Leprosy: A Perspective of the Results of Experimental Study of the Disease

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To cite this article: H. Bayon (1915) Leprosy: A Perspective of the Results of Experimental Study of the Disease, Annals of Tropical Medicine & Parasitology, 9:1, 1-90, DOI: [10.1080/00034983.1915.11687672](https://doi.org/10.1080/00034983.1915.11687672)

To link to this article: <http://dx.doi.org/10.1080/00034983.1915.11687672>

Published online: 24 Mar 2016.

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LEPROSY: A PERSPECTIVE OF THE RESULTS OF EXPERIMENTAL STUDY OF THE DISEASE

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(Received for publication 18 August, 1914)

PLATES I—VI

CONTENTS

I—INTRODUCTION	I
II—THE CLINICAL NOSOLOGY OF LEPROSY	4
III—MICROSCOPICAL FEATURES OF LEPROUS LESIONS	9
IV—MORPHOLOGY AND STAINING PROPERTIES OF HANSEN'S 'BACILLUS'	18
Analogy with the <i>Mycobacterium tuberculosis</i>	20
V—ARTIFICIAL CULTIVATION OF THE MICRO-ORGANISM OF LEPROSY	23
VI—EXPERIMENTAL TRANSMISSION TO ANIMALS	31
Rat-Leprosy and its Relation to the Human Disease	40
VII—SEROLOGICAL TESTS AND REACTIONS IN LEPROSY	47
VIII—COMMUNICABILITY AND CONTAGION	55
Is the transmission through an intermediate arthropod probable?	60
IX—EARLY AND DIFFERENTIAL DIAGNOSIS. PROGNOSIS	64
X—TREATMENT, SPECIFIC AND PALLIATIVE	70
XI—PREVENTION. HOME AND ASYLUM SEGREGATION. SETTLEMENTS	73
XII—DISCUSSION OF RESULTS AND CONCLUSIONS	77
EXPLANATION OF PLATES	80

I. INTRODUCTION

Leprosy is the name applied to all clinical manifestations produced by an infection with the micro-organism commonly known as 'Hansen's bacillus' (*Mycobacterium leprae*).

It is a disease that has been recognised and feared for centuries, possibly already as far back as 2400 B.C., or in any case about 1300 B.C. (Ebers papyrus). Leprosy as described in Leviticus does

not, however, correspond exactly to the symptoms we know in more modern times. It should, moreover, not be forgotten that the word 'leprosy' is but an approximate rendering of the expression 'zaraath' in the original Hebrew.

Not only is leprosy the 'most ancient disease,' but it is also a widely spread, cosmopolitan scourge, which nearly rivals consumption, syphilis and cancer, if not in numbers, at least in the variety of climatic conditions under which it can flourish and increase. Though at the present day it is found, to any considerable extent, practically only in tropical and sub-tropical countries, it is known that numerous lepers existed in France, Germany, Great Britain, and other countries of Europe throughout the Middle Ages. Opinions differ whether it was imported into Europe from the East through the returning Crusaders. The disease still lingers in Turkey, Russia, the Balkan States, Norway, Spain, Portugal, parts of Italy, etc., in the form of small endemic foci. However, the ruthless individual and, in some cases, collective segregation in the thirteenth and fourteenth centuries, aided no doubt by the improving hygienic conditions of all classes, succeeded in bringing about a practically complete extinction of leprosy in Middle Europe and Great Britain. In addition to this, various plague epidemics also helped in sweeping to an early grave, in a somewhat selective fashion, the vagrant and pauper lepers sooner and quicker than individuals belonging to better situated classes.

The slow if intermittent course of the disease, the extensive mutilations and repulsive features, which are an outstanding symptom of its more advanced stages, have rendered leprosy a subject of terror and horror from time immemorial. That it is contagious has been known for centuries, but it is no doubt mainly due to aesthetic reasons that the fear it engendered was quite out of proportion to the degree in which it is communicable, under usual circumstances, from the diseased to the healthy.

Leprosy presents numerous peculiarities in its pathognomonic features. Not only is its infectivity extremely variable under slightly dissimilar or even identical circumstances, but its period of incubation varies also within very wide limits, anything between one year and twenty-five or thirty. The 'causa prima morbi' has been

known for years and years, and yet the fundamental bases of all bacteriological research, viz., artificial cultivation of the micro-organism and the experimental transmission of the disease, have presented insurmountable difficulties up to the present day. Indeed, these bases are still matters under discussion, and in any case successful results can only be achieved after numerous, repeated, prolonged, pertinacious attempts. The large numbers of bacteria which may be present in single leprotic lesions are certainly not surpassed in any other disease, with the possible exception of bubonic plague.

An excellent instance showing the influence that bacteriology exercises on clinical medicine is to be found in the effects resulting from the discovery of the 'bacillus' of leprosy by Armauer Hansen in 1872. It is true that definite knowledge of the morphology of the micro-organism was only obtained after Neisser had succeeded in demonstrating it by means of an 'acid-fast' stain in 1879. However, from the moment the bacterial origin of the disease was recognised, the communicability of leprosy became scientifically established, and all doubts in that connection could only be the outcome of an incomplete or lacking comprehension of the application of the laws of biology to practical medicine.

On the other hand the extreme difficulty encountered in transmitting the disease to animals, the repeated lack of success attending the inoculation of leprosy material into human beings (with one exception: Arning), have allowed much doubt to arise regarding the exact fashion in which leprosy is transmitted. Even the purely bacteriological observation of the fact that apparently the 'bacilli' could not be artificially cultivated, and isolated from the lesions they produced, has seriously hampered the therapeutic outlook.

Leprosy slowly and surely became the disease of negations; it could not be experimentally transmitted, its bacterium could not be isolated in artificial culture, and so to complete the list, leprosy could not be treated, let alone arrested, and no hope of cure could be entertained.

It is my intention to show whether recent experimental work allows, enables, or justifies us in taking a more active and positive view of the situation.

II. THE CLINICAL NOSOLOGY OF LEPROSY

Two clinical types of the disease are generally distinguished and no more. Such views are partly owing to the influence of Hansen, who considered that it was not necessary to make further sub-divisions because practically all lepers presented features at one time or another of their existence (that is, if they lived long enough) which allowed them to be classed either as cases of (i) nodular (hypertrophic) leprosy, or (ii) maculo-anaesthetic, otherwise called atrophic, smooth leprosy.

From a purely clinical point of view this classification holds good, however, only within certain limits. It is a commonly accepted rule of nosology that bedside or clinical nomenclature does not take into consideration so much the eventual course of a disease, as its etiology and the symptoms and appearances which, however fleeting and changeable, can be brought under a definite scheme of relative incidental constancy. The classification used in relation to recognised clinical types of tuberculosis, syphilis, and other complaints, which often run a chronic course and vary largely in their symptomatology, seems clearly to show which are the determining factors ruling the designation of clinical entities.

It is no doubt quite correct, from a general point of view, to state, as Hansen did, that a 'mixed' leper (i.e., a patient who from the very beginning shows features of both the nodular and maculo-anaesthetic type) who lives long enough and undergoes a natural process of elimination of the great majority of the acid-fast 'bacilli' from his lesions, will eventually be classifiable as a purely anaesthetic leper. Many of these instances of 'lepra mixta,' however, do not reach this ultimate stage, because death steps in before completion of the process of evolution into a different type, and in any case the primary condition may last for many years.

Without unnecessarily labouring this point any further, I believe that there is quite sufficient justification in considering every single case of leprosy as classifiable on the basis of the clinical and bacterioscopic features at the time of examination, irrespective of the expected course of the disease later on. In other words, the clinical diagnosis is to be considered of a temporary nature, as far as the naked eye appearances (and to a certain extent also the bacterioscopic results) are concerned. The diagnosis leprosy is the

only unchangeable feature, though it may need modification by the adjectives 'arrested' or possibly even 'cured.'

Leaving aside sub-divisions founded on partial or purely localised symptoms, I believe that on examination of any great number of lepers, in any part of the world, more or less numerous specimens of the following varieties or even distinct types of the disease may be distinguished.

1. Nodular type with more or less marked or diffuse tuberosities which generally are most developed on the face, but of course can also affect any other part of the body, including (though somewhat rarely) the scalp, the soles of the feet, the tongue, and the palms of the hands. Leprous nodules should contain numerous acid-fast micro-organisms, and in certain instances may be located as loose or movable small lumps which can be shelled out from under the skin.

Nodular leprosy may give rise to visceral lesions, which are remarkable for the enormous quantity of acid-fast 'bacilli' that can be detected accumulated in the tissues of the spleen, liver, testicles, lymphatic glands and lungs.

2. Maculo-anaesthetic type with more or less numerous spots which have a slight predilection for the trunk (chest, back, buttocks) but are certainly also very frequently present on the limbs. The spots in advanced cases may show a greater or lesser amount of anaesthesia. It should be noted that often the anaesthesia is definitely localized in portions not showing any maculae. In many cases, however, the anaesthesia is by no means complete, and should more correctly be termed paraesthesia. The patients cannot distinguish hot and cold, sharp or blunt in the affected areas, but are still sensitive to touch. In early stages the maculae may present a ringed appearance; the centre then may be normal in relation to sense of touch, etc., whilst the outer ring, if anything, is slightly hyperaesthetic.

The maculae appear to be the result of the localisation (and possibly disintegration) of a small number of casual micro-organisms in the skin. The anaesthetic areas are due to the 'bacilli' invading the sheath of the nerves, causing a proliferation of connective tissue, which brings about a slow degeneration of the corresponding nerve fibres. In advanced cases the bacilli invade

the ganglia of the spinal cord, hence the practical impossibility, under certain circumstances, of distinguishing leprosy clinically from syringomyelia.

3. Mixed or combined leprosy, that is, cases where from the very earliest noticeable onset of the disease, and for years afterwards, definite areas of paraesthesia (insensibility to heat and cold, incapacity of distinguishing blunt from sharp) and anaesthesia can be made out, accompanied by maculae and small nodules teeming with acid-fast bacteria.

An excellent description of this type has been given by Glück, who called it '*lepra tubero-anaesthetica*.'

These three main types can be sub-divided into the following relatively rare varieties and singular forms:

1. Lupoid or serpiginous leprosy. Among the 2,000 lepers I have had under observation in South Africa I have only met with the disease three times. Another instance of the variety was seen in London. It is recognisable as leprosy by the presence of nerve-lesions, but acid-fast micro-organisms are very scarce indeed in any of the superficial patches. The expression 'patches' is used because the skin-lesions are much more raised and thickened than mere 'maculae,' and yet do not deserve the appellation of nodules, being too flat and extensive. They spread by forming peculiar confluent configurations, which can be best recognised by referring to Pl. V, fig. 1.

The patches are a peculiar coppery colour, and do not show any marked tendency to break down and ulcerate, which in addition to other peculiarities distinguishes them from lupus.

At times single patches whose colour, texture and general appearance corresponds closely to that of these serpiginous lesions, are noticeable in cases of leprosy, whose remaining clinical features differ in no other fashion from the usual nodular type.

In other instances the patches may not be confluent and serpiginous, but are distributed unevenly all over the body, varying in size from the diameter of a threepenny-bit to the extent of a man's hand or more. They may appear relatively rapidly, within a fortnight or so, and are accompanied by localised paraesthesia. In such case the diagnosis usually presents considerable difficulty, because acid-fast bacteria may be practically absent in the lesions and nasal mucosa.

Jadassohn has described somewhat similar varieties of leprosy as the 'tuberkulid' type, in view of the resemblance which microscopical specimens of the lesions bear to tuberculosis of the skin.

2. Many cases of maculo-anaesthetic leprosy begin with paraesthesia, numbness, and a peculiar 'leathery' feeling, usually of the ring and little finger of one hand, or tingling sensations with small areas of definite anaesthesia may be present in a hand or foot. Such conditions can last for a considerable time, as much as three or more years, before definite maculae make their appearance. Some cases, after a prolonged premonitory stage of this nature, may develop nodules and finish as definite hypertrophic leprosy.

Maculo-anaesthetic lepers may heal in such a fashion as to allow hardly any traces of their spots being visible to the naked eye; the trained observer may just be able to make out a simple configurated discoloration or slight livido. Needless to say, definite areas of anaesthesia are usually easily made out in these patients. As long as these conditions last it appears quite correct to classify them as simple paraesthetic or anaesthetic leprosy.

3. Under certain circumstances maculae or spots may appear before any nerve symptoms are traceable. Even to the experienced clinician the leprotic nature of the spots may appear doubtful, other conclusive symptoms being absent and possibly no history of contact being available, though the latter has but a relative value. In these rare occasions only prolonged observation, aided and controlled by the microscope, can afford us certainty in diagnosis. Eventually, in the course of time, a definite maculo-anaesthetic stage is reached, but during this initial period the condition is one of simple macular leprosy.

When dealing with dark-skinned races great care must be taken not to mistake for macular leprosy one of the numerous tineae which have been so ably classified and investigated by Castellani.

4. In some instances leprotic symptoms are seen which are somewhat too prominent to deserve still the name of 'maculae' or spots. The edges are considerably more raised than is usually the case in smooth leprous lesions, owing to active proliferation of the superficial dermal tissue. The periphery is studded with numerous minute papulae, which have a somewhat vesicular appearance. The central portion may or may not participate in this process of granulation, but a certain degree of desquamation is generally

present. In any case the appearance of the inner area is angrier and more 'active-looking' than what is seen in the usual run of maculae, though parts of the surface do not usually participate to such a marked degree in the process of granulation and eruption noticeable at the margin.

It may be objected that practically all maculae of lepers go through periods of increased activity or exacerbation, during which they may show some of the appearances described. However, the case illustrated in Pl. V, fig. 2, has remained in this condition for over three years, and moreover, the localisation of the lesion is somewhat peculiar. In addition, the maculae of many lepers never reach the condition of marginate proliferation shown in the photograph.

Of course this whole condition is but the result of an intensified tissue reaction, such as generally takes place to a much lesser degree in most maculae. The diagnosis, however, may still present difficulties, because, as in the instance illustrated, other definite leprotic symptoms, such as anaesthesia, may be absent or cannot be detected at the time of examination. I should like to draw attention to the existence of these intensified 'maculae' without insisting on their separate classification.

5. Diffuse or hyperaemic leprosy is also scarcely a separate variety, but simply an initial or premonitory stage of nodular leprosy. It consists in a peculiar diffuse, puffy swelling of the eyebrows, the lobes of the ears and the alae nasi, which in addition takes on a peculiar pinkish-bluish hue. This condition may last for years and imperceptibly merge into the well-known condition of leprosy generally known as 'facies leonina.' In rare instances the disease may not make further progress, but eventually improves and leaves, as the only trace, a peculiar wrinkled and dry appearance of the skin of the face. I have so far not found any of such arrested cases without smaller or larger areas of anaesthesia.

These three types and five varieties or peculiar diversities from the usual clinical appearances of leprosy appear to me to cover all forms of leprosy, as far as I have been able to observe them. In addition, there are numerous combinations which can result through atypical and transitory appearances of the disease mixing in varying proportions.

Bullae, ulcers, suppurations and necrosis may considerably alter and add complexity to the clinical features of the symptomatology of leprosy. They should, however, be considered as complications of the primary infection; moreover, they are too variable and inconstant to allow definite systematization.

Careful description of the majority of these symptoms is also given by Abraham (1910) where special stress is laid on the fact, and rightly too, that the diagnosis is in many cases but the description of a stage of the disease.

These various sub-divisions have not been made to complicate further a diagnosis which under usual circumstances is already sufficiently difficult, but on the contrary to induce a careful observation of the various phenomena of a disease whose correct, exact, and above all early recognition is at all times a matter of considerable importance.

On two occasions I have noticed in lepers peculiar psoriasis-like maculae, but in these instances the possibility of psoriasis and leprosy occurring together could not be excluded.

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III. MICROSCOPICAL FEATURES OF LEPROUS LESIONS

The minute anatomy of leprotic lesions or histo-pathology of leprosy is the study, by means of the microscope, of the relationship or direct and indirect action of the lepra-bacterium to and on the tissues it has invaded. Accordingly, every investigation or analysis of the appearances detected by the microscope must take into consideration not only the presence or absence of acid-fast 'bacilli,' but also, in the former eventuality, the quantity and localisation of the 'bacilli' discernible in the sections being examined. Accordingly it is to be understood that the microscopical diagnosis of a leprosy lesion is bacterioscopic and histo-analytic.

Good descriptions of the microscopical appearances of leprosy have been given by Lie, MacLeod, Jadassohn and others, and an even prolonged observation of the material available in South Africa does not bring to light any new facts of fundamental importance, except to show once more the necessity of clearly distinguishing between leprosy and tuberculosis by means of animal experiments and any other methods available for the purpose. In referring to the lesions found in the spleens of lepers, MacLeod (1910) expresses his view as follows (page 314):

'In the spleen, in addition to leprosy infiltrations in the trabeculae, pulp and malpighian corpuscles, extensive necrotic masses have been described by Arning (Schäffer, *Leprosy*, 1900, I, p. 11) like those of tuberculosis with typical Langhans giant cells. Such cases have to be further verified from the point of view of tuberculosis before they can be finally accepted.'

In several autopsies (5) at Robben Island I have found in the spleen of nodular lepers lesions similar to, if not identical with, those described and illustrated by Schäffer. The inoculation experiments into guinea-pigs were, however, positive; that is, the animals experimented upon died within two to four months with extensive generalized lesions of a tuberculous nature.

These investigations are by no means concluded, and they have the limited value of single instances. They simply show that 'tuberculous' lesions in a leper are not necessarily always caused by Hansen's 'bacillus' alone.

The uncompromising standpoint of Hansen, that leprosy and tuberculosis were so absolutely distinct from each other that no single common feature was thinkable, is no more defensible or convenient, not even from a didactic point of view. At the present day we have learnt through the more intimate knowledge of many maladies and the properties of numerous pathogenic micro-organisms, that dissimilar diseases can be caused by microbes which are practically indistinguishable, and that on the other hand analogous pathological conditions can be brought about by micro-organisms which behave in a totally different fashion in artificial culture and laboratory tests. As cases in point it is only necessary to mention at random yaws and syphilis; kala-azar, infantile splenomegaly and oriental sore; typhoid and paratyphoid; human

and bovine tuberculosis, plague and pseudo-tuberculosis. Pathology has learnt the truth of Goethe's dictum 'Alles ist Ubergang.' The increasing exactitude of clinical methods of observation ought to enable us to avoid the pitfall of considering two allied diseases as identical, since we understand that hard and fast types are only extant for the purpose of classification.

For some time discussion has been rife whether leprotic tissue ever contained giant cells of the Langhans type. It is now practically unanimously admitted by those who have had opportunity of seeing a sufficient number of slides from different cases, that giant cells do occur in typical leprotic tissues, for they have been observed by Thoma, Jadassohn, Ramon y Cajal, Rikli, Schaeffer, Dohi, Babes, Kedrowsky, Matsuda, Gurd, Bayon and G. W. Robertson (verbal communication). Even Lie, who originally held that giant cells were only present in leprosy when the disease was complicated by tuberculosis, now admits their presence, with the reservation that they are not morphologically absolutely identical to the Langhans type found in tuberculosis (verbal communication).

In discussing the nosology of leprosy, stress was laid on the temporary nature of many conditions in leprosy, as a result of the extremely chronic course of the disease and the facility with which it can be complicated by other infections. In addition we have to consider the multifarious appearances of the disease *per se*. These factors influence also the histological features to a considerable extent, so that it is not possible to state, except in a somewhat general fashion, which are the microscopical features that render the diagnosis 'leprosy' certain in any section. No single element is of decisive value, except the presence of numerous acid-fast rods, and this even with several qualifications. Hansen's 'bacillus' is generally only to be found in large numbers in advanced nodules and nerve-lesions, and is practically absent from maculae and leprotic papulae, that is, only to be detected after a very prolonged search and by special methods.

Unna's definition of a leproma is as follows:—

' a diffuse granuloma, whose peculiarity consists, on the one hand, in its limitation to the connective tissue elements, and specially to the lymphatic system of the skin, and on the other in the enormous growth of organisms, whose number far exceeds

anything we are accustomed to find in other infectious diseases. . . . To the paucity of the cellular elements and the preponderance of the organisms dormant in the bacillary mucus, the remarkable indolence and relative benignancy of these growths may be ascribed.' (Unna-Walker; *The Histopathology of the Diseases of the Skin*, 1896, p. 616.)

Jadassohn sums up his investigations on the subject in the following words* (l.c. p. 871):—

'The leprosy bacillus produces a non-characteristic type of inflammation, attended by the formation of granulomatous tissues with different features of a degenerative character, which can even deserve to be classified as necrosis; this may in some instances take on a tuberculous appearance, signalised by sclerosis, and direct or indirect destruction (Untergang) of various specific parenchymata. As a rule the leprosy bacillus causes only an indolent reaction and the resistance displayed by tissue against its luxuriant growth (Wucherung) and toxins is quite remarkable. Deposits of bacilli may be detected even in tissue which otherwise appears to be quite normal, and in cells which cannot be shown to be altered in any known fashion. The histological features are also very variable as a result of the diversity of clinical types.'

'The typical leproma, wherever it may be situated in the body, has the broad characteristics of other infective granulomata, with certain peculiarities which render its diagnosis possible' (MacLeod).

It is evident from what has been said above that distinctive features need not necessarily be present in many lesions which from their occurrence and localisation we know to be definitely leprotic. By avoiding generalisation, and considering single types and anatomical situations by themselves, it is, however, possible to recognise certain definite, recurring, important features.

Skin. Nodules. Numerous acid-fast rods occur, especially in matted groups, there is absence of advanced necrosis (except in the presence of open sores), and no caseation or giant cells with a necrotic centre. Giant cells containing single acid-fast 'bacilli' may, however, be present, but generally they are not numerous, and show fewer peripheral nuclei than is the case in tuberculosis. The 'bacilli' may be scattered loosely in the parenchyma of the nodule

* Translated by the Author of this paper.

or may have invaded various cells of endothelial and fibroblastic origin, in which case it is especially remarkable that the structure of the protoplasm and nucleus or even the morphology of the bacterial acid-fast rods has not suffered in any noticeable fashion. Plasma cells are rare as opposed to yaws and syphilis, where they are especially numerous.

A peculiar narrow band of hyaline, glassy tissue, containing no 'bacilli,' is often noticeable just under the epidermis.

Acid-fast bacteria may be present in such quantities that in stained sections (Ziehl-Nielsen) the whole tissue appears a dull red to the naked eye. In other instances 'bacilli,' though very numerous, are distributed singly or by twos and threes, and can only be detected with high-power lenses.

Skin. Patches. Acid-fast bacteria are not numerous. They can only be detected with great difficulty. They are not bunched or massed, but present in little groups of few 'bacilli,' which may apparently be situated extra-cellularly or they may have invaded cells without causing any alteration in the structure of either protoplasm or nucleus.

Giant cells with numerous peripheral nuclei are often present. At times a peculiar coagulation or discrete necrosis of the tissue may be noted in parts, which shows hardly any definite structure. It has a filamentary appearance and stains easily with eosin. Such small areas of degeneration are circumscribed and show one or two giant-cells at the periphery.

The vessels and capillaries can be seen partaking in a process of proliferation, accompanied by an increase in the number of endothelial cells forming their walls.

The epidermis is often found thinner than usual, and the epithelial villi are somewhat flattened out, or the epithelium may appear as a border of uniform breadth.

Spindle-shaped cells (young connective tissue cells) may be numerous, and plasma cells are not infrequent.

Skin. Maculae. Nodules and patches partake of the nature of infectious granulomata. The macula belongs, however, to another pathological group, which can be compared with a condition of slight chronic irritation, possibly not very dissimilar to that seen in Erythema perstans.

Various degrees of perivascular cellular deposit correspond to the different intensity of eruption in single maculae, but, as a rule, a slight infiltration of spindle and round cells can be detected surrounding the capillaries and sweat-glands. The hair-follicles may also undergo a similar process of localised infiltration and proliferation. Giant cells may be present, but hardly any acid-fast bacilli, unless nodules are to be found in other parts of the body.

The histological appearances I have described agree with the view that maculae are a local anaphylactic symptom, caused by the toxic products set free by the lepra-bacilli, after disintegration induced through the agency of the defensive properties of the tissues involved. This process takes place, however, when only few germs are present, because lepra 'bacilli' in common with other acid-fast micro-organisms are very resistant.

Regarding the changes occurring in the peripheral nervous system, the suggestion has been made by Lie that 'bacilli' are only present in maculae at the very beginning, and that later they disappear into the nerve-endings and finally ascend along the peripheral nerves. It can, however, be objected that in many cases anaesthesia appears to set in without the primary production of maculae in the corresponding area, and that many maculae do not show any definite anaesthetic symptoms, though they have lasted for years.

The other hypothesis considers the neuritis to be a descending process (a contrast to the 'ascending' process put forward by Lie), and accordingly the result of deposit following generalised infection. In any case, though the nerves may be involved in any single type of leprosy, it is in the maculo-anaesthetic type that this invasion and localisation gives rise to the most striking and apparently relatively rapid results.

In thickened peripheral nerves, under certain circumstances, numerous 'bacilli' may be found, as in skin lesions. Generally they are situated in massed groups in the spindle-cells of the perineurium, or loose in the interstitial lymphatic spaces; at times they may be distributed with a certain regularity in the cells of the endoneurium, so that they appear to be in rows rather than in clumps. In the course of time they may get eliminated and leave behind a marked thickening, consisting of connective tissue with a

few stray degenerated and fragmented nerve fibres, in which the general disposition of a nerve-bundle is still recognisable.

Practically every organ of the body has been found to be the site of leprotic lesions by some observer or other, but deposits of lepra-bacilli are more usually found in the lungs, liver, spleen and testes. In the lungs the frequent complication with tuberculosis is very disconcerting, and in many instances a decision as to the pathological process involved can only be arrived at by tests with inoculated guinea-pigs, though it is quite possible that even this crucial experiment may not have an absolutely decisive value. Babes gave considerable attention to the question of the lesions found in the lungs of lepers, and has come to the following conclusions which well deserve to be quoted in full:

- (1) The lungs are normal, and do not contain lepra bacilli.
- (2) They appear healthy to the naked eye and under the microscope, but notwithstanding contain leprosy micro-organisms.
- (3) They show the features of hypostatic pneumonia or broncho-pneumonia, without any leprosy micro-organisms being recognisable, whilst pneumococci and streptococci are present.
- (4) They may show signs of tubercular localisation with excavations, caseous pneumonia and peribronchial nodules, tubercle bacilli and without the leprosy micro-organisms.
- (5) In one single case he found caseous degeneration without any tubercle or leprosy bacilli or other bacteria.
- (6) In cases of chronic interstitial pneumonia peribronchial foci of a leprosy nature were noticed.
- (7) The lungs may be the seat of extensive desquamative or fibrinous localisation of a leprosy nature, with countless lepra bacilli, which may be accompanied by the formation of vomicae.
- (8) Gangrenous bronchial cavities, and bronchial affections of a leprosy nature, were found in the centre of necrotic foci or surrounded by an interstitial or desquamative pneumonia.
- (9) Cases exist where leprosy and tuberculous lesions combine, and accordingly are very difficult to diagnose correctly.

The lesions of leprosy lungs are very similar to those of tubercle, but it must be remarked that leprosy runs a more chronic course, the resulting tissues are more solid, caseate less frequently, and are less prone to be destroyed or eliminated. When considered from this standpoint leprosy lesions in the lungs resemble the late manifestations of syphilis of the lungs.

We are thus enabled to distinguish not only a chronic diffuse interstitial or trabecular form of leprosy of the lungs and a sclerotic nodular form, but also an acute, and at times caseating, parenchymatous variety of the disease. In the latter we also find fibrinous-pneumonic catarrhal lesions.

In all cases he succeeded in proving, by means of cultures, and in some cases also by microscopical examination in the bronchial forms, the presence of diphtheroids in company with the lepra bacilli. These organisms are associated at times and in varying manner with bacilli of the coli group; at other times with filamentary, branching micro-organisms or with streptococci or pneumococci in the acute pneumonic or caseating varieties ('Lepra; Handbuch der pathogenen Micro-organismen' of Kolle-Wassermann, 1906, *Ergänzungsband*, pp. 174-175).'

Leprotic lesions of the other organs may be accompanied by a greater or lesser degree of amyloid degeneration. Amyloid of the spleen, liver, kidneys, may be present in lepers who die with the features of anaesthetic cases, but typical leprotic lesions of the inner organs are generally only found in nodular cases.

Liver. The most frequent change noted is a peculiar interstitial infiltration, accompanied by numerous acid-fast rods situated in 'lepra-cells,' that is, mononucleated round cells whose protoplasm is swollen out and riddled with vacuoles. The liver cells may also contain 'bacilli,' though this is not frequent. Generally the parenchymatous cells are but slightly altered, except for the presence of lardaceous disease, and under certain circumstances may contain a deposit of brownish-yellow pigment. The capillaries appear dilated and may also contain lepra-micro-organisms, which may have invaded the endothelium or lie loosely in the lumen.

In common with the other organs it is often very difficult to decide in sections of the liver whether we are dealing with simple deposits of 'bacilli' which have been carried by the blood stream and have accumulated passively in the walls of the capillaries, or whether we are dealing with a chronic but progressive pathological process involving multiplication of the germs and an ever increasing local spread of the leprous lesions.

In single cases giant cells and necrosis were detected, but I fear that in these instances a complicating tuberculosis could not be excluded. The same applies to the similar alterations seen in the spleen.

Spleen. In the spleen the acid-fast bacteria can be so numerous that their presence can be detected by the naked eye on staining. They may be scattered about in small clumps in the pulp, especially in the neighbourhood of the capillaries. The presence of lepra-cells may be under certain circumstances a noticeable feature of the lesion. Though a spleen may be in an advanced

stage of leprotic invasion the resulting enlargement may be hardly noticeable.

Testicles. The connective tissue between the tubuli is seen to have proliferated actively, and to contain more or less numerous acid-fast rods, some lying loosely, others enclosed in lepra-cells and in the endothelium of capillaries.

Numerous degrees of connective tissue proliferation can be found in the testicles from different patients, and under certain circumstances even from different parts of the same testicle. The bacilli present also vary very much in numbers—from few bacilli, which can only be detected by means of an oil-immersion lens, to deposits rivalling in numbers those seen in the nodules of some lepers.

Lymphatic glands. There is no doubt that the bronchial, mesenteric, and other lymphatic glands can be affected by a pure leprous infiltration, which microscopically shows very numerous acid-fast rods enclosed in cells of different sizes, some with hypertrophied protoplasm containing numerous vacuoles. Lymphatic glands may also be the seat of a mixed infection with tuberculosis and show necrosis and caseation.

From this brief survey it will be seen that in dealing with the microscopical diagnosis of leprotic lesions we are continually faced with the difficulty of distinguishing lepra from tuberculosis, and that in many instances the decision must be left with the results of inoculation into guinea-pigs.

It should not be forgotten that leprosy is a slower and more chronic complaint than even tuberculosis, and that in certain instances the possibility is given that a tubercle which has spontaneously healed may be invaded by Hansen's 'bacillus,' in which case the crucial experiment on animals would give a negative result, though the histological lesions might show a definite tuberculous character.

With the exception of cases where the presence of numerous giant cells of the Langhans type, or very similar in appearance to those seen in tuberculosis, coupled with necrosis or caseation, render the presence of a mixed infection with tubercle probable, the main microscopical features of a leprotic lesion can be summed up in the following words:

Very numerous acid-fast micro-organisms, singly or in matted

clumps, lie loose in the tissues and lymphatics or wedged in compact masses in interstitial spaces. Similar acid-fast bacteria may be present in varying numbers in the protoplasm of various cells, in which under certain circumstances vacuoles can be detected. The endothelial cells of the lymphatics may also show a marked degree of bacterial invasion. The tissue reaction and production of connective tissue is relatively insignificant in all instances, and the resulting degeneration or necrosis of the tissues affected is quite minimal in proportion to the number of germs present in the lesions.

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IV. MORPHOLOGY AND STAINING PROPERTIES OF HANSEN'S 'BACILLUS'

The *Mycobacterium leprae* belongs to a group of acid-fast bacteria which in morphology and staining reactions are very similar to the *Mycobacterium tuberculosis*. The group may be considered to consist of the micro-organisms causing spontaneous tuberculous disease in human beings, cattle, horses, pigs, birds, etc. All these bacteria are relatively easily isolated on artificial media, at body heat, from the lesions in warm-blooded animals, with morphological and tinctorial properties analogous to those which may be seen in infected tissues. A sub-division of this group embraces several acid-fast germs, which are generally present in diseased tissues in enormous quantities and are extremely difficult to isolate in artificial culture. This sub-division may be considered to include the *Mycobacterium leprae*, the *M. leprae rodentium* (rat leprosy 'bacillus'), and the micro-organism of Johne's disease in cattle, and that causing the analogous disease of sheep mentioned by Twort and Ingram, Vukovic, McGowan. It is quite evident

that a classification based on such principles cannot be satisfactory from a bacteriological standpoint, but it is simply brought forward to show once more that the leprosy 'bacillus' does not stand absolutely alone in many of its peculiarities.

Lehmann and Neumann's (1912) definition of the group *Mycobacterium* is the following (p. 582):

'Thin, slender rods, often showing typical dichotomous branching, at times giving rise to filaments, with or without branching. If stained with warm carbol-fuchsin, the colouring matter cannot be extracted by acids, that is to say, the bacteria are acid-fast and behave towards stains somewhat like the spores of common fission-fungi. In some species the acid-fast properties are but slightly developed; in fact, may even be absent.'

According to Lehmann and Neumann's definition, the mycobacteria are not true 'bacilli,' and the possibility of micro-organisms of the group showing true branching is recognised, as also the fact that acid-fastness is a property which varies in different bacteria belonging to the group. These admissions are important in view of the fact that lately some bacteriologists have denied both conclusions when applied to the microbe of leprosy.

A satisfactory classification of Hansen's 'bacillus' is not a matter of purely theoretical interest. It has definite practical importance, because we have reason to expect that an exact knowledge of its bionomics will help isolation by means of artificial culture, and in such a fashion clear up the numerous obscure points in connection with the epidemiology and therapeutics of leprosy.

The irregular morphology of the micro-organism of leprosy tends to confirm the view that it is not a true 'bacillus,' because of the lack of constancy in shape, thickness and length, which in addition to various other features connected with the presence of endogenous spores, flagella, etc., determines the diagnosis 'bacillus.' The lepra bacterium is markedly pleomorphic, that is to say, in smears from nodules single germs can be detected which vary in thickness between 0.3μ and 0.5μ , and whose length may be anything between 1μ and 5μ and in rarer instances even 6μ or 7μ .

Hansen's 'bacillus' is often seen to contain small, fine granules (Babes-Ernst) which are not as acid-proof as the rest of the

bacterium. At times, peculiar hyaline breaks can be detected in the rods; they have been considered to be spores.

Another peculiarity of the bacillus is its breaking up into small coccoid bodies, which Deycke considered to be a sign of degeneration, but which the observations of Martinez-Santamaria seem to indicate are possibly developmental stages prior to multiplication.

The reasons for which it is possible to classify Hansen's 'bacillus' as the acid-fast stage of a *Mycobacterium* closely allied to the *Actinomyces* are based on morphological grounds and deductions by analogy, in addition to the interpretation of cultural attempts.

The morphology of Hansen's 'bacillus,' when examined with high-power lenses (say 2 mm. apochromatic, comp. eyepiece No. 12) and in sufficiently thin smears, can be seen to be exceptionally variable; structures with one end tapering and the other definitely thickened (clubbed) are mixed with rods of uniform thickness but of different lengths and fragments, which seem to consist of a series or chain of small beadlike coccoid bacteria.

At times in smears taken from nodules branching forms are seen; they are, however, rare. These peculiar pleomorphic appearances, especially the clubbed and branching forms, are typical of the fragments of actinomycotic germs having the tendency to break up into acid-fast fragments. The variations in morphology have lately been commented upon by Galli-Valerio, who, in discussing the relationship of the genera *Corynebacterium*, *Mycobacterium* and *Actinomyces*, has not failed to note the numerous points of contact between these groups.

From the standpoint of analogy we know from the observations of Petrone (1884), Metschnikoff (1888), Fischel (1892), Babes and Levaditi (1897), Schulze (1899), Lubarsch (1899), Lehmann and Neumann (1912), Galli-Valerio (1912), Foulerton, and others, that true branching can occur in *Mycobacterium tuberculosis* and that its appearances in sputum and tissues of experimental animals are at times distinctly like those brought about by actinomycotic germs, especially in the production of radiary deposits of bacteria. Abbot and Gildersleeve have noted similar appearances in connection with 'saprophytic' micro-organisms. Further, observations of Silberschmidt (1899), Galli-Valerio (1910), Birt and Leishman, and

others, have made us acquainted with a group of germs which clearly can be classed with the Actinomyces or Streptothrix class, yet in artificial cultures and on injection into animals show numerous acid-fast fragments very similar to *M. tuberculosis*.

That an acid-fast rod seen in tissues, can be found to be a filamentary branching micro-organism in artificial cultures, is an observation which has been made so repeatedly by those working with *A. caprae*, Birt and Leishman's Streptothrix, that there is no necessity to dilate further on the subject.

Accordingly we may deduce that it is by no means far-fetched to suggest that Hansen's 'bacillus' may present a filamentary, acid-labile appearance in artificial culture, though the *M. tuberculosis* is consistently acid-fast on the usual laboratory media: and even in this instance Frei and Pokschischewsky, and later Wherry, have shown that under certain circumstances this property can be made to vary.

The interpretation of the cultural results of investigators whose bacteriological technique was not open to criticism (Beauchamp Williams) shows us that in the great majority of cases their culture tubes have either remained sterile for months and months (Fraser and Fletcher), or that their repeated efforts were only rewarded by the isolation of a singularly pleomorphic diphtheroid with slight acid-resisting properties, that is to say, that after prolonged staining with carbol-fuchsin it could be, and was, only partially bleached by a weak acid such as one per cent. sulphuric. This diphtheroid was usually found to have peculiar filamentary forms.

The relationship of the genus Corynebacteria to the Actinomyces is also very close; to give an example out of a numerous series we have the *Corynebacterium necrophorum* (Lehman and Neumann) which Schmorl considers as a Streptothrix and other authors as an Actinomyces.

As a matter of fact, the bacteriological literature of the last ten years contains numerous, indeed very numerous, hints that a strict separation of bacteria on cultural characteristics alone is extremely difficult, to say the very least, because of the existence of very many micro-organisms which do not conform in every case with any single distinctive test or feature.

It will be seen that, though definite reasons are extant to

postulate that Hansen's 'bacillus' belongs in reality to the Actinomyces, Actinobacteria or ray-fungus group, still the last conclusive test is a matter of surmounting the difficulties inherent to the artificial isolation and cultivation of this bacterium.

STAINING PROPERTIES OF HANSEN'S 'BACILLUS.'

In a recently published study on the bacteriology of human and rat leprosy Wolbach and Honeij (1914) come to the conclusion that :

'The possibility that the non-acid-fast and acid-fast organisms isolated from cases of leprosy are related and may be converted one into the other is one we must take, however reluctantly, into consideration, because of the great length of time the leprosy bacillus resides in the human body and the variety of conditions it is subjected to by virtue of the stage of the lesion and anatomical situation. The loss and acquisition of properties as distinctive as that of acid-resistance are well known in the field of bacteriology and indeed the changes undergone by the tubercle bacillus towards staining reactions is the strongest claim for the possibility.

Very numerous methods have been published with the purpose of communicating a strictly specific stain for the leprosy micro-organism, that is, a stain which would show up in some distinctive colour Hansen's 'bacillus,' whilst all other bacteria, however similar but not identical, would not take the same hue. The majority of these methods are based on the property of the *M. leprae* of taking up carbol-fuchsin or a similar stain more readily than Koch's 'bacillus,' and, moreover, on the greater resistance, as a rule, of the latter to the bleaching properties of mineral acids or strong alkalis.

Accordingly it will be seen that we are dealing with differences in degree and not in quality, and as to be expected, such methods of differentiation are apt to fail in a fair proportion of cases and be unreliable in the remaining instances.

Our experience in dealing with the sections and smears in the laboratory at Robben Island is that to obtain well stained leprosy bacilli in sections it is advisable to use 2½ per cent. carbolic in making up the fuchsin solution, to stain in the warm solution one or two hours according to thickness of section, and to differentiate with one per cent. hydrochloric acid in the common methylated spirit of commerce. Counterstain with alum-haematoxylin.

Skin fragments are always fixed in absolute alcohol, specimens from organs in 4 per cent. formaldehyde. Embedding in paraffin is advisable, though excellent sections can also be got in celloidin.

For the quick staining of nasal smears, etc., Pappenheim's carbol-fuchsin-methylene-blue-coralline method gives reliable results.

Unna has described a method of distinguishing lepra 'bacilli' which have been fixed alive from those that were brought dead into the fluid. The validity of this distinction is, however, only founded on circumstantial evidence.

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V. ARTIFICIAL CULTIVATION OF THE MICRO-ORGANISM OF LEPROSY

The first attempts to cultivate Hansen's "bacillus" were made by Sir Patrick Manson many years ago, at a time when aniline dyes had not yet been introduced into bacteriological technique. Later on, in 1882, Hansen thought he had succeeded in getting the "bacillus" to grow artificially in some serum contained between a microscope slide and slip, but he never followed the matter any further after mentioning this observation.

Neisser in 1886 considered that multiplication of "bacilli" from a nodule had taken place on cooked egg and blood serum. In any case he was not able to get further generations to grow.

Bordoni-Uffreduzzi in 1887 cultivated from the bone marrow of a case of leprosy a partially acid-fast or acid-resistant micro-organism, which, from the description given and the specimens seen, I would consider to be morphologically a diphtheroid. It was not quite as acid-fast as the *Bacillus leprae* in tissues.

Campana from 1889 onwards has described micro-organisms, which he cultivated anaerobically from the nodules of lepers. I have been able to examine the culture: it is a mixture of cocci, and coli-like organisms, none of which are acid-fast or even acid-resisting. There appears to be a sad lack of technique in isolating these cultures, an opinion also apparently shared by Wasserman.

Kanthack and Barclay, in 1891, cultivated a micro-organism of varying acid-fast properties from a leproma. Originally they considered it to be leprosy, but later on they withdrew their claim.

Levy in 1898 cultivated from a leper a slightly acid-fast, filamentary organism, which in later publications he considered identical to that isolated by Czaplewski in the same year from another case of leprosy. No animal experiments succeeded with these micro-organisms.

Spronk, also in 1898, was successful in isolating a diphtheroid from lepromas. He carried out some agglutination experiments with it, which, however, appear

not to have had conclusive results owing to incomplete knowledge of the agglutinating properties of sera at that time.

Babes in 1899 isolated on several occasions, from nodules and the inner organs of lepers, an acid-resisting diphtheroid, illustrations of which he has given, and which I consider extremely suggestive. Unfortunately he did not follow the work up, as he later considered that these diphtheroids were contaminations.

Barannikow in 1899 cultivated also a diphtheroid from lepers, very similar to the one isolated by Bordoni-Uffreduzzi, Spronk, Babes, Levy, Czaplewsky. This he considered was a pleomorphic stage of Hansen's "bacillus."

Kedrowsky published his first results in 1900. Using placental-extract-agar, he succeeded in isolating from the nodules of lepers an extremely pleomorphic micro-organism, with varying acid-resisting properties.

Weil in 1906 succeeded in getting what he thought was a multiplication of "bacilli" by injecting leper serum into a hen's egg, which he incubated at 37°C. He was not able to carry this further than one, the first, generation.

Rost published his first results in 1904. He made a great point of the fact that the least trace of salt would not allow the culture to succeed. The medium used was the extract from rotten fish. Semple in 1905 was sent to confirm Rost's results and found that his isolations were due to faulty bacteriological technique. This was also the opinion of other bacteriologists who had occasion to examine his work.

Rost's culture is a dark red, wrinkled, dry culture. It is markedly chromogenic, especially on gelatine at room temperature, under which conditions it grows quite easily. At 37° C. it grows rapidly on most of the usual culture media, sometimes within 48 hours.

Morphologically it is a slightly acid-resisting streptothrix, with acid-fast fragments; this property varies, however, in different culture tubes. It is Gram-positive.

It resembles Grassberger's isolation from butter in culture and under the microscope. It has not produced leprotic lesions in animals.

Shiga (1909) isolated on potato-serum-glycerine a pleomorphic, partially acid-resisting diphtheroid.

Clegg in 1909 published his results and concludes with the following summary :

1. The leprosy bacillus was first cultivated from leprosy material in symbiosis with other unidentified bacteria and amoeba, and later from other cases in symbiosis with amoeba and cholera vibriion.
2. By heating a symbiotic culture of amoeba, cholera, and leprosy for half an hour at 60°C. and incubating, the leprosy bacillus was obtained in pure culture.
3. The leprosy bacillus, isolated in this manner, grows readily on the ordinary laboratory culture media.
4. The bacillus is pathogenic for guinea-pigs, subcutaneous inoculations having caused lesions, which macroscopically and microscopically resemble the leprosy lesions of the human subjects.

Clegg's culture is granular, dry, yellow, grows at room temperature on gelatine or any of the common laboratory media. I have found difficulty in getting the strain to grow in the incubator. It is acid-fast, alcohol-fast, and Gram-positive. Morphologically it consists of short plump rods, very similar in appearance to the timothy grass bacillus; at times, however, it may resemble the "Smegma bacillus," and accordingly consist of slender matted rods.

On injection into animals it does not produce lesions comparable with leprosy in man.

Currie, Brinckerhoff and Hollmann in 1910 succeeded after several failures, in growing acid-fast rods in symbiosis with cholera vibriones and amoebae. They divided up their cultures into four "strains," and found that one was practically identical with Clegg's culture from Manila.

Serra (1910) cultivated anaerobically from several cases (three of seven attempted) a peculiar micro-organism which is Gram-positive, but not acid-fast, as it can be bleached by 2 per cent. nitric acid. Morphologically it appears to be a "diphtheroid."

Twort in 1910 by using his "ericoline" method isolated from the nasal discharge of a leper, on egg-medium to which he had added ground-up tubercle bacilli, an acid-fast rod, which grew very slowly indeed, and was morphologically identical with the "bacilli" found in tissues. He was not able to carry the culture further than the first generation, but still his incomplete results deserve consideration, in view of his success with John's "bacillus."

Duval in 1910 and the following years published various results in connection with the isolation of Hansen's "bacillus."

His first publication was founded on Clegg's results, and the isolation of the acid-fast micro-organisms was made with amoebae in the fashion identical with that of Clegg. The micro-organism in question appeared, however, to differ from that isolated by the latter. In later publications Duval found he could dispense with the amoebae and cultivate the "bacilli" from the nasal discharge of lepers simply by adding amino-acids to the culture media. Later on, even the addition of the amino-acids does not seem to be indispensable, for an isolation is mentioned on Novy-Mac Neal's blood-agar. The last papers deal with isolation by means of Kedrowsky's placental juice agar, which had been re-discovered by Wellman and published as "Wellman's placental agar." Animal experiments failed to produce typical leprosy lesions.

Duval's so-called culture of lepra is a bright yellow, moist, smooth culture. It grows easily and abundantly on gelatine by room temperature and can be easily regained in pure culture on common agar from the organs of animals that have been inoculated with it. At 37° C. it takes about three days to grow on any of the current laboratory media.

Morphologically it is coccoid in appearance, but under circumstances, when injected into animals and sometimes on artificial media, it is apt to present a somewhat more elongated appearance, but at no time closely resembles Hansen's "bacillus."

It is acid-fast and alcohol-fast. Gram-positive.

Its cultural and morphological characteristics cause it to resemble markedly a saprophytic acid-fast micro-organism isolated by Nabarro from London milk. Therefore it is not astonishing that animal experiments did not succeed in producing any lesions analogous to those found in lepers, and that at the International Medical Congress in London (1913) this author admitted he had no culture of leprosy to show or hand round.

Kedrowsky's paper published in 1910 deserves special mention in view of the care with which the experiments have been carried out. They took ten years to complete.

His first isolations from the nodules of three lepers gave as a result two distinct bacteria; one was a non-acid-fast filamentary, interlacing, branching micro-organism, the other was a slightly acid-resisting diphtheroid. He also cultivated

other micro-organisms, which, however, from his pictures and descriptions are easily seen to be but variations of these two groups. He injected these various bacteria strains singly, into mice and rabbits, in different fashions (under the dura, intravenously and intraperitoneally) and observed the animals for prolonged periods, in some cases over two years. He found that, whatever micro-organism he had injected, the result was practically the same in all cases; very numerous acid-fast micro-organisms of the "tubercle bacillus" type in the viscera, from which they could be regained in pure culture as acid-fast rods. The resulting lesions resembled in some cases the chronic type of tuberculosis induced in rabbits by injections of human tuberculosis; in others the lesions were strikingly similar to those occurring in visceral leprosy of human beings.

Kedrowsky's acid-fast culture of "Hansen's Bacillus" is a moist, creamy, smooth or wrinkled ivory-white culture which resembles avian tuberculosis to a very marked extent. It grows only at incubator temperature on special media, such as placental-juice-agar, glycerine-agar, horse-serum-nutrose-agar or any similar medium suitable for tubercle. Multiplication is generally apparent within ten to fourteen days, but may take three weeks to four weeks or more to attain its maximum.

No growth takes place at room temperature or on gelatine.

It is acid-fast, cannot be bleached by 20 per cent. nitric acid in one minute after staining for five minutes with warm carbol-fuchsin. It is alcohol-fast, will withstand absolute alcohol for ten minutes. Gram-positive. Morphologically it is markedly pleomorphic, and resembles avian tuberculosis in this respect, in fact I do not believe that these two bacteria can be distinguished from one another under the microscope, except that Kedrowsky's strain of *lepra* is more apt to show clubbed shapes than even avian tubercle.

Williams in 1911 isolated diphtheroids and streptothrices from the nodules of lepers. He considered them to be pleomorphic stages of Hansen's "bacillus," but was not able to produce any typical lesions in animals with the micro-organisms isolated.

Currie, Clegg and Hollmann express their opinion on these cultures in the following terms:—

"This investigator considers that his work tends to confirm the work of Rost, Deycke, and Clegg, i.e., that all these investigators have, by different methods, isolated the same organism, which latter is very pleomorphic. He seems, however, to base this opinion on very little data other than that the organisms in question were all grown from lepromata, and that local nodules were produced in animals by inoculation of some of these cultures."

Bayon (1911) published the first confirmatory results of Kedrowsky's isolations, above all in relation to the existence of filamentary non-acid-fast micro-organisms in cultures taken with all aseptic precautions from leprosy nodules. He also confirmed the possibility of isolating on various media diphtheroids which were slightly acid resisting. Both bacteria acquired acid-fast properties after injection into animals. This author considered that the identification of bacteria isolated from lepers was the most important point in connection with the bacteriological work, and accordingly carried out extensive investigations by means of numerous experiments on animals, serological tests and observations on human beings. He found that Kedrowsky's view that the parent form of Hansen's "bacillus" is a filamentary, interlacing, branching, non-acid-fast micro-organism is correct, and that this pleomorphic property is shared by several other acid-fast bacteria, e.g., the smegma "bacillus," some saprophytes, such as the acid-fast rod found in tap-water, etc. His comparative experiments with Duval's, Rost's, Clegg's cultures

persuaded him that they behave in culture, on common gelatine at room temperature, and in animal experiments, like the usual ubiquitous, acid-fast micro-organisms found in grass, dung, milk, butter, earth, etc. This observation he confirmed by serological tests, which showed that these cultures when used as antigens do not react specifically with any lepers' serum. The lesions produced in animals are not like the lesions of rat or human leprosy. On the other hand, he found that, given sufficient time for incubation, and notwithstanding a very heavy percentage of failures, Kedrowsky's strain was capable of producing in rats, mice and rabbits lesions extremely similar to those occurring in visceral lepra of human beings. To obviate as much as possible any experimental error, the culture was injected into guinea-pigs and fowls to determine whether, as Babes had suggested, it might not be a tubercle strain which had infected Kedrowsky's animals. Small doses (five to ten loopfuls) did not cause any lesions in guinea-pigs or fowls, even after prolonged observation.

The serological tests employed also showed this strain to be capable of reacting specifically with the serum of certain lepers. A filtered cultural extract when injected into lepers caused a rise of temperature to take place. This reaction, however, has no specific value, as it can be brought about by many different substances, and is, moreover, not constant.

Bayon's culture (in the diphtheroid stage) was studied by Priestley, who compared it with numerous (namely, 48) other micro-organisms from various sources, showing somewhat similar morphological features, with the intention of bringing evidence to bear on the point, whether this diphtheroid could possibly be an ubiquitous saprophyte, whose presence in the skin of lepers had only casuistic, and not etiological importance.

Priestley found that morphologically the "bacilli" were very irregular in shape, clubbing was very marked, polar granules could be detected by Neisser's stain. Gram-positive. On serum they formed raised, white circular colonies, like Klebs-Loeffler "bacillus"; on agar, very minute, circular, greyish-white colonies; no growth on gelatine; on broth, very slight growth, very stringy deposit; no growth on potato. Non-virulent. They fermented dextrose and laevulose, but not saccharose, lactose, maltose, mannite, dulcitol, glycerine, dextrite, galactose, did not clot milk. Unfortunately the study was not completed at the time, and no further details were published because all attention had to be concentrated in attempting to bring the peculiar results of some American authors in relation with the observations made on Kedrowsky's culture and the acid-fast micro-organism isolated from rats inoculated with acid-labile cultures from lepers.

Numerous experiments on animals showed, however, that the acid-fast stage of the filamentary micro-organism was capable of producing in rabbits, rats and mice lesions very similar to those obtained by Kedrowsky in his experiments, and which accordingly were analogous to the lesions observed in leprosy of the human being.

The result of these numerous experiments, prolonged over several years (4), was accordingly that Kedrowsky's isolation was true leprosy, and that the cultures of some of the other authors appear to be accidental.

Reenstierna (1913) succeeded in cultivating from the blood and nodule of a leper an acid-fast rod, which was morphologically similar to Hansen's "bacillus" seen in tissues, and numerous acid-labile bacteria. The acid-fast rods were isolated in pure culture by the means of 10 per cent. antiformin, and lasted four generations in their acid-fast condition, and then turned acid-labile.

A pure culture isolated from these acid-labile bacteria showed on single occasions the presence of acid-fast micro-organisms.

A monkey (*Macacus rhesus*) was injected in the brain and ischiatic nerve with a pure culture of the acid-fast rod isolated from the blood of a leper. This animal showed peculiar maculae on the chest and face, which contained acid-fast micro-organisms. The death of the monkey took place three months after injection, and the inner organs showed numerous caseating nodules which contained big bundles of acid-fast rods, which were mostly situated extra-cellularly.

Another *Macacus rhesus* was injected with a pure culture of the acid-labile micro-organism isolated from the blood of a leper. Forty-two days after, it developed blisters on its fingers and toes, which contained acid-labile and acid-fast bacteria. Shortly after the animal was killed, and acid-fast rods were found at the site of injection, and in caseating inguinal and sacral lymphatic glands.

A third *M. rhesus* was injected with a culture of the acid-labile micro-organism, which was isolated from a single bacterium by means of Burri's Indian ink method. This animal lived eight months, and though during its life it developed a spot which contained diphtheroids and a contracture, the autopsy revealed no leprotic lesions.

Reenstierna concludes from his numerous observations that the bacillus of leprosy is not only morphologically but also biologically closely related to the tubercle "bacillus."

His experiments deserve special consideration, because they belong to the few which have been undertaken without the preconceived *idée fixe* that leprosy and tubercle are absolutely distinct diseases in every single particular, and that Hansen's "bacillus" is acid-fast from beginning to end of its existence, notwithstanding that there is sufficient evidence to show that either statement need go unchallenged.

Stanziale (1913) cultivated from the eye of a rabbit, which had been inoculated 128 days before with a fragment of leprotic nodule under anaerobic conditions, on agar-egg-yolk, an acid-fast rod very similar to that of tuberculosis. The original culture took a month to develop, but on other media the colonies were already apparent after twenty-four to forty-eight hours. On agar and broth the culture resembles tubercle, except for the fact that it is more abundant. Apparently the resistance to the bleaching properties of acids varies, though the bacterium contains granules which are markedly acid-fast. Gram-positive. Numerous clubbed shapes similar to those seen in *Corynebacterium diphtheriae*. Non-pathogenic for animals.

Wolbach and Honeij (1914) have lately isolated a diphtheroid from a case of leprosy. It was originally cultivated aerobically on ascitic fluid dextrose agar, and appeared within ten days in the form of a translucent whitish band around the piece of gland tissue.

"When first isolated the growth was poor on bouillon, with or without glycerin, and on plain agar, dextrose agar and glycerin agar. After several months' cultivation the bacillus grew readily on these media. No growth has been obtained upon potato, with or without the addition of 0.5 to 1 per cent. sodium carbonate. Glycerin does not favour the growth of this bacillus." Gram-positive. After staining with carbol-fuchsin (how long?) they resisted decolourization with 1 per cent. hydrochloric acid in 70 per cent. alcohol; 20 per cent. sulphuric acid left the bacilli from litmus milk distinctly red, after staining by Gabbett's method for tubercle. No lesions were obtained on inoculation into Japanese waltzing mice, guinea-pigs, rabbits and white rats. The methods of inoculation were intravenous, subcutaneous and intraperitoneal.

Wolbach and Honeij consider this culture to be identical with the diphtheroid which has so often been isolated from cases of leprosy, and put in a plea for more full data about any micro-organisms which may be cultivated in future.

These are the results obtained in the course of upwards of thirty years of bacteriological investigation of an extremely widely spread disease. No doubt hundreds of negative results have been obtained and not published, but it can be said that as a rule every time the problem has been tackled by a competent bacteriologist the culture and isolation of a diphtheroid or filamentary germ has been the result. This has also apparently been the case with the investigations of Fraser and Fletcher, who, however, discarded all diphtheroids because of their ubiquity, a standpoint which would considerably simplify pathology. The micro-organisms of syphilis, of tuberculosis, of cholera, could also, on similar grounds, simply be ruled out of court, as far as their etiological significance is concerned.

The main point has, however, always been that as a rule these diphtheroids, though slightly or partially acid-resisting, did not turn absolutely acid-fast on injection into animals, with the exception of the instances mentioned.

It should be understood that every experiment connected with leprosy should be repeated scores of times, because evidently if the matter were simple it would have been solved from the very beginning. The crucial experiment to be carried out with any culture isolated from a leper is not only to get it to acquire the acid-fast properties and the morphology of the 'bacillus' seen in tissues, but also to succeed in producing lesions analogous to those seen in lepers and in rats spontaneously infected with *M. leprae muris*. Bearing in mind the great difficulties encountered in transmitting leprosy to animals through the injection or inoculation of nodules teeming with 'bacilli,' we must be prepared to face series and series of negative results. As negative results, however numerous, are powerless to destroy a single positive observation, it must be admitted that Kedrowsky has published micro-photographs and drawings of lesions in rabbits and mice which are strikingly like those produced by the inoculation of human and rat 'virus' in rabbits and rats. Such specimens have not been published by any other author, excepting those to be found at the end of this paper; the corresponding deduction should not be difficult. (Plate II, fig. 11.)

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VI. THE EXPERIMENTAL TRANSMISSION OF LEPROSY TO ANIMALS

Leprosy is definitely known to be a bacterial disease, and therefore it should not and cannot be impossible to transmit it to animals by experimental inoculation, if it is considered that practically all pathogenic bacteria can be made to produce in animals diseases similar or analogous to those caused in man. In fact, the existence of a disease in rats, extremely similar to leprosy, ought to throw light on this vexed question and postulate the possibility of the experimental infection of laboratory animals.

In estimating the value of any experiments made for the purpose of inoculating animals with leprosy, it should be remembered that but fourteen years ago it was universally denied that syphilis could be given to rabbits or monkeys. Even scientists like A. Neisser upheld this belief, which, as we now know, was absolutely erroneous and totally unfounded. Syphilis is extremely contagious, develops comparatively rapidly, therefore it is not astonishing that

the transmission to animals should be a relatively easy matter, much more so than leprosy. Yet, even after the communication of the first successful inoculations of syphilis to rabbits and monkeys, numerous negative experiments were published, accompanied by the statement that the sores produced on the testis of rabbits, etc., were not produced by the syphilitic virus but were due to the effects of contaminating bacteria.

These recent happenings should induce more attention being paid to the evidence which has accumulated in the course of time, showing that though in the great majority of cases leprotic products, when inoculated into animals, are eliminated without leaving any definite traces, still multiplication and conclusive dissemination of the bacilli does take place in a small number of instances.

In 1881, Neisser, after twenty-four unsuccessful attempts on rabbits, injected two dogs with leprous nodules, and concluded from the results that leprosy developed locally at the site of inoculation.

1883. Damsch grafted lepromata in the anterior eye chamber of two rabbits. The animals died after 139 and 219 days. Apparently a slight increase in the quantity of acid-fast germs had taken place. He also inoculated two cats in the abdomen with leprous nodules. After 120 days numerous bacilli were found in the newly-formed tissue round the atrophied nodules.

1888. Vossius carried out experiments in a similar fashion to Damsch on rabbits and had identical results. He also considered that the acid-fast germs had multiplied.

1885-6. Melcher and Ortmann inoculated four rabbits in the same way. They succeeded in getting, after four to ten months, definite metastases and deposits of acid-fast germs in the spleen, liver, caecum, pleura, and pericardium. They stained these germs with Baumgarten's differential stain, and found that they had the staining properties of Hansen's "bacillus."

1887. Wesener injected several rabbits with leprous nodules, and in two animals out of eight, after periods of four and a half months and eight months respectively, he found lesions apparently identical with those described by Melcher and Ortmann—that is, nodules from the size of a pinhead to that of a pea in the lungs, on the pleura, on the epiploon, in the liver, in the lymphatic glands, spleen, kidneys, caecum, and peritoneal surface. Caseation and giant cells were present. In the eyes of the rabbits he obtained after six and eight months a congregation of round cells choked up with acid-fast micro-organisms. He considered that the generalised lesions were due to tuberculosis, and that the ocular lesions were caused by dead bacilli, because acid-fast germs can be demonstrated in the eye of the rabbit after inoculation with nodules which have been kept for years in alcohol.

1901. Barannikow confirmed these results on one rabbit.

1893. Wnukow inoculated twenty rabbits with leprous nodules in various fashions (intraocularly, subcutaneously, intraperitoneally). In fourteen rabbits he got lesions which he considered to be of tuberculous nature. No confirmatory tests with guinea-pigs appear to have been made.

1893. Tedeschi inoculated a leproma into the dura of a monkey. The animal died after eight days; that is far too brief a period for any conclusions to be drawn.

1902. Ivanow injected several guinea-pigs with leprous nodules. In one case the animal was killed after eight months and found to have nodules in the epiploon, which Ivanow considered were due to multiplication of the bacilli.

1905. Thiroux inoculated five rabbits with leprous material. The animals lived thirteen to twenty months, and presented various lesions at autopsy, which Thiroux considered to be tuberculous, after positive inoculation of two guinea-pigs.

1906. Nicolle inoculated monkeys with ground-up nodules, and succeeded in getting localised lesions.

1909. Marchoux and Bourret inoculated a chimpanzee under the skin of the ear with a freshly-excised leprous nodule. It apparently increased in size during three months, and then began to be resorbed. An examination of the blood showed a few leucocytes with badly-staining bacilli. The animal died ninety-six days after inoculation. The nodule had reached the size of a split pea, and under the microscope was shown to consist of three layers. In the middle were the remains of the original tissue, quite necrosed, with a few loose acid-fast germs. Around this was a considerable number of lymphocytes, enclosing numerous bacilli, and at the periphery organised connective tissue with a few cells filled with bacilli. The authors considered that a proliferation of the original germs had taken place.

1909. Sugai inoculated Japanese dancing mice intraperitoneally with an emulsion of fresh leprous nodules, and found as a result the development of miliary granulomata on the peritoneal lining, especially in the hepatic region and epiploon. Also the bronchial and peritoneal glands showed characteristic leprous lesions. All contained acid-fast germs. The attempt to transmit the disease from these to other mice failed.

1909. Kitasato appears to have successfully inoculated an orang-outang on the cornea. Only scanty details were, however, given.

1909. Stanziale reports upon experiments on rabbits. In one typical case he inoculated into the eye of the animal a fragment of leproma. During the first few days a marked hyperaemia developed round the opening in the cornea. Soon afterwards a constant diminution in the size of the nodule could be made out, accompanied by the formation of an opalescent exudation, which took its departure from the inoculated piece of tissue and spread out as a fan-shaped segment. After twenty days the nodule became stationary, and remained so during fifteen to twenty days without any noticeable change taking place. After forty days the nodule began slowly to increase till it had trebled its original size. In the same time small grey nodules made their appearance, and could clearly be distinguished on the surface of the inoculated tissue. These little nodules attained the size of a pin's head. Some appeared to be adherent, while others were loose and independent. After the initial hyperaemia due to the operation had disappeared, a new formation of blood vessels took place, which spun a delicate network round the piece of tissue inoculated. After seventy days the rabbit's eye was enucleated, part of the tissue was used for histological observations and the rest was grafted into the cornea of two other rabbits. In one the graft got resorbed without any further results in the course of two months. In the other rabbit the graft began to increase in size after fifty days, and produced similar changes to those described in the foregoing animal. The experiments are being continued by the author, but to date the results obtained are: thirty-one rabbits have been inoculated, and in eight it was possible to produce leprous ocular lesions. In some of the positive cases the

material was taken eighteen to nineteen hours after excision from the patient. In all cases in which the inoculation succeeded the Wassermann reaction was positive. As a control Stanziale inoculated lepra nodules into the abdomen of another rabbit, and found at intervals after a month the reaction constantly negative. The same negative result was achieved after grafting into the cornea of rabbits pieces of human skin or dead leprous nodules.

These experiments of Stanziale have been most carefully carried out, and full descriptive details are given; the only defect is, however, that no metastases in the inner organs are mentioned.

1911. Duval inoculated a series of animals—namely, four rats, four white mice, and four Japanese dancing mice—with grumous material taken from an acute case of human leprosy which had developed numerous soft subcutaneous leprous masses and had repeated attacks of leprous fever. A small quantity of material was used in each case—namely 0.5 c.cm. emulsified in 1 c.cm. of normal saline solution. Some were injected intraperitoneally, others subcutaneously.

The two white mice which received intraperitoneal injections died fourteen days after the inoculation. At the autopsy both showed a general infection of the peritoneum with a pure growth of the *M. lepræ*, while the mesentery, omentum, visceral and parietal peritoneum contained numerous minute, firm greyish-white nodules, which on microscopic section proved to be typical leprous lesions. The most surprising feature was the occurrence of a slightly turbid, semigelatinous exudate, which microscopically consisted almost entirely of large mononucleated cells (macrophages). Great numbers of these cells were filled with acid-fast bacilli, and scarcely any were found that did not contain a few. No remarks are made about the other animals.

1911. Courret fed two goldfish on teased nodules from a leper. No other food was allowed the animals until they had disposed of the leprosy tissue, after which they were cleansed and transferred to a clean aquarium.

The first was examined twenty-four days later; acid-fast organisms had not been found in the faeces for three days before the animal was killed. No evidence of infection was apparent externally or internally. Films made from the omentum and other organs showed a few scattered acid-fast bacilli. The average number of bacilli to the slide was about four, and no change in morphology was seen. The second fish was examined after thirty-seven days. The findings were similar to those in the first one. With reference to these experiments, it should not be forgotten that tap water appears to harbour acid-fast germs frequently, as shown by Brehm, Beitzke, Schern, and Dold. The tap water at the Lister Institute in London and of the Public Health Laboratory in Cape Town, also contains acid-fast germs; I have also seen them in the taps at Stockholm. (See Plate IV, fig. 20.)

Serra (1911 and 1913) describes a series of experiments he has carried out on rabbits by means of the intra-ocular method.

His results on the whole seem to correspond to those of Stanziale, but it is extremely difficult to unravel any definite statements as to the facts observed from a mass of secondary detail. Too much stress seems to be laid on the Wassermann reaction observed in some of the rabbits inoculated, and no details are given as to way in which it has been carried out; whilst also in this case no metastases in the inner organs are mentioned.

It is to be hoped that other following publications will bring more light on the subject.

Ch. Nicolle and Blaizot succeeded in producing in *Macacus sinicus*, by inoculating fragments of leprous tissue, local lesions very similar to those of dermal

leprosy in man. They repeated these experiments on three monkeys (bonnet chinos) and one chimpanzee, and reported on the results in 1911.

One monkey received sixteen inoculations *in toto*, but none of them ever generalised, and the resulting nodules got slowly resorbed in the course of time.

A second monkey died without showing any visceral lesions. The experimental lepromas were in course of development, and showed numerous acid-fast micro-organisms under the microscope.

A third monkey received nine inoculations at intervals varying between a week and twenty-five days. The resulting nodules softened, caseated and broke down. The pus showed a few degenerated "bacilli" among numerous polynuclear cells.

The chimpanzee received eight inoculations in the course of four months. One injection was followed by the development of a local nodule, which was followed later on by several little nodosities, which soon became confluent. This lesion only lasted about a fortnight and then got resorbed.

In these cases, therefore, we had a temporary or negative result in most cases, and a localised success in one experiment.

Bayon (1912) injected four rats on two occasions in the testes with ground-up nodules from a case of leprosy from Mauritius. Two rats did not show any macroscopic lesions, even after four months. One rat, however, developed, four weeks afterwards, a nodule at the site of inoculation, which grew to the size of a small pea. On puncture it showed acid-fast germs and necrosed tissue, some of which, no doubt, represented the original cells injected. After five weeks the rat died, but no acid-fast micro-organisms were found in the organs. Microscopical sections were made of liver, spleen, and testes. The disease, if transmitted, was localised. The whole of the nodule was then injected subcutaneously into two other young rats. Three months after inoculation, one of the rats was losing fur on the surface of its abdomen, without there being any signs of the usual rat scabies about the ears or tail. Small shotty nodules could be felt under the skin.

The other rat developed, three months after the second injection, a nodule in the left testis. This broke down, and was found to contain acid-fast rods in great quantity. This rat was killed four months after inoculation, the slight wound caused by the nodule breaking down having healed. At the site of injection and in the corresponding inguinal glands numerous acid-fast rods were found. One of these small glands was inoculated into the testes of another rat, and on killing it six months afterwards no acid-fast micro-organisms were found in the testes, but definite deposits were present in the inguinal glands, spleen and liver. A multiplication must have taken place, because the acid-fast bacteria detected in these organs were evidently more numerous than the relatively small quantity injected. (Plate III, Fig. 14.)

At Robben Island, during 1912, 1913 and 1914, thirty experiments on rabbits were undertaken by means of the intra-ocular method. Exact data will be published in due course, when the histological study of the resulting specimens is undertaken.

It is, however, worthy of note that one single rabbit of the thirty inoculated has shown permanent lesions—that is, minute white, vascularised nodules in the cornea and on the iris. This animal was operated upon 1st November, 1912; nodule from Pat. No. 1294.

As a rule the remaining animals developed inflammatory appearances similar to those described by Stanziale, but in the course of time the inoculated fragment of leprotic tissue got resorbed, all signs of inflammation or production of new tissue subsided, and in conclusion only a linear scar remained as a trace of the operation.

One animal, however, still shows numerous minute leprotic lesions one year and seven months after inoculation.

I do not wish to admit a definite communication of leprosy to these animals, till I have been able to achieve the results accomplished with the rats—that is, the transmission of the virus through several generations, and deposits in the inner organs.

Reenstierna (1912) injected a *Macacus rhesus* under the mucous membrane of the nose with 0.5 c.cm. of an emulsion made from a leproma containing numerous “bacilli.” The animal died forty-two days after inoculation. The inner organs showed no alteration, but the nose had developed a perforation of the septum; moreover, there was extensive ulceration of the upper lip and nasal mucous membrane. The microscope revealed numerous extra-cellularly situated acid-fast rods in the nasal secretion and sections of the diseased tissues. In addition an acid-labile but Gram-positive filamentary germ was present with fragments which, morphologically, were similar to lepra “bacilli.”

Another *M. rhesus* was injected intra-peritoneally and subcutaneously with the same emulsion as in the previous experiment. The monkey died fifty-nine days afterwards, and showed numerous caseating nodules in the liver, spleen, lung and mediastinal lymph-glands. These lesions contained numerous acid-fast rods.

Five guinea-pigs were inoculated with the caseating nodules from the spleen; they died within three to five weeks and showed localised lesions which contained very numerous acid-fast rods.

A third *M. rhesus* monkey was injected with the same emulsion intraperitoneally and subcutaneously. It died six months afterwards, and developed small nodules at the sites of injection which contained acid-fast rods. A cherry-sized nodule which developed on the upper-lip contained numerous acid-fast intra-cellular “bacilli” and vacuolated cells. Acid-fasts were also found in the liver, spleen and bone-marrow.

These are the successful or reputed successful attempts to transmit leprosy to animals by means of injection or inoculation of leprosy tissues.

As will be seen, they are certainly more numerous and have been more carefully observed, than the isolated statements in connection with the communication of syphilis to animals, which were to be found in literature only so short a time ago as the first year of this century. And yet syphilis can be communicated to rabbits with relative ease. In dealing with leprosy, where even direct inoculation of human beings has failed (except in Arning's case) one can but expect to find much more serious difficulties, such as:

(1) Lack of knowledge in relation to the bionomics of Hansen's ‘bacillus.’

It does not seem to be understood that though attendants in leper asylums, and persons living with lepers, must often come in contact with numerous ‘bacilli’ which we know nodular lepers cast

about them, yet only a very small proportion ever develop the disease in a clinically recognisable form. In other words, in the great majority of cases either the 'bacilli' remain absolutely quiescent in the body or get harmlessly eliminated.

Therefore it should not astonish us that a great proportion of the animals inoculated eliminate the acid-fast bacteria injected after a longer or shorter period.

(2) The difficulty of proving whether any 'bacilli' seen in experimental lesions are simple deposits of dead acid-fast bacteria or whether they are alive and in course of multiplication.

This is really an outcome of No. 1, as it depends on an incapacity in comprehending how extremely passive, inert and resistant Hansen's 'bacillus' is.

It is true that Campana, Wesener and others have shown that it is possible to bring about lesions in animals very similar to those described by the experimenters who claim having transmitted leprosy to rabbits or rats, by simply injecting tissues containing numerous 'bacilli' which had been autoclaved or kept in alcohol for months. As we know of no method of cultivating directly the acid-fast germs seen in leprosy with their original morphology and staining properties, it is of course difficult to refute this argument except by pointing to the analogy with rat-leprosy, where, though we know that the 'virus' used in experiments is living because it can be indefinitely transmitted, still, except for the latter particular, the lesions caused by killed and living virus are extremely similar.

(3) The similarity existing between the lesions produced in rabbits and those found in experimental tuberculosis.

This is the argument which settled the results of Melcher and Ortmann, Wesener and others. At the time leprosy and tuberculosis were considered to be as easily distinguishable histologically and bacterioscopically as they are clinically. Further study has, however, shown that this is not the case, and that under certain conditions only experiments with guinea-pigs can decide whether we are dealing with lesions brought about by Koch's or Hansen's 'bacillus.'

Taking into careful consideration the previous experiments and personal experience, in addition to the interpretation of the clinical notes made on lepers who have been under observation for fifteen

and more years in South Africa,* no other conclusion can be arrived at than that leprosy is directly, experimentally, communicable from human beings to rats and rabbits; that a long time of incubation must be allowed for; that the great majority of animals eliminate the 'bacilli' injected after a shorter or longer period of quiescent deposit.

We have, therefore, under experimental conditions an analogous counterpart of what is happening daily with people who contract leprosy, for even prolonged exposure to infection causes the disease to develop only in a small percentage. Those who show clinical symptoms of the contagion appear to eliminate the majority or practically all their 'bacilli' if they live long enough to become what is called an 'arrested' case. Such an 'arrested' case is a leper who is known to have had numerous visible lesions teeming with acid-fast rods, but who for the time being only shows scars and traces of the disease with no 'bacilli.' Such cases relapse at times, or may show small bacillary deposits in their inner organs at death, but even then there can be no doubt that they have succeeded in eliminating or destroying millions and millions of 'bacilli' from or in their nodules.

A somewhat analogous observation is often made at autopsies in connection with tuberculosis of the lungs. It is then seen that very many bacillary infections of this organ do not develop into clinical tubercles, but heal with scarring.

All these considerations should, and do, give a satisfactory explanation of many negative results and condone the scepticism with which many successful experiments have been received. Conclusive histological specimens like those shown in Plate III, fig. 14 cannot be ignored, especially as experimental results agree in an exceptional manner with clinical observation.

Once more, these conclusions have to be arrived at:

(1) Leprosy is experimentally transmissible to animals such as the rabbit and the rat. Allowance must be made for the fact that the great majority of inoculations do not succeed, owing to the 'bacilli' being eliminated or destroyed without leaving any visible trace.

* This shows that in single instances lepers get rid of nearly all the acid-fast germs from their lesions.

(2) The incubation period is very long, and the resulting lesions in the inner organs may not be visible to the naked eye.

(3) In rabbits the bacillary deposits in the inner organs resemble tuberculosis. In such cases the question can only be decided by means of guinea-pig inoculations.

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ON RAT LEPROSY AND ITS RELATION TO THE HUMAN DISEASE

A disease extremely similar to leprosy, not only in its clinical features but also from an histological and bacteriological point of view, was discovered in rats by Stephansky in Odessa, in 1903. Its presence among the sewer rats of Berlin was confirmed by Lydia Rabinowitch the same year. Both these observers considered that rat leprosy could not be transmitted experimentally from one animal to the other, and that the acid-fast micro-organism found in enormous quantities in the lesions of the animals affected could not be cultivated on nutrient media.

George Dean had studied this same disease at Elstree, near London, for some time, and published his results nearly contemporaneously with Stephansky and Rabinowitch. He was, however, successful in transmitting rat leprosy through several generations of rodents, a result which has since been amply confirmed by Marchoux and others. G. Dean's cultural attempts only succeeded in isolating a diphtheroid, which showed filamentary forms, and much to his astonishment reacted specifically with the serum of lepers. The results of his agglutination experiments were :

- '1. The serum of rats inoculated with rat-leprosy, i.e., with acid-fast "bacilli," agglutinated the diphtheroid. Normal rat's serum had no agglutinating properties for this micro-organism.
2. The serum from a case of human leprosy agglutinated the acid-fast micro-organism from the rat. Normal human serum had no agglutinating power.
3. Normal human serum and the serum from a tuberculous patient failed to agglutinate the diphtheroid, whereas the serum from a case of leprosy had distinct agglutinating properties.'

These carefully planned tests, in addition to the histological appearances, the cultural and experimental behaviour of the micro-organism causing the disease in rats, lead us to believe that rat leprosy is possibly related to human leprosy in a manner similar to that existing between bovine and human tuberculosis.

Marchoux has carried out very carefully-planned experiments with the strain of rat leprosy he discovered in Paris, and has come to the following conclusions :—

- '1. That only six in a thousand sewer rats in Paris present marked leprotic lesions, but that 5 per cent. harbour acid-fast micro-organisms (*bacille de Stephansky*).
2. That the inguinal glands appear to be the first attacked by the disease.

3. That the lung acts as a filter in arresting the germs and then directing them towards the mediastinal glands.
4. That by simply placing the virus of the disease on the scarified or depilated skin, an infection can be brought about in rats even more easily than by subcutaneous injections.
5. That intact skin or even the bare skin of very young rats does not allow the penetration of the virus.
6. Rat leprosy is a disease peculiar to the rat. Mice can be infected, it is true, but with less ease than is the case with rats. Attempts to infect through the scarified or depilated skin do not succeed as often as subcutaneous injection in mice. In such cases one finds amongst the "bacilli" involution forms similar to those met with in rats injected with human leprosy.
7. *Mycobacterium leprae murium*, like Hansen's "bacillus" is a parasite of the mesodermal cells. It does not live at the expense of its host, but of the same substances which nourish the cell containing it.
8. Granular bacilli are dead.
9. A first culture is relatively easy to obtain. Further sub-plants are not obtainable.
10. The bacillus disappears rapidly in contaminated media (*en milieu impur*).
11. It does not resist desiccation.
12. It is not killed by a temperature of 60° C. during five minutes. It dies after being exposed at the same temperature for fifteen minutes.
13. Infection takes place through the skin, and accordingly superficial surface regions are generally more intensely affected.
14. Infection follows the lymphatic stream.
15. The point of inoculation is not always the most heavily infected spot.
16. Male rats can be infected by depositing some of the virus under the prepuce without causing any lesions of the mucous membranes.
17. However, the spontaneous disease does not seem to be transmitted in this fashion.
18. Insects do not carry the disease.
19. The sarcoptes of rat scabies play only an indirect rôle in the diffusion of the disease.
20. The immediate contact of a skin abrasion with a diseased surface or with freshly contaminated objects is the usual mode of contagion.
21. By introducing a large number of micro-organisms through the digestive tract a primary pulmonary infection can be produced.
22. The lymphatic glands of artificially inoculated rats are generally very small; those of spontaneously diseased rats, on the contrary, generally much enlarged.
23. Inoculation generally produces an infection of the lymphatic glands. Impure virus has to be injected to produce the muscular and cutaneous type of the disease.

I have quoted extensively these results of Marchoux and Sorel, because not only all experiments have been carefully and systematically worked out, but the majority of the observations made seem to agree so completely with what we know of the pathology of human leprosy.

Currie and Hollmann also carried out experiments with rat leprosy, and in two papers on the subject came to the following conclusions:

'1. In some cases of artificially acquired rat leprosy the onset is with broncho-pneumonia, accompanied by a septicaemia and without any other demonstrable lesions.

2. In other cases of this disease pneumonia is a very early lesion, but we cannot positively state that it is always the first lesion.

3. That the animal may die in the pneumonic stage before other lesions present themselves, or it may develop pneumonic symptoms and recover from the same only to develop later the well-known lesions.

4. That during the stage of the disease in which the animal is very ill certain mites (*Laelaps echidninus*) were found to be very numerous on the animals' bodies.

5. That during the stage of the disease in which septicaemia is marked, these mites' digestive tracts contain the bacilli of rat leprosy in considerable numbers, and, therefore, these parasites may be one means of transmitting the disease. This latter probability is, of course, not proven.'

In a later paper, published in 1912, these authors add the following to the previous conclusions:

'1. In the disease we are dealing with, whether the animal is inoculated by a laboratory method or simply allowed to develop the disease from coming into contact with infected rats, i.e., the natural mode of infection—the lesions met with are practically the same.

2. With the exception of the local lesion, occasionally produced at the site of artificial inoculation, infection of the viscera seems to usually precede the lesions of the skin.

3. Of the visceral lesions, a broncho-pneumonia is often the earliest and most constant. Infection of the spleen is also often an early event.

4. The heart blood of infected rats often contains the bacilli of rat leprosy, and no difficulty is experienced in demonstrating the presence of acid-fast bacilli in the mites contained on the bodies of these animals when the latter's heart blood contains the organisms.

5. The fact that these mites contain the bacilli so frequently naturally leads one to suspect that they may be one of the means of transmitting the disease from rat to rat, but up to the present time we have no evidence that such is the case.

ATTEMPTS TO CULTIVATE THE BACILLUS OF RAT LEPROSY

As reported in our first paper, we have made many attempts to cultivate the bacillus of rat leprosy on artificial culture media, both on the media ordinarily employed in the laboratory and by the method of Clegg in symbiosis with amoeba and cholera. We have now to report that we have continued these experiments for nearly a year, and that our results have been entirely negative, not having secured a single culture of an organism which we considered to be the bacillus of rat leprosy. In one of our attempts to cultivate this organism from the ulcer on the abdomen of a leprosy rat, we succeeded in growing what appeared to be an acid-fast streptothrix. As one might expect to obtain such organism on an exposed surface of that kind, we regarded this culture as an accidental contamination, and not the bacillus of rat leprosy.'

It is hardly feasible to bring these results in correlation with anything observed in human leprosy, except for the fact that also these authors have found the disease can be transmitted by means of inoculation from one animal to another, an experiment which did not succeed in the hands of earlier observers. In a similar fashion the transmission of human leprosy to animals has failed time after time, and yet under exceptionally favourable circumstances it can be successfully achieved. The repeated attempts to cultivate the micro-organism of the disease, which only resulted in the isolation of acid-fast filamentary, branching bacteria (diphtheroids are not mentioned) which were considered to be contaminations, are also worth noting, because this observation coincides with the results of much of the work done on the bacteriology of human leprosy.

Bayon (1912) succeeded in isolating on fish-juice-agar from the spleen of a rat which had been injected with a ground-up nodule from a spontaneously diseased rodent, a moist, ivory-white, creamy growth, which multiplied in sub-cultures very slowly at 37° C. on the media generally used for the artificial cultivation of tubercle. This culture produced in rats the identical glandular and visceral lesions observed in rats injected with the virus from spontaneously diseased animals. The glands and organs infected were teeming with acid-fast micro-organisms, which caused little or no tissue reaction and a very minimal production of giant cells (Plate III, figs. 16 and 17).

The culture does not grow at room temperature or on common gelatine. It is difficult to isolate again from the inner organs of the animals into which it has been injected. Guinea-pigs, fowls and rabbits do not show any lesions if inoculated with small quantities (five to ten loops), but if a culture slope or more is introduced intra-abdominally, after a time caseating, necrosed nodules are produced on the surface of the peritoneum and the omental glands can be considerably enlarged, showing big masses of acid-fast micro-organisms. The necrosis and caseation are partially due, I believe, to the mechanical foreign-body action of the large numbers of resistant micro-organisms injected.

No growth could be obtained under anaerobic conditions.

In an oxygen atmosphere the cultures develop somewhat more

rapidly; after ten to fourteen days a thick growth is discernible, whilst under ordinary conditions, at 37° C., three or four weeks are needed.

No multiplication was obtained on gelatine at room temperature or on common agar in the incubator.

No pigment was produced on any of the following media: fish-juice-glycerine-agar, glycerine-agar, glucose-agar, glycerine-potato, rice-glycerine-milk, sterilised wedges of rabbit's liver + glycerine, Dorset's egg-medium. All these media were suitable for growing the micro-organism.

Morphologically the culture is a short rod, with a marked tendency to pleomorphism; clubbed shapes are frequently seen, and at times true branching can be detected. The length of the rods varies; in fact, the microscopical appearances are very similar to those of a culture of avian tuberculosis, which it also resembles from a cultural point of view.

It is acid-fast, i.e., cannot be bleached by one minute's treatment with 20 per cent. H_2SO_4 after having been stained for five minutes with warm carbol-fuchsin. It is also alcohol-fast. After soaking for six hours in warm alcohol its staining properties are unimpaired.

It is Gram positive.

Very numerous attempts to isolate the same micro-organism from several other cases of rat leprosy failed completely. Marchoux is therefore not quite correct in saying that: 'Bayon, au contraire, l'aurait cultivé assez facilement.' (l.c. p. 23.)

Further cultural results have been published by Hollmann, Chapin, Zinsser and Carey, Marchoux and Sorel, and, of course, Wellman. None of these cultures have succeeded in producing leprotic lesions.

After Stephansky's and Rabinowitch's and Dean's observations, rat lepra was found in Australia by J. R. Bull, in New South Wales by Tidswell, in the United States by Wherry, McCoy, Walker, in Roumania by Mezinescu and Alexandrescu, in Japan by Jitoyo and Sakaki, in Paris by Marchoux, in New Caledonia by Leboeuf, in Ipswich by Petrie and Macalister (see Pl. I, fig. 4), in India by the Plague Commission, in Queensland by Priestley.

Though rat lepra seems to be spread nearly all over the world, still Brinckerhoff examined 16,000 rats in the Hawaii Islands without finding any trace of an animal affected with the disease.

In Cape Town I have had now 1,378 sewer rats examined without having succeeded in a single instance in discovering a marked case of the disease.*

Dr. G. W. Robertson remembers, however, to have noticed one animal the lesions of which contained numerous acid-fast rods, in the course of plague investigations, when about 30,000 rats were examined.

Mezinescu succeeded in preparing from the ground-up nodules of leprosy rats an antigen which was capable of absorbing complement when linked up with the serum of lepers; a further proof of the relationship of both diseases, though, on the other hand, it must be admitted that the serum of lepers is similar to that of syphilitics in this respect, because it is capable of reacting with specific and certain non-specific antigens. A distinction can only be made by carefully titrating all the elements of the haemolytic system, and varying the proportions of antigen and antibody in a suitable fashion; up to the present this has only been done in quite a minimal proportion of cases.

Rats are not the only animals affected by a disease akin to leprosy. Acid-fast micro-organisms which belong to the tubercle group, but are not pathogenic for guinea-pigs in small quantities, and are only cultivable with extreme difficulty, cause diseases in cattle, horses, sheep, and possibly goats. The cattle disease has been named by K. F. Meyer 'Enteritis hypertrophica bovis specifica.'

Twort and Ingram, Vukovic, M'Fadyean, McGowan, have described 'Johne's disease' in the sheep. This disease differs from rat-leprosy in so far that the symptoms are mostly confined to the digestive tract.

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*My thanks are due to Dr. Mitchell and Dr. J. Anderson of Capetown for procuring these rats.

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VII. THE SEROLOGY OF LEPROSY AS A MEANS OF DIAGNOSIS OF THE DISEASE AND FOR THE PURPOSE OF CONTROLLING SPECIFIC TREATMENT

Soon after the adaptation of Bordet-Gengou's complement fixation to the diagnosis of syphilis by Wassermann and his co-workers, Eitner modified this test to suit the special conditions of leprosy, and prepared his antigen by means of a saline extract from a leproma. He found that the blood of lepers contained, as he thought at the time, specific anti-bodies, and accordingly was able to bring about the absorption of complement when linked up with an antigen prepared according to his method. In the course of time it became evident that Wassermann's test for syphilis could not claim to be absolutely specific. Accordingly Eitner amplified his experiments, and found that the serum of lepers was also capable of giving a positive reaction when linked up with the alcoholic extract from a guinea-pig's heart, and that therefore, also in this particular instance, the serum of lepers and that of syphilitics behaved in a similar fashion.

Numerous and various experiments were then carried out with different antigens by several investigators, and the serum of lepers was carefully compared with that of syphilitics and tubercular patients. As far as the original Wassermann test of syphilis is concerned, its relation to leprosy can be aptly summed up in the conclusions of Howard Fox (l.c.):—

- '1. A positive Wassermann reaction is frequently obtained in cases of leprosy giving no history or symptom whatever of syphilis.
2. The reaction is at times very strong, inhibition of haemolysis being complete.
3. The reaction occurs chiefly in the tubercular and mixed forms of the disease, especially in advanced and active cases.
4. In the cases of the maculo-anaesthetic and purely trophic type the reaction is generally negative.
5. The value of the test is not affected in the slightest by the results found in leprosy.'

On the other hand, if we consider the test being made with an antigen prepared in various fashions from the nodules of lepers (Eitner's test or its modifications), one finds on reviewing the literature on the subject that, with a few differences, the results mainly agree with Jeanselme's conclusions, which are the following :

'1. Eitner's reaction applied to syphilitic sera is positive in 85 per cent. of all cases examined.

2. Eitner's reaction with the serum of healthy individuals or that of syphilitics in whom the disease is quiescent: 100 per cent. negative.

3. Wassermann's reaction applied to lepers: Practically the same conclusions as Howard Fox.'

Eliasberg has shown that the serum of lepers is at times capable of inhibiting haemolysis by itself, even small quantities as 0.4 c.c. being sufficient. A similar observation has been made by Ehlers and Bourret.

Noguchi's 'Luetin' reaction was found to be negative in eleven lepers who were free from obvious signs of syphilis (but gave a Wassermann reaction) by Clegg.

Incidentally it can here be mentioned that, according to Rocamora's and also Jeanselme's experience, salvarsan has no influence whatever on the Wassermann reaction in lepers.

Evidently neither Wassermann's nor Eitner's test can be considered strictly specific for syphilis or leprosy. It remains, however, to be seen whether a test could be devised in which by using pure cultures of 'Hansen's bacillus' a clear, specific, definite reaction might be obtained.

Currie and Clegg approached the problem with the intention of proving the identity of the acid-fast bacteria they had cultivated from lepers, and after numerous experiments concluded that:

'1. They were unable to differentiate by the method of Bordet and Gengou the leprosy bacillus from certain other acid-fast micro-organisms.

2. Extracts of certain acid-fast bacilli, other than *B. leprae*, will deflect the complement when combined with leper's serum.

3. They were able to produce specific agglutinins for *B. leprae* by injecting a horse with the cultivated lepra bacilli.'

The explanation of these results is given by Much and his co-workers, Hössli, Lescke and Deilmann, who have shown that all acid-fast micro-organisms are more or less closely related and their chemical constituents are similar. Much sums up his results in the following words (l.c. 1912):

'We were able to show—chiefly by the reaction of immune bodies—a relationship between tubercle and lepra bacilli and other acid-fast bacilli, which is due to inherent qualities common to all these organisms. Thus tuberculous and tubercle immunised persons responded to the reaction of complement-fixation, not only with tubercle, but also with other acid-fast bacilli, though not equally with all,

and with certain sorts more than with others. A table which I have prepared shows the quantitative differences in these reactions, and according to this table the lepra bacilli have the closest resemblance to the tubercle bacilli.

In the same way leprous sera react not only against lepra bacilli, which we obtained from leprous tubercles, but they give also a specific reaction in the same scale of relationship with tubercle and (other) non-pathogenic acid-fast bacilli. These reactions are absolutely specific.'

Much's observations and experiments show clearly that, as was to be expected, the specific result of any serological test carried out with acid-fast micro-organisms is apt to be masked by the interference of a group-reaction. This is similar in its effects to that observed on trying to differentiate from a serological standpoint various bacteria of the typhoid or para-typhoid group. It is no doubt also analogous to the results of precipitation tests when being adapted to identify the blood of closely-related animals.

FIG. 1.

Diagram showing two complement fixation tests for the identification of acid-fast micro-organisms isolated from lepers.

Both serum and antigen are diluted in falling dosis and mixed in varying proportions.

Clear circles indicate complete haemolysis, dark circles absolute inhibition; spots of varying sizes correspond to the stages between haemolysis and inhibition.

Dark circles in the middle vertical line are controls of antigen, serum, complement.

H. R. Dean having shown that this difficulty can be obviated by linking up antigen and antibody in varying dilutions, Bayon carried out some experiments on the same lines with the intention of getting rid of the group-reaction without having recourse to

Weichardt's complicated technique. These tests require the greatest care, because the antibodies of leprosy sera are never very strong, and dilutions capable of reacting above $1/150$ are the exception. The antigen was prepared by alternately freezing and rapidly thawing, and then shaking mechanically, various acid-fast cultures in distilled water. The principal factor consisted in the variation of the proportions of antigen and antibody, which can be best explained by referring to the figure on p. 49, in which the dark rings represent complete haemolysis and the clear rings complement-absorption. It will be seen that in all the rows the leprosy serum was diluted in falling quantities, $1/5$, $1/10$, $1/20$, etc. In the first row the antigen was used undiluted, in the second $1/2$, in the third $1/4$, and so forth. By this method not only a control was achieved unobtainable by any other technique, but, moreover, very satisfactory and reliable results were arrived at. It was found possible to distinguish, from a serological point of view, cultures of various acid-fast bacteria, unless they were too similar or closely related, e.g., bovine and human tubercle. In this fashion Kedrowsky's strain of leprosy was found to react specifically with the serum of lepers in a dilution of antigen which gave no result with Duval's or Rost's micro-organisms.

This test can be applied to the diagnosis of leprosy, but unfortunately, in common with many other laboratory methods, it fails in those cases of early anaesthetic leprosy, which are the most difficult to diagnose clinically.

In the instance illustrated in fig. 1 the serum of a nodular leper was tried against antigens made with the leprosy cultures of Kedrowsky and Duval. It will be seen that though Kedrowsky's micro-organism reacted even in a dilution of $1/4$ with serum diluted $1/40$, Duval's bacterium ceased to give any absorption after mixing $1/2$ with serum $1/5$. These results have lately been confirmed by Kritschewsky and Bierger, who however did not grade their dilutions. In the second series of fig. 1 we see a test carried out with the serum of a rabbit which had been repeatedly injected intravenously with several slopes of Duval's culture. The serum of this animal was used against an antigen made with Duval's 'lepra,' and another consisting of Moeller's 'mist-bacillus' isolated from horse-dung. The result is that very little difference can be made

out, showing that Duval's so-called 'leprosy-culture' is very closely related to a harmless, ubiquitous saprophyte.

These results were confirmed in course by the fact that the etiological significance of this isolation had to be abandoned by its author.

Moellers (1913) examined the sera from thirty-two lepers, using as antigen the following products: Alttuberkulin Höchst, Perlsucht-tuberkulin Höchst, Tuberkelbazillenemulsion T.O.I., Neues Tuberkulin T.R. He sums up his results in the following fashion:

(1) The serum of mixed and nodular lepers gave a positive fixation of the complement in 95 to 100 per cent. of cases examined when tested against various tuberculins. Anaesthetic varieties of the disease reacted only in 25 per cent.

(2) In the serum of lepers the amboceptors for bacillary emulsions are more developed than those for preparations made from the cultural liquid.

(3) It is not possible to draw any conclusion as to the presence of tuberculosis in a leper who shows the presence of 'tuberculous antibodies' in his serum.

(4) The complement absorption properties of leprotic sera tested with tubercular substances are in direct proportion to the extent of mixed and nodular features in lepers. Accordingly it appears that this inherent quality of the serum depends on the greater or lesser spread of the leprotic lesions (Krankheitsherde); this is confirmed by the observation that the reaction was negative in arrested cases.

Kritschewsky and Bierger (1913) found that the serum of lepers gave a definite positive complement fixation test with an antigen made with Kedrowsky's culture. Duval's 'lepra' did not react in the same remarkable manner. A close similarity in relation to serological tests was found to exist between the leprosy 'bacillus' taken from tissues and that isolated by Kedrowsky. *M. tuberculosis* appeared also to be closely related to the latter micro-organisms.

These authors conclude that Kedrowsky's isolation is true leprosy, and that Duval's chromogenic culture is not etiologically connected with the disease.

Gaucher and Abrami, Sugai and others, have tested the agglutinating properties of lepers' sera towards Hansen's 'bacillus' separated from ground-up nodules. Such experiments are somewhat vitiated from the fact that acid-fast rods are prone to show spontaneous clumping.

Summing up these different independent observations it cannot be definitely stated that it is not possible, with due care and attention, to carry out serological tests showing the etiological relationship of any given micro-organism to leprosy. In the case of acid-fast bacteria the group-reaction must be obviated. The difficulties are superior to those encountered with other germs; they are, however, not insurmountable, as Harris and Langford are inclined to believe.

TUBERCULIN AND SIMILAR TESTS IN LEPROSY

Abraham, Goldschmidt, Babes and Kalindero, observed practically at the same time, in 1891, that lepers react with a rise of temperature to injections with 'Alt-tuberkulin.' Though this observation was repeatedly confirmed, the tendency was to consider that the reaction was due to a co-existent tuberculous infection. Babes, however, examined seven lepers after death, who during life had reacted to tuberculin, and found in four chronic tuberculosis of the lungs, whilst the remaining three were without any signs of infection with *M. tuberculosis*. Guinea-pig experiments were negative.

Sir Malcolm Morris and Colcott Fox have observed very violent reactions in anaesthetic lepers; in the former case bullae appeared all over the arms.

Babes, having given considerable attention to the subject, is of the opinion that some lepers react with quite a small dose, others only after repeated larger injections. A general reaction takes place after about twenty-four hours, in some instances, however, after eight to ten, or even as short a time as only two hours, and as a rule lasts longer than in the case of tuberculosis. The first can be followed by a second or even third rise of temperature. Under certain circumstances an extremely marked reaction may follow an

injection of less than one mmg., lasting several weeks and endangering the life of the patient.

Jadassohn has, however, been unable to produce any reaction with tuberculin in four cases he examined. It will be seen that the evidence is contradictory, but if we take into consideration the relative close relationship of leprosy and tuberculosis from many points of view, it cannot appear improbable that lepers should react to various tuberculin tests.

In previous communications Bayon was inclined to consider that intra-dermal test after Mantoux's method, carried out with a cultural extract made from Kedrowsky's strain of leprosy, might have a specific and diagnostic value. Further investigations have, however, shown that similar local and general reactions can be brought about by the extracts of several acid-fast micro-organisms such as *M. phlei*, Moellers 'mist-bacillus' and Duval's so-called 'lepra.' It is true that as a rule the reaction is not as marked with the latter substances, but the difference is only one of degree.

On the other hand, lepers who do not react to a tuberculin test may show very definite local reactions after intra-dermal injection with one c.cm. of a 10 per cent. dilution of the extract from Kedrowsky's culture. This may consist of a copper-coloured patch appearing at the site of injection or in more marked cases in the production of blisters and infiltration (Plate V, figs. 3 and 4).

One patient at Robben Island, under observation of Dr. W. L. Stuart, developed reddening and infiltration and a rise of temperature to 100° F. even after injection of minimal doses corresponding to one c.cm. of a 1/250 dilution of cultural extract. Other nodular lepers again did not react even after injection of 3 c.cm. Both extremes are exceptional; as a rule one or two c.cm. will be followed by a rise of temperature and an intra-dermal injection will result in varying degrees of discoloration. Pattison injected ten lepers (four nerve cases, four mixed and two nodular) with one c.cm. 1/10 dilution; all reacted either locally or generally. The local reaction consisted usually of a dark patch at the site of injection surrounded by a red zone, which might be swollen and tender.

All these tests have, it is true, confirmatory value, but at the present stage they are insufficient as a decisive help to diagnosis.

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VIII. COMMUNICABILITY AND CONTAGIOUSNESS OF LEPROSY

Exact and repeated observations carried out during the last thirty years have definitely proved that leprosy is an infectious or communicable disease. The 'wisdom of centuries,' to quote Sambon's expression, had never doubted this fact. It is only due to superficial clinical observers of the XIXth century that hereditary and other irrelevant factors have lately been at all considered, even for a short time, in connection with the disease.

The statement is often made that nothing is known about the way in which leprosy is communicated from the diseased to the healthy; but as a matter of fact, the question has been carefully studied and the results are quite as definite, if not more so, than any obtained in many other infectious complaints, such as measles or scarlet fever.

Our knowledge of the contagiousness of leprosy is founded on the following observations:

(1) That it is a disease due to a definite specific micro-organism which has only been found in lepers, their excreta or immediate surroundings.

(2) That in Northern Germany, where leprosy had been re-introduced from Russia in modern times, it was seen to have spread very slowly and concentrically around the first imported cases and their contacts.

(3) That on the island of Oesel, the population of which had practically remained stationary during the last fifty-five years, Lohk, Talwik, and Dehio were able to show that out of sixty-three cases of leprosy only in eight could previous contact with lepers not be traced.

(4) That with one exception (Da Costa) all cases, in which contact cannot be proved, originate in countries or districts where leprosy is fairly common; but that in the relatively rare instances where leprosy has been contracted in countries in which the disease is not indigenous, such as the United Kingdom, Southern Germany, Holland, it is possible to prove the intimate contact with other lepers, who in their turn had contracted the disease abroad.

(5) In countries where leprosy is rare, such as the Valais, the Riviera, Alpes Maritimes, the disease is always found bound to definite foci or families.

(6) That the countries which have carried out a thorough and efficient system of segregation have been rewarded by a gradual and constant diminution of the disease. (Norway, Iceland, Germany, Sandwich Islands, Philippine Islands.)

(7) That where segregation has been abandoned, or loosely carried out, or not enforced at all, the scourge has usually attacked an ever increasing number of individuals. (India, Basutoland, Dutch Indies).

The grounds on which the contagiousness is denied are, I believe, the following:

(1) That medical men and attendants never contract the disease in leper-asylums.

This statement is not quite correct. Infection under these circumstances is not frequent, but still several cases can be brought forward showing that attendants and medical men do contract the disease. In South Africa the Medical Superintendent of a Leper Asylum contracted leprosy. Further instances of professional infection have been published by Ehlers, Vidal, Jeanselme, Nicolas, and others.

In one case of which I know, a missionary to lepers, trusting no doubt to the low degree of infectivity of the disease, allowed his little girl to play with leper children. She developed the malady whilst at school in Europe.

Published and unpublished cases of infection among religious persons who have attended lepers are also known to exist. (Three priests at Molokai, Father Boglioli in New Orleans, two nuns, a missionary, a lady missionary.)

On similar grounds it has been attempted to deny the infectiousness of tuberculosis, the deduction being based on statistics showing the low ratio of marital and professional infection.

(2) Because the disease cannot be transmitted to animals, and inoculation experiments on human beings have failed.

This also is not quite correct. The first part of this argument would have allowed us fifteen years ago to deny the contagiousness of syphilis. As a matter of fact, leprosy is transmissible to laboratory animals such as the rabbit or rat, as repeated experiments have shown. That this possibility is not more generally recognised is due to the fact that the lesions may be localised and fail to develop at all in a very great proportion of experiments, and often resembles tuberculosis to a certain extent.

As to the inoculations which Danielssen, Profeta, Cagnina, Bargilli, carried out on themselves and others, the results, it is true, were negative, but in view of the knowledge we have lately acquired of the bionomics of the leprosy micro-organism, they have only proved that experimental inoculation with small quantities of leprosy material is incapable of producing the disease in the human being in every case.

In Arning's well-known case of the convict Keanu who was pardoned on condition he allowed himself to be inoculated with leprosy, the disease did develop, but the experiment is somewhat spoiled by the fact that the man had lepers among his relatives and was in contact with them before and after inoculation.

(3) That in Norway leprosy diminished considerably in the course of sixty years, but that only about a quarter of the lepers were ever segregated at one time.

This is not quite correct; it is true that only a small proportion

of all the lepers known to exist were placed under strict segregation, that is, in special asylums, but these were the cases unable, incapable or unwilling to carry out segregation at home. All the rest were avoiding at home all contact with their relations, etc., under medical supervision. In this sense the system was one of efficient universal segregation.

A further similar argument, often brought forward by non-contagionists, is that leprosy disappeared in the Middle Ages from England, France, Germany, etc., without strict measures of segregation having been resorted to.

It appears to me that the measures adopted to prevent the spread of the disease were extremely severe. Lepers were not allowed into churches or market places, had to carry a distinctive dress, and had to make their presence known by a bell or clapper. In a few words the intimate contact between the healthy and the diseased, which gives rise to the most favourable conditions for transmission, was most radically avoided. I also believe that plague directly and indirectly swept away a great proportion of the leper population, as they were feeble, and during times of epidemics and commotion would receive no alms. This observation has been confirmed to a certain extent in India in modern times.

It will be seen that non-contagionist arguments are founded mostly on negative evidence. Positive figures bearing on the contagiousness of leprosy are available from Norway, Japan, and the Sandwich Islands, and they unanimously point to the same moral.

Kitasato's statistics from Japan show that children of lepers become leprosy in a proportion of only 7·95 per cent. of the total. Matrimonial infection was proven in 3·8 per cent. cases, whilst persons living under the same roof contracted leprosy in a proportion of only 2·7 per cent. Brothers and sisters infect each other in a ratio of 4·2 per cent. These figures may need correcting according to the latest statistical methods. However, they roughly correspond to the experience gained in Norway where Sand and Lies' figures differ somewhat, but show that the children of a leprosy mother are more frequently infected than those whose father alone is diseased. This proves that the more intimate contact between mother and child leads to a greater percentage of acquisition of the scourge.

Sand's statistics from Norway show that in 357 married couples in which the father alone was a leper, 1,241 children were born, of which 63, equal to a proportion of 4·9 per cent., became lepers. In 138 other married couples observed, the mother only was a leper; of 533 children born of these unions 56, or 10·5 per cent., developed leprosy. In 17 couples both parents were diseased; of the resulting 63 children 8, or 12·7 per cent., became infected.

Lies' figures from South-Western Norway give somewhat similar results. 230 married couples in which the father only was a leper had 769 children, of which 79, or 10·2 per cent., contracted the disease. In 223 married couples the mother only was leprous; of 648 children, 106 of these, otherwise 16·36 per cent., became lepers. In 28 instances both parents were lepers; out of 79 children 29 fell victims to leprosy, that is, 39·19 per cent.

McCoy and Goodhues' observations have been made in the Sandwich Islands, and relate mostly to cases of infection noted among the kokuas or voluntary helpers of the lepers at the Molokai settlement. Their conclusions show that:

(1) Of 119 men, practically all Hawaiians or persons of mixed Hawaiian blood, living in the same house with the lepers, five, i.e., 4·2 per cent., developed leprosy.

(2) Of 106 women, practically all Hawaiians or persons of mixed Hawaiian blood, living in the same house with lepers, five, i.e., 4·7 per cent., developed leprosy.

(3) Of 12 women, all Caucasians, who lived in such contact with lepers as is necessary in administering to their bodily and spiritual wants, none developed the disease.

(4) Of 23 men living under the same conditions in contact with lepers, three, i.e., 13 per cent., developed the disease.

(5) The shortest period in which the disease developed after the person entered the settlement was three years (two cases), and the longest seventeen years.

In a report made in 1886 it is asserted that of 178 kokuas, 17 became lepers in a year. In a later report, made in 1888, it is remarked that of 66 kokuas examined 23 were found to have become lepers.

Such a condition of affairs does not exist at the present time at Molokai, and the change for the better is no doubt due to the great

improvements made in the sanitary conditions of the settlement in recent years.

Of course it should not be forgotten that, as the kokuas are drawn from a population in which leprosy is not very uncommon, it is quite possible that a certain number of cases came to the settlement in a stage of incubation.

Hollman examined carefully the conditions affecting the development of leprosy in the children of lepers at the Molokai Settlement, and came to the following conclusions:

(1) It is shown that 40 per cent. of the children born of parents of whom one or both were lepers died under one year.

(2) 32 per cent. of the males who were exposed ten or more years developed leprosy.

(3) 4 per cent. of the females whose average time of exposure was less than five years developed leprosy.

(4) 10 per cent. of the males exposed for more than seven years developed the disease.

(5) 13 per cent. of the females exposed from one to seventeen years, and under observation seven or more years, became lepers.

(6) The average time of exposure of the cases which developed leprosy was five years.

Accordingly, the danger of contracting leprosy for children born of leprous parents increases with the length of exposure.

Incidentally these investigations show that heredity does not play any important rôle in the causation of leprosy. Also, if it did, the disease would soon die out in any country.

The figures and conclusions show so clearly that contagion or infection through immediate contact is the usual mode of communication, that it appears rather far-fetched to seek an insect carrier of the scourge.

As a matter of fact, all experiments to prove this mode of transmission have so far failed, though it appears quite probable that the common house-fly can suck up the germs of the disease from open sores, carry them about for several days, and disseminate them in such a fashion.

The horrid sight of flies swarming and hovering over the purulent sores and round the nostrils of leprous beggars is well known to the traveller in eastern countries.

Graham-Smith, having shown that house-flies can harbour the bacteria of tuberculosis for twelve days or more, it seemed probable that the micro-organism of leprosy would show an equally long permanence in the fly-intestine.

Leboeuf examined numerous specimens of *Musca domestica* caught on the sores of lepers, in the wards, and in houses not further than 150 metres from the hospital.

He found leprotic 'globi' in the intestines of flies captured and kept for twenty-four hours, and acid-fast rods in flies thirty-six hours after feeding. His conclusions are that:

(1) *Musca domestica* can absorb enormous numbers of Hansen's 'bacilli' by nourishing itself on sores containing these germs.

(2) The 'bacilli' can be found in abundance and, apparently, excellent condition, in the excreta of the infected house-flies.

(3) It does not seem that multiplication takes place in the digestive tract of *Musca domestica*, but in any case there are no signs of degeneration.

(4) *Musca domestica* possibly plays an important part in the dissemination of leprosy by depositing its excrements on the mucous membranes or small abrasions of the skin of healthy people living in the immediate vicinity of lepers whose sores contain 'bacilli.'

It will be seen that in any case the fly does not do more than eventually disseminate the micro-organisms it has ingested, in a similar fashion to flies disseminating typhoid.

As far as our knowledge goes, no insect plays a real rôle of transmission in any bacterial disease. Moreover, transmission implies a more or less complicated developmental cycle in the body of the intermediate host, after which a protozoon can be inoculated by the proboscis of a biting or stinging insect. With bacteria a contaminatory communication through the faeces or by the regurgitation of the crop contents takes place. This is the case in bubonic plague or typhoid.

The fly is eminently adapted for a contaminatory or mechanical method of dissemination, but the difficulties inherent to the communication of leprosy to animals will render experimental work in this direction very difficult to accomplish.

It will be seen that the intimate personal contact, as found between a child and its mother, gives the most favourable circumstances for the acquisition of leprosy.

In South Africa, where the use of coloured and native servants and nurses for children is very widespread, it is not astonishing to find that about 40 to 50 per cent. of the white (Caucasian) patients under segregation cannot tell where they have contracted leprosy. Leprosy is quite widespread in the native population. In single instances, after a great deal of investigation, I was able to find out that the disease could be traced to a coloured nurse or servant who had evident signs of leprosy or eventually had been segregated in some asylum of the Union, the disease developing in the child many years afterwards.

Native labourers suffering from leprosy appear to be the source of contagion in many other cases. The Cape of Good Hope Leprosy Commission of 1895, having given careful attention to this matter, quotes several observations which support these views:

‘An individual may be leprosy for many months, and it may be for a year or longer without showing outward signs of leprosy, and during that time may have communicated the disease to several without being aware of the fact that he is a leper himself. Hence arises the difficulty of knowing how and when the healthy may have been in contact with the contaminated. It is self-evident that the length of the period of incubation, and the possibility that during the period of incubation one individual may communicate the disease to another, greatly add to the difficulty of proving the source of contagion. Hence one may readily understand that statement of many lepers, that they had never been in close contact with a leper, or had never seen a leper, and consequently do not know how they got the disease. In many cases, however, possibly in by far the greater majority, it may be shown that at some period or other those who have acquired the disease have been in contact with a person or persons suffering from the disease; and even where direct contact cannot be proved, indirect means of acquiring leprosy, such as the use of the same bedding, or articles of clothing, or utensils, or a pipe, or implements used by a leper, or living in a room occupied by a leper, or attending to a leper, may be proved to have been present at some time or other in the life history of those who have contracted the disease.

In the evidence given before your Commission, Dr. A. J. J. Simons, of Malmesbury, who, in the course of an extensive practice reaching over a period of years, had many opportunities of observing the disease, gives a very instructive history of the course of leprosy on a certain farm in that division. In the case under consideration the leprosy was first noticed by him in a coloured man, a bastard Hottentot; next a little girl, the farmer's daughter got the disease; next another coloured man on the farm, a wagon driver who used to be great friends with the bastard Hottentot became diseased; after the wagon driver his master, the farmer, became leprosy; next a girl who came to the farm to attend the farmer's daughter and nurse her; and finally the farmer's niece who frequently visited the farm, spent the day there and was generally intimate with the leper daughter of the farmer. Everybody who is acquainted with the patriarchal

mode of life of the South African farmers, and who knows the habits of our rural population, will admit that the account given by Dr. Simons is a history typical of what happens in every country district in South Africa generally.'

' Dr. Nieuwoudt, Darling, records the following cases: (1) A patient, in whose family, apparently, the disease was not present, was waited on by a leprous servant, and developed the disease in a mixed form. Later on a boy who attended on him, etc., got the disease and died; later on the gentleman's daughter developed the disease in the tubercular form and is still here, though her father has since died. (2) An old man had the disease in whose family the disease did not exist, so far as known. His brother's son, who wore the same hat of his, got the disease; and another man outside this family, and of a clean family, in whose bed the patient slept, also developed the disease.'

' Dr. Newnham, Aliwal, knows a case where a farmer was clearly infected by his native coachman who had been long a leper. Master and servant when travelling together used the same horn drinking cup.'

' Dr. Vanes, M.L.A., of Humansdorp, writes: "In a family living at Patentie there were four children affected, the parents being healthy." With regard to these last cases it must be noted that many examples may be cited, which prove that children get the disease before the parents. Such cases appear to your Commission to plead powerfully in favour of the contagiousness of leprosy and as powerfully against its heredity. More especially in those cases in which no remote family taint can be shown.

Dr. Barry, of Bedford, quotes the case of a Dutch farmer, V.H., who states that he got the disease through handling a spade used by a leper Hottentot.'

These observations might possibly be set aside by the hypercritical if they did not agree in a striking fashion with the inferences deduced from the investigation of the spread of leprosy in many other parts of the world.

We know that at the present moment about twenty-five to fifty lepers or more are living in England: and yet of these only one has acquired the disease in the United Kingdom (mother and father were lepers). The simple precautions these unfortunates are able to take to keep themselves separated from their families have been sufficient to prevent contagion.

As a contrast we have India, where the last census appears to show an increase of lepers in the last ten years from 100,000 to 110,000.

The modern medical eye looks, therefore, upon leprosy as a disease which is definitely contagious, but to a very slight degree

under proper sanitary conditions. In situations where hygienic precautions are defective and the contact between the diseased and the healthy is unnecessarily immediate, where a leper is obliged to sleep in the same bed with other members of the family, and personal cleanliness apt to be in abeyance, the danger of contagion is certainly present to a markedly increased extent.

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IX. EARLY AND DIFFERENTIAL DIAGNOSIS. PROGNOSIS

The early recognition of leprosy presents difficulties commensurate with its importance; for at times the symptoms may be so vague and indefinite that in the absence of conclusive microscopical evidence a correct diagnosis can only be made by a process of exclusion. Cases in which nodules containing numerous acid-fast rods, or in which typical maculae accompanied by anaesthesia or even contractures can be detected, cannot generally be considered as early conditions. Moreover, these ought to be diagnosable by someone who has a practical knowledge of the disease. It is in connection with slight and evanescent symptoms that serious difficulties arise, for such indefinite appearances are generally the only ones noticeable during the prodromal stage.

Lepers with very slight and atypical lesions are not necessarily early cases from the chronological point of view, because the slight areas of anaesthesia or discoloration may have existed unnoticed for years.

Sir Patrick Manson mentions the case of a gentleman who developed leprosy five years after noting in his diary a long series of headaches, transient fever attacks and progressive deterioration of health and vigour. These prodromal symptoms were followed three years afterwards by profuse perspiration which occurred without obvious cause. Such carefully observed cases are not frequent, and in view of the abnormal length of the period of incubation of leprosy it is often impossible for the patient to remember the occurrence of slight indefinite prodromal symptoms.

What in many cases is apparently the onset of the disease is but the more marked appearance of symptoms which have been present for a long time. Correspondingly very slight evidences of leprosy may be the traces of much more apparent previous pathological processes. It is accordingly often practically impossible to say whether we are dealing with an early case, though the symptoms may not be conclusive.

It should not be taken for granted that any case showing leprotic symptoms necessarily will progress and become irrecoverable through deformities and mutilations because leprosy may get arrested in the incipient stage.

A disease with such multiform variety of clinical features is naturally often extremely difficult to recognise in its first stages, not only because of its tendency to produce symptoms which are not typical for any single condition and common to several ailments, but also because of the corresponding variety of initial appearances.

As a rule anaesthetic cases begin with a peculiar numbness in a digit, preferably the little finger of one or both hands. This numbness the patients compare to feeling that their fingers are covered with leather. On plunging the hand in warm water a peculiar sensation is noticed in so far as the finger or fingers affected feel the pain caused by the heat to a much lesser degree. The same symptoms may first show themselves in a little toe. On observation it may be seen that the fingers affected are glossier, more shiny than the corresponding or other fingers of the same hand. On taking exercise in warm weather it will be noticed that these areas are much less apt to perspire. Contemporary with these anaesthetic symptoms maculae or discoloration may be present or not in other parts of the body. Under some circumstances the maculae can be so slight

as to amount to little more than a peculiar discoloration very similar to *cutis marmorata* or mottled skin due to effects of cold, or they may take the shape of slight red lines which may form a closed figure. In course of time a case like this becomes a definite maculo-anaesthetic leper, or develops nodular features. A third alternative is, that the symptoms may slowly but surely disappear, leaving hardly any trace.

The insensibility to heat and cold may be accompanied or heralded by formication and shooting neuralgic pains in the limbs affected. Profuse sweating precedes often the anhidrosis.

Pigmented spots may appear on various parts of the body, varying in colour from a light lemon yellow to a dark dirty brown. On looking at the spots under various angles of light incidence it will be noticed that the skin does not reflect the light everywhere in the same fashion, but is rougher in parts and appears covered with a slight farinaceous deposit which consists of desquamating superficial epithelial cells; the surface is intersected with very fine wrinkles, and has a dry atrophied appearance.

Another early stage consists in puffiness and infiltration round the *alae nasi*, or thickening of the lobes of the ears and loss of the eyebrows, accompanied often by intensive irritation and itching of the neck and back of the scalp of the head. In such instances epistaxis and dryness of the nostrils may be followed by a persistent cold in the nose.

A further early stage may be shown by a small pimple or blind boil, appearing in some part of the body, generally the face, this being followed by an outcrop of typical small nodules, superficial or subcutaneous. Under certain circumstances some sore or wound may be found to heal with extreme difficulty, or a slight abrasion may turn into a chronic ulcer; these have often been considered to form the initial sore or lesion of leprosy. They are at times, however, but a symptom of an infection which is already fully developed.

In dealing with such extremely early cases one should never fail to map out the extent and measure the intensity of the paraesthetic symptoms, remembering that in the beginning maculae are usually hyperaesthetic; pin-pricks, etc., are painful which under ordinary circumstances would cause hardly any discomfort; the sense of

touch can be unimpaired. Special value is to be laid on the faculty of recognising blunt and sharp (a penholder or a sharpened lead pencil will do for the purpose) and in each case a trial with two test tubes filled with warm (50°-60° C.) water, and cold water should be used to discover the patient's sensibility in distinguishing hot and cold in the affected areas. Slight muscular atrophy of the interossei should be looked for.

In all doubtful cases a microscopical examination of maculae or discolorations should be undertaken, though the interpretation of any histological lesions observed is a matter requiring expert knowledge. Needless to say, acid-fast rods should be searched for in the nasal mucous membrane; they may be present for a short time and then disappear for longer or shorter intervals.

Small nodules can be grouped up and treated with Anti-formin, centrifuged and the sediment examined for bundles of acid-fast rods. This method should, however, be only used in conjunction with an histological examination, because single acid-fast micro-organisms, without the lesions described elsewhere, are not sufficient to diagnose leprosy.

The fusiform thickening of the ulnar or other nerves, which is one of the cardinal symptoms of anaesthetic leprosy, as a rule does not come into practical consideration as a help in the early diagnosis of leprosy, because in the initial stages it is not usually present to a sufficient degree to render its detection easy. Moreover, such swellings are often deeply seated, and therefore not accessible in clinical examination.

DIFFERENTIAL DIAGNOSIS

Apart from the histological and serological features which have already been discussed, the differentiation of leprosy from other skin lesions, which are somewhat similar in appearance, is generally based on the assumption that leprosy is an extremely slow and intractable disease, and that its manifestations are essentially indolent in character.

Much has been written on the difficulty of distinguishing leprosy from syphilis. There can be no gainsaying that in very rare instances—a case has been illustrated by Graham Little—a

momentary confusion can arise, but a practical knowledge of both complaints soon shows that they must be quite different in their naked eye appearances.

Syphilis and yaws as a rule produce, in all stages, lesions which are more vascular, angrier, with a more active and proliferating appearance than leprosy, which is an eminently indolent, torpid, slow pathological process.

This difference is also applicable to the scars left by ulcers in these diseases. Syphilitic scars are usually rough, with numerous small fleshy warts and excrescences, and their margins are irregular with numerous small pockets and indentations. At times peculiar minute bridges of tissue can be observed under which a sound or needle can be passed. All these appearances are the result of a process of active proliferation and production of cicatricial tissue. Leprosy leaves scars which are smooth, shiny, and usually flush with or gradually merging into the surrounding healthy skin.

Accordingly any circinate macular efflorescences in syphilis and yaws should be more raised, redder, bleed more easily than a corresponding leprotic manifestation. In addition they should respond to mercury or salvarsan.

Practically every macular leper shows at least incapacity of distinguishing blunt from sharp and hot from cold (thermanæsthesia) in some area of his body. Without this crucial test it is not advisable to diagnose leprosy, however typical the lesions may appear to the naked eye, unless the opinion can be confirmed by the microscope.

Leucoderma in the negro and dark-skinned races is often mistaken for leprosy. Here again the lack of anaesthetic or thermæsthetic symptoms, the uniformity in hue and spread of the white spots, ought to facilitate a decision.

Lupus and tuberculosis of the skin are the pathological processes whose manifestations may cause considerable difficulty. However, lupus is rarely multiple, has an early tendency to break down and ulcerate, forming scars at its periphery. Lupus is more friable and bleeds less easily, and though more destructive than leprosy is usually somewhat more amenable to local treatment.

Pellagra ought not to be confused with leprosy, and *vice-versa*. Pellagra is symmetrical, strictly confined to parts generally exposed

to the action of the sun: there are no marked disturbances of sensibility in the areas affected, and the lesions are much more uniform and regular than is usually the case with lepra. The edges are not indented or irregular. In doubtful cases the microscope should decide.

The ringed circinate maculae seen in Caucasians in early stages of trypanosomiasis are not easily distinguished from some phases of early macular leprosy; in fact in one case to my knowledge the presence of the diagnosis was only cleared up by finding trypanosomes in the blood. Leprotic lesions are, however, more permanent and are not as fleeting as the similar eruption in trypanosome disease ('trypanides').

Syringomyelia, especially in its initial stages, is extremely difficult to distinguish from lepra, unless oculo-pupillar paralysis (consisting in myosis, diminution of the eyelid aperture and decreased prominence of the eyeball, Moritz) is present in the former eventuality, or typical maculae can be detected in the latter. A search for clumped acid-fast rods should be made. Early leprosy, moreover, does not often show such generalised lesions as syringomyelia.

In advanced cases, symptoms on the part of the medulla oblongata, scoliosis, and the absence or presence of thickened nerves, ought to help the diagnosis.

The absence or presence of thermanæsthetic and analgetic symptoms should be carefully investigated when dealing with coloured races, for numerous skin diseases due to fungi cause lesions which resemble leprosy in quite a disconcerting fashion. Here, again, microscopical evidence should not be missed.

In conclusion, it need only be added that in many instances the locality from which a patient comes, etc., the possibility or probability of contagion, are facts which, though they cannot carry conviction in every case, still may on the other hand simplify the diagnosis. It will be seen that very often recourse will have to be made to trained microscopical and bacteriological examination of excised fragments of skin.

The extreme variability of all the initial features of leprosy and the chronic course of the complaint, allow only a most guarded prognosis to be stated in any single case of the disease. It cannot

be denied that, given skilful medical attendance and healthy surroundings, even this most dreaded complaint can be held in check for comparatively long periods. It is true that little can be done for advanced cases, except from the standpoint of surgery. Early cases, however, will show but little impairment of their general health under favourable conditions and are quite capable of living a useful life for years and years.

From what has been said in connection with early diagnosis, it is evident that it is not safe to predict in the early stages what course leprosy is going to take; as a rule, cases which have begun with indefinite anaesthetic symptoms, last longer than those whose nodules have appeared in batches or have shown an extensive appearance of simultaneous patches.

The extensive mutilations of many anaesthetic lepers are but too often due to lack of attention to trifling casual wounds and burns.

X. THE TREATMENT OF LEPROSY

Not only nearly every imaginable drug, but in addition poisons and venoms, have been tried on lepers with the intention of discovering a cure, but this notwithstanding we have yet to find a prompt and sure method of treatment.

The present position can, however, be summed up in the words that even the most useful therapeutic substance still requires the help of an early diagnosis and proper hygienic conditions; but that at no time has the outlook regarding the treatment of leprosy been so hopeful as at the present moment.

In its initial stages leprosy affects the general well-being and appearance of an individual to such a slight extent that any therapeutic effort which succeeds in arresting the disease in its early stages in a fair proportion of cases would practically amount to a cure.

Spontaneous remissions of the disease, and spontaneous apparent 'cures' take place, however, in a small proportion of lepers, and can last for several years, in some instances as long as 15 years or more, after which the disease may again become virulent and rapidly carry its victim to the grave.

Therefore any drug or method of treatment must stand the test of time—five years or more—and have been carried out on a sufficient number of patients.

Without taking into consideration these important factors it is absolutely irresponsible to speak of cure in a chronic, slow, intractable malady such as leprosy.

A review of all therapeutic attempts would fill a volume by itself. I may, however, be allowed to give the results of the experiments made at Robben Island, and in South Africa generally.

For all advanced nodular stages Chaulmugra oil, or better still its refined constituent 'anti-leprol,' injected intra-muscularly 3-5 c.cm. at a time, is still the best palliative I know of. The injections should be repeated every three days and the course last five months or more if the patient can stand it, because at times the injections may become very painful. Chaulmugra oil and Antileprol can also be given internally in small capsules.

Antileprol is decidedly preferable for the latter mode of treatment, as it does not cause the gastric disturbances which are the outstanding feature of the unrefined oil. Doses varying between 15 m. and ten times that quantity can be taken daily.

Chaulmugra oil is a product of the seeds of the *Taraktogenos kursii*, whilst the oil extracted from *Gynocardia odorata* ought to be called false chaulmugra (D. Hooper; Article on *Taraktogenos kursii* in 'The Agricultural Ledger,' 1905, No. 5). It appears that substitution and adulteration of this oil is extensively practised, owing to the difficulty of keeping up a regular supply of the seeds of the *Taraktogenos kursii*. Further particulars relative to this important subject are to be found in the paper by Hooper, which no doubt explains the variable results obtained in treating lepers with chaulmugra oils from different sources.

Brocq and Pomaret mix 70 parts of chaulmugra oil with 30 of eucalyptus oil, and find that the injections of this product are much less painful than the pure oil.

Early macular cases appear to respond better to other forms of treatment. A cultural extract has been prepared from Kedrowsky's isolation of the micro-organism of leprosy on similar lines to Koch's Alt-Tuberkulin. It contains accordingly the water-soluble toxic constituents of the bacillus, which, however, in the case of Hansen's

germ are very feeble indeed, so that much higher concentrations have to be injected than is the case in the analogous treatment of tuberculosis by tuberculine.

Dr. MacLeod of Charing Cross Hospital, and Dr. T. S. Davies, Resident Medical Officer of the Pretoria Asylum, have made use of this substance on single chosen cases. The results in both instances have been very satisfactory. The maculae or spots have slowly faded away.

Dr. MacLeod's patient, a young lady from the West Indies, has improved to such an extent that the disease is no more diagnosable. I am authorised to say that other therapeutic efforts failed to bring about any change for the better, and that the patient has now been observed for over two years without any remission taking place. On the contrary a further subjective improvement has so far taken place that muscular pains which were present in the arm affected have disappeared.

Dr. Sidney Davies's first patient, a little girl of $8\frac{1}{2}$ years, was covered with dusky red patches all over her body. These faded away in the course of treatment extended over eighteen months, leaving only a slight discoloration (Pl. VI, fig. 6).

Later, six other lepers were injected with the same cultural extract at Pretoria, with the result that a remarkable improvement was brought about in two (this includes the patient already mentioned), marked improvement became noticeable in three, and slight improvement in the remaining two.

The injections are being continued, and at the time of writing further progress has been made, that is to say, that the maculae have continued fading and in some cases have disappeared, leaving only a trace of faint discoloration. Details will be published in due course.

It now remains to be seen whether these results will stand the test of time, and whether the same amelioration takes place in larger experimental series.

This method of treatment does not appear to be of real advantage in advanced nodular cases. The injection of one or two cubic centimetres of the cultural extract causes a rise in temperature which is accompanied by the appearance of bacilli in the blood. This may possibly lead to dissemination of the germs of the

disease. If the individual affected is young and otherwise healthy, and the leprotic symptoms not marked, a course of injections beginning with one cubic centimetre hypodermically every three days may be distinctly beneficial. The treatment should be continued for some time even after the maculae have disappeared.

The surgical treatment of leprosy requires most careful and constant attention. Fingers, toes, hands and feet are constantly getting septic, and prompt surgical intervention can really work marvels. Eye complaints, which are exceedingly frequent among lepers, are amenable to a certain extent to operative procedures, but relapses often follow even after the most skilful intervention.

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XI. PREVENTION, ASYLUMS AND HOME-SEGREGATION. SETTLEMENTS AND LEPER COLONIES

The trend of all recent research has been to prove conclusively that though leprosy is communicable from the diseased to the healthy by direct and indirect contact, still relatively simple precautions are sufficient to reduce the peril of infection to a considerable extent. Thus the probability of the scourge rapidly spreading and giving rise to an extensive epidemic is certainly remote. On the other hand, if hygienic precautions are neglected, the danger for the immediate surrounding and family of a leper is by no means to be despised, in view of the gravity of the disease.

The fortitude with which some nations view the slow but continuous increase of leprosy in their midst deserves to be explained, at least to obviate its being misunderstood for some less admirable virtue.

If the news spread that robbers or thugs or wild tribesmen were killing, torturing or maiming about five hundred or a thousand

people a year, I have no doubt that expeditionary corps, the police, and all the full weight of official indignation, would be employed to crush the criminals out of existence, and quite rightly so. On the other hand, an acid-fast micro-organism, against which we have hardly any chance of defending ourselves unless we are armed with the sharpest weapons of preventive medicine, is allowed to corrupt the bodies and souls of hundreds and thousands of new victims yearly without a single protest being heard. This is due to the fact that a biological mode of thought has not yet permeated the body politic, and that accordingly it is not yet sufficiently understood that public health means public wealth and individual health. We know of no other method of eradicating leprosy from a country than by segregation. All the critics of this method of dealing with the disease have no other practicable suggestion to make. It is true that by improving the hygienic conditions of the homes and lives of the poorer population, by carrying through an efficient and widespread sanitary inspection, leprosy could be slowly and definitely stamped out; but to deal with the scourge promptly nothing else can be suggested but isolation. The only argument that can be brought to bear against segregation is on the score of expense. In some instances parsimony and reluctance to invest money in public health matters have been veiled by the sentiment that it would be cruel to separate a leper from his family and his friends. Two facts are, however, overlooked. One is that when an individual develops leprosy in a severe and noticeable form, he need not trouble about his friends: they leave him of their own accord. The other is that consideration of the feelings of one may mean the misery of the whole family. In South Africa one leper infected in the course of time, directly and indirectly, sixteen other members of his family.

It is erroneous to believe that all lepers being segregated are compulsorily detained, however penurious may be the conditions offered by an asylum. Many are but too glad to find a refuge, a shelter from the dreadful conditions and inhuman circumstances under which they had to exist in the outer world.

The new introduction of a scheme of segregation requires careful preparation, because experience teaches us that the mere building of asylums is not sufficient to eradicate successfully the disease.

Efficient isolation presupposes adequate, skilful, sympathetic medical attendance in asylums, and when such is forthcoming many of the terrors of segregation disappear. Even in leprosy-ridden countries it is necessary for the medical profession to learn to diagnose leprosy, especially in its early stages. The public must be persuaded of the fact that there is no credit or advantage to be gained from having even only a few hundred or few thousand lepers hidden away in the midst of the community.

In Johannesburg a prominent political man had a leper for about ten years as his gardener; the boy was repeatedly diagnosed as a syphilitic. The mixed case of leprosy figured in Abraham's chapter on the disease in Allbutt and Rolleston's *System of Medicine*, page 682, toured South Africa with an operatic company, was laid up in Johannesburg with an acute leprotic attack, was visited and treated by a medical man who failed to recognise the malady. Numerous similar instances could be quoted, all showing that, for a system of segregation to succeed, it needs above all the intelligent co-operation of the general medical public. Without it all efforts are of little use.

There can be no doubt that segregation in asylums, if properly carried out, is in every case an expensive matter. No doubt it is more expensive still, in the long run, if adopted in an incomplete fashion, because the sum total eventually employed will have failed to bring about a corresponding diminution of leprosy.

The Union of South Africa is at the present moment spending quite £100,000 a year on its lepers (according to the estimates for 1913-14, £97,800), and is segregating certainly not more than half the number of lepers which are believed to exist in the territories of the Union. Under the circumstances the question arises whether these stupendous efforts and large sum of money would not be better employed in stamping out diseases which are more infective, such as typhoid or syphilis, and show a better chance of responding to treatment.

Unfortunately we are dealing with a subject which is but rarely, if ever, approached without a certain preconceived view and sentiment. The general public, on the one hand, considers leprosy to be extremely contagious, shuns and has an absolutely fanatic terror and horror of the disease. As a contrast, the patients them-

selves and their families cannot as a rule be persuaded to take the simplest measures to prevent an immediate spread of the scourge. In face of this dilemma nothing but segregation seems to meet the requirements of both parties.

An alternative to isolation in asylums is home segregation, which, however, as a rule, fails to have the desired effect if not aided by constant inspection, which may become so irksome that many prefer to take refuge in asylums. In South Africa it has not been a success, though in Norway it has been possible to introduce the system on a large scale.

When dealing with numerous lepers, such as are to be found among native populations, a system of segregation in asylums does not seem to be advisable on the score of efficiency, expense, and practicability. In these instances isolation in settlements with natural boundaries (a river, steep hills, on islands, etc.) appears to be by far the best solution. Wives can then accompany their husbands and the usual amenities of kraal-life (cattle, agriculture) need not be dispensed with. A central hospital for the infirm and blind, a dispensary for dressings and ambulatory medical attendance, a home for untainted children, should be provided, but the inhabitants of the settlement, whether lepers or healthy, would have to work for themselves; the only restriction placed on them is that they are not allowed to leave a certain district or province.

Amongst natives generally, especially in South Africa, pure maculo-anaesthetic leprosy is by far the commoner type of the disease. Many of these anaesthetic cases are by no means incapable of work; in fact, graduated exercise and manual labour is distinctly beneficial to their general good health. In asylums, strapping young natives, with a simple contracture or a few maculae, slide into a life of sloth, mope about the wards and yards, and if re-infection can take place, certainly expose themselves to its danger to an unnecessarily increased extent and jeopardise accordingly their slender but possible chance of recovery.

Asylums for lepers cannot be done away with; they are equally necessary, if not more so, than hospitals for the mentally afflicted. Where feasible, they should be supplemented by settlements or leper colonies, and in exceptional and carefully selected cases by home segregation.

By these means there is every reason to believe that leprosy would soon become extinct in any country, however a firm and extensive hold it may have taken, however unsuccessful previous half-hearted attempts of prevention may have been, however long the scourge may have existed in the past.

XII. CONCLUSIONS

Though numerous questions are yet unanswered in the pathology of leprosy, and many points are still under discussion, it cannot be denied that the researches of the last ten or fifteen years have opened up further fields of fruitful investigation, and helped to elucidate several obscure problems.

It is true that the results of some experimental observations are so diametrically opposed that it appears hardly possible that both can be correct, at least not in their entirety. This is no new feature in the study of diseases whose investigation presents more than ordinary difficulties. Malaria is a good example. First of all bacteria were isolated time after time from patients, and it was sturdily maintained they were the etiological factor of the disease. Then the protozoa in the erythrocytes were stated to be artefacts by men eminent in various branches of medicine. Later on the plasmodia were found in marsh-water and so forth. Finally, the present conclusive standpoint was reached, but the path to truth was strewn with the thorns of controversy and deeply indented with the pit-falls of erroneous deductions.

This comparison explains the present position of leprosy research. The exercise of sound and reasoned scientific criticism ought to enable us to unravel, in course of time, the delicate and elusive thread of positive fact from the tangled skein of mistaken interpretations of essentially correct, but irrelevant observations.

The main conclusions which can be deduced from a perspective review of recent experimental study of leprosy appear to be concentrated in the following main points:

Cultivation of Hansen's 'bacillus.'

Any micro-organism isolated from lepers which claims to correspond to the acid-fast rod seen in lesions should be identified

by injection into animals and the following production of the well-known histological features of lepromas.

The culture of Kedrowsky and those similar to this type are the only ones to fulfil this essential postulate.

Clinical features of leprosy.

In addition to the nodular, maculo-anaesthetic, and mixed types, a further variety is recognisable, with thick raised patches, which may be more or less confluent and circinate, containing numerous giant cells, and very scanty acid-fast rods.

Histological appearances of typical leprotic lesions.

In dermal nodules and corresponding lepromas of inner organs, there occur numerous matted masses of acid-fast rods, intra-cellularly and extra-cellularly situated, very slight tissue reaction and scanty giant cells.

The lesions of inner organs which show caseation, necrosis or numerous giant cells of the Langhans type, appear in some cases to be due to tuberculous complications. Guinea-pig inoculations only can conclusively decide the nature of such appearances.

Maculae show the features of slight chronic irritation due to the action of minute doses of bacterial toxins. This, in addition to the external resemblance between maculae and the erythema produced by injecting the water-soluble contents of various acid-fast cultures into lepers, seems to postulate that leprotic maculae may be the result of a local reaction similar to the one resulting in von Pirquet's and similar tests for tuberculosis.

Rat leprosy.

This spontaneous disease presents numerous points of resemblance to leprosy, and may yet be found to be etiologically related to the human malady.

Its experimental transmission in rodents only causes analogous but not identical effects to the spontaneous disease.

Transmission to animals.

The negative results of numerous experimental inoculations of human beings, and the relative low infectivity of leprosy, should prepare us to face very numerous unsuccessful results in dealing

with this question. It is only by injecting a large series of animals in various ways, and then observing them for prolonged periods, that deposits of acid-fast 'bacilli' can be produced in the inner organs which have the essential histological features of the leproma.

Serology.

Wasserman's test is incapable of distinguishing in every case syphilis from leprosy. The same applies to Eitner's test. Noguchi's luetin test is negative in lepers whose disease is not complicated by syphilis.

Leprotic sera often show spontaneous absorption of complement. The serological distinction of leprosy and tuberculosis is not possible in every case. Tuberculine tests may be present in lepers showing no clinical symptoms of tuberculosis.

Agglutination is so far of little value owing to self-clumping of acid-fast bacteria and low titer of leper sera.

Contagiousness.

The communicability of leprosy by direct and indirect contact, especially under defective hygienic conditions, has been established by numerous repeated and independent clinical observations.

Treatment.

Leprosy, especially the macular variety, is subject to spontaneous remissions and self-cures.

Chaulmugra oil is indicated for nodular cases; cultural extract for macular lepers (as far as the present experience goes).

Prevention.

Registration and sanitary inspection of lepers' habitations; segregation in asylums, settlements, or colonies; early separation of children from leprous parents; betterment of hygienic conditions where leprosy has spread extensively.

EXPLANATION OF PLATES I-VI

PLATE I

- Fig. 1. Filamentary interlacing, branching, non-acid-fast germ cultivated from the nodule of a leper on horse-serum-nutrose-agar. Some of the original acid-fast rods from the leprous lesion are still to be seen, and the acid-labile bacteria have grouped themselves in a peculiar fashion round the 'globi.' This culture was injected into a rat, acquired acid-fast properties, and could be then regained in pure culture as an acid-fast 'bacillus.' Stain: Ziehl-Neelsen. Magnification, 1,000 diameters.
- Fig. 2. Diphtheroid, pleomorphic, filamentary and bacillary germ, isolated from the nodules of a leper. It is considered to be a further developmental stage of the previous micro-organism. These bacteria are slightly acid-resisting, and regained acid-fast properties after injection into animals. Third sub-culture on placental-juice-glycerine-agar. A slight multiplication of the original acid-fast rods may have taken place. Stain: Ziehl-Neelsen. Magnification, 1,300 diameters.
- Fig. 3. Acid-fast stage of the bacteria of leprosy which are commonly met with in tissues. ('Hansen's bacillus,' *Mycobacterium leprae*.) Pure culture with which all identification experiments have been carried out. Two months' culture at 37°C. on fish-juice-glycerine-agar. From a micro-photograph. Stain: Ziehl-Neelsen. Magnification, 500 diameters.
- Fig. 4. Section of omental gland from a spontaneously leprous rat, found in Ipswich by Drs. Petrie and Macalister. The similarity to the lesions seen in human leprosy is very striking. Stain: Ziehl-Neelsen. Magnification, 500 diameters.
- Fig. 5. Nodules produced in the kidney of a rabbit by the intravenous injection of a culture of 'Moeller's smegma bacillus.' This lesion simulates leprosy in one detail only: the presence of massed acid-fast micro-organisms. Stain: Ziehl-Neelsen. Magnification, 500 diameters.
- Fig. 6. Section from the skin of a leprous rat, showing the enormous quantities of micro-organisms which cause the lesions. The thick, purple masses consist almost entirely of 'bacilli'; the blue spots are the nuclei of the connective tissue.
- From a colour-photograph taken by Sanger-Sheppard's method. Stain: Gram. Magnification, 400 diameters.

[Plates I-IV have already been published by the author in the *S. Afr. Med. Record* (1913), XI, pp. 201-222.]

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PLATE II

- Fig. 7. Lesions produced in the liver of a rabbit after intravenous injection of the acid-fast culture of 'Hansen's bacillus.' Similar appearances can be brought about by the intravenous injection of cultures of human and avian tuberculosis, and under circumstances by the inoculation of leprosy 'virus.' Stain : Ziehl-Neelsen. Magnification, 500 diameters.
- Fig. 8. Lung of a mouse which has been injected intraperitoneally with Kedrowsky's strain of leprosy. The enormous quantity of 'bacilli' present has caused no appreciable tissue reaction of a tuberculous nature. Stain : Ziehl-Neelsen. Magnification, 150 diameters.
- Fig. 9. Spleen of a monkey injected intraperitoneally with Kedrowsky's strain of leprosy. Also in this instance the numerous bacteria have not brought about a tissue reaction of a tuberculous nature. Stain : Ziehl-Neelsen. Magnification, 35 diameters.
- Fig. 10. Omental gland of a rabbit, which received an intravenous injection of Kedrowsky's strain of leprosy. The section is teeming with acid-fast 'bacilli' which have not caused the death of the cells they have invaded, because the nuclei are still capable of staining, and have not appreciably altered in morphology. Stain : Ziehl-Neelsen. Magnification, 25 diameters.
- Fig. 11. Spleen of a mouse which had been injected intraperitoneally with an emulsion of Kedrowsky's strain of leprosy. The red patches are groups of cells which are crammed with acid-fast rods. Similar lesions are sometimes seen in the spleen of lepers. Stain : Ziehl-Neelsen. Magnification, 25 diameters.
- Fig. 12. Portion of the mouse spleen shown in fig. 11, but under increased magnification. The 'bacilli' are seen to have nearly completely filled the protoplasm of the cells without inducing necrosis or caseation. No giant cells of the Langhans type are to be detected. These are the points which on the whole distinguish this lesion from one of 'tubercular' nature, i.e., caused by Koch's 'bacillus.' Stain : Ziehl-Neelsen. Magnification, 230 diameters.

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PLATE III

- Fig. 13. Localised lesion produced in the testes of a rat by the injection of human leper 'virus.' Stain : Ziehl-Neelsen. Magnification, 500 diameters.
- Fig. 14. Leprous lesions in the spleen of a rat six months after injection of a ground-up inguinal gland from the preceding animal. Drawing made from three different portions of the slide. The peculiar hyaline increase in size of protoplasm of the cells invaded by the 'bacilli' is specially noticeable. Stain : Ziehl-Neelsen. Magnification, 500 diameters.
- Fig. 15. Section through the skin of a rat suffering from spontaneous rat leprosy. The acid-fast 'bacilli' of the disease have congregated round the shaft of a hair-follicle. (According to Borel may have been deposited there by *Demodex*.) Stain : Ziehl-Neelsen. Magnification, 35 diameters.
- Fig. 16. Small, solitary deposit of 'bacilli' in the omentum of a rat, one month after intraperitoneal injection with ground-up 'virus' from a spontaneously infected rat. The micro-organisms are markedly granular, yet juice of the spleen of this animal produced a pure culture of the germ, the only one achieved out of very numerous attempts. Stain : Ziehl-Neelsen. Magnification, 700 diameters.
- Fig. 17. Thorax gland of a white rat injected intraperitoneally with an artificial culture of rat leprosy. The lesion is identical with that produced by the injection of 'virus.' Stain : Ziehl-Neelsen. Magnification, 500 diameters.
- Fig. 18. Small deposit of acid-fast micro-organisms detected in a nodule of the abdomen of a mouse injected with an emulsion of a leprosy culture which had been heated for an hour at 60°C. Showing that, killed or alive, leprosy micro-organisms are capable of producing similar lesions. Stain : Ziehl-Neelsen. Magnification, 300 diameters.

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PLATE IV

- Fig. 19. Filamentary, interlacing, branching, partially acid-fast and acid-resisting germ isolated from the pleura of a man, by Birt and Leishman. It will be seen that it shows marked clubbed fragments (so-called involution forms), and also some which are definitely 'bacillary' in appearance. The resistance to the bleaching properties of mineral acids varies also considerably. From a pure culture on glucose-agar. Stain: Ziehl-Neelsen. Magnification, 800 diameters.
- Fig. 20. Acid-fast bacteria from the water-tap at the Lister Institute. Here also marked pleomorphism and variable acid-fastness is noticeable, but in this case the culture is not known to be pure, because the micro-organism was not isolated on artificial media. Similar acid-fast rods have been found in the scraping from a water-tap in the Public Health Laboratory at Cape Town and in Stockholm; also in mule's dung at Robben Island. These observations show the ubiquity of acid-fast rods. Stain: Ziehl-Neelsen. Magnification, 600 diameters.
- Fig. 21. Section marked 'Experimental Leprosy, Monkey,' sent by Professor Duval, and considered by this author to be diagnosable as leprosy. Stain: Haematoxylin-Eosin. Magnification, 60 diameters.
- Fig. 22. True branching in tubercle-bacillus from sputum of consumptive. From a drawing by Mr. W. D. Severn. Stain: Ziehl-Neelsen. Magnification, 2,250 diameters.
- Fig. 23. Pure culture of Duval's strain of leprosy. Its coccoid appearance shows it to be morphologically very similar to the ubiquitous group of saprophytic acid-fast micro-organisms, therefore quite different from 'Hansen's bacillus.' From a micro-photograph. Stain: Ziehl-Neelsen. Magnification, 1,100 diameters.
- Fig. 24. Mononuclear cells from the peritoneal cavity of a guinea-pig, forty-eight hours after injection with a chromogenic strain of an acid-fast micro-organism. (Duval's 'lepra.') Stain: Ziehl-Neelsen. Magnification, 1,800 diameters.

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PLATE V

- Fig. 1. Front and back view of an off-coloured Cape-boy, with serpiginous or lupoid leprosy. The presence of nerve-lesions and similar appearances on single other cases of leprosy, allow the inference that the disease is due to an infection through Hansen's 'bacillus,' though acid-fast micro-organisms are very scarce indeed in the skin-eruption.
- Fig. 2. Leprous patch of face, apparently taking its origin from the eye, in a Fingo native. The borders are more raised and the surface rougher than is usually the case in leprosy. Similar patches are present on the loins of this case. No anaesthesia or paraesthesia detectable.
- Fig. 3. Arm of nodular leper 24 hours after intradermal injection of 10 minims of cultural extract. There is a copper-coloured areola round the site of injection, in the centre of which a small sore has developed.
- Fig. 4. Arm of an arrested anaesthetic leper, 24 hours after intradermal injection of 10 minims of cultural extract. Numerous blisters; intense local reaction, rise of temperature to 101° F., malaise, pains. All symptoms passed within three days.

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PLATE VI

- Fig. 5. Diagrams of case before treatment (12.9.12). On face, infiltrated and thickened patches, red in colour. On legs, erythematous patches, reddish in colour. Over feet, purplish flush.
- Fig. 6. Diagrams of case after treatment (6.5.14). There are faintly pinkish-red flat discolorations on the face. There is a flat brown macula on right upper arm, below the shoulder. The other yellow discolorations are very difficult to chart, as many of the edges are not well defined. There is a faintly light purple flush on the limbs, and the insides of the hands are a darker shade of the same.

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