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# Study of Lepra Reaction<sup>1</sup>

A. Mukherjee and S. Ghosh<sup>2</sup>

Although much information is available on the subject of lepra reaction its appearance in a patient with lepromatous leprosy is unpredictable. Biopsy examination of the reaction has shown fibrinoid and necrotic changes of the collagenous element (9). Similar observations have also been made by others and it has been suggested that hypersensitivity plays a role in such cases (13, 14, 22). "Fibrinoid" deposits in histopathologic material in certain human diseases led us to suspect their possible origin in fibrinogen or a closely related protein (4.7). That plasma heparin-precipitable-fraction (HPF) may, like fibrinogen, be also involved in the pathogenesis of fibrinoid lesions has been suggested on the basis of observations in experimental animals (24). Meyers (17) suggested that an increase in plasma HPF due to "allergic vasculitis" could possibly provoke intravascular fibrin formation in leprosy. However, Rogers (23) observed that the incidence of coronary thrombosis, cerebrovascular accident or pulmonary embolism is much lower in patients with leprosy than in the general population. The possibility of intravascular coagulation in cutaneous blood vessels initiated by a leprotic process has

neither been substantiated nor ruled out. A concomitant study of plasma fibrinogen as well as plasma HPF along with the status of fibrinolysis and hemostasis in lepra reaction was, therefore, undertaken. Histopathologic study of the biopsied materials from skin lesions was also done to find any possible correlation.

#### MATERIALS AND METHODS

Twenty patients (15 males, 5 females) having reaction in lepromatous leprosy (acute lepromatous infiltration-ALI) belonging to an age group between 20 and 56 years were selected from the outpatient clinic of the Leprosy Research Department, School of Tropical Medicine, Calcutta. Diagnosis and classification were made on the basis of clinical, bacteriologic, immunologic (lepromin test) and histologic examination. Routine treatment for the reaction was instituted after the investigations were carried out. The cases were followed till subsidence of the reaction (SR) when the same investigations were repeated. As control, 15 patients of a stable lepromatous variety (SL), 7 stable tuberculoid (ST), and 10 cases of reaction in tuberculoid leprosy (TR) of comparable age and sex groups were chosen from the same clinic. Six healthy normal individuals (HN) from the staff and students of the institute were included among the control groups. The subjects under study were free from any concomitant parasitic disease.

- The investigative study comprised:
  - quantitation of plasma fibrinogen by the method of Nath and Debnath (<sup>20</sup>)

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<sup>&</sup>lt;sup>2</sup>A. Mukherjee, M. D. (C. U.), Ph.D. (C. U.), D. T. M. &H. (C. U.), D.C.P. (Cal.), Reader, Department of Pathology; S. Ghosh, M.B.B.S. (C. U.), D. Bact. (Lond.), Ph.D. (C. U.), D.T.M. (Cal.), M.C. Path. (Lond.), Professor, Head, Department of Leprology, School of Tropical Medicine, Calcutta, India.

- determination of plasma heparinprecipitable-fraction (HPF) by a) semiquantitative method of Harville et al (<sup>11</sup>) as well as by b) spectrophotometric method (<sup>6</sup>)
- assessment of plasma-fibrinolytic activity by determination of the euglobulin lysis time (5)
- 4) ascertainment of hemostatic status from:
  - a) prothrombin time (PT) by the one stage method of Quick (<sup>21</sup>)
  - b) partial thromboplastin time or , PTTK (<sup>15</sup>)
  - c) thromboplastin generation test or TGT (<sup>3</sup>)
  - d) platelet study (8)
  - e) histopathological study of the biopsied material from skin was made after hematoxylin & eosin stain (H&E), and Weigert's stain for fibrin.

#### RESULTS

Values for plasma fibrinogen, HPF and euglobulin lysis time are shown in Table 1.

Fibrinogen. Values exceeded 600 mg% in most of the cases (85%) of ALI while 30% of the patients showed values above 700 mg%. The range varied from 543 mg% to 770 mg% and the mean value was 652 mg%. When reaction subsided fibrinogen level decreased and except in two cases it was within 600 mg%. Mean value came down to 559 mg%. The decrease in the post-reactive stage was found highly significant (P-ratio < 0.001). In the control series of cases, its range was from 303 mg% to 497 mg% and mean value 400 mg% in the HN group. These were respectively 248 mg% to 454 mg% and 351 mg% in ST patients. In TR the respective values were 298 mg% to 652 mg% with a mean of 475 mg%, while in SL these were 397 mg% to 775 mg% and a mean of 586 mg%. Statistical analysis showed that the difference between values obtained in ALI and SL groups was significant (P-ratio < 0.005, > 0.001), while it was highly significant (Pratio < 0.001) when the findings of ALI patients were compared with those of other control groups.

Heparin-precipitable fraction. The qualitative test (semiquantitative) was positive in

LEPROMATOUS LEPROSY			TUBERCULOID LEPROSY		
Lepra r acute	reaction subsided	Stable	Reaction	Stable	Normal healthy
20 (15/5)	20 (15/5)	15 (11/4)	10 (7/3)	7 (5/2)	6 (5/1)
534-770	494-624	397-779	298-652	248-454	303-497
652	559	586	475	351	400
±59.2	±32.3	±94.5	±88.6	±51.6	±48.6
(++ to ++++)(+ to ++)		(±or -)	(-)	(-)	(-)
194-890	112-408	Not done	Not done	Not done	87-195
376.7	207.7				128
102 330	104 206	05 252	08 218	08 108	121 204
260	176	153	162	140	171
	LEPROMA Lepra 1 acute 20 (15/5) 534-770 652 ±59.2 (++ to ++++ 194-890 376.7 192-330 260	LEPROMATOUS LEPROSY Lepra reaction acute subsided 20 (15/5) 20 (15/5) 534-770 494-624 652 559 ±59.2 ±32.3 (++ to ++++)(+ to ++) 194-890 112-408 376.7 207.7 192-330 104-206 260 176	LEPROMATOUS LEPROSY         Lepra reaction       Stable         20 (15/5)       20 (15/5)       15 (11/4)         534-770       494-624       397-779         652       559       586 $\pm$ 59.2 $\pm$ 32.3 $\pm$ 94.5         (++ to ++++)(+ to ++)       ( $\pm$ or -)         194-890       112-408       Not done         376.7       207.7       104-206       95-252         260       176       153	LEPROMATOUS LEPROSY       TUBERCUL         Lepra reaction       acute       subsided       Stable       Reaction         20 (15/5)       20 (15/5)       15 (11/4)       10 (7/3)         534-770       494-624       397-779       298-652         652       559       586       475 $\pm$ 59.2 $\pm$ 32.3 $\pm$ 94.5 $\pm$ 88.6         (++ to ++++)(+ to ++)       ( $\pm$ or -)       (-)         194-890       112-408       Not done       Not done         376.7       207.7       104-206       95-252       98-218         260       176       153       162	LEPROMATOUS LEPROSY       TUBERCULOID LEPROSY         Lepra reaction       acute       subsided       Stable       Reaction       Stable         20 (15/5)       20 (15/5)       15 (11/4)       10 (7/3)       7 (5/2)         534-770       494-624       397-779       298-652       248-454         652       559       586       475       351 $\pm$ 59.2 $\pm$ 32.3 $\pm$ 94.5 $\pm$ 88.6 $\pm$ 51.6         (++ to ++++)(+ to ++)       ( $\pm$ or -)       (-)       (-)         194-890       112-408       Not done       Not done       Not done         376.7       207.7       207.7       104-206       95-252       98-218       98-198         260       176       153       162       149

 

 TABLE 1. Values for plasma fibrinogen, HPF and euglobulin lysis time in different stages and types of leprosy and normal individuals.

a + = mild; ++ = moderate; +++ = high; ++++ = very high;  $\pm = doubtful$ ; - = negative.

all patients during lepra reaction, the degree of positivity, varying from mild to very high (i.e., 1+ to 4+). Chemical quantitation revealed that the mean value was 376 mg%. In 90% of the patients with ALI the value surpassed the highest level (195 mg%) observed in the normal group. Thirty percent of cases showed values more than double the highest normal and the range varied between 194 mg% and 890 mg%. In all the cases values diminished significantly in the post-reactive phase when the range varied between 118 mg% and 408 mg% with a mean value of 207.7 mg%.

The qualitative test was negative in all groups of the control series. Quantitation revealed that the range varied from 87 mg% to 195 mg% and mean value was 128 mg% in the healthy normal group. Therefore, quantitation was not done in other control groups.

**Euglobulin lysis time.** The timing in minutes varied from 192 to 330 in AL1. Mean value was 260 minutes. In 65% the values exceeded the maximum limit of 241 minutes observed in HN. After subsidence of reaction, the values varied between 104 and 206 minutes and mean value fell to 176 minutes.

Among control groups, lysis time was found to be within 241 minutes, in all persons except two of SL group where the highest value reached 252 minutes and the mean value was only 153 minutes.

A comparison between the values for fibrinogen, HPF, and euglobulin lysis time obtained in different varieties of leprosy is shown in Figure 1.

Hemostatic status. PTTK was found to be raised in 50% of ALI patients. TGT was abnormal in 55% of the cases (including cases showing raised PTTK), but PT was normal except in two cases where it was slightly increased. Correction studies with normal plasma/serum indicated a deficit of serum factor in six (30%), plasma factor in three (15%) and both plasma and serum factors in two other (10%) patients. The abnormalities were found fully reversed in the post-reactive state. Examination of peripheral blood smear and clot retraction showed that the quality and quantity of the thrombocytes were normal. Among control groups, values were within normal range except in one of ST and three of SL groups who showed raised values for PTTK and slightly poor thromboplastin generation.



FIG. 1. Values for plasma fibrinogen, HPF, and fibrinolytic activity in different types of leprosy.

**Histopathology.** In addition to the usual leprosy histology, inter- and intracellular edema, collection of ploymorphonuclear neutrophils and eosinophils were observed in patients with reaction.

In acute lepromatous infiltration there were varying degrees of cutaneous necrosis, vasculitis (Fig. 2) and intravascular deposits (Fig. 3). Weigert's stain showed that the intravascular deposits, the walls of many cutaneous blood vessels and the proteinous exudate in the interstitial tissue had the tinctorial character of fibrin (Fig. 4). Another very interesting observation was frequent obliteration of the lumen of some blood vessels by a mass of cellular elements enmeshed in fibrin threads which appeared like a thrombus. In a few of them a small central gap was also noticed, consistent with partial recanalization in an organizing thrombus (Fig. 5).

Similar intravascular fibrin deposits, or features recognizable as thrombosis were found neither in other types of reaction (*viz*, TR) nor even in the same cases of acute lepromatous infiltration after the subsidence of acute stage.



FIG. 2. Vasculitis in a cutaneous blood vessel in a case of acute lepromatous infiltration. H & E stain X 440.



FIG. 3. Fibrin deposit inside a dermal blood vessel in a case of acute lepra reaction. H & E stain X 440.

#### DISCUSSION

The present observations show that the values for plasma fibrinogen and HPF were most increased in acute lepra reaction. The stable lepromatous group also had some increase in values for these two fractions, but no significant abnormality was detected in the nonlepromatous group. The characteristic high degrees of positivity for plasma HPF-a cold precipitable fibrinogen-like protein-tend to indicate its possible relation with raised cryoprotein level in lepra reaction observed by some workers (16.25). Meyers (17) reported increase of and correlation between plasma HPF and fibrinogen levels (2) to explain the defects observed in cases in leprosy and the present findings are in of kala-azar. The impact of leprosy for a



FIG. 4. Fibrin clot in a dermal blood vessel in case of acute lepra reaction. Weigert's stain X 440

agreement with his observations. After subsidence of reaction, fibrinogen and HPF levels were even lower than those in most cases of stable lepromatous group.

Euglobulin lysis time was found raised during acute lepra reaction, but it was normal in other groups of cases. This shows that the fibrinolytic activity of plasma diminished during reaction. In the post-reactive phase, this became normal again. Meyers (18), however, found significant impairment of fibrinolysis in all patients with leprosy. He observed that the impairment was maximum in the lepra reaction group while the nonlepromatous patients revealed only mildest deviation. The findings of Japanese workers (12, 26) are at variance with those of Meyers (18) who attributed this to ethnic origin.

The abnormalities in hemostatic status seen in lepra reaction were found to be reversible. Our previous studies (1) suggested deficit of some coagulation factors singly or in combination, in a few cases of leprosy. The precise cause of these defects could not, however, be defined with certainty. The defects in the nature of either serum or plasma factor deficiency were found most frequently in cases of lepra reaction. It was a rare finding in the other groups.

No inadequacy of the platelets (qualitative or quantitative) was apparent. The basic abnormality can thus be explained in a number of ways. Hyperglobulinemia, a usual feature (19) with advanced cases of leprosy, could act by interfering with the synthesis of coagulation factors as suggested by Basu et al



FIG. 5. An enmeshed mass of cellular elements inside an obliquely cut dermal blood vessel. There is a central gap possibly denoting beginning of recanalization. H & E stain X 120.

prolonged period may bring about a temporary decompensation of hepatic function (unpublished data) when the synthesis of coagulation factors might also be affected. But consistent findings of raised plasma fibrinogen and HPF as well as diminished plasma fibrinolytic activity tend to point towards a disorder of the homeostatic balance in physiological fibrinolysis.

Another very significant observation in this study is deposition of fibrin in the dermis and some dermal microvessels in the lesions of acute lepra reaction. The dermal vascular endothelium, whose integrity determines adequate elaboration of plasminogen activators, is extensively damaged by the prolonged leprotic lesions that usually spare the major vessels. Excess of fibrin deposition over removal by fibrinolysis underlines some form of chronic inflammation (10). This in its turn, may lead to a vicious cycle of elevation of plasma fibrinogen and deposition of fibrin aided by an impaired plasma fibrinolytic activity. As a result of intradermal vascular thrombosis, appreciable amounts of coagulation factors might be consumed thus depicting poor thromboplastin generation. These findings tend to indicate that during the course of this mycobacterial disease, periodically there might occur generalized Shwartzman-type of reaction when alteration in fibrinogen (qualitative and quantitative) leads to its precipitation in small blood vessels of the lepromatous tissue, this being an immediate cause of the vascular damage observed. Such occurrences seem to be synchronous with episodes of lepra reaction.

#### SUMMARY

The present work, undertaken with a view to elucidating the mechanism of lepra reaction, reports significant increase of plasma levels of fibrinogen and a closely related protein, heparin-precipitable-fraction (HPF), in cases of acute lepra reaction. Fibrinolytic activity has also been found to be impaired in them. This may account for the periodic episodes of fibrin deposition in histopathologic material including dermal blood vessels, which were conspicuous during acute reaction. These patients also revealed variable deficiency in some of the coagulation factors possibly as a result of "consumptive coagulopathy." The relevance of the findings to episodes of lepra reaction has been discussed.

#### RESUMEN

Este trabajo, que se llevó a cabo con el propósito de elucidar el mecanismo de la reacción leprosa, reporta un aumento significativo en el plasma de los niveles de fibrinógeno y una proteina estrechamente relacionada, la fracción precipitable con heparina (FPH), en casos de reacción leprosa aguda. También se ha encontrado que la actividad fibrinolítica está alterada. Esto puede explicar los episodios periódicos de deposición de fibrina en material histopatológico, incluyendo en vasos sanguíneos del dermis, que son muy notorios durante reacciones agudas. Estos pacientes también presentaron deficiencias variables en algunos de los factores de coagulación—posiblemente como resultado de una "coagulopatía consuntiva." Se discute la relevancia de estos hallazgos a episodios de reacción leprosa.

### RÉSUMÉ

Ce travail a été entrepris en vue d'élucider le mécanisme de la Réaction Lépreuse. On rapporte ici une augmentation significative des taux plasmatiques du fibrinogène, ainsi que d'une protéine étroitement apparentée, la fraction précipitable à l'héparine (HPF), dans les cas de réactions lépreuses aigués. On a également observé des troubles de l'activité fibrinolytique chez ces patients. Ces observations peuvent expliquer les épisodes périodiques de déposition de fibrine dans des specimens histopathologiques avec vaisseaux sanguins dans le derme, caractéristiques que l'on peut observer au cours de la réaction aigué. Ces malades ont également témoigné d'un déficit variable au niveau de certains facteurs de coagulation; ceci pourrait résulter d'une "coagulopathie de consomption." On discute de la pertinence de ces observations, en rapport avec les épisodes de réaction lépreuse.

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