimes producing a definite acanthotic change.

EPIDERMAL CHANGES

Character of Epidermis	Number of Cases
Papillae wholly flat	18
Papillae partly flat	8
Acanthotic	2
Normal	4

Table 1

Atrophy of Sweat Glands.—Infiltrative lepromatous lesions almost invariably involve the coil glands by embedding them in granulomatous tissue, leading to atrophy and loss of function, but not destruction of the epithelial structures. In the regressive lesions under study, the infiltrations about the sweat glands are among those most strikingly reduced in extent. The ready infiltration of the coil glands in leprosy has always been attributed to their rich capillary bed. It is reasonable to attribute the ready regression of foci in these areas to the same factor.

Atrophy of the Corium.—The presence of infiltrative foci in the corium leads to much distortion and disarrangement of the coarse collagen fibers. Large nodular lesions compress many out of existence. When such lesions regress there is no evidence of any regeneration of collagen fibers. Rarely there is some proliferation of elastic tissue as described by Milasch,³ seen in one of the present cases. More often the collagen fibers are simply atrophic, and the corium as a whole is thinned, or edematous in appearance. Often the collagen fibers stain peculiarly, retaining a little hematoxylin, and failing to take acid fuchsin. Rarely nuclear remnants are left behind in distorted areas. In three cases lipids are deposited, some apparently within and between collagen fibers, without the presence of cells, and quite separate from the lipid deposits associated with granulomas.

DISTRIBUTION OF FOCI IN DIFFERENT LAYERS OF THE SKIN
IN 10 POSITIVE AND 10 NEGATIVE CASES

Site of Foci	Bacterioscopy	
	Positive	Negative
Superficial	5+	3+
Middle	6+	2+
Deep	6+	1+

Table 2

Persistence of Deeply Seated Foci.—The deeper foci, those infiltrating the subcutaneous tissue, usually invading discrete fat lobules, appear to undergo regressive changes much less readily than the superficial foci. Comparison of lesions indicates that the proportionately small number of deep foci in the bacterioscopically negative cases is due to their original absence, not to healing processes, which would leave some residue.

Just as activity in a chronic leprous lesion is usually more pronounced in the superficial areas, so also regressive changes appear to take place here more readily. It might be said that the changes, whether progressive or regressive, seem to be more active nearer

the surface of the skin. The importance of this is that lesions of lesser extent or duration, which have not so extensively infiltrated deeper parts of the skin, may be expected to respond to treatment, or to regress, better than others. Here again it is possible that the capillary blood supply is a determining factor. In several cases there are many bacilli in the deeper foci, and comparatively few in the superficial.

Vascular Changes.—The author⁴ called attention to the frequency and importance of bacillary infection of blood vessels in a majority of lepromatous lesions. These lesions with bacilli in endothelial cells provide a continuous source of organisms for further spread of the disease by way of the blood stream, and production of new lesions of hematogenous origin.

In the present cases no example of vascular infection has been encountered, with bacilli either in vessel walls or in endothelial cells. Lesions of vessels without bacilli are observed in seven cases. In these, cellular infiltration of the vessel wall indicates a vessel formerly infected. Venules and capillaries with large prominent endothelial cells are outspoken in many lesions.

In one case there is infiltration of the superficial vessels by neutrophilic granular leukocytes in a most striking manner. This is in a 40-year-old white woman with leprosy of 19 years duration which has improved tremendously on promin therapy. Bacilli were found in a single focus in a single section of several searched, and nowhere in relation to the blood vessels.

Polymorphonuclear Neutrophilic Leukocytes.—These cells are ordinarily absent from the chronic leprous granuloma, occurring only in the presence of ulceration, or in small numbers in acute reactive inflammatory phases, or from unrelated secondary processes.

In most of the regressive lesions they are also absent. However in seven cases, including the above with vascular infiltration, they are found, once in considerable numbers infiltrating all the granulomatous foci. In two cases these cells are observed invading large globi which seem to be undergoing disintegration. In no case is phagocytosis of bacilli by the granular leukocytes observed.

Lipids.—All lepromatous lesions and leprous granulations contain large quantities of lipids. These are present in the vacuolated cells in the earliest lesions, even as in the epithelioid cells in tuberculosis, but in leprosy continue to increase in quantity with the chronicity of the lesion, making old solid lesions greasy in texture. The lipids are mixtures of fatty materials including much neutral fat, but are free of cholesterin.

The lipids persist beyond the life or activity of the leprous lesion. Leprous foci which appear totally obsolete are not scars, but

collections of fat-laden cells. Many of these are vacuolated, and are of the same appearance as the original bacillus-containing cells.

It has often been suggested that the lipids and waxes present in the bacillary body of the tubercle bacillus act as a barrier to the action of chemical or therapeutic agents, these organisms being possessed of a high resistance to chemical destruction. In the present studies obsolete bacillus-free cellular foci are as rich in lipids as foci containing bacilli, and there is no question that bacilli are often removed from, or disappear from, the lesions in its presence. Thus it is not possible to argue from these studies that the cellular lipid, presumably derived from the host, but possibly also from the bacilli, plays a role in experimental therapy. That it does play an important part in the histiogenesis of the lesion is another matter.

Fibrosis.—Scarring is not a feature of the regressive leprous lesion. Intense scarring occurs in the healing of ulcerated lesions, but in the more common non-ulcerated lesion it is usually absent. In one case there is intercellular fibrosis in most of the foci, which is regarded as an accentuation of the usual connective tissue framework of the lepromatous granulation. In two cases there is similar fibrosis about sweat glands. A third case is one in which the previous biopsy showed a peculiarly large number of fibroblasts in the granulomas, which condition persists two years later, although most of the bacilli are gone.

Tubercle Formation.—One of the questions raised in this study was whether regression of the disease might lead to reversion from the lepromatous to the milder tuberculoid form of the disease, with histologic tubercle formation and only rare organisms. All the cases in this study were examples of mixed and lepromatous leprosy clinically. In two of the biopsies epithelioid cells are observed, and in one of these the distribution of foci suggests that the case might have possessed tuberculoid features at some time in the past. The previous biopsy in this case likewise shows epithelioid cells. Thus in these cases it is believed the traces of tuberculoid changes must properly be attributed to an earlier process.

In a third case there are giant cell-epithelioid cell formations, apparently of recent origin. Some are proliferations about disintegrating globi. Others are mixtures of epithelioid cells and foreign body type giant cells. However, these are small, and are embedded in lepromatous tissue of the usual sort. Thus, in none of the cases is there any suggestion of conversion to any other type of leprosy.

MODE OF ACTION OF PROMIN

Daily intravenous injections of promin produce high but transitory blood levels. Clinical improvement is characterized by:

- (1) Prevention, or healing, of secondary infection, especially of the upper respiratory tract, and of ulcers of the extremities.
- (2) Elimination of the often severe acute reactions which are associated with exacerbation of the disease.
- (3) Prevention of formation of new lesions.

These histologic studies suggest that promin effectively rids the blood vessels of bacilli. The bacteriostatic action of promin appears adequate to do this. There is little or no evidence that promin succeeds in destroying bacilli in the cells of the tissues. Most of the atrophic regressive changes seen in the tissues are also seen occasionally in cases which regress spontaneously, or in cases which improve spontaneously in the intervals between periods of activity. Leprosy has a certain tendency to be a self-limited disease, never destructive in character.

The long time required for promin treatment to show beneficial action, and the very slow eradication of organisms from the tissues, indicate that the genuine improvement under prolonged treatment stems from the eradication of vascular lesions, eliminating the dissemination of organisms by way of the blood stream, and preventing the development of new lesions of hematogenous origin. But the slow process of destruction of bacteria in tissue cells appears to occur at much the same rate as in the common periods of remission, which are a normal characteristic of most cases of untreated leprosy. Certain unusual features, such as the persistence of deep foci, and the ready regression of infiltrations of sweat glands, suggest that a luxurious blood supply favors the regression of focal lesions.

The absence of acute reactions under promin treatment strongly suggests that blood stream dissemination of bacilli is essential for their production. In the absence of these acute reactions the lesions have a natural tendency to regress. There are, to be sure, exceptions. There are lesions with their bacilli which persist, even when other lesions in the same patient vanish. The persistence of some cellular reaction well beyond the disappearance of organisms in bacterioscopically negative lesions suggests that the criterion of presence or absence of demonstrable bacilli is not a wholly reliable indicator.

SUMMARY AND CONCLUSIONS

Under promin treatment, the improvement in leprosy is not accompanied by characteristic cellular changes. Those which do occur are predominantly atrophic in character, with extremely slow and gradual lessening of numbers of organisms in the lesions to the

point of final disappearance in 10 of 32 cases examined. These changes do not differ materially from similar changes occurring in spontaneous remission without treatment of any sort, or during interim periods of inactivity or regression between phases of acute activity.

The important finding is that promin appears to eliminate bacillary infection of the blood vessels and blood stream, thereby preventing the formation of new lesions. The atrophy of focal lesions is also more apparent in areas with a more generous blood supply. The results indicate strongly that the best results may be expected in those cases in which treatment is begun in a comparatively early stage of the disease.

A more powerful bactericidal agent than promin appears necessary for the chemical destruction of bacilli within tissue cells, and especially those within globi.

REFERENCES

1. FAGET, G. H.; POGGE, R. C.; et alli.: The Promin Treatment of Leprosy. Pub. Health Reports, 58: 1729-41, 1943.
2. COWDRY, E. V.: Cytological Studies of Globi in Leprosy. Am. J. Path., 16: 103-136, 1940.
3. MILASCH, G. P.: Ueber die Veränderungen des elastischen Gewebes bei Lepra. Virch. Arch., 292: 216-219, 1934.
4. FITE, G. L.: The Vascular Lesions of Leprosy. Intern. J. Leprosy, 9: 193-202, 1941.