INTRODUCTION
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HISTORICAL REFERENCES ON LEPROSY

Ancient Medical Literature

The origin of Leprosy is yet to be established. When, from where and how it started its first ravaging run is not clearly known. The references available in ancient medical literature are not very precise in meaning and some found to have covered wider range of diseases of the skin. The question wherefrom Leprosy started its ravage first is also not free from dispute. According to Bargmann (1897), Egypt is the first place where Leprosy was detected and correctly described thousands of years before the birth of Christ. Whether Leprosy passed on from Egypt to India, or from India to China, or it existed simultaneously in all the three countries, cannot be clearly proved. But there are records to confirm that at one stage in the ancient days, the ravaging disease existed in all the above three countries, India, East Africa and China.

Rogers in his 'Croonian lecture' (1924) referred to some Egyptian record of 1350 B.C. to say that Leprosy was found among Negro slaves during the rule of Dameses II. This was disputed by Buffer as he could not find any case of mutilation among the mummies he examined. Nonetheless, the
tradition goes that Leprosy was first found in the upper region of the Nile. There are references, Pacha (1914) and Baron (1957), that India is the original home of Leprosy. It is true that the Rig Veda Samhita (1400 B.C.) is perhaps the only ancient document having authentic references on Leprosy. The other ancient document of India, Sushruta Samhita (600 B.C.) had described Leprosy under Vata Shonita and Kustha diseases characterised as hyperasthesia, anaesthesia and deformities. The name Kustha has been used for various kinds of skin diseases in general, one of which described as Aruna Kustha corresponds to Leprosy. Of all the varieties of Kustha described by Sushruta Samhita, one group has been explained having the symptoms of anaesthesia and deformities and another with signs of ulcerations and falling of fingers.

Nothing interesting has been found in the ancient medical literature about the existence of Leprosy in China. There is a reference (Wong and Wo 1932) that a disciple of Confucious died of Leprosy during Chou dynasty. But nothing definite could be found from any literature except after 7th Century A.D. There are references that Leprosy was present in Japan in the 7th Century before Christ. There are plenty of references in Greek-Roman literature (Lucerfius, Calsus etc.). With the fall of Greek - Roman civilisation, medical science had to face a set back for some time in Europe, but Arabians kept it alive
through their study of Greek and Indian literature, which was later recovered in Europe from Arabian writings.

The term Leprosy had been used with different meanings by different writers causing confusion about its concept which prevailed for a long time. Some used Leprosy as a term for general skin disease. Greeks used it for psoriasis and for Leprosy used the term Elephanthis Graecorum. Arabians used "Lepra" for Leprosy and in certain writings ad "Djudsum". The terms Zaraath of Old Testament and Lepra of New Testament possibly meant Leprosy. In certain translation of the Bible the very term Leprosy had been used and according to some interpretations of the Bible the term Leper was used for the disease. The word, therefore, ran through in a variety of related forms with different meanings and interpretations. According to one interpretation, the meaning of the word itself is that peels off and as such was used for inner branch of trees. The Latin origin of the word is "Liber" and as liber used as writing paper, the term also carried the meaning of a book and from that the term library came in. The term Library and Leprosy, therefore, have the same origin.
The wars and conquests by Darius and Xerxes in 480 B.C. perhaps broke the boundaries of Leprosy zone for the first time and spread the disease from Asia - Africa to Europe. Xerxes while returning from his march in Europe left thousands of people behind and they were perhaps the original source of Leprosy coming in Europe. The spreading of the disease was initially quite slow, but it was only for a shortwhile. Leprosy was unknown in Italy till the return of Pompey's troops from the East in 62 B.C. and Galen wrote of the existence of Leprosy in Germany in 180 A.D. Three - four hundred years later the disease became widespread in Europe and after the fall of Rome, it became extensively common in all countries of Europe.

According to Newman the first Lepros hospital was built in Nottingham in 625 or 638 A.D. and the second one in Ireland in 867. The disease gradually spread over all Europe and it was at its height in Europe in 12th century. It is interesting to note that the decline of the disease in Europe also started soon and by the 17th century, it had practically no trace in most of the European countries, except in a very few persistant pockets. How and due to what measures this decline occured, are not clearly known. Prophylactic measures, better diet and living conditions were undoubtedly the major contributory factors responsible for the control and reduction of the incidences of
the disease. Isolation of the active cases, reduction of overcrowding of the people and avoidance of close contact between infected and non-infected were perhaps the most important measures adopted to eradicate the disease from Europe.

**Leprosy in America**

Leprosy was dying and practically died in Europe, but found a new home in America through the slaves of Africa and migrants from Europe and China. It is only the Eskimos of the Arctic circle and the Bering Strait regions who could keep themselves free from any attack of Leprosy, perhaps because they had no contact, or whatsoever contact came, could not survive under the climate to affect others. In fact, Leprosy was entirely an imported disease in most of the States of America, except in certain States of Western and Southern America i.e. Texas, Florida etc. Nevertheless, the disease spread over and affected areas after areas, people after people, exactly in the same way as happened in Great Britain i.e. through infiltration of people from endemic areas. Leprosy thus increased in many States and is still remaining a problem in certain States.

More recently, the few islands of pacific which were once free and away from the clutches of Leprosy, had also been brought in the domain of Leprosy perhaps through the Chinese immigrants. The existence of the disease in Hawai was recorded in 1835 and a number of cases was also found in Nauru and New
Calidonia. As in other places, the disease started very slowly at the initial stage, but very soon took a widespread character infecting larger and larger number of people.

**Aetiology**

In Sushruta Samhita Leprosy has been described as contagious and communicable disease, which spreads from infected persons to healthy ones by touch and breath, through uses of common bed, utensils and clothings. The basic factor responsible for spreading of the disease is, therefore, close contact with the diseased person, according to Sushruta Samhita. Chinese writings of the 7th Century and severe isolation measures adopted in Europe in the middle ages confirm the above concept of the contagious character of the disease.

This view prevailed as the universally accepted theory till the seventeenth century, when the hereditary theory came up and gradually started negating the theory of its communicable character. Danielssen and Boeck of Norway strongly upheld this hereditary view in 1848, and as there was not enough data, at that time, in support of the contagious theory, the hereditary theory received the maximum recognition from all quarters and was further strengthened by the report of the special committee of the Royal College of Physicians of London (1862). Their line of thinking was that leprosy was a constitutional disease associated with cachexia and blood dyscrasia.
This hereditary view still prevails in certain parts of the world, mainly because incidences of disease in more than one member of a family are quite high due to close contact between the healthy and diseased person.

But this hereditary theory was not left long to go unchallenged and the contagious theory soon started coming back with newer data and findings. Even before the leprosy bacillus was discovered and isolated, a number of objective reports based on prolonged observations came out in support of the contagious view. In 1869, Drognant and Landre, and in 1875 all the thirteen medical men in reporting to the British Guina Leprosy Commission supported the contagious theory. Brousse (1879) in his book based on years of experiences in Trinidad Leper Asylum, Hills in his report (1881) on British Guina Leper Asylum and Leloir's and Hawaii report in 1886, which are a few of the many important publications, ultimately brought the universal recognition to contagious theory of the disease.

Another theory came up in the mean time, which attracted the attention of the research minds for some time. It was the fish theory of Jonathan Hutchinson (1863) and Dharmendra (1960). The theory claimed that (a) excessive consumption of fish alone or together with milk or (b) consumption of decomposed fish or (c) consumption of fish suffering from leprosy like diseases could cause leprosy. But this theory did not prevail longer,
because it was soon found that people who had never taken fish had been attacked with Leprosy, and the people eating fish as a regular item had been completely free from Leprosy infections.

However, it is now a confirmed fact that Leprosy is an infective disease and that the causative organism is Mycobacterium Leprae, popularly known as Hansen's bacillus or lepra bacillus. The organism was discovered by Dr. G. Armauer Hansen in 1868, confirmed by his publication in 1874.

The remarkable significance of Hansen's discovery was not only not appreciated at the beginning, but was also challenged by the then leading leprologist, Danielssen and Boeck (1848), who attributed leprosy to multiple causes and claimed that the "rods" they had observed were the correct causes of the disease. But very soon recognition to Hansen's bacillus as the specific agent was declared in Germany by Neisser (1879), in France by Brocq (1885), Leloir (1886) and Besnier (1887). Thus, all other hypothesis previously built and claimed gradually got reduced to a position of secondary importance or no importance at all.

Since then immense research work has been done and is still being done all over the world to know the details of the character and movements of the bacillus, but unfortunately many things still remain unknown, particularly how the bacillus passes from the diseased to healthy body. But there is no doubt
today about the fact that the causative organism is the *Mycobacterium leprae*, because (a) the bacillus is constantly found in all leprous lesions, (b) uniform cellular reactions are observed when provoked by the organism or its chemical fraction and (c) the bacillus is not found in healthy persons.

*Mycobacterium leprae (Bacteriology)*

The organism is a *Schizomycoete* belonging to the group *Actinomycetales*, of the family *Mycobacteriaceae* and genus *Mycobacterium*. They are acid-fast because of their property of resisting decolourisation by acids after they are stained with strong basic dyes. The bacilli may differ in shape or size, but are usually straight like rods or may look sometimes slightly curved, having length 1 to 8 μ and width 0.2 to 0.5 μ with rounded or blunt ends. Instead of staining solidly and evenly, they may resemble diphtheroids and show granular staining, confined to the poles or distributed throughout their length. Clubbed forms are also found sometimes with lateral buds and branches, or the bacilli may look like oval body with greater diameter from 0.8 to 1.6 μ.

The leprosy bacilli are usually found in bunch called globi which look like bundles of cigars. The clumps of bacilli are said to be found with a lipid like substance, called the glia. As *Mycobacterium leprae* is found in both intracellular and
extracellular glial masses, it is considered that they are covered in a capsule-like membrane (Babes - 1901). This observation has been further confirmed by Hanks (1961). The organisms are non-motile and non-sporing, and in size, morphology or acid-fast staining character they closely resemble *Myco.* tuberculosis. But they look more deeply stained with carbol fuchsin and with Gram's stain. Their capacity to resist decolourisation with weak mineral acids is lesser than that of *Myco.* tuberculosis. *Myco.* leprae has larger and more defined granules and is more commonly found in intracellular position. The morphology of *Myco.* leprae as revealed by classical optics was described by Lohnis (1922) and confirmed by Baldrock (1923).

**Electron Microscopy**

The details of the internal structure of the bacilli can be deduced from the shadow of the electron microgram. Ultrathin section of tissue or cell can also give some information. The first electron microscopical studies of Bishop et al. (1943) showed that leprosy bacilli might appear as a filament, clear in the electron beam, with denser polar ends and that the bacilli were different in appearance from tubercle bacillus grown in culture. The dense condensation at the poles often appear as rod-shaped inclusions and such inclusions may also be seen in other parts of the cytoplasm of the bacilli. Experiment with other bacilli in the same process show the cytoplasm vacuolized.
Denny (1934) showed the mass of bacilli contained in a limiting membrane with the bacilli concentrically arranged around its edge. Nees et al. (1958; 1960) demonstrated three morphological types, i.e. normal, degenerated and segmented, of which the degenerated forms are found in greater proportion. de Souza - Arauja (1955, 1959) confirmed by electron microscopy the bacillary membrane, glia and granules. Richards and Cade (1948), Chatterjee et al. (1955a, b), Lc. Badzean and Valentine (1958, 1959, 1960) claimed that on an average 56.3% of the leprosy bacilli are degenerated in untreated cases of lepromatous leprosy, whereas in rat leprosy the degenerated form was only 5%. Malfati and Jonqueres (1953) showed by electron microscopy that the percentage of degenerated form can increase considerably after treatment with sulphone. The bacilli on treatment show shrunken cytoplasm and empty cell membrane. Malfati (1952) Haedicke, et al. (1952), Terada (1953), Kooij (1958) and Immeda (1958) supported and confirmed the above observations.

Yamamoto et al. (1968) described the morphology of ultrasection of bacillus. The cell wall of the organism is about 6 μm and consists of outer and inner layers which are electron dense and a central layer which is less dense. Cytoplasm of the bacilli is moderately electron dense and has a relatively homogenous appearance. In treated cases only the cytoplasm shows condensation at the polar ends and sometimes granules
(13-36 μm) and these are believed by Bishop et al. (1948) as nuclear structure. The nuclear apparatus is composed of moderately electron dense threads about 9 μm wide which show distinct coiling along the long axis of bacillary bodies. The nuclear threads appear to be embedded in an electron transparent matrix. In treated cases no clear threads are found. Brieger and Glaubert (1956) also found dense threads and granules in transverse ultra thin section of leprosy bacilli. Chatterjee et al. (1955a, b) expressed the view that a slow phase of multiplication results in solid, homogenously dense bacilli while a rapid phase results in the forms possessing alternate light and dark regions.

Vitro culture

Innumerable attempts so far made to cultivate Myco. leprae in vitro have failed to give any positive results. Kedrowski (1901), Williams (1911), Bayon (1912) Duval and Wellman (1912) and Sarkar (1962) isolated diphtheroid like non-acid fast organisms. Clegg (1909), Post (1911), Williams (1911) Duval and Wellman (1912) McCoy (1914) Currie, Clegg and Holdman (1912) and many others reported about chromogenic acid fast organisms and non-chromogenic forms were also reported by Duval (1910) Duval and Wellman (1912) Soule and McKinley (1932), McKinley and Verder (1923) Soule (1934) McKinley and de Leon (1937). Anaerobic forms were also isolated by Ducrey,
Sera and others, but most of their works could not be reproduced by Schlössmann (1923), Duval and Holt (1934a,b), Lowe and Dharmendra (1937), Dharmendra & Lowe (1938). In analyzing all available publications on bacteriology of leprosy it was concluded that the organism isolated by various workers could not be proved to be *Mycobacterium leprae*. The isolated organism might, therefore, be either (a) contaminated organism which had nothing to do with leprosy as such, or (b) the leprosy bacillus might have different stages of life, or (c) they were something different so far not isolated, but were closely associated with leprosy bacilli.

Hanks (1945) reported that *Mycobacteria* form a spectrum ascending from saprophyte and intermediate form to higher species such as *M. tuberculosis* which are pathogenic to animals. *M. leprae* murium cannot be cultivated in vitro and can infect only a few species of rodents. *M. leprae* is still uncultivable in vitro and is infective only to man. In this series, the increasing selectivity of host species may well be related to an increased necessity of organism for intracellular existence, limiting the ability of the organism to gain energy from in vitro substrates and requiring protection afforded to it by the host's cell wall from humoral components or secretions. It is logical that in as much as intracellular survival is associated with low oxygen requirements, oxygen becomes
increasingly toxic for the mycobacteria at the upper end of the spectrum. This hypothesis may explain the difficulty encountered in cultivating Myco. leprae and suggests numerous avenues of approach to the problem of cultivation. Many workers including Shepard (1967), Fjelde (1957) etc. studied the behaviour of different mycobacteria using different types of tissue culture. Ranadive et al. (1958) isolated an acid-fast organism from cases of human lepromatous leprosy in a tissue culture system consisting of the SEG fibrocytic cell line derived from human foetal spinal ganglia. The organism designated the XCC bacillus, can be grown and maintained in the conditioned fluid of stock.

**Experimental Incubation**

All attempts to infect animals with leprosy organism have failed to give any uniform and satisfactory results. The injected bacilli do not multiply but retain their morphological and staining characteristics for more than twelve months. All the experiments, so far made, confirm that the only animal susceptible to the organism is man.

But the question whether infection can be induced in human beings through skin is debatable. Klingmuller (1930), Jeanselme (1934), Danielssen and Boeck (1848), Krofeta (1884) could not offer enough proof of transmissions of the organism.
by inoculation. Arning (1886) Marchoux (1934), De Langen (1933), Lagoudaky (1936, 1937) Porritt and Olsen (1946) reported some favourable results of their research on experimental inoculation. Anyway, all the experiments confirm that the normal animals are not susceptible to leprosy infection and all efforts for experimental inoculation have not yet resulted in any indisputable positive findings.

However, some of the works which claim to have obtained some success are reported below:

**Monkey**

Nicolle (1905) Beenstirna (1926), Soule and McKinley (1932) Collier (1940) reported positive results in the transmission of human leprosy to monkeys. Tharmendra and Mukherjee (1944), Cochrane et al. (1945) reported negative results of their experiments in injecting human leprosy to splenectomised monkeys. Lai (1955) claimed positive results of his experiments on Taiwan monkeys.

**Hamster**

Majority of the workers such as Adler (1937) Tharmendra and Lowe (1940) Burnet (1940) reported negative results of their experiments. Chatterjee (1958) reported success in all his experiments, which are still to be confirmed by further works.
In mice also majority reports are negative. De Souza Arauja (1928, 1929), Shiga (1936), Nojima (1939) Yamamoto (1939) claimed some amount of success, which, however was disputed by Sellard and Pinkerton (1936), Suzaki (1939), Burnet (1940) as they did not observe any sign of multiplication of the bacilli. Chatterjee (1958b,c,d) demonstrated both multiplication and generalisation of Myco. leprae in selected hybrid black mice by using tissue free bacillus suspension, which are awaiting confirmation by further studies.

Rats and other Animals

Fite (1941,b) de Souza Arauja (1941), Barman (1945), Sato (1949), Tanimura and Nishimura (1953), Mitsuda (1941), Ota and Sato (1941), Ota and Nitto (1941) Sato (1951), and many others had tried experimental inoculation in all kinds of animals, fish, birds, frogs, fowl, pig, chicken etc. and in various methods, but no conclusive results could be obtained with regard to successful transmission of Myco. leprae from the diseased to the non-diseased. Ota and Sato claimed in 1941 that they had succeeded in producing local lesions in breast muscle of hen and concluded that of all the laboratory animals, fowl was the most susceptible and in them the disease could be transmitted up to certain generations.
However, the fact remains, in spite of whatever progress has been made in the field of experimental inoculation, that the objective of the search is still to be achieved and the various experiments claiming certain amount of success are under further study and observations.

Pathology of Leprosy

Our inability to cultivate the causative organism of Leprosy artificially, to observe the evolution of the disease in experimental methods, to establish the specific means of transmissions of the disease from diseased to healthy persons has kept the door open for various kinds of subjective inferences and hypothesis to grow. The research and studies on the pathology of the leprosy are, therefore, conditioned by these limitations of our basic knowledge about the disease.

As in the case of other mycobacterium, the most successful reaction to the primary lodgement of *Myco. leprae* at the site of introduction would be their complete suppression in so effective a manner that neither the histological picture, which morbid anatomists seek to recognize, nor the clinical lesions which the physicians strive to identify, are allowed to develop. This is observed in the case of those contacts of leprosy patients (Figueroed and Desai, 1949) who escape histological or clinical evidence of infection although they show a
temporary presence of acid-fast bacilli in the dermis and a
graded, but more lasting, immunological transformation from a
lepromin negative to a lepromin positive condition. It is
presumed that the leprosy bacilli enter into the body through
breach of skin or breach of mucous membrane, but it was shown
(Khanolkar, 1951) that infection may also occur through healthy
skin. The bacilli float about as inert particle in the fluid
watershed and the superficial lymphatic network of the dermis
to all the parts of skin under the epidermis. Then the evolu-
tion of the diseased process depends on the susceptibility of
the individual to leprous infection and this depends on multiple
factors, the knowledge of which is still imperfect such as na-
tural immunity, acquired immunity or some secondary factors
etc. when the suppression of invading organisms is for a while
incomplete - in other words, where there is an initial failure
of the defence mechanism - the mycobacteria adapt themselves
to the new environment in the dermis, slowly multiply and
spread around in the outer layers of the cutis. The defence
mechanism of the human host slowly and very gradually comes
into operation. It is not yet known whether there is a very
early and evanescent phase of tissue response comprising of
changes in the bloodcapillaries, fluid exudation, and a poly-
morphonuclear cell migration to the site of the deposition of
the mycobacteria. The bacilli are ingested by wandering
histocytes but it takes some considerable time to completely
digest the micro-organisms. In the skin biopsies of certain presumably healthy contacts, it was noticed (Khanolkar, 1951) that such cells packed with acid-fast rods and broken-down bacilli, are called fuchsinophil cells because of the retention of basic dye in the cytoplasmic contents in spite of decolorization with weak acids. Presumably this stage may continue for months, even several years, and may finally terminate without any clinical evidence of the disease. It may, therefore, be considered as a 'Silent Phase' of infection. The further evolution of the disease, that is in those persons in whom spontaneous recovery does not take place, usually proceeds at a leisurely pace, with periods of quiescence, interspersed with spurts of abrupt activity.

The leprosy bacilli spread along the lymphatics into regional lymphatic gland or carried along with peri-neural lymphatics to the nerve trunk. Recently it has been shown by electron microscopy (Nishiura et al, 1957) that bacilli is taken up by the phagocytic activity of axon of the nerves. Recent tissue culture studies of the spinal ganglia (Nakai, 1955, 1956) have revealed pinocytosis and a tropistic reaction of the growth cones of the axons. From this finding, it is possible that growth cones of the regenerating axons catch leprosy bacillus and engulf them into exoplasm. In the pinocytosis of the growth cones of the axones, the vacuoles move in the
centripetal direction in the axons. This finding suggests the presence of centripetal stream of axoplasm which would transport the engulfed bacilli towards the spinal ganglion cells. It was also demonstrated by Nishura et al. (1957) that cytoplasm of the Schwann cells which surrounds the normal nerve fibres did not show the presence of bacilli but only in Schwann cells of Bunher cord which probably phagocytosed the bacilli in the empty axon. The leprosy bacilli then multiply in the axoplasm of the nerve fibres and later phagocytosed by the Schwann cells and often remain there dormant in that sheltered location for long periods of time. Under the stimulus of certain supervening changes in the function of the body, as during adolescence, puberty, pregnancy and the onset of mild maladies, the bacilli begin to proliferate in the nerve fibres and appear in large numbers in the intercalated zones, from which they burst out in the endo and perineural tissues. There, they are taken up by the histiocytes which gradually become transformed either into lepra cells or into epithelioid cells depending upon the immunological response of the host to the presence of leprosy bacilli (Khanolkar, 1961). The pathological alterations and the subsequent signs which are observed in the nerves and in the skin are dependent upon distribution of the inflammatory exudate in them and upon the functional impairment of the nerve supply to the cutaneous blood vessels and to the deeper cells of the epidermis.
The pathological changes in leprosy had been described by many workers and here below an attempt is being made to summarise their findings.

**Skin**

Diffuse, infiltration, localised patch with slight or marked infiltration, nodules may be present. Scaling and ulceration may be found.

**Nerves**

Both the cutaneous nerves and nerve trunks may be involved, the affected nerves are thickened sometimes markedly, often unilateral but bilateral and symmetrical in lepromatous cases. The thickening may be present over large parts of the course or in some limited parts only. The thickened nerve is hard and usually tender to touch. There may be round or oval swelling along the course of thickened nerve indicating the position of a nerve abscess. In chronic long standing cases, instead of being thickened, the nerves may be thick and atrophic and consist of little more than bundles of fibrous tissue.

**Lymph Glands**

Regional lymph glands may be enlarged and in some cases slightly generalised glandular enlargement may be found. The changes are more marked in the superficial lymph glands, the glands in the thoracic and abdominal cavities show less marked
changes. The enlarged lymph glands may burst, produce chronic ulcers and sinuses discharging pus.

**Bones**

The bone marrow may be infected and contain lepra bacilli. There may be leprous periostitis, enlargement of nutritive canals of the bones and even cyst formation in the bone. Degenerative changes may be present in the joints.

In the areas supplied by the affected nerves, trophic changes will be found in the bones. The changes in the bones are of trophic nature and results from the combined effect of neurocirculatory changes following on nerve involvement. As a result of pressure and injury on the affected part, there may be ulceration and secondary infection. The small bones of hands and feet are generally affected. The primary changes include decalcification, diffuse rarefaction, concentric atrophy and there may be complete absorption and destruction of bones. The most marked bony changes are found in secondary infection following an ulceration in the affected parts. These include periostitis, sclerosis, necrosis and complete or partial absorption of the bones and degenerative changes in the small joints.

**Eyes**

Leprous lesions include episcleritis, conjunctivitis, keratitis, iritis, irido-cyclitis and panophthalmitis. When the
eyes are involved due to affection of their nerve supply, there may be lagophthalmos, ectropion of the lower eyelid and the anaesthetic eye may be infected with secondary infection.

Gastro Intestinal Tract

There is leprous infiltration or nodulation of the mucous membrane of the lips, tongue and pharynx. Leprous changes have been reported in teeth, specially in the pulp; stomach and intestine do not usually show any gross changes but on microscopic examination may show presence of lepra cells and lepra bacilli. Nodules and ulcers in the intestine have also been found. The liver and spleen may show enlargement. Secondary amyloidosis of the spleen and liver may be present in advanced cases. The gall bladder is rarely affected.

Respiratory Tract

The upper part of respiratory tract, the nose, larynx may show infiltration, nodulation and ulceration, scarring etc. The affection may extend down to trachea, bronchi and bronchioles but lung parenchyma is usually not affected.

Circulatory system

The peripheral blood vessels, both the arteries and the veins may show sclerosis and the presence of leprosy bacilli in the walls. Proliferation of endothelium also is found. Heart and large vessels do not show any change.
Urogenital system:

The kidney, bladder, ovaries etc. do not show any macroscopic changes but microscopically may reveal the presence of leprosy bacillus and lepra cells. In advanced cases, secondary amyloidosis may be seen in the renal glomerules. Testis may show microscopic involvement, hypertrophy and swelling later followed by atrophy, hyalin degeneration of the tubules may be present. In the case of testis, the affection may be marked enough to produce gynaecomastia, i.e. enlargement of the male breast. The presence of leprosy bacilli in the placenta of infective cases of leprosy has been demonstrated but the bacilli are more common on the maternal side than on the foetal side.

Glands of the internal secretion

Microscopic evidence of infection is found in the glands of the internal secretion only in the case of testis, the affection is marked enough to produce symptoms such as gynaecomastia and loss of hair etc.

Histopathology

The histological reactions may be grouped under the following:

- Lepromatous leprosy shows a granulomatous infiltrate.
  Bellow a narrow free zone, directly beneath the epidermis, the 
  infiltrate is massive in the upper and middle portions of the
dermis. In the lower dermis and in the subcutaneous fat, on the other hand, it shows a patchy distribution around the arteries, the veins and the nerves. Histiocytes and lepra cells predominate but, in addition there are lymphocytes, plasma cells and, in older lesions, fibroblasts. Lepra or Virchow cells develop from histiocytes. They are large foamy cells, resembling those of xanthoma. On staining with Ziehl-Neelsen or Fite stain, innumerable bacilli are found, particularly in lepra cells where they may lie in bundles or large clumps, called globules. Lepra, unlike Mycobacterium tuberculosis is not strongly acid-fast and as such sections must be decolorised lightly if suspected (Allan, 1948). In older lesions the develop into fibroblasts and the number of lepra decreases.

Tuberculoid leprosy shows a tuberculoid infiltrate. Patient with tuberculoid leprosy has fairly good immunity against lepra bacillas. This explains, in accordance with Jadassohn - Lewandowsky law, the scarcity or the absence of the bacilli and the tuberculoid tissue response. Sections may show almost pure epithelioid cell tubercle, so that differentiation from sarcoidosis may be difficult. However, a thorough search usually will reveal invasion and destruction of nerves in the dermis or the subcutaneous tissue by epithelioid cell tubercles, which never occur in sarcoidosis. In some cases the
tubercles show a moderate admixture of lymphocytes and contain giant cells. Caseation necrosis, however, does not occur in the skin. Lepra bacilli may be absent in the lesions of tuberculoid leprosy but not infrequently they are found in small numbers after a prolonged search (Arnold, 1945).

Indeterminate leprosy shows only lymphocytic infiltration around the vessels and the nerves of the dermis. Lepra bacilli are found only with difficulty, if at all (Canizares, 1949). Dimorphous leprosy shows histologically lepromatous and tuberculoid lesions. Lepra bacilli are present specially in the lesions of the lepromatous type (Fernandez, Doull & Calcott, 1956).

Lesions in the large peripheral nerves occur in almost every case of leprosy, regardless of type. The histologic appearance of the neural lesions corresponds to that of the cutaneous lesions (Fardo-Castello, Tiant & Pinteyro, 1947). The nerve lesions of lepromatous leprosy show large vacuolated Virchow cells and numerous lepra bacilli. In tuberculoid leprosy one observes in the nerves an extensive infiltrate of epithelioid cell tubercles containing few or no bacilli. However, in contrast with the cutaneous lesions caseation necrosis may occur in the neural lesions of tuberculoid leprosy. In occasional instances, massive caseation of the tuberculoid lesions with complete destruction of nerve tissue occurs.
Histocchemistry

Extensive studies have been made on the histocchemistry of leprous lesions in recent times with the help of different improved staining methods and much light has been thrown on the chemical constituents of leprous lesion. Histochemical methods have been used by some workers in the classification of leprosy (Boramendi 1955, Bergel 1958, Convit et al. 1960).

It was Virchow (1860, 1861) who first claimed that vacuoles in the lepra cells were due to a state of hydropsy. Herrmann (1923) demonstrated a mixture of cholesterol, glycerol and fatty acids in lepra cells. Mitsuda (1928) reported that lepra cells contained lipoid and byeproduct of destruction of leprosy bacillus. Ueda (1949) reported that the chief component of lepra cell was lecithin like fat and that a large quantity of cholesterol is present when there is necrosis of lepra cells. Fite (1951) concluded that vacuoles in lepra cells were made up of a combination of neutral fats, fatty acids and their esters excluding cholesterol.

Harada (1955) observed that phagocytosed bacilli and the cytoplasm of lepra cells undergo fatty degeneration and the neutral fat is discharged into the blood. Ortmann et al. (1956) demonstrated that, inclusions in lepra cells consisted mainly of lipids, polysaccharides and protein components while Sugal (1958)
found phospholipids (lecithin) fatty acids, a small amount of neutral fat and at times sterol.

Wells (1957) demonstrated alkaline, acid phosphatase and non-specific esterase in different types of leprous lesions. In the tuberculoid type of leprosy, acid phosphatase was diffusely present with somewhat greater concentration in the giant cells and epithelioid cells and also present in lymphocytic mass. Strong esterase activity was found in the cytoplasm of giant cells and other large branched cells of the infiltrate. No esterase was found in the epithelioid cells, lymphocytes or plasma cells. The heaviest concentration of esterase activity was found in lepromatous leprosy, specially in lepra cells.

According to Papler et al. (1958), there is more acid phosphatase in lepromatous leprosy than in tuberculoid types. Non-specific esterase, sulfatase was present in the infiltrate of both forms of leprosy.

Imaeda (1960) studied lepra cells with the help of electron stains of various purified lipids and observed that opaque droplet of lepra cells contained lipoprotein. The minute vesicles which arise from disintegration of opaque droplet are composed of phosphatide. The foamy structure, the terminal phase of opaque droplet contains fatty acids, their esters or lower molecular substances. The electron-transparent zone
around leprosy bacilli does not consist of a lipoid phase but of a water phase in which are dissolved the metabolites of the bacilli.

**Review of Biochemistry**

Much work has been done on the biochemical aspects of leprosy in recent years. Reversal of albumin globulin ratio has been reported by Lundin and Boss (1958) and many other workers. It is also reported that during lepra reaction the proportion of globulin increases considerably. Lundin and Boss (loc. cit.) did not find any definite relationship between the total serum calcium and phosphorus in a study of 85 cases.

In leprosy, serum lipids are higher than normal while lipolytic enzyme activity is lower. The higher lipids and lower lipase activity shows correlation between the two and indicates a disturbance in the fat metabolism in leprosy (Gokhale and Godbole, 1957). The cholesterol content of serum of leprosy patients has been found to be lower than that of normal healthy individuals but there has been no difference in the total lipids and phosphatide levels (Kusaka, 1958). Sayama (1958) reports that the serum lipo-protein Sβ of T Cases was 9.2 to 11.1 with a mean of 10.3 while Sβ in L cases showed a wide variation from 3.4 to 13.7 with a mean of 6.6.
Values in respect of blood sugar, uric acid, alkaline phosphatase, cholinesterase activity, cholesterol and serum calcium do not show any appreciable change neither during the reactive phase nor when it is controlled. Hyperlipaemia, hypercupraemia and high E.S.R. are found in reactions in leprosy. They seem to be interrelated. They suggest a disturbance in lipid metabolism during reactions in leprosy (Patau et al., 1962). From Khanolkar's observations (1959, 1960) it may well be postulated that hyperlipaemia in the reactive states is the expression of an overburdened reticulo-endothelial system which is no longer able to contain the multiplying bacilli, their breakdown products and products of their metabolic activity set up in the R.E. Cells. The R.E. cells have an important function in the metabolism and the excretion of cholesterol and lipids (LUZIO, 1960). The possibility that an overloaded reticulo-endothelial system might allow the lipids to pass into the blood causing reaction to appear can not be ruled out lightly.

As early as 1928, hyper-cupraemia was observed in patients with infections by Krebs. Brondestrup (1953) recorded moderate rise in serum copper in acute hepatitis, the copper level falling gradually as the infection subsided. Hypercupraemia has been observed in pregnancy, various infections, Hodgkin's disease, acute leukaemia, lymphosarcoma, aplastic anaemia, hyperthyroidism, haemochromatosis, pernicious anaemia (Cart-
wright, 1955). Ramu (1962) recorded increased copper values in the erythrocyte in the reactive states contrary to the observation of Gubler et al. (1953) that R.B.C. copper is more or less constant whereas plasma copper is increased in many instances of chronic infections.

In a group of subjects of leprosy Seali (1960) has studied the data of the serum aldolase content and the serum transaminase reactions (glutamic-oxalacetic and glutamic-pyruvic transaminase) and has found considerable increase of serum aldolase and a noticeable decrease of transaminase reactions. The author has stressed the analogy existing in the aldolase content in muscular protopathic disease and in leprosy, he has pointed out some doubts concerning the interpretation of the hansenian myodystrophic processes as due to a prior process of neuritis. The decreased values of transaminase enzymes is referred to the general syndrome of microergic deficit, which develops in chronic leprous conditions.

Tigano et al. (1956) while analysing the results of their researches on the behaviour of C - Protein, of protidogram of some serum lability tests in a group of lepers with different clinical forms found the presence of C - reactive protein in more than half of the cases, increase of alpha - 2 and gamma-globulins in almost every case with a corresponding high
percentage of C-reactive protein and increase of alpha-globulins.

E.S.R. is controlled by composition of the plasma with special reference to its content fibrinogen, serum globulin, lipids and certain products of tissue destruction. The sedimentation rate is increased in nephrosis where it may be due to lipaemia. The raised erythrocyte sedimentation rate in the reactive states in leprosy, therefore, is probably associated with the lipaemia.

The Object and Scheme of present investigation

Human serum contains many enzymes concerned with the reaction of transamination. As many as 22 amino acids undergo transamination and each probably has its own specific enzymes. Glutamic oxalacetic transaminase (GOT) and Glutamic pyruvic transaminase (GPT) are the two enzymes which are widely distributed in animal and human tissues and serum. Cohen and Hekhuis (1940) gave a detailed account of these enzymes in various tissues of the body. These were supplemented by Wroblewski in 1958. They reported the highest amount in heart, liver, skeletal muscle and kidney tissue in decreasing order.

Raised titre of serum glutamic oxalacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) occur in conditions which involve death or injury to a large number of metabolically-active cells specially those of...
myocardium and liver parenchyma as they are rich in these enzymes. In myocardial infarction G O T is raised in proportion to the amount of muscle destroyed (e.g. up to 300 units or even more) while G P T is less elevated (seldom to more than 100 units). Increase in these enzymes occurs in all types of liver diseases (Wroblewski and La-Due 1956, Wroblewski, 1957). In infective hepatitis both enzyme levels are greatly increased (e.g. up to and even over 1000 units for both, whereas in cirrhosis G O T is raised more than G P T (in Juvenile cirrhosis G O T up to 800 units and G P T to 250 units, and normal levels in inactive cirrhosis). In obstructive Jaundice both enzymes show moderate elevations (40 to 100 units for both enzymes). Increase in activity occurs in pancreatitis, muscle trauma and secondary Carcinoma of the liver. Similarly high figures have been obtained in case of pseudo-hypertrophic muscular distrophy.

Normally there is a slight diffusion of transaminase enzyme from intact skeletal muscle which accounts for the normal serum activity of transaminase (Zeirlar, 1956). Dystrophic muscle, however, shows increased permeability and a much greater efflux of transaminase as compared with normal muscle and it has a greatly reduced total transaminase content (Dreyfus et al., loc. cit.). In neurogenic muscular atrophy normal levels of transaminase activity are obtained even when the rate of muscular wasting is much greater than that of muscular distrophy.
There is yet no substantial explanation for this differential increase in serum transaminase activity in cases of pseudohypertrophic muscular dystrophy which does not rise in other types of myopathies including the ones secondary to diseases of nervous system. The rate of transaminase release reflects in part the rapidity of tissue destruction and in part amount of tissue involved.

Studies of various works have proved beyond doubt that transaminase estimation, specially $\text{SGOT}$ is a specific test which becomes enhanced only when these enzymes are liberated into the circulation as a result of necrosis of tissues containing these enzymes.

We are handicapped in our knowledge of leprosy relating to some aspects as are known in any other disease of similar importance. While there can be no doubt that Mycobacterium leprae is the essential cause of the disease, it fails to meet a single one of Koch's postulates in that it can not always be found readily in the diseased person, attempt to cultivate the organism has been unsuccessful and that leprosy can not be reproduced in animals. As a consequence of this, our knowledge of many aspects of leprosy is faulty or incomplete and while it is impossible here to avoid making definite statements on
on which conclusions must be based, it is of importance to remember that both statement and conclusions may need radical revision in the light of further research.

The present study is concerned with the estimation of serum Glutamic oxalacetic transaminase (G O T) and Glutamic Pyruvic transaminase (G P T) in leprosy patients in different stages and to correlate different conditions of the patients with the changes in the activities of the above mentioned transaminases. An attempt has also been made to study $.G.O.T. and $.G.P.T. contents in the soluble protein extracts from skin of lepromatous and non-lepromatous cases and compare them with those from skins of normal patients. Estimation of transaminase activities in liver tissue extracts from a few normal persons, patients of infective hepatitis and patients of lepromatous leprosy with reaction has been undertaken to make a comparative study so that role of liver and extent of its damage in lepromatous form may be assessed.

This study is expected to throw some light on the degree of transaminase activities in serum, skin extracts and liver tissue extracts vis-a-vis the extent of cellular necrosis in various tissues affected by leprosy. It may show some light on the pathogenesis of reactions in lepromatous and non-lepromatous forms.