Lysosomes—Their Relationship with Vitamin E and Leprosy

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INTRODUCTION
Leprosy is an infectious disease probably due to 'organic susceptibility'. Immunological studies of the disease have shown that, in the pair bacillus-host, the latter seems to be the main factor in its pathogenesis.

Therefore it will be interesting to investigate the biological, biochemical and immunological conditions that prepare the organic susceptibility which facilitates or impairs the growth of M. leprae. This paper is a partial attempt to unveil the pathogenic mechanism of the leprosy infection through modern knowledge on lysosomes.

LYSOSOMES
Lysosomes were discovered by De Duve in 1955, and the CIBA Foundation dedicated a symposium1 to them. They are subcellular cytoplasmic organelles which enclose hydrolytic enzymes, mainly acid phosphatase, with only one membrane. These corpuscles are formed by enzymes, lipids, peptides, aminoacids, nucleotides, metals, etc.; they are found in most animal cells, especially in liver, kidney, spleen, intestine, leukocytes, macrophages, etc.

The enzymes contained in the lysosomes are of the hydrolytic type; they act mainly in acid pH and show their activity on biopolymers. These enzymes are generally proteases, phosphatases, glycosidas, etc.; the most important enzymes isolated were: acid phosphatases, cathepsin, ribonuclease, arylsulfatase, beta-glucuronidase and beta-galactosidase. The activity of the acid phosphatase is especially important as it indicates the lysosomic enzymatic complex.

Lysosomes are formed by 2 elements: the membrane and the hydrolytic enzymes contained inside it.

The membrane differs from that of other subcellular corpuscles as mitochondria—with double membrane—because of its simple structure. This single membrane of lipoproteic nature acts as a barrier between lysosomic enzymes and substrates. Thus the enzymes remain inactive as long as the lipoproteic membrane is untouched.

It has been proved lately that lysosomes are involved in the mechanism of morphologic changes, catabolic disorders, autolytic processes, necrosis, and infections and inflammatory processes, etc. They initiate intracellular digestion and a great number of catabolic processes, being therefore connected to the pathogenesis of several morbid processes. They would be mainly connected with phagocytosis and the destruction of alien substances.

LYSOSOMES AND VITAMIN E
The lipoproteic nature of this single membrane in the lysosomes suggested a relationship between these corpuscles and the compounds connected with the auto-oxidation of lipids such as Vitamin E—well known biological antioxidant—as the attack of subcellular particles is generally initiated through their membranes.

Damage of the lysosomic membrane and lysosomes themselves were connected to the conditions which cause auto-oxidation of lipids, such as irradiation peroxides, systems that form free radicals, vitamin E deficiency, etc.

Experimental studies2,3,4 have shown that these conditions damage the lysosomic membrane. Besides these, other alterations as osmotic pressure, pH, detergents, freezing, etc., cause the previously mentioned damage.

These studies led to experiences on nutritional Vitamin E deficiency and muscular dystrophies in relation to lysosomes.
Tappel et al. have shown that in muscular dystrophies, genetic as well as nutritional ones, caused by Vitamin E deficiency, there is a high proportion of lysosomal enzymes originated in the macrophages, in direct relationship to the catabolic processes of the muscle. These, in turn, are evidenced in histological manifestations of muscular disorganization and exertion of products of muscular degradation. Lysosomal alterations have also been shown to occur in other alterations caused by Vitamin E deficiency, such as encephalomalacia in chickens. Homogenates of chicken brains in chickens with Vitamin E deficiency and symptoms of encephalomalacia show important increase in lysosomal activity.

The explanations of these facts would be as follows: Vitamin E deficiency causes an increase in peroxidation of lipids, damaging cells and its subcellular components, among which lysosomes are counted. As these are broken, lysosomal enzymes are freed, and they alter cells causing an invasion of macrophages and muscular catabolism.

On the other hand, Desai et al. have shown that the lysosomes isolated in rat livers are extraordinarily labile to the auto-oxidation produced by systems that form free radicals, such as linolate emulsions, ultra-violet radiation, and gamma radiation. Sawant et al. have proved that irradiation frees lysosomal enzymes in in vitro systems such as arylsulfatases, beta-glucuronidase, acid phosphatases and ribonucleases.

In conclusion, both peroxidation and irradiation cause selective damage on the lipoprotein membrane of lysosomes through the activity of the free radicals generated by the mentioned systems.

LYSOSOMES AND LEPROSY

The electronic-microscopic study of the leprosy cell allowed the discovery by Yamamoto, Imaeda and Nishihara of subcellular elements called 'opaque droplets' or 'opaque bodies'. The histochemical study of these elements identified them as lysosomes. At this stage of knowledge on these subcellular corpuscles, study of their connection with the histogenesis, pathogenesis and chemotherapy of leprosy was started.

Cytotoxic techniques show clear evidence of the existence of acid phosphatases in those 'opaque droplets' that Brieger and Allen identify as lysosomes.

The lysosomes, in the appearance of a thin granular substance, are found in the leprosy cell around the leprosy bacillus. They are also found in other infections, such as those by tuberculosis bacillus and staphylococci.

Chemotherapy with DDS and similar compounds alters the contents of this lysosomal substances, in the sense that administration of such chemotherapy increases the contents.

It was also seen that bacilli disintegrate in that substance of abundant hydrolytic enzyme content. When bacterial disintegration occurs a foamy structure appears around the lysosomal substance.

The lysosomal activity of the leprosy cell has also been connected with the clinical evolution of leprosy patients, with the degree of ease with which the leprosy bacillus develops, and with the natural immunity to this disease.

Karat suggests that DDS acts through the lysosomes, which, by freeing hydrolytic enzymes, kill the M. leprae and help the removal of bacillary rests.

Recent experiences tend to show that Schwann cells are rich in lysosomes and immunity to leprosy rests partially in them. There can also be a connection between the lack of response to the antileprotic chemotherapy and the deficient content of lysosomes in the cells or the decrease or inhibition of lysosomal activity that occurs in certain cases.

Interpretation of these facts is as follows: lysosomes are subcellular corpuscles with a lipoprotein membrane, very sensitive to auto-oxidation processes which have the important function of destroying M. leprae. Therefore any element that tends to protect the lipoprotein membrane and also the lysosome, indirectly helps destroying M. leprae. That is the case of the biological antioxidants, potent inhibitors of
auto-oxidation, and of DDS, biological anti-oxidant with Vitamin E-type of activity, as shown by Bergel.

VITAMIN E AND LEPROSY

In 1951 Bergel made the first complete description of the possible relation between leprosy and Vitamin E. Later on, this investigator carried out many experimental trials which have confirmed this type of relation. Other authors have also confirmed part of these trials.

Of this series of experimental trials, the most important facts that show the connection between Vitamin E and leprosy are summarized below: 

(a) development of M. leprae inoculated in rats and mice under prooxidant and severely prooxidant diets; 
(b) biological antioxidant activity, manifested as anti ceroid activity, of chemotherapeutic antimicrobial agents, especially antileptotics. Bergel has proved the biological antioxidant activity—similar to that of Vitamin E—of the DDS, both in vitro and in vivo, which would be due to the presence of its 2 free amino groups in position 1-4; 
(c) therapeutic activity of a great number of biological antioxidants as those already mentioned and of Vitamin E. It has also been established that prooxidant diets favour the development of experimental infections caused by other mycobacteria as BCG, M. tuberculosis Vallee, M. fortuitum Penso, etc.

COMMENTS

This reveals the importance of lysosomes in the pathogenesis and cure of leprosy and also the important role of antioxidants, especially Vitamin E in the protection of the lipoprotein membrane of lysosomes. An increase in the biological oxidations through the formation of free radicals destroys the lipoprotein membrane of lysosomes and therefore they cannot destroy M. leprae, which develops freely and originates the disease. The administration of DDS and other biological antioxidants, by impairing auto-oxidant processes would protect the lipoprotein membrane of lysosomes increasing therefore the defensive capacity of the organism against M. leprae. Hence, the antileptous chemotherapy acts on M. leprae indirectly through the lysosomes. In this sense it differs from antituberculosis chemotherapy which, according to Rast, acts directly on M. tuberculosis.

This confirms the fact that leprosy needs a special biological susceptibility for its development, which is conditioned by the lysosomal activity. This explains why M. leprae experimentally inoculated does not develop in normal animals under normal conditions, as Bergel has sustained.

SUMMARY

This is a review of the experimental facts that connect lysosomes with leprosy and Vitamin E. Leprosy infection develops in an auto-oxidant susceptibility which favours destruction of the lipoprotein membrane of lysosomes. Lysosomes, due to their destructive activity of M. leprae, represent one of the natural mechanisms of defence against leprosy infections. The antileptous activity of the sulfones and other antileptotics would be indirect and through its biological antioxidant capacity which protects the lipoprotein membrane of lysosomes, natural agents of destruction of M. leprae.

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