This book is for reference only and must not be taken from the ante-room.
TROPICAL
MEDICINE AND HYGIENE
Plate I.

1. 2. 3. 4. 5.

6. 7. 8. 9. 10.


16. 17. 18. 19. 20.

21.

22. 23.

A Terzi del Bale & Damelsson Ltd lith.

TROPICAL MEDICINE AND HYGIENE.—Part I.
PLATE I.

STAINED WITH LEISHMAN'S STAIN.

Figs.
1 to 5. Stages of benign tertian parasite. *Plasmodium vivax*.
7, 8, 9. Characteristic degeneration of red corpuscles containing benign tertian parasites (Schüffner's dots).
10 to 15. Stages of quartan parasite. *Plasmodium malariae*.
16, 17. Stages of malignant tertian (sub-tertian) which are seen in peripheral blood. *Plasmodium falciparum*.
18. Male gametocyte, malignant tertian (sub-tertian).
19. Female gametocyte malignant tertian (sub-tertian).
20. Double infection with malignant tertian (sub-tertian) parasites of a red corpuscle; basophilic granules in red corpuscle.
22, 23. *Amoeba coli*. 
PLATE II.

Stained with Hæmatoxylin or Eosin and Hæmatoxylin.

Figs.
1, 2. Normal variations in red blood corpuscles.
3, 4. Nucleated red blood corpuscles.
6, 7. Abnormal variation in size and colour.
8. Abnormal shapes, poikilocytes.

Malignant Tertian Parasites (Sub-Tertian) Stained with Carbol Thionin.

Figs.
10. Young form, rings.
11. Half-grown parasite.
12. Full-grown parasite.
13 & 15. Are full grown and sporulating parasites, as seen in sections of organs shrunk by the spirit and other processes.
16 to 19. Development of the gametocytes of malignant tertian.
22, 23. Quartan parasites, half-grown and sporulating.
24 to 27. Sporozoa of cattle and horses.
Abnormal shapes, basophilic granules.

IGNANT TERTIAN TES (Sus-T. PHIONIN, tertian parasite, half-grown and sporoziates,)

MALIGNANT TERTIAN PARASITES (SUB-TERTIAN, STAINED WITH CARBOL THIONIN.)

Figs.
10. Young form, tings.
11. Half grown parasite.
12. Full grown parasite.
13. Sporulating parasite.
15 & 15. Are full grown and sporulating parasites, as seen in sections of organs shrunk by the spirit and other processes.
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1. 2. 3. 4. 5.

6. 7. 8. 9.


16. 17. 18. 19.

20. 21. 22. 23.

24. 25. 26. 27.

TROPICAL MEDICINE AND HYGIENE.—Part I.
TROPICAL MEDICINE
AND
HYGIENE

BY

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IN THREE PARTS, WITH COLOURED AND OTHER ILLUSTRATIONS

PART I.
DISEASES DUE TO PROTOZOA

SECOND EDITION

London
JOHN BALE, SONS & DANIELSSON, LTD.
OXFORD HOUSE
83-91, GREAT TITCHFIELD STREET, OXFORD STREET, W.
1913
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PREFACE.

The exigencies of tropical practice require most medical men to be practical sanitarians as well as clinicians.

It is with this in view that in the present work, while due attention has been paid to the clinical features, treatment and nursing of tropical diseases, special prominence has been given to their etiology and prevention.

Owing to the recent advances in the knowledge of the etiology of many tropical diseases the subject of their prophylaxis is a very promising one, since the general principles on which efficient and economical preventive measures should be based are now well understood.

In the application of such general principles local conditions must be carefully considered, and thus in describing the various methods to be adopted those suitable for certain localities have been given as types.

In the spread of many tropical diseases intermediate hosts play an important part, and the life-history of such hosts, often insects, has been considered at some length, as a knowledge of this subject is essential to the proper understanding of the rationale of the preventive measures proposed.

An attempt has been made to group the diseases treated of according to their known or probable causation. Thus, in the first part those diseases are dealt with which, like Malaria, are known to be due to Protozoa, and others, such as Yellow Fever, which are probably due to such organisms.

In the second part diseases due to the higher forms of animal life are considered.
The third part is devoted to bacterial diseases, to the effects of certain animal and vegetable poisons, and to certain diseases the causation of which is unknown or but imperfectly understood.

The advantages of this arrangement are considerable, as the general outline of the prophylactic measures required differs for the diseases described in each part.

Thus the measures described in the first part are mostly directed against arthropoda, insects or arachnida, which act as intermediate or alternative hosts for the malarial and other protozoal parasites. The measures described in the third part, including as they do those for dealing with cholera, enteric fever and plague, involve the consideration of the protection of water supplies, the disposal of sewage, disinfection and other sanitary problems; while the measures dealt with in the second part include some directed against insects, as in the case of filariasis, and others, e.g., those for the prevention of endemic hæmaturia and ankylostomiasis, dealing with the water supplies and sewage disposal; in both cases, however, involving somewhat different problems from those discussed in the other two parts of this work.

Suitable technical methods of a simple character, as well as data and measurements in common use, are given in an appendix to each part.

We are much indebted to numerous friends and past students of the London School of Tropical Medicine for valuable hints and aid in revision of proofs. Major J. B. Smith, Major J. H. McDonald, of the I.M.S., Dr. Venis, and Dr. H. B. Newham must be specially mentioned. The charts used for the illustrations are in most instances those of patients at the Albert Dock Hospital of the Seamen's Hospital Society, to which is attached the London School of Tropical Medicine.
PREFACE TO THE SECOND EDITION.

With the steady advances made the division into parts according to the class of organisms causing the diseases has been justified. Even with intestinal diseases where very different organisms may, as in dysentery, cause similar symptoms, our knowledge is getting more definite. In deference to the views expressed by some kindly critics an alteration has been made in the arrangement which it is hoped diminishes the amount of repetition.

C. W. D.
**CONTENTS.**

<table>
<thead>
<tr>
<th>CHAPTER I.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction, Classification, and Life History of Protozoa</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHAPTER II.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporozoa, General</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHAPTER III.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign Tertian, Quartan, and Subtertian Malaria</td>
<td>14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHAPTER IV.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis, Pathology, and Treatment of Benign Tertian and Quartan Malaria</td>
<td>32</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHAPTER V.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis, Prognosis, and Treatment of Subtertian Malarial Fever; Management and Nursing; Complications; Special Cases; Malarial Cachexia; Sequelae</td>
<td>40</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHAPTER VI.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis and Etiology of Subtertian Malarial Fever; Mosquitoes; Notable Dates</td>
<td>69</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHAPTER VII.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prognosis, Susceptibility, Pathological Anatomy and Treatment of Blackwater Fever; Nursing; Piroplasma; Prophylaxis</td>
<td>88</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHAPTER VIII.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Piroplasmosis...</td>
<td>111</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHAPTER IX.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Geographical Distribution, Clinical Course, Diagnosis and Treatment of Yellow Fever; Prophylaxis; Ship Epidemics</td>
<td>115</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHAPTER X.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Geographical Distribution, Clinical History, Varieties, Diagnosis, Prognosis, Pathological Anatomy, and Treatment of Sleeping Sickness; Nursing; Etiology...</td>
<td>131</td>
</tr>
</tbody>
</table>
CONTENTS

CHAPTER XI.
Definition, Geographical Distribution, Clinical Course, Pathological Anatomy, Diagnosis, Prognosis, Etiology and Treatment of Kala-azar; Digestive, Respiratory and Cutaneous Systems; Prevention; Varieties.—Clinical Course, Pathology, Etiology and Treatment of Juvenile Kala-azar. Canine Leishmania ... ... ... ... 151

CHAPTER XII.
Etiology, Diagnosis, Treatment and Prevention of Oriental Sore ... ... ... ... ... ... ... 176

CHAPTER XIII.
Incubation, Clinical Course, Complications, Prognosis, Diagnosis, Morbid Anatomy, Etiology and Treatment of Relapsing Fever ... ... ... ... ... ... 183

CHAPTER XIV.
Diagnosis and Treatment of Tick Fever; Prophylaxis; Varieties ... ... ... ... ... ... ... 202

CHAPTER XV.
Diseases associated with Spirochætae in the Tissues ... ... 211

CHAPTER XVI.
Intestinal Protozoa, &c. ... ... ... ... ... ... ... 225

CHAPTER XVII.
Prophylaxis in Protozoal Diseases: Résumé ... ... ... 237

APPENDICES.
(i) Notable Dates—(ii) Important Measurements—(iii) Ticks 262

INDEX... ... ... ... ... ... ... ... 267
<table>
<thead>
<tr>
<th>LIST OF ILLUSTRATIONS.</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLATE I, containing 23 coloured figures</td>
<td>Frontispiece</td>
</tr>
<tr>
<td>PLATE II, containing 27 coloured figures</td>
<td>Frontispiece</td>
</tr>
<tr>
<td><strong>FIG.</strong> 1.—Showing the Development of Coccidia</td>
<td>5</td>
</tr>
<tr>
<td>2.—Piroplasmata</td>
<td>11</td>
</tr>
<tr>
<td>3.—Hæmogregarines of Frog</td>
<td>12</td>
</tr>
<tr>
<td>4.—Arrangement of the Red Cells in a Fresh Fluid Film</td>
<td>15</td>
</tr>
<tr>
<td>5.—Detail of Method of making Blood Films</td>
<td>16</td>
</tr>
<tr>
<td>6.—Asexual and Sexual Phases in the Development of the Quartan Parasite</td>
<td>18</td>
</tr>
<tr>
<td>7.—Asexual and Sexual Phases in the Development of the Benign Tertian Parasite, <em>Plasmodium vivax</em></td>
<td>19</td>
</tr>
<tr>
<td>8.—Asexual Phases in the Development of the Malignant Malarial Parasite, <em>P. falciparum</em></td>
<td>25</td>
</tr>
<tr>
<td>9.—Showing the Development of Malarial Parasite</td>
<td>27</td>
</tr>
<tr>
<td>10.—Temperature Chart of Simple Benign Tertian Fever</td>
<td>34</td>
</tr>
<tr>
<td>11.—</td>
<td>35</td>
</tr>
<tr>
<td>12.—</td>
<td>36</td>
</tr>
<tr>
<td>13.—</td>
<td>37</td>
</tr>
<tr>
<td>14.—</td>
<td>41</td>
</tr>
<tr>
<td>15.—</td>
<td>42</td>
</tr>
<tr>
<td>16.—</td>
<td>42</td>
</tr>
<tr>
<td>17.—</td>
<td>42</td>
</tr>
<tr>
<td>18.—</td>
<td>42</td>
</tr>
<tr>
<td>19.—</td>
<td>43</td>
</tr>
<tr>
<td>20.—Parasites in Capillaries of Pancreas</td>
<td>46</td>
</tr>
<tr>
<td>21.— Capillary from Intestine</td>
<td>47</td>
</tr>
<tr>
<td>22.—Culicine male and female and Anopheline male and female</td>
<td>73</td>
</tr>
<tr>
<td>23.—Various forms of Wing Scales</td>
<td>74</td>
</tr>
</tbody>
</table>
LIST OF ILLUSTRATIONS

Fig. 24.—Lateral Views of Anopheleline and Culicine, Anopheleline and Culicine viewed from above, head of Corethra and Megarhinina .......................... 76

" 25.—Diagram showing percentage of Negroes harbouring Malaria Parasites ............... 82

" 26.—Diagram showing percentage of Negroes' bodies having enlarged spleens ........ 83

" 27.—Diagram showing percentage of Negroes' bodies having pigmented spleens .......... 85

" 28.—Temperature Chart of mild attack of Blackwater Fever .................. 92

" 29.— " " severe " .......................... 92

" 30.— " " relapsing case of Blackwater Fever .......................... 93

" 31.—Spectra ................................ 98

" 32.—Rabbit's kidney in health during experimental hæmoglobinuria, and in suppression of urine following Blackwater Fever .................. 100

" 33.—A renal tubule showing normal condition, commencing deposit in hæmoglobinuria and obstruction of the tubules in the pyramid .................. 101

" 34.—Temperature Chart of Yellow Fever simplex .......................... 117

" 35.— " " severe attack of Yellow Fever .......................... 118

" 36.— " " Trypanosomiasis, with adminis-tration of soamin .................. 132

" 37.— " " Trypanosomiasis, third and fifth weeks .................. 132

" 38.— " " Trypanosomiasis, three months later .......................... 133

" 39.— " " Trypanosomiasis, with intra-venous injections of tartar emetic .................. 133

" 40.— " " Trypanosomiasis .......................... 134

" 41.— " " , later condition .......................... 134

" 42.—Child with Trypanosomiasis ................................ 136

" 43.—Glossina morsitans ................................ 145

" 44.—Trypanosomes multiplying asexually by longitudinal division .................. 148

" 45.—Temperature Chart of Kala-azar simulating typhoid .......................... 154

" 46.— " " " , later, showing inter-mittent type .......................... 154

" 47.— " " " , undulating type .......................... 155
LIST OF ILLUSTRATIONS

Fig. 48.—Film showing Parasites of Kala-azar—Leishman-Donovan Bodies ... ... ... ... 165
" 49.—Trypanosomes and the altered forms found in culture 169
" 50.—A case of Leishmaniasis from South America ... face 176
" 51.—Growths on face, neck and left arm, in a case of Oriental Sore ... ... ... ... face 178
" 52.—Growths on neck (× 2), from case in fig. 51 ... " 180
" 53.—Temperature Chart of case of Relapsing Fever from India ... ... ... ... ... ... 185
" 54.—Spirillum obermeieri ... ... ... ... ... ... 194
" 55.—Pediculus vestimentorum ... ... ... ... ... 197
" 56.—Ornithodorus moubata ... ... ... ... ... 207
" 57.—Case of Yaws ... ... ... ... ... ... face 216
" 58.—" " on Sole of Foot ... ... ... " 216
" 59.—" " involving Trunk and Limbs ... " 218
" 60.—Granuloma of the Pudenda ... ... ... " 222
" 61.—Neuration of Wing of Culicidæ ... ... ... 243
" 62.—Sections of Drains ... ... ... ... ... 247
" 63.—Phlebotomus ... ... ... ... ... 259
" 64.—Balantidium coli ... ... ... ... ... 227
" 65.—Scheme of Development of Amœba ... ... ... 228
" 66.—Temperature Chart of Hepatic Abscess with Irregular Pyrexia ... ... ... ... ... ... 233
" 67.—Temperature Chart in Amœbiasis with Liver Abscess yielding to Ipecacuanha ... ... ... ... ... 234
" 68.—Neuration of Wing of Ixodes ... ... ... ... 265
" 69.—Sections of Drains ... ... ... ... ... 247
" 70.—Phlebotomus ... ... ... ... ... 259
" 71.—Mouth-parts of Argasina ... ... ... ... 266
" 72.—" " Rhipicephalus ... ... ... ... 265
" 73.—" " Argasina ... ... ... ... 266
INTRODUCTORY.

The term Tropical Diseases is a convenient one, though not capable of logical definition. Few diseases are limited to the Tropics or even subtropical regions. As employed in this work, it is meant to include all diseases which are not commonly seen or recognized in England but which are prevalent in tropical regions, and a few other diseases which present peculiar characteristics, or require special prophylactic measures in the Tropics.

The peculiar distribution of many of the diseases met with in the Tropics is due to the fact that the parasites causing them require special conditions for their extracorporeal existence. These conditions in the case of parasites such as ankylostomes, which do not require an intermediate host, are mainly warmth and moisture. Where, however, the parasites, like those of malaria, require an alternative host for their development, the conditions determining the distribution of disease are not purely meteorological, but include various other factors affecting the life of alternative hosts—in that instance, certain species of mosquitoes. These other factors include the presence or absence of special soil, of water suitable for breeding places, of suitable food for larvæ, and so forth. The absence of natural enemies of larvæ or adult forms of the insect hosts has also to be considered.

The distribution of such alternative hosts and, therefore, of their parasites and the diseases caused by them, has a great tendency to be local and apparently erratic,
and to vary from time to time without any obvious reason. With closer study the reasons for such variations can sometimes be traced. The varying results of prophylactic measures directed against such diseases, though on the whole satisfactory, are often explicable by the variations in these factors when the causes of the variations are known.

The distinction between plants and animals, so obvious in the higher members of these kingdoms, is less definite in the unicellular organisms. Such distinctions as the presence or absence of chlorophyll, the absorption or assimilation of nitrogen and carbon from their inorganic compounds, or only from higher organic compounds, are not conclusive. Those organisms most closely related to the vegetable kingdom and those that appear to be animal may either be motile or non-motile. In so many instances is it impossible to determine whether the lowly unicellular organisms are animal or vegetable, that Haeckel proposes to make a separate kingdom of such forms which he calls Protista.

The unicellular organisms approximating in most of their characters to the animal kingdom are known as the Protozoa.

In warmer countries the diseases due to parasites with characters in the main animal are of more special importance than those caused by parasites of the same division in cold climates. The diseases of cold climates are usually due to parasites like bacilli, which are allied to the vegetable kingdom. Many of these diseases are world-wide in their distribution.

The protozoa for this reason are first considered. Protozoa are unicellular organisms. The cells may be aggregated together in masses, or may occur singly. Frequently parts of the cells are specially modified for special purposes, such as locomotion, so that flagella or cilia are formed, whilst in other instances a part only of the cell is contractile and exhibits amœboid movement.

Many of the protozoa are non-parasitic; others are
parasitic only in the lower animals. Some are parasitic during a portion only of their existence, whilst others are parasitic in entirely different animals during the different stages of development.

It is proposed to consider in detail only the protozoa parasitic in man, with brief reference to protozoa parasitic in other animals.

The knowledge of disease-causing protozoa is advancing so rapidly that some information as to parasites of other animals may at any time become of importance in human pathology.

The Protozoa are divided into four groups:—

(1) *Sarcodina* include all forms which move by the protrusion of protoplasm either as blunt and broad processes or sharp and thin processes. They may be naked or covered in part with shells. Multiplication is by budding or fission; occasionally spores are formed.

(2) *Mastigophora* or *Flagellata* are provided with motile apparatus specialized for the purpose and consisting of one or more flagella. All parts of the cell enter into the formation of the flagellum. The body is usually of a well-defined shape and covered with a cuticle or membrane. Multiplication is by longitudinal fission.

(3) *Sporozoa* are unicellular parasites living during a portion of their life in cells and multiplying by the division of the whole or part of the protoplasm into young organisms commonly called "spores," more correctly termed "merozoites."

(4) *Ciliata* (*Infusoria*). The motor apparatus is in the form of cilia which may be either simple or united into membranes. These are formed from the ectosarc only. Reproduction is effected by transverse division or budding. Rarely spores are formed.

Of these classes it will be convenient to consider first the Sporozoa.

Researches, especially those of Schaudinn, have gone far to throw doubt on this classification, for his work, if confirmed, would prove that the distinction between the
flagellata and the sporozoa is not a sound one, as flagellates have a quiescent stage when they resemble sporozoa. Much more work is necessary in connection with the protozoa and their sexual cycles and transformations before we can safely alter the present usual classification, and any premature attempts at regrouping these organisms are to be deprecated.

*Development and Life-history.*—This is not known in all the genera, but where it is fully known two methods of multiplication can be shown to occur—*asexual* or vegetative, and *sexual*. As a type of the life-history and method of reproduction of the sporozoa that of coccidia may be taken as an example. The analogies with the development of the malaria parasites will be considered with them.

In the coccidia, entrance to the warm-blooded host is gained through the alimentary canal. The young coccidia spores, *sporozoites*, are set free from the cyst in which they are contained by the action of the digestive juices and penetrate into the epithelial cells of the intestinal mucosa, or of one of the appendages of the intestine such as the bile passages and the liver.

When the young coccidia have entered such a cell they grow until they have entirely filled and destroyed it. Division of the protoplasm of the coccidium now takes place. The outer part of this has formed a cyst wall, and thus a cyst is formed containing a large number of young coccidia or spores. The cyst wall then ruptures, the young coccidia are liberated and pass into other intestinal or hepatic cells. The process is repeated over and over again, and massive tumours are thus formed by the coccidia which have multiplied asexually. Coccidia which develop into asexual forms are known as "schizonts." Some of the spores of young coccidia develop in a different manner. No division of the cell contents takes place, but the protoplasm remains undivided with a single nucleus. A weak spot in the cyst wall, known as the micropyle, is present. Such forms are the female
INTRODUCTORY

forms, *macrogametes*, of the coccidia. Again, in other coccidial cells, when they have reached their maximum stage of growth, the cell contents divide into a mass of bodies smaller and more actively motile than the spores. The small actively motile bodies are the male fertilizing elements equivalent to spermatozoa, and are known as *microgametes*. When the cyst containing them ruptures the microgametes are set free and penetrate through the micropyle of the macrogamete and fertilize it.

In the fertilized macrogamete, now known as the oöcyst, various changes occur and the micropyle is closed

---

**Fig. 1.**—Diagram of development of Coccidia. Endogenous life includes the asexual cycle and the fertilization of the macrogamete by the microgamete. The further development does not require an alternate host. It takes place on the ground.
so that the cyst wall is complete. The cyst is discharged and passed with the faeces of the host. Development of the contents takes place, the cell mass divides into four, and in each of these four divisions two spores—"sporozoites"—are formed. This stage of development takes place in the oöcysts as they lie on the ground, no host being necessary in this stage. This is the sexual form of multiplication. Ultimately, when the cyst is swallowed by a suitable host, the capsule is dissolved, the sporozoites are liberated in the alimentary canal and enter cells in the mucosa or pass up the bile ducts in the liver and there recommence the cycle of events described, multiplying asexually to form massive tumours, or becoming sexual forms, gametocytes, male or female.

This protozoal infection is common in rabbits; it has been described in man, but is certainly extremely rare. It forms a good example of a sporozoal organism, parasitic during its stages of growth and asexual multiplication, but not throughout the whole of its sexual development (fig. 1).

The general plan of development of the parasites of malaria resembles this to some extent, but there are important differences.

By coccidia no second host is required. Conjugation takes place in the warm-blooded host and full sexual development outside under ordinary conditions, but for many of the protozoa a second host is required and the development in this second or alternate host differs from that in the first host.

Intermediate and definitive hosts are more precise terms. The definitive host is the host in which the sexual processes of multiplication or reproduction are carried out. In the case of the parasites of malaria the definitive host is the mosquito.

Intermediate hosts are those in which the asexual method of multiplication is carried out; e.g., man is the intermediate host of the malaria parasite.

Insects or other alternate hosts are not required for
the propagation of all the various protozoa which cause disease, as in some, such as the coccidia and *Amoeba coli*, part of the development takes place in earth or in water without an alternative host.

Invertebrate hosts: The commonest alternative hosts, either intermediate or definitive, are insects, but some of the ticks, ixodinae and argasinae, may also serve as hosts.

Insects are infected with animal parasites in various ways:

1. The blood-sucking insects draw up with the blood any small parasites present in that fluid, such as the parasites of malaria. These parasites developing and multiplying in the insect host are ultimately injected into a warm-blooded host—man in this instance—and multiply again in that host.

2. In other cases, as in the development of piroplasmata and the spirochaeta in ticks, the development of the parasites taken up with the blood is continued in the eggs of the host, and the full development does not take place till the eggs are hatched and the young ticks are sufficiently developed to bite a warm-blooded host, when they will transmit the infection.

3. The parasites drawn up with the blood may develop in the lumen or walls of the alimentary canal and the sporozoites may be discharged with the faeces.

4. The larvæ of the invertebrate host living in water become infected directly through their food with protozoa. These then develop and, as in the case of a monocystis described by Ross, multiply after encystment, so that when the insect has attained its perfect form—the imago—it harbours very numerous parasites which are deposited with the excrement and then live an independent existence till they re-enter other larvæ. It is possible that many of the flagellata are thus transmitted.

Protozoa are not the only parasites for which invertebrates act as hosts. Several of the metazoa are conveyed in a similar manner. Bacteria also can be conveyed by such hosts. In some instances the insects merely act
as mechanical carriers. Thus the ordinary house-fly may, after alighting on the excreta of a typhoid patient, carry the bacilli to human food, such as milk, directly. In other instances, blood-sucking insects take up bacteria, such as those of plague and leprosy, and may, in the former case at least, infect other animals.

The bacteria present in the water in which larvæ live are taken up by such larvæ, and in some instances, e.g., *Bacillus pyocyaneus*, the bacteria continue to live during the various stages of development of the larvæ and may be widely distributed by the adult insect or imago. The conveyance of helminthes and of vegetable organisms by insects will be considered in Part II and Part III.

**Origin of Parasites.**

The question is sometimes raised as to the origin of parasites, and particularly of such parasites as are found only in so recent (geologically) a development as man. No direct genealogy can be drawn up for these parasites; they must be derived from pre-existing non-parasitic forms which gradually became parasitic during one, probably the sexual, cycle, and later parasitic throughout their entire cycle. Possibly, this change first took place in birds or bats, and by development from them those parasites, which are now parasitic in man only, were developed. The intervening links are lost and any explanation can be merely hypothetical.
**Table of the Important Groups of Parasites.**

<table>
<thead>
<tr>
<th>Protista—Unicellular organisms.</th>
<th>Metazoa</th>
<th>Animal Parasites, Part II.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristics</strong></td>
<td><strong>Protozoa</strong></td>
<td><strong>Characteristics</strong></td>
</tr>
<tr>
<td>mainly those of the vegetable kingdom, &amp;c.</td>
<td>mainly those of the animal kingdom.</td>
<td></td>
</tr>
<tr>
<td>Bacteria to be considered, Part III.</td>
<td>Sarcodina—represented by the Amoeba colit.</td>
<td>Mastigophora—including Spi-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>rochaete, Leishman-Donovan bodies, Try-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pansomes, Trichomonas and Lamblia in man.</td>
</tr>
<tr>
<td>Telosporidia</td>
<td>Neosporidia</td>
<td></td>
</tr>
<tr>
<td>Gregarinida—Parasitic in earth-worms and many invertebrata. Coccidia: parasitic in many animals, very common in rabbits. Have been observed in man. Species (?)</td>
<td>Hæmosporidia</td>
<td>Hemo- gregarinida—In reptiles and few mammals.</td>
</tr>
<tr>
<td>Babesia or Piroplasma—Parasitic in cattle, horses, sheep, dogs, &amp;c.</td>
<td>Hæmamœba—Including H. relicta (proteosomes in birds and at least three species of plasmodia, the cause of malaria in man.</td>
<td></td>
</tr>
</tbody>
</table>
CHAPTER II.

The diseases caused by sporozoa are of special importance as they include those caused by the parasites of malaria as well as trypanosomiasis, one form of dysentery, and other ailments. They are therefore considered first, and with them other diseases, probably caused by allied parasites.

The classification of the Sporozoa is still in dispute, and various schemes have been propounded from time to time. There is no authoritative classification at present. The scheme here given is a useful one, but is not to be regarded as final or as even universally accepted.

SPOROZOA.

(A) Those in which the entire protoplasm, with the exception of dead residual masses, divides into spores, the parent protozoon disappearing in the process.

Telosporidia, e.g., parasites of malaria, coccidia, &c. In this group are included the sporozoa that cause the most important diseases of man and the lower animals—malaria, Texas fever, &c.

The group is variously divided by different authors and protozoologists. The classification here given is convenient for the purpose: (1) Gregarinida; (2) Coccidia; (3) Hæmosporidia; (4) Hæmogregarinida.

(1) Gregarinida.—The body is of a constant elongated form. They are distinguished by their peculiar creeping movements. They are parasitic in cells of the intestinal walls of the various invertebrates during the early part of their existence, and later are free in the intestinal cavity or its appendages, where they become encysted,
and the cell contents have been shown in rare instances to undergo division into spores.

Reproduction.—Sexual reproduction by the conjugation of two cells which resemble each other.

(2) Coccidia.—Of a spherical or oval shape, and contained in definite cyst walls when mature; only the youngest forms are motile. Fecundation by the conjugation of dissimilar cells. They are parasitic in cells of warm-blooded animals and invertebrates, and frequently form massive tumours. They have been described in man, but little is known at present of human diseases caused by them. Very common in rabbits.

![Fig. 2.—Piroplasmata.](image)

(3) Haemopirodia or Haemocytozoa.—Parasites of the red blood corpuscles of warm-blooded animals; do not form cysts in such hosts; are parasitic throughout their whole existence, the sexual phase taking place in invertebrates, e.g., insects or ticks. The young forms have active amoeboid movement. They are divided into two main groups:

(a) Haemamœbae, which form pigment, and usually divide into a large number of spores. The definitive hosts are mosquitoes.

(b) Piroplasmata (fig. 2), which do not form pigment; divide into two or more young parasites. Ticks are the definitive hosts. Piroplasmata have been described in man, probably erroneously; common in cattle, sheep, horses, dogs, &c., and usually lead to extensive blood destruction, e.g., Texas fever in cattle, and haemoglobinuria in sheep and dogs. Careful search has been made in men in cases of blackwater fever for piroplasmata, but with negative results.
(4) *Haemogregarinida* are, by many authors, included in the *Haemosporidia*. The young forms are found in red corpuscles of reptiles (fig. 3), and in a few instances in red blood corpuscles of mammals, as in the Indian rat and the African jerboa. They may also be found in leucocytes, as in the dog and in the palm squirrel. Older forms moving like gregarines are found free in the blood plasma. Sporulation takes place in cells of solid viscera, such as the liver and in the bone-marrow. It appears to be doubtful what are the definitive hosts; in the dog *haemogregarine*, the host, is an *iodina*. The parasites do not form pigment, and differ from the *haemosporidia*, in the restricted sense, in the structure of the nucleus of the young parasite. The nucleus stains with basic stain, and the chromatin is distributed in fine granules throughout the nucleus. Segmentation does not take place whilst the parasites are present in the blood. No *haemogregarines* are known to occur in man, and it is only recently that they have been found in mammals and birds (fig. 3).

(B) Only a portion of the protoplasm of the cell divides into spores. The parent protozoon still remains alive, further growth takes place, and again, part of the
new protoplasm divides into spores. This process, repeated indefinitely, leads to the formation of large masses composed of spores enclosed in the much distended parent cells.

**Neosporidia, e.g., Sarcosporidia.**—The Neosporidia are too little studied to be fully considered at present. They are divided into *Myxosporidia*, which occur in fishes and in silkworms, and *Sarcosporidia*, which are very common in the muscles of domesticated animals, and are rarely found in man. They are known to cause one disease in man, but recorded cases are rare.

The parasite *Rhinosporidium kinealyi* described by Minchin and Fantham, belongs to the Neosporidia. It occurs in tumours of the septum nasi in natives of India. The tumours are vascular pedunculated growths, in which can be seen, as yellow points, bodies containing large numbers of the parasites embedded in the connective tissues.

The youngest parasites consist of granular protoplasm enclosed by a hyaline membrane and containing numerous nuclei. As the parasite grows a thick capsule forms, and from the layer of cells in contact with this, numerous other cells are formed and pushed towards the centre. The older cells increase in size and become multinuclear, and the protoplasm segments into numerous uninuclear pansporoblasts which, in their turn, give rise to numerous spores.

Nothing is known as to the method in which infection is spread, and the diseases caused by them are not common.

The parasite has also been recorded by Beattie as occurring in aural polypi, also in Indian natives.
CHAPTER III.

DISEASES CAUSED BY HÆMOSPORIDIA.

The *hæmosporidia* are responsible for most important diseases, and malaria in its three main forms is due to parasites of this group. It is possible that there are more than three species of malaria parasites, but three are clearly to be distinguished from each other, and to understand the clinical manifestations, the diagnosis and prophylaxis of the disease, a sound knowledge of these three species is required. The clinical manifestations vary according to the species of parasite, but in all, pyrexia, slow development of anaemia, and other toxic symptoms occur, and in all the parasites are found in the red corpuscles and the definitive host is a mosquito, some species of Anopheline.

The parasites, the cause of malaria, require a careful and detailed study. They may be examined while still living in the freshly shed blood, and certain vital functions, such as the amœboid movements and those of the pigment in the interior of the parasites, can only be seen in such preparations. Other changes take place in the living parasites after the blood is shed; these are the alterations in the sexual forms or gametocytes which become actively sexual. The detailed structure can be best made out in stained specimens.

For the complete study of the parasites both methods of examination must be employed. The blood may be obtained by pricking the tip of the finger or the lobe of the ear. The latter situation is most convenient in children. The skin must be clean and should be rubbed over with alcohol and ether before the puncture is made.
Preparation of Blood Films.—The essential in the preparation of blood films for examination of the parasites is that the film should be so thin that the red corpuscles lie flat over a considerable part of the film. With fresh blood this result can be attained if the slides and cover-glasses are free from grease and grit so that the blood can run rapidly; and if the drop of blood is so small that it does not fill the whole space between the slide and cover-glass, the edge of the film will always be too thick and the centre will contain too few corpuscles.

Fig. 4.—Indicating the arrangement of the red cells in the different parts of a fresh fluid film. (a) Edge where corpuscles overlap each other, so that parasites in them are not readily seen. (b) Centre so thin that the red cells are scanty. (c) The best part of the film for examination. Red cells numerous and all flat, so that parasites are easily found and seen.

The space between should look opalescent and in it the corpuscles lie side by side and flat (fig. 4, c). Dried films are best made with two slides. The drop of blood should be taken up on the extreme edge of the lower surface of one slide, and then this slide brought into contact with the upper surface of a second slide at an angle of about 45°. The blood will run along the edge of contact, and if the upper slide is pushed so as to glide over the surface of the lower slide, a film of blood suitable for examination will be left behind (fig. 5).
For general blood work Leishman's modification of Romanowsky's stain is the most generally useful. This is the solution in pure methylic alcohol of the precipitate formed when polychrome methyl blue and eosin in watery solutions are mixed.

Unfixed films must be used. There are three stages in the process of staining:

1. The solution of Leishman's stain is placed on the slide so as to cover the film. This fixes the film and the stain penetrates the corpuscles, but little staining occurs. Time, half to one minute. The solution must not be allowed to dry on the film.

![Fig. 5](image)

2. Distilled water is added to the solution of the stain in methylic alcohol that has been placed on the slide, and the water is rapidly mixed with the solution. The amount should be sufficient to cause an abundant precipitate of the stain and the mixture should appear pink. The water should be about double the amount of the solution used. It is during this stage that staining takes place. Time required, five minutes or more. It is best to
examine with a low power under the microscope in order to see if the leucocytes are well stained, and the nuclei a rich purple, before proceeding to the next step, i.e., clearing.

(3) Clearing. The mixture of the water and precipitated stain should be flushed off with distilled water. A drop of distilled water should be left on the films, which should be examined under the microscope. The red corpuscles should not be blue, and water can be left on until these appear red. This takes half a minute or more. The water can now be poured off and the film stood on its edge and allowed to dry. It may be blotted, but fibres from blotting paper are so often mistaken for spirochaetæ or filariae that this is not recommended.

Parasites of Benign Tertian and Quartan, Plasmodium vivax and Plasmodium malariae.—The living parasites in their earliest stage are colourless bodies in the interior of the red corpuscles. They can be distinguished from vacuoles or rifts in the red corpuscles by the less sharply defined edge and by a slight opalescence, so that they do not appear quite so translucent. Amœboid movement can frequently be seen, and this is often active though the pseudopodia at this stage are small. The quivering, oscillatory movement of the hæmoglobin forming the edge of a vacuole must not be mistaken for amœboid movement.

The parasites may be called amœbulae; in the fresh blood the parasites in this early stage have not obviously altered the red corpuscle which contains them. Some enlargement of the corpuscle may be seen in an infection with the parasite of benign tertian malaria.

There is, however, already a change, as the red corpuscles infected with benign tertian parasites do not crenate as readily as the uninfected corpuscles. Sometimes when all the other red corpuscles in a field are crenated, those containing the young forms are not crenated. On the contrary, in a subtertian infection, the corpuscles containing parasites crenate more readily; sometimes the only crenated corpuscle to be seen will be
one containing the subtertian parasite. In a subtertian infection the red corpuscles containing the parasites may be altered in colour, appearing more yellow, the so-called "brassy bodies."

There is a difference in the size of the youngest parasite of benign tertian and quartan, as the quartan "spores" are the larger, but both are considerably larger than the youngest forms of the subtertian parasites.

**Fig. 6.**—*a* to *f*, Phases in the asexual development of the quartan parasite; *x* to *z*, phases in the sexual development.

In the blood examined a few hours later in either tertian or quartan malaria the parasite will be larger and the amœboid movements greater in extent, so that the parasites are much more irregular in shape. As a rule the amœboid activity is greater in tertian and the pseudopodia are often finer and much more irregular in shape. Pigment will be present in both; that in tertian varies in colour from light brown, almost yellow, to dark brown, nearly black, in rare instances. In quartan the
granules are coarser and always black. The red corpuscles containing the benign tertian parasites are swollen so that they are larger and paler than the average. In a quartan infection they are slightly smaller, and very slightly darker in colour than the average.

If the blood be examined at intervals of a few hours these developments are gradually seen to become more pronounced. The parasites increase in size, more and more pigment is formed, brown and fine in the tertian, coarse and black in the quartan. The changes in the red corpuscles become more marked (figs. 6 and 7).

![Diagram](https://via.placeholder.com/150)

Fig. 7.—a to f, Phases in the asexual development of the benign tertian parasite *Plasmodium vivax*; x to z, phases in the sexual development.

At length the parasites nearly fill the red corpuscles that contain them; this requires rather less than two days with the tertian parasite, and less than three days with the quartan. Amœboid movements at this stage cease. The full growth is thus accomplished, the pabulum
contained in the red corpuscle is exhausted, and the further changes are those leading to multiplication and reproduction. This may be asexual or sexual. In the former, the most frequently seen, the first changes that are observed in the fresh blood are that the pigment aggregates in a clump in the interior of the parasite. This clump is at first loose, so that the individual grains of pigment are easily distinguished, but these soon become so closely packed that it appears almost as a solid block of pigment. By this time traces of the division in the parasite will be visible. At first these are only seen with difficulty, but soon become more marked, so that the whole of the protoplasm, except a minute residuum round the pigment, is divided into a series of oval unpigmented masses, five to ten in number in quartan and eighteen to twenty-four in benign tertian. Very rarely a larger or smaller number of those ovoid masses—spores—may be found in these sporulating parasites. The red corpuscles containing the parasites soon burst, and the spores, pigment, residual protoplasm, and any fluid or solid residue of the red corpuscle, probably including toxic substances, are set free in the blood plasma. The pigment is taken up by leucocytes, usually by the large mononuclear leucocytes.

The spores do not long remain free in the peripheral blood; they rapidly try to enter other red corpuscles. Many must fail to do so and be rapidly destroyed, as the number of young parasites found is far less than it would be if all the spores were able to enter red corpuscles; nor does the rapid increase in the number of parasites occur with the successive sporulations as might be expected.

This process of reproduction is commonly termed sporulation, but is more correctly termed schizogony. The sporulating parasites would then be known as schizonts and the spores as merozoites.

Sexual Phase.—Sporogony. The parasites destined for a sexual life in benign tertian and quartan malaria are
not unlike full-grown parasites before any indication of sporulation has taken place. When nearly full-grown they can be distinguished from these, because there is always a rounded space enclosed in the parasite free from pigment and slightly more refractile to light; through the cytoplasm of this the pigment is scattered. These forms may be found at any period, and are usually less numerous than the *schizonts*. They undergo no further development in the peripheral blood.

In the shed blood further development takes place, and can be observed in a thin blood film under the microscope. The sexual forms, *gametocytes*, are potentially male and female in the freshly shed blood, but it is practically impossible, in the parasites of benign tertian and quartan, to distinguish at first the males from the females. After a short time, if the blood has been exposed to air or has had water added to it, and still more rapidly in the stomach of the mosquito, they become sexually active.

*Sexual Multiplication.*—The first change that can be seen is that the parasites become more definitely rounded and the pigment appears to be in active movement, indicating movements in the protoplasm. The remnants of the red corpuscles which had enclosed them disappear.

In both male and female forms the next stage is the extrusion of a considerable part of the protoplasm, so that there are two bodies of unequal size, the smaller being the polar body. The females ordinarily do not undergo any further change, as seen on the slide; they are now in the receptive condition awaiting fertilization, and are called *macrogametes*. The males do change. In the larger of the two masses, into which the parasite has divided, violent movement of its pigment occurs, and it suddenly projects three, four, or five thin, long flagella, which are free from pigment and actively motile, lashing the neighbouring red corpuscles. These flagella, known as *microgametes*, are the male fertilizing elements, the equivalent of spermatozoa. After a time they detach
themselves from the mass of residual protoplasm in which the pigment is included, and swim freely in the blood plasma. They have been seen to fertilize the female or macrogamete. The residual protoplasm and pigment are swallowed by surrounding leucocytes, usually the large mononuclear ones, rarely the polymorphonuclear. The pigment is not digested by these leucocytes, but is carried by them to the spleen or liver, and there deposited in cells and connective tissue.

Parasites in all stages in benign tertian and quartan malaria may be seen in a series of consecutive examinations. The sporulating forms are not so numerous in the peripheral blood as the younger forms, as a considerable proportion of the corpuscles containing the full-grown and sporulating forms seem to be detained in the splenic sinuses. At any one time either all the parasites are about the same age, or those of one set are twenty-four hours older or younger than the others. It is very unusual to find parasites in the intermediate stages of growth; it follows from this that the sporulation of a large number of the parasites is nearly synchronous.

If there is only one generation the successive sporulations are at intervals of forty-eight hours in the tertian and seventy-two in the quartan. If there are two generations, in tertian they will sporulate on successive days, but the sporulation of the individuals of each generation is synchronous.

In quartan there may be at the same time, one, two, or three generations. Where there are three they will sporulate on three consecutive days. Where there are two generations, on two consecutive days with one day's interval.

Parasites in Subtertian Malaria.—The results of the examination of fresh blood in subtertian fever (malignant tertian) differ in important points.

In the great majority of cases during the febrile period only small parasites free from pigment are found. These are usually actively ameboid, but the changes in shape
are slight. The smallest forms are smaller than any forms in benign tertian or quartan. The red corpuscle containing the parasite crenates readily, but the corpuscle is usually of the average size and colour; sometimes it is more yellow and brassy.

**Table of Differences between the Parasites of Malaria.**

<table>
<thead>
<tr>
<th></th>
<th>Benign tertian, <em>P. vivax</em></th>
<th>Quartan, <em>P. malariae</em></th>
<th>Subtertian, <em>P. falciparum</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Length of cycle, <em>i.e.</em>, interval between one sporulation and the next</td>
<td>48 hours ...</td>
<td>72 hours ...</td>
<td>Uncertain, often about 48 hours or rather less.</td>
</tr>
<tr>
<td>(2) Size of mature parasite</td>
<td>Larger than the average red corpuscle</td>
<td>Slightly smaller than the average red corpuscle</td>
<td>About half the diameter of an average red corpuscle.</td>
</tr>
<tr>
<td>(3) Number of &quot;spores&quot;</td>
<td>18—24 ...</td>
<td>6—10 ...</td>
<td>Variable, 6—30.</td>
</tr>
<tr>
<td>(4) Amoeboid movement</td>
<td>Active and extensive</td>
<td>Sluggish ...</td>
<td>Very active, but range of movement not extensive.</td>
</tr>
<tr>
<td>(5) Gametocytes</td>
<td>Rounded bodies</td>
<td>Rounded bodies</td>
<td>Sausage-shaped bodies, &quot;crescents.&quot;</td>
</tr>
<tr>
<td>(6) Pigment</td>
<td>Finely divided and brown</td>
<td>Coarse and black</td>
<td>Black and at first finely divided, but soon aggregating into coarse clumps.</td>
</tr>
<tr>
<td>(7) Effect on red corpuscle serving as host</td>
<td>Causes it to swell and become paler. Does not crenate so readily. In stained specimens Schüffners' dots often found</td>
<td>Red corpuscle becomes slightly smaller and darker</td>
<td>The young parasite causes little or no alteration, but sometimes the corpuscles become yellower—&quot;brassy bodies.&quot; The older parasites decolorize the red corpuscles irregularly and cause them to become adhesive.</td>
</tr>
</tbody>
</table>

Parasites at this stage may be found at each successive examination extending over a period of several days, but are usually more numerous at one time than at another. At some of the examinations they may not be found, whilst a few hours later they may be numerous. It is common to find a few slightly larger parasites with more
extensive amoeboid movements, and containing finely divided black pigment (fig. 8, a, b).

More advanced stages are very rarely seen in the peripheral blood, but parasites with the pigment aggregated in a dense black block, and even sporulating, are occasionally found. Sometimes, usually just before death, such forms may even be numerous (fig. 8, c, d, e). In these cases the red cells containing the more advanced parasites are often found in clumps; they agglutinate because of their stickiness. These advanced forms are abundant in the capillaries in the internal organs and appear to be accidental only in the peripheral circulation. The change induced by the parasite in the red cells is such that these become sticky and adhere to each other and to the walls of the blood-vessels, especially in the capillaries in the internal organs where the current is slow and uniform.

In addition to the young forms of the parasites, gametocytes are also found in the peripheral blood. These are not present in the early stages of the fever, and are rarely numerous when there is pyrexia, and young forms are abundant; they are more common after the pyrexia has disappeared, and when no young forms can be found, and are therefore numerous during convalescence from a febrile attack.

The gametocytes of subtertian malaria are of a special shape and quite different from the sporocytes of subtertian or the gametocytes of the other forms of malaria. They are sausage-shaped bodies, longer than the diameter of a red corpuscle, and the ends are free from pigment; this is aggregated into a clump near the centre (fig. 8, x). In the freshly shed blood they are still enclosed in a red corpuscle, but this is almost colourless and stretched out by the parasite. Gametocytes in all species develop from some of the "ring" forms. Why this form develops instead of asexual sporulating forms is uncertain. Possibly the formation of some antibodies renders the conditions of life less favourable for the parasite, and then
the more resistant sexual forms are produced instead of asexual schizonts. Ross gives reasons for believing that they take ten days to form. In the earlier stages they affect the red cells like schizonts and cause them to become adhesive, but by the time the gametocyte is fully developed the red cell is reduced to a mere decolorized shell and is no longer adhesive, and so circulates with the blood throughout the body and in the peripheral circulation. If these gametocytes, the potentially sexual

Fig. 8.—a to e, Phases in the asexual development of the malignant malarial parasite; P. falciparum, x to z, phases in the sexual development—xyz, of the female; x'y'z', of the male.
forms, are examined closely, it will be seen that in some there is a space free from pigment in the centre of the clump of pigment; these are the female forms. In the others there is no such clear space, and the pigment clump is larger and less regular. These are the male forms (fig. 8, x').

If watched for a time varying with different cases, and in the same case on different occasions, the gametocytes are seen to become actively sexual. The first change in both is that the parasites become shorter and broader, first ovoid and finally circular or spheroidal. This is spoken of as the "transformation" of the crescents. The remnants of the red corpuscle disappear. One or two small refractile globules, the polar bodies, are extruded, and there is much agitation of the pigment.

The females—macrogametes—unless fertilized undergo no further change (fig. 8, y, z). The males' flagellate and the flagella "microgametes" ultimately separate from the residual protoplasm which contains all the pigment and swim about freely in the blood plasma (fig. 8, y', z'). They have been seen to enter and fertilize the female or macrogamete. This is the first stage in the sexual cycle of the malaria parasites. The macrogamete when fertilized is a zygote, i.e., the product of conjugation. . . . This zygote is actively motile, creeping and moving like a gregarine. It is at this stage known as the travelling vermicule or oökinet. In the coccidia, it may be remembered, the zygote is non-motile and is called the "oöcyst." The further changes in the zygote, by which the contents ultimately divide into a mass of minute thread-like bodies, the sporozoites, takes place in the stomach wall of the mosquito between the epithelial and musculo-membranous layers (fig. 9). This series of events is known as the sexual, exogenous, or mosquito cycle, and by parasitologists as sporogony. The sporozoites ultimately, in eight days or more according to the temperature, accumulate in cells in the salivary glands of the mosquito and are injected with the saliva of that insect into man. After this, in about
eight to fourteen days, the young amœboid forms of the parasite will be found in the man so injected if he be susceptible.

*Stained Films.*—In blood films stained by Leishman's method the various stages can also conveniently be studied, and certain points in the cell structure can only be brought out in such specimens.

Leishman's stain is practically a triple stain; it contains eosin, which has a special affinity for formed material but not for parts of cells actively concerned in growth or reproduction. It is a so-called acid stain, and stains the haemoglobin in blood and some of the granules in certain leucocytes. It stains faintly the protoplasm of some of the leucocytes. The methylene blue has been altered by the polychroming so that two stains are present,
both basic: A blue, the unaltered methylene blue, which stains the ordinary cell protoplasm of actively growing cells, parts of the nuclei, granules said to be basophilic in some of the red corpuscles, and faintly but diffusely other degenerate red corpuscles. It also stains the nuclei of any red corpuscles that still possess them, and stains faintly the blood platelets.

The altered methylene blue, red in colour, but a deeper red than that of eosin, has a special affinity for certain substances constantly present in actively growing cells known as chromatin. In the nuclei this substance is in abundance and especially concerned in processes of multiplication and reproduction.

Of the blood elements this red polychrome methylene blue stains the nuclei of the leucocytes so that, as they are also stained with the unaltered methylene blue, they appear purple. It also stains granules present in the protoplasm of some of the large mononuclear leucocytes, and granules or a network in the blood platelets.

As regards the parasites of malaria the young forms with Leishman stain show a nodule of chromatin contained in a large non-staining nucleus, a so-called "vesicular nucleus." This vesicular nucleus is surrounded by a narrow rim of protoplasm which stains blue with the unaltered methylene blue. The whole forms the "ring form" of the parasite and in the stained specimen, as in the unstained, it is difficult to distinguish between the different species of parasites in this stage (Plate I, 1, 7, 10, 16).

The older the parasite is the more abundant the protoplasm surrounding the vesicular nucleus becomes, as growth is mainly by an increase in the protoplasm. Where the protoplasm is relatively abundant the parasite is not a young one. A ring form that is still small, when from the relative amount of the protoplasm it is known not to be young, is probably a subtertian parasite. A very small ring form is also probably a subtertian, as the very young subtertian parasites are smaller than either tertian or quartan.
The chromatin nodules in half-grown benign tertian and quartan are easily distinguished. The vesicular nucleus is still present and the chromatin no longer appears to be a solid block, as it seems to be composed of several fragments. In deeply stained films of benign tertian granules staining red, Schüffner's dots can be seen throughout the red corpuscle containing the parasites (Plate I, 7, 8, 9).

Later in both tertian and quartan forms the vesicular nucleus and the chromatin mass break up and the whole parasite stains irregularly blue.

Before sporulation, chromatin masses again appear in the periphery of the parasite. At first these are few, but later they are more numerous, one corresponding to each spore or division into which the protoplasm divides. When fully formed each spore contains a nodule of chromatin embedded in an oval mass of protoplasm which stains blue. The vesicular nucleus is indicated by less deep staining near the chromatin, but is not sharply defined as it is in the spore after it has entered the red corpuscles (Plate I, 4, 5, 14, 15, and Plate II, 10 to 23).

The corresponding forms in subtertian malaria are very rarely found in the peripheral blood.

The gametocytes of quartan and tertian can be readily recognized in the stained specimens.

The space free from pigment does not stain with the unaltered methylene blue, but contains numerous granules usually forming a clump of chromatin, which stains less deeply than the chromatin of the sporocytes.

In a stained flagellum a narrow strip of chromatin is seen in the middle. The polar bodies also contain chromatin.

In the gametocytes of subtertian malaria—crescents—chromatin is in a different state of aggregation in the males and the females. In the females the chromatin forms a nearly solid block in the centre of the clear space enclosed by a ring of pigment. In the males, the chromatin
is more abundant but does not form a solid block, but a series of coarse granules scattered about between and beyond the grains of pigment (Plate I, 18, 19). The chromatin in the gametocytes of all forms of malaria stains only with the altered forms of methylene blue. It does not stain with haematoxylin or with most basic stains (Plate II).

It is doubtful if all the parasites described here as "subtertian" are of one and the same species. By some of the Italian authorities they are subdivided into three species, viz., pigmented quotidian, unpigmented quotidian, and malignant tertian, whilst others attempt to subdivide into two species only. Any classification based on the periodicity of the fever with this class of parasites is unreliable, as there is not a sufficient synchronicity in the stages of the parasite for any marked regularity to be expected. In practice one type of fever may pass gradually into another type without any change in the characters of the parasites found.

In the majority of cases there are few or no pigmented parasites to be found in the peripheral blood, but in these cases, if fatal, the full-grown parasites found in the internal organs are always pigmented.

As regards the inquiry as to the differentiation into species of the parasites having gametocytes of a sausage-shape—crescents—we find:

1. That the length of cycle is very difficult to ascertain, as the later stages of development are not found in the peripheral blood, and that parasites of all stages may be present at the same time.

2. That the parasites are comparatively small, but full-grown parasites from less than half to two-thirds the diameter of the red corpuscle are to be found in the same case.

3. That all may be actively amoeboid, that in all the pigment when first seen is finely divided, and that in all in the older parasites the pigment is coarse and black.

4. The number of spores varies within very wide
limits. In some cases the number of spores found is small in all the sporulating parasites seen. In others the number of spores formed is large in all. Speaking generally, it is much rarer to find the parasites with six to eight spores than those with a larger number.

(5) Effect on the red blood corpuscle: This certainly varies, but does so as much from day to day in the same patient as in different persons. Brassy bodies may be very numerous on one day, but though the patient is not treated and the parasites continue to be numerous, none at all may be found two or three days later.

(6) Toxic Effects.—Hæmolysis may be marked or very slight, and in some countries these hæmolytic effects are very common and in others rare. In most forms of malaria there are changes in the red cells similar to those found in other diseases where toxic blood changes occur, e.g. pernicious anæmia (Plate II, 1—5). This may indicate a difference in species. Other effects, such as albuminuria, are common in some districts and rare in others. In these cases no morphological differences in the parasites can be demonstrated. It is possible that there are different species of parasites, but it cannot be considered as proved. Possibly the differences in toxic effects of the parasites may be affected by variations in the environment of the parasites during their sexual or exogenous cycle, as in different places different mosquitoes serve as hosts, and slight alterations in temperature markedly affect the rate of growth and development of the parasites whilst developing in the mosquitoes.
CHAPTER IV.

DISEASES CAUSED BY HÆMOSPORIDIA IN MAN.

MALARIA.

(Synonyms: Ague Fever, Marsh Fever, Paludism, Intermittent Fever, &c.)

MALARIA is the general term applied to the diseases caused by the human hæmosporidia commonly known as the parasites of malaria. There are three main clinical types due respectively to the three species of parasites: Benign Tertian (P. vivax); Quartan (P. malariae); and Subtertian, or malignant tertian, usually irregularly remittent or intermittent (P. falciparum). The prominent symptoms are those of febrile disturbance; the fever may be regularly periodic, irregularly intermittent, or remittent and followed by a variable degree of anaemia. Later visceral changes, especially enlargement of the spleen and pigmentation of the spleen and liver, may occur. The febrile symptoms yield readily to treatment by quinine.

The parasites are conveyed from man to man by various species of mosquitoes, belonging to the subfamily Anophelina. There are at least three species of parasites and the symptoms differ according to the species of the parasite with which the patient is infected.

Geographical Distribution.—Malaria occurs in most tropical and subtropical countries, with the exception of certain groups of islands, such as the Seychelles in the Indian Ocean, Fiji, the Society and Friendly Islands in the South Pacific, Barbados and St. Helena in the Atlantic Ocean. In temperate regions the distribution is more irregular, and is frequently limited to low-lying
country, and the course of rivers or their estuaries. Elevation has a decided effect in temperate regions, but in equatorial districts malaria may be still common 4,000 or 5,000 ft. above the sea.

The topographical distribution of malaria is affected by many conditions, such as density of population, but is mainly determined by the species of mosquito present, and the abundance of suitable breeding places for such mosquitoes.

Clinical Varieties of Malaria, and Species Associated with these Varieties.

Benign tertian; Tertian Fever. Geographical Distribution.—It occurs in all the malarial tropical countries, but is rarer in Africa than in the East. In subtropical and temperate countries a larger proportion of the cases are benign tertian, and it occurs further north than the other forms of malaria. It used to be common in some parts of Great Britain and, rarely, cases still occur.

The clinical course of an attack of benign tertian malaria is regular, though in a first attack of a severe type the periodicity may not be well marked. The attacks of pyrexia are short, lasting some six or eight hours. The temperature rises suddenly, and there is a rigor, often so severe that the bed on which the patient is lying is shaken.

The temperature often rises to 105°F., or more, and the pulse is quick and bounding. The urine presents the usual febrile characters. The skin is cold and the features pinched, whilst the lips may have a bluish tinge. Following the cold stage is the hot stage, and during this the patient still has fever, usually high, severe headache, and the skin is dry. This stage may last for two or three hours, and is succeeded by a sweating stage during which the temperature rapidly falls. With the onset of the diaphoresis the patient becomes much more comfortable, and the temperature rapidly falls to or
below normal, when, beyond a certain amount of debility, or sometimes a mild form of collapse, the patient will feel well and be able to resume his occupation.

The next day, and till forty-eight hours after the occurrence of the rigor, the patient remains to all appearances in normal health. At the end of this period there is another similar pyrexial attack, and on each alternate day, in an untreated case, these attacks of pyrexia recur. Even without active treatment, sooner or later the paroxysms diminish in severity, and gradually disappear altogether, and the temperature may remain

![Graph](image)

**Fig. 10.—Simple Benign Tertian.**

normal or subnormal for two or three weeks, when another series of febrile paroxysms on alternate days will occur. These attacks of tertian fever alternating with apyrexial intervals may continue for two or three years. During the whole time the patient is suffering from infection with parasites of malaria, and visceral changes, especially enlargement of the spleen, are likely to occur, as well as anaemia and general debility. Death is unusual even if treatment be neglected, and a fatal result is usually due to concomitant disease.

In a simple benign tertian the character of the pyrexial paroxysms and the regular periodicity of their recurrence enable diagnosis to be made readily. Blood examina-
tion showing the presence of the parasites confirms this diagnosis, and it is the only way in which it can be made if the patient is seen during the apyrexial interval. In many cases of the disease the fever is quotidian, that is, a pyrexial attack occurs every day. This is the so-called double tertian, and is due to the co-existence of two generations of the parasite maturing on alternate days. Sometimes the double character of the infection is obvious clinically, as the pyrexial attacks vary in severity, being alternately severe and mild (fig. 11). In a double tertian the more frequent recurrence of the pyrexia causes more rapid development of anaemia and debility, and the prognosis therefore is more serious. The nature of the disease may be suspected from the completeness of the apyrexial intervals, from the shortness of the pyrexial attacks, and in some cases because the pyrexia occurs in the morning, whilst in most forms of quotidian intermittent fever the pyrexia is in the evening. A certain diagnosis cannot be made without an examination of the blood. As the name implies the prognosis, as regards life, is favourable. The fever is distressing but, as a rule, not dangerous. Cerebral symptoms are usually delirium and such symptoms as occur in any febrile condition. Rarely coma occurs, and in exceptional cases may be fatal.
The disease has a depressing mental effect and may lead to actual insanity, which as a rule terminates when effective anti-malarial treatment is undertaken.

Quartan Malaria.—Clinically, this form closely resembles benign tertian, but differs from it in that in a simple infection the pyrexial attacks occur with an interval of two days between them (fig. 12). The character of each attack is similar to that of benign tertian in that the onset is sudden, the stages of fever marked and the total duration a few hours only. Quartan malaria is less widely distributed than benign tertian, but also occurs throughout the Tropics, and in subtropical and even temperate climates. In some districts cases are as numerous as those of benign tertian, or even more so. As a rule in such countries quartan will be commoner amongst the poorer classes and tertian amongst the well-to-do, but no race or class is exempt. The reason for the irregular distribution of quartan is not known. Double and triple infections of quartan malaria occur, due to two or three generations of the parasite being present in the same patient, and reaching maturity at intervals of twenty-four hours. With three generations the fever would be quotidian, with two generations there would be fever on two days and then a day free from fever, followed again by two days with fever and so on (fig. 13). The effects of quartan malaria are very similar to those of benign tertian, but it is more dangerous to life, especially in cases of disturbed cardiac action, such as in beri-beri.
It persists for a longer time, and often yields less readily to quinine.

**Clinical Diagnosis.**—The single and double infections are easy to diagnose because of the peculiar periodicity. In a triple infection the quotidian periodicity may not only be confused with double tertian, but with any diseases in which quotidian fever occurs. Prognosis is good in uncomplicated cases if well treated.

In some cases the parasites are scanty, but even in small numbers may give rise to occasional attacks of fever or, without any pyrexia, to malaise. It is perhaps more frequently overlooked than any other form of malaria.

![Fig. 13.—Double Quartan.](image)
each other, consequently parasites of intermediate ages are rarely met with. The sporulation of these parasites leads to rupture of the red corpuscles, when the spores, together with the remains of the parasites, pigment, and any other products of the metabolism of the parasites, are set free in the plasma.

The simplest explanation of the observed clinical phenomena is that amongst these varied products are (1) toxins that act on the heat-controlling centre, (2) haemolytic toxins, variable in amount, and (3) toxins affecting innervation. Blood serum taken before a rigor and passed through a Berkefeld filter will, when injected into a healthy man, cause a febrile paroxysm similar to that which occurs in malaria. Of the bodies set free, the spores rapidly enter other red corpuscles, and recommence the cycle, or failing to do this are destroyed by phagocytes or by the blood plasma, and this destruction is facilitated by the action of quinine. The pigment is taken up by the leucocytes, usually by the large mononuclear or hyaline cells, and ultimately deposited in the spleen, which becomes, in a chronic case, of a deep slate black colour. It is also deposited in the connective tissue cells of the liver. In an earlier stage the spleen may merely appear to be congested, but on microscopic examination abundant deposits of pigment will be seen even then.

The symptoms, therefore, are toxic, and the severity will in part be due to the amount of the toxin, which depends in the main on the number of parasites present. Parasites may be present in small numbers without causing pyrexia, though usually malaise, and perhaps anemia, will be caused.

The actual number of parasites required to cause fever has been estimated by Gray and, by a more accurate method, by Ross. The numbers can only be considered as approximate, and probably vary in different persons. The usual limit—pyrogenic limit—according to these observers is about 250 per cubic millimetre; as the
volume of the blood is about 3,000,000 cubic millimetres, it follows that a man might be infected by 600,000,000 parasites without having "fever." When the fever is well established the parasites remain in about the same number, showing that only a small proportion of the merozoites formed infect red corpuscles. The birth-rate and death-rate of the "spores" must balance when the parasites remain constant in number.

_Treatment._—Quinine in any form and in moderate doses will rapidly relieve the symptoms, but to prevent relapses must be continued in diminished doses for months. The patient should be kept in bed, not only during the pyrexial period, but in the intervals, for two or three days after a pyrexial attack. Quinine is far more effective in a person kept at a uniform temperature in bed and on light diet. The bowels must be kept open. Simple rest and diet will often, without any medicine, cause temporary disappearance of the symptoms if the bowels are kept free. No reliance can be placed on this apparent recovery, as relapse will occur even if the patient is kept in bed.

The effect of the quinine, either directly or indirectly, is to reduce the number of parasites, but it takes some days to reduce them so much that they cannot be found after a protracted search.
CHAPTER V.

SUBTERTIAN MALARIAL FEVER.

MALIGNANT TERTIAN, subtertian, æstivo-autumnal, and tropical malaria are some of the names applied to the remaining forms of malaria, viz., those due to infection by parasites, which pass the later part of their asexual stage in the visceral capillaries (Plasmodium falciparum). Young forms and gametocytes are found in the peripheral blood. The gametocytes are the sausage-shaped bodies known as "crescents." It is not certain whether there is more than one species of these parasites. The geographical distribution of this is more limited than of other forms of malaria. It is the commonest form in the Tropics, and was called by Koch tropical fever. In temperate regions it is not found as far north as benign tertian, and in the south of Europe it occurs later in the year than other forms of malaria, i.e., in the summer and early autumn, and was, therefore, called by the Italians æstivo-autumnal.

Clinically it has a less regular and definite course than the other forms, and the stages of the pyrexial attack are ill-defined, and last longer, whilst the periodicity is uncertain.

There is a liability to sudden onset of pernicious symptoms, often fatal, even in cases apparently not very severe. Hence the name malignant tertian. Sometimes before the fever there are aching pains in the back and legs; as in other forms of malaria these myalgic pains may become worse with the onset of the fever, or, in other cases, disappear.

The pyrexia presents few diagnostic characters. The
tendency, so marked in tertian and quartan, for the parasites all to sporulate about the same time is less constant. Subtertian parasites of all ages may be found at the same time in blood removed from the viscera, though a majority may be about the same age. The pyrexial attack following sporulation is therefore necessarily less defined, as the toxin is being liberated during a far longer period. The cold stage is less often marked by a rigor, frequently merely by a feeling of chilliness; the hot stage is prolonged and the sweating stage is often intermittent, consisting of a series of attacks of dia-

![Graph showing subtertian malaria with definite tertian periodicity.](image)

**Fig. 14.**—Subtertian Malaria with definite Tertian Periodicity.

phoresis with hot dry intervals; the whole pyrexial period may last for more than twenty-four hours. The interval in such cases is short, as the whole cycle of development of the parasite appears to be under forty-eight hours (figs. 14 and 15).

In other cases the pyrexial attack is still more prolonged, and the interval correspondingly shortened. Not uncommonly in a severe attack there is no interval during which the temperature is normal, but merely a remission. Such a fever is therefore not intermittent, but remittent (fig. 16). Vomiting is common and may be persistent. When exceptionally severe and bilious, particularly if
Fig. 15.—Subtertian Malaria. Periodicity still definite.

Fig. 16.—Subtertian Malaria. Periodicity indefinite.

Fig. 17.—Subtertian Malaria (untreated). Slight fever only. No definite periodicity. Diagnosis based on blood examination.

Fig. 18.—Severe Subtertian Malaria (treated).
associated with jaundice, it is often popularly called bilious remittent fever. Constipation is the rule, but there are exceptions. In many of the cases of this form of malaria, when the parasites, though not very numerous, are not difficult to find, the temperature is not high, sometimes not exceeding 100° or 101° F. (fig. 17).

Hyperpyrexia has been frequently described, and there can be no doubt that, as in other toxic diseases, it must occur. In most of the recorded cases there has been no blood examination and no post-mortem examination, so that the malarial nature is not proved. Fig. 19 is of a case in which the temperature was at one time over 108° F., and the recovery under quinine is a proof that it was malaria.

In benign tertian, in spite of the severe attacks of fever, the patient may be in good health during the intervals. In subtertian this is exceptional. The patient may be able to be up and force himself to attend to business or pleasure, but these attempts at "fighting the fever" are responsible for many serious errors of judgment, as well as causing serious risk to the patient.

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**Fig. 19.**—Hyperpyrexia in Malaria.
Children are said by some to suffer little or not at all, and there is a certain amount of truth in this as they may, whilst harbouring the parasites, be capable of playing about and taking interest in their surroundings. Careful inquiry, however, will usually show that during a great part of the day they are listless, do not take food, or otherwise show signs of ill-health. They have usually a definite enlargement of the spleen.

Labial herpes is common in malaria, but as a rule does not occur till late in the attack, and frequently occurs when the fever begins to subside.

The great peculiarity of subtertian fever is the liability, with little or no warning, to the so-called pernicious manifestations. These are in the main due to blood stasis in different organs of the body, caused by the numbers of red corpuscles containing the parasites adhering to the walls of the capillaries and to each other, and so obstructing the circulation in that organ. This may occur in any organ, and the effects and clinical manifestations vary accordingly.

(1) When stasis of the blood occurs in the capillaries of the central nervous system the danger is great, and a large number of deaths are due to this condition. The symptoms vary in adults and in children.

In adults the patient usually has a flushed face and appears to be dull and stupid with slow speech and uncertain gait. In appearance and demeanour he is not unlike a man in the early stages of intoxication. This stupor may pass off in mild cases, but in others rapidly increases, and a condition of coma supervenes. There are no convulsions in the great majority of cases and no localizing symptoms. In a fatal case the coma deepens, the breathing becomes stertorous and the conjunctivae insensitive. Even at this stage recovery may occur with energetic treatment, or rarely even without it. Recovery when it occurs is rapid and complete, the patient in twenty-four hours may appear to be in fair health. There is no more striking instance of the effects of vigorous treatment than in a case of this kind.
If untreated and the patient recovers, the attack usually recurs, and is then fatal; very rarely does he survive two attacks at short intervals without antimalarial treatment.

In children the onset is less gradual; usually the first thing noticed is a convulsion. When this has occurred other convulsions rapidly follow, the child remains comatose between the convulsions, and death occurs in four to twelve hours from the first attack.

Even when the convulsions have continued for two or three hours, recovery is the rule with energetic treatment, and is complete.

Such convulsions are the usual evidence of cerebral malaria up to the fifth year of life. After this period coma without convulsions begins to be more common, and after the tenth year convulsions are highly exceptional. In these cerebral cases the temperature may be little raised, or temperature up to 105° F. may be noted. They are not associated with hyperpyrexia.

(2) The lungs may be a preferential site, and there is increased rapidity of breathing. Provided that the condition of the heart and lungs is sound there is comparatively little danger. The congestion of the lungs induced, though it may give rise to suspicion of pneumonia, does not seem to be serious in itself. In any condition of cardiac disease, or in pulmonary conditions such as emphysema and bronchitis, the danger is greater, as the effect of such diseases is aggravated. In cases of tuberculosis there is often hæmoptysis.

(3) If the abdominal viscera, and particularly the intestinal capillaries, are blocked, the congestion induced may lead to a condition of collapse—the algide form of malaria. In such cases the congestion of a part or the whole of the intestinal wall may be sufficient for hæmorrhage to take place into the lumen of the alimentary canal, and hæmatemesis, melæna, or hæmorrhage from the rectum may result, according to the portion of the alimentary canal involved. Occasionally, with or without such hæmorrhage, the nutrition of the superficial layers
of the mucosa is sufficiently impaired to render this membrane vulnerable to the vegetable organisms, bacilli and cocci, present in the alimentary canal. In that case extensive superficial necrosis occurs and ulceration may result, which will of course persist after the malarial attack has been relieved or has passed off (figs. 20 and 21).

![Parasites in Capillaries of Pancreas.](image)

(4) The capillaries in the heart may contain blood in a similar condition of stasis. This is probably one of the causes of the cardiac failure that frequently occurs in malaria. Persons with old organic cardiac mischief, pericardial adhesions, or fatty degeneration of the heart should, therefore, not be exposed to the risk of acquiring malaria. The mortality from malaria in chronic alcoholic subjects, and in persons with beri-beri, is probably due
to this stasis in cardiac capillaries in part, but may occur with quartan malaria, especially in cases of beri-beri, and so may be due to a direct toxic effect on the cardiac nerves. (5) The blood-pressure is usually raised as a result of such stasis, and actual hæmorrhages are not infrequent and may occur in any part of the body. Where there is old atheroma in the cerebral vessels, fatal cerebral hæmorrhage may occur.

Complications.—Albuminuria in some places is common during a febrile attack; in other places it is unusual. In children nephritis is a common sequela, but in adults it is rare; this nephritis is sometimes fatal. In many malarious countries this sequela is not met with. Hæmoglobinuria, and its possible relationship to malaria, will be considered under blackwater fever. Glycosuria may occur during the febrile attacks, but is rare. Hæmorrhages may occur from various parts of the body. Epistaxis is common. Hæmatemesis, melæna, passage of blood by rectum, though rare, have been seen on many occasions. Hæmaturia has been recorded, but is very rare. Neuritis, peripheral and multiple, is often described, but in most instances it is more probably due to alcohol, arsenic, and sometimes to beri-beri; as a rare sequela it does occur, and then rapid improvement takes place with quinine treatment. Still more rarely paraplegia may

Fig. 21.—Parasites in Capillary from Intestine.
follow an acute cerebro-spinal attack. Neuralgia is often attributed to malaria, and migraine has been ascribed to the same cause, but there is little evidence that there is any connection between these diseases and malaria. Attacks not unlike "petit mal" may occur with malaria, and may recur as long as the malarial infection persists, but they are rare.

Repeated congestion may be in part the cause of the chronic enlargement of the spleen, of some of the fibrotic changes in the liver and other organs, and of the tendency of pregnant women to abort, but the influence of toxins in inducing these conditions cannot be excluded.

(6) The mechanical effects due to the temporary blood stasis caused by the capillaries of one or two or more organs being partially blocked by corpuscles containing parasites will lead to congestion of those organs and to an inadequate supply of freshly oxygenated blood. Waste products also are not removed sufficiently rapidly, and, it has been pointed out that the interference with the circulation will result in a local accumulation of the malarial toxin. Cerebral or other local symptoms are mainly a combination of the effects in each organ, but in such cases extra work is always thrown on the heart, and cardiac failure may be the result. The immediate effects of this condition have been considered; they constitute the main danger to life in this disease. Sequelæ of the condition are not so common, though even temporary impairment of the nutrition of certain parts of the body, rendering the tissues more vulnerable, may lead to chronic changes. The frequency with which tuberculosis in the West Indies dates from attacks of malarial fever may be taken as an instance. The blood changes, according to Newham, do not as a rule affect the opsonic index; and therefore do not, in themselves, render the person more susceptible to bacterial diseases.

In subtertian malaria, as in other forms of malaria, the effects of toxins must be considered as well as the effects of the blood stasis—this only peculiar to
subtertian malaria. The effect of the substances—toxins—liberated when the red corpuscles containing the parasites break up, is irregular but more or less continuous. The tendency is for a considerable but variable proportion of the parasites to be fully developed and therefore to rupture the corpuscles which contain them about the same time. The toxic effects, as instanced by the pyrexia and vomiting, will then tend to show slight periodicity. Other evidence of toxæmia, such as hæmolysis, is variable. In some cases, even when the fever is high, there is little or no hæmolysis, in others it is marked. When the infection has continued for a long time there is always anæmia, but not necessarily severe anæmia. Of probable toxic causation are certain further symptoms which are more common in some places than in others, though morphologically the parasites in the different places are indistinguishable. These include (a) Albu-minuria, which may be transient, appearing and disappearing with each attack of fever, or occurring much as it does in scarlet fever, as a definite sequela of the disease. (b) Neuritis, which may be general or may occur mainly in the legs, and lead to a paresis with loss of knee-jerks, muscular tenderness, and rapid wasting of the muscles. In some of these cases there is some disturbance of the higher cerebral functions, such as loss of memory. These cases are often confounded with alcoholism, and may be associated with it. Rapid improvement takes place under quinine.

Diagnosis.—On the clinical symptoms alone, even during the stage of pernicious attacks, certain diagnosis is impossible; suspicion only is warranted. Certainty one way or the other is essential, as for any case persistent treatment, and for severe cases energetic treatment, is necessary. It is also essential that the possibility of malaria should be excluded in many cases, as without this time will be wasted before the real disease, possibly tractable, is diagnosed. The only satisfactory method is by blood examination. With
well-made films, either fresh, or preferably stained by Leishman's method, the parasites can be found usually with little difficulty. The essential is that the films, whether wet or dry, are so spread that in considerable portions of the film the corpuscles are lying flat and separate from one another.

The evidences of malaria derived from blood examinations are:

(1) Discovery of parasites. This is conclusive, but in persons who have been taking quinine the non-discovery does not prove that the patient has not got malaria. In the intervals between attacks of fever, whether after treatment or naturally, a prolonged search may be necessary before the parasites are found.

(2) Pigmented leucocytes, usually the large mononuclear or hyaline leucocytes. These are conclusive of recent malaria. They are often very scanty, so that it is only rarely that they aid in the diagnosis unless a prolonged search be made.

(3) Increase in the relative proportion of the large mononuclear leucocytes, without any increase in the total number of leucocytes. In malaria and for a variable period after malaria the proportion of large mononuclear leucocytes is raised to 15 per cent. or even more. This change is not affected by the administration of quinine, and is more marked when there is no pyrexia. It is therefore of great value in just those cases of malaria in which the parasites are not to be found. It does not, however, prove that the malaria is still present, as the change is so persistent, but, as a rule, it indicates past malaria. If there is a coexisting disease such as pneumonia, sepsis, or even acute hepatitis, which produces an increase in the number of polymorphonuclear leucocytes, this change will completely mask the mononuclear increase of malaria in a differential count. In children it is of less value, as in them an increase in the large mononuclear leucocytes is fairly common without any disease.
Prognosis is good, but energetic treatment may be required, and relapses will generally occur unless the treatment be prolonged for months after the last onset of a febrile attack. When pernicious symptoms supervene there is great danger, and, unless these can be speedily controlled, death will occur. If the recognition of the nature of the disease is made early the patient will usually be saved.

The case mortality among hospital patients is small where the diagnosis is made accurately, and also in private, but the number of deaths due to malaria untreated or inefficiently treated is large, but impossible to calculate. The high mortality in the Tropics, India, Africa, &c., is largely attributable to fever, both amongst Europeans and natives, and is the main cause of the high infantile mortality from convulsions.

The prognosis is much less favourable when malaria occurs in persons suffering from other diseases. Organic cardiac disease, and diseases such as beri-beri or chronic alcoholism, which affect the innervation of the heart, render the prognosis less favourable. When there is atheroma of the cerebral vessels, fatal cerebral hæmorrhage may occur. Syphilis in a person with malaria will not yield to antisyphilitic treatment till the malaria is treated.

Pathological Anatomy.—The general appearances may be inferred from the symptoms. In an acute case there is always congestion of some of the organs, and in those in which blood stasis has occurred this may be extreme. Parasites will be found in the cells in the capillaries or, if the examination is too long after death, pigment from the breaking down of these parasites. Cloudy swelling of the cells of the liver and kidneys is usually present.

The special changes consist of the deposits of malarial pigment in the connective tissue cells of the liver and in the parenchymatous cells of the spleen.

This pigment is fine and intracellular when derived from recent malarial infection, and intravascular when
parasites are present. It is much coarser and not obviously intracellular when derived from an old infection. In cases where hæmolysis has been great, hæmosiderin may be found abundantly in the hepatic cells, in cells in the convoluted tubules of the kidneys and sometimes in the spleen. Granules giving the reactions of iron (in its inorganic combinations) may also be present.

Large hæmorrhages are exceptional, but small subserous hæmorrhages or punctate extravasations in the organs such as the brain are more common. The lymphatic glands are sometimes enlarged, and rarely Peyer's patches. More commonly the Malpighian bodies in the spleen are enlarged and, as they are not pigmented, stand out boldly as white spots against the blackish background of the parenchyma.

Decomposition is not usually rapid, but the parasites die shortly after the death of their host. Blackening of organs from decomposition must not be mistaken for malarial pigmentation. If the examination be made shortly after death the spleen is always firm, but when the rigor mortis of the tissues has passed off, an event that occurs earlier than the disappearance of rigor mortis of the voluntary muscles, it is softer and more flaccid, but only becomes diffusent in the early stages of putrefaction.

Accumulations of parasites are found in the capillaries in various organs; even in the same case they may be found in many organs, less commonly they may be found only in the capillaries of one organ.

In fatal cases the capillaries of the brain, heart, intestines and other abdominal viscera are thus affected most frequently, but in other organs, such as the lungs, the capillaries may be found in the same condition.

Whatever organ is involved is markedly congested, and sometimes is of a dull slaty colour from the pigment contained in the parasites or in the cells in the parenchyma.

The spleen is always engorged and tumid, and this is shown by the tense smooth capsule free from wrinkles
and the broad rounded edge of the organ. It is not necessarily much above the average weight when death occurs early in the course of the disease, and then it usually weighs 10 to 15 oz., rarely more in an adult.

Examined microscopically malarial pigment is always found, but in early cases the spleen to the naked eye may appear red; the dense black colour sometimes seen is found in chronic cases, and may be only the remnant of malaria previously contracted.

The liver also is pigmented, and the pigment is deposited mainly in the cells between the lobules, so much so that in some cases the outlines of the lobules appear to be pencilled out in black.

*Treatment.*—Many drugs have been employed, quinine, methylene blue, arsenic, opium, &c., but of these only the first two have a marked effect on the parasites. Though the inorganic compounds of arsenic have little effect on the parasites the organic compounds, such as atoxyl, soamin and salvarsan, have a marked effect and may be of value in the rare cases where the parasites are quinine resistant. Since the general adoption of blood examination has led to a sure diagnosis, the value of quinine in malaria has been fully confirmed.

Any of the salts of quinine may be used. The ethyl carbonate, euquinine, has the great advantage of being tasteless, and is used for children and such adults as have great distaste for quinine. It is too expensive for general use.

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<th></th>
<th>Percentage of alkaloid</th>
<th>Solubility in water</th>
<th>Equivalent doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinina</td>
<td>100</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>Q. hydrochloride</td>
<td>81·8</td>
<td>1 in 40</td>
<td>10 grains</td>
</tr>
<tr>
<td>Q. bihydrochloride</td>
<td>72</td>
<td>1 in 1</td>
<td>11·4 &quot;</td>
</tr>
<tr>
<td>Q. sulphate</td>
<td>73·5</td>
<td>1 in 800</td>
<td>11·1 &quot;</td>
</tr>
<tr>
<td>Q. bisulphate</td>
<td>59·1</td>
<td>1 in 11</td>
<td>13·8 &quot;</td>
</tr>
<tr>
<td>Q. hydrobromide</td>
<td>76·6</td>
<td>1 in 45</td>
<td>10·9 &quot;</td>
</tr>
<tr>
<td>Q. bihydrobromide</td>
<td>60</td>
<td>1 in 7</td>
<td>13·6 &quot;</td>
</tr>
<tr>
<td>Q. ethyl carbonate</td>
<td>81·8</td>
<td>Nil</td>
<td>10 &quot;</td>
</tr>
<tr>
<td>Q. tannate</td>
<td>30</td>
<td>Nil</td>
<td>27·2 &quot;</td>
</tr>
</tbody>
</table>
The form in which quinine is taken is of some importance. The amount of anhydrous quinine in the various salts differs, and the solubility of the salts also varies, as shown in the subjoined table, which also shows the doses of the common preparations of quinine equivalent as regards the amount of quinine to 10 gr. of the hydrochlorate.

With a perfectly healthy stomach and a free secretion of hydrochloric acid, all these salts will be converted into the hydrochloride or bihydrochloride before they are absorbed, so that in that case the varying amounts of quinine only are of importance.

When the stomach is not healthy or, as is so often the case in malaria, the acid secretion is not normal, the case is different, and at the best the quinine will be more slowly absorbed, or at the worst only absorbed in small part. The same occurs with an empty stomach as then there is little or no acid secreted; and for the same reason, if the contents of the stomach do not excite gastric secretion, as when they are mainly water or watery, vegetable food solution and absorption of the less soluble preparations of quinine will not be complete.

The acid set free in the case of the sulphates will be sulphuric acid, which is not of much value in the digestive processes, and, acting as an astringent, may increase the tendency already marked in malaria to digestive disturbances.

When the hydrobromide is used, and still more with the bihydrobromide, the amount of bromine has to be considered, as in 10 grains of bihydrobromide there is bromide equivalent to about 3 gr. of potassium bromide. Where this drug is used as a prophylactic for long periods, mental depression may occur not only from the quinine but also from the bromine.

The hydrochloride contains a larger proportion, 81.8 per cent., of quinine; it is a little more expensive but not sufficiently so to prevent its general use. It is more soluble (1 part in 40 of water) and less irritating. The
bihydrochloride contains 72 per cent. of quinine; it should always be used for intramuscular and intravascular injections as it is soluble in one part of water. It is also best for rectal injections.

Quinine may be given (1) by the mouth; (2) by the rectum; (3) by intramuscular injection; (4) by intravenous injection.

(1) By the mouth is on the whole the most convenient method, and it suffices in the vast majority of cases. The quinine should be given in solution dissolved in water with the addition of an acid when a rapid effect is desired and in all cases for treatment of the acute conditions; hydrochloric or hydrobromic is the best, but sulphuric or tartaric acid may be used. Lime juice, either fresh or preserved, sherry and other acid solutions may also be used as solvents. When given in solution it is certainly and rapidly absorbed, but the taste to many people is nauseating.

Freshly made pills, made by the addition to quinine sulphate or hydrochlorate of a small crystal of tartaric acid and a drop of water, have no disadvantage.

Sugar-coated pills, tabloids, or tablets or old pills must not be used, as they are frequently passed undissolved. Compressed uncoated tablets are occasionally, but rarely, passed in this way under ordinary circumstances. They may be used for prophylaxis, during convalescence, and in mild attacks, if the tongue be clean and there are no symptoms of dyspepsia, but should not be relied upon in severe attacks. They are convenient when travelling as they can be readily broken up and dissolved if required. Before using tablets in cases of fever, typhoid fever must be excluded. Fatal haemorrhage has occurred in cases of typhoid where quinine tablets have been given. Quinine is sometimes taken in cigarette papers, but it is not certain that taken in this way the quinine will be absorbed, and in many places gelatine capsules are used, but the gelatine often becomes hard and is not dissolved in the stomach.

(2) Administration by the rectum results in very rapid
absorption. It is particularly useful when there is much vomiting and when it is desired to give frequent large doses, as in comatose cases or in children with convulsions, as it is necessary that large doses should be absorbed, and that these doses should be repeated at short intervals. A preliminary enema is not advisable except when the rectum is loaded with faeces.

The hydrochloride or bihydrochloride, dissolved in the minimum amount of acid and freely diluted, up to four or six ounces in an adult, should be used and injected very slowly.

The injection must be given warm, and with a fairly long tube (a No. 8 Jaques catheter fixed on the nozzle of a glass syringe is a convenient instrument to use) to be sure that it is retained.

In children it is necessary for the nurse to keep the buttocks pressed together to ensure the retention of the quinine solution till it is absorbed. Irritation and inflammation of the rectum are said to follow this method of administration, when the sulphate dissolved in sulphuric acid is given, but even then these results are exceptional.

(3) Intramuscular injection has many advocates. The results are good but no better, even if as good, in comatose cases than rectal injections. It is assumed that absorption is rapid. The quinine is, however, precipitated in the muscle, and is gradually absorbed; the great advantage of its administration is that it is being continuously absorbed. It is particularly useful in persons with chronic dyspepsia or gastric irritability, and a comparatively small dose (10 gr. daily or on alternate days) of quinine is required.

Precautions.—Unless antiseptic precautions are adopted there is danger of tetanus or formation of abscesses, and the injection must be made into a large muscle. Semple has shown that however strict these precautions may be, if there are any tetanus spores in the body, or introduced shortly after the injection, these will multiply at the site of the quinine injection and tetanus occur.
Some of the Indian authorities before using the quinine injections inject antitetanus serum.

(4) Intravenous injections are used in pernicious cases by some; it is doubtful if the results are better than those obtained by rectal injection. In the strengths often used Semple has shown that much of the quinine is precipitated and that much greater dilution is required for the quinine solution to be miscible with the blood. W. M. James advocates such dilute solution as 1 in 150 of normal saline, either subcutaneously or by intravenous injection. He gives 30 gr. of the bihydrochloride in 10 oz. of normal saline and uses it when the infections are large, or when for other reasons he suspects the probability of the onset of cerebral or other crisis.

Dosage.—This is most important. It may be stated with confidence that, where the diagnosis is verified by blood examination, treatment with quinine never fails if the doses be sufficient and there is time for the drug to act.

In many cases small doses will suffice; even the amount of quinine contained in a drachm of Easton's syrup may bring the temperature down to normal. Ten to fifteen grains of any of the salts of quinine daily will usually suffice for benign tertian and quartan, and sometimes for subtertian. It is more uniformly satisfactory to give 30 gr. daily till the fever is down and then reduce the amount. Where it is absolutely necessary to economize the quinine, it will be better to give a single dose before an expected rigor, as a smaller dose will then suffice to relieve the pyrexia.

In severe cases with pernicious symptoms no time should be lost; moderate or even large doses so often fail, that if life is to be saved the risks of quinine poisoning must be faced. In such cases in adults a single dose of 20 gr. should be given at once, preferably per rectum, and repeated in an hour, and 10 gr. given every hour till improvement takes place, usually a matter of some four or six hours. Even in young children
5-gr. doses may be given at corresponding intervals in the same manner. If there is any sign of cardiac failure, stimulants, preferably alcoholic, must be freely administered. Every effort must be made to keep the patient alive, as recovery is certain if the quinine has time to act. Hot packs in adults and hot baths in children are beneficial and must be used in addition to quinine.

The time of giving quinine with reference to fever is not considered to be of so much importance now as it was. The action of the quinine is more decided if it is given when the spores are set free, and therefore in benign tertian and quartan a small dose given before the rigor is more effective than the same dose later. It is in the period immediately before the onset of fever that sporulation occurs and, therefore, when quinine acts best; and there is no advantage in reducing the temperature artificially, as by the use of antipyretics, before giving the quinine, except that vomiting is less likely to ensue and the headache is less. In all cases of malaria, treatment with quinine must be continued for a long period after the disappearance of the symptoms.

A commonly successful practice is to give 10 gr. daily for one week, every other day for two weeks, and twice a week for a month, and 15 gr. once a week for two months. In the majority of cases, even if large doses of quinine have been given during the pyrexial period, relapses will occur unless the use of the drug be persisted in. In the experience of the writer the intermittent administration of quinine is not so satisfactory as a regular daily dose of 5 gr. of the hydrochloride of quinine. If given during a meal, say breakfast, the uncoated tabloids can be used. In a few cases of benign tertian a three months' course is not sufficient, but in the vast majority of cases it is in subtertian malaria.

In malaria there is usually constipation; this should be relieved, preferably by saline aperients, but calomel and calomel and jalap are used by many.

Antipyretics, such as phenacetin, are not advisable in
severe cases on account of the risk of cardiac failure. In mild cases, if the headache be severe, they give relief and are harmless.

Management.—One of the points that is constantly arising in connection with malaria is the advisability of allowing the patient to work during the intervals of an attack or, in the case of subtertian, when the patient is still suffering from a low type of fever. In both cases recovery is delayed by any attempt at getting up, exposure of any kind, or work, whether physical or mental.

In benign tertian and quartan fever it may be permissible for urgent work to be done during the apyrexial interval. This should be restricted as far as possible to routine work. It must always be remembered that work done under these conditions is inferior. With the subtertian fever, even though the temperature be normal or nearly so, no responsible work should be undertaken as the patient is incapable of acting with judgment. Instances of grave errors resulting in serious calamities are common. A very decided stand has, therefore, to be taken in these cases, as one of the prominent symptoms is an obstinacy which leads the patient to insist on doing work when he is mentally incapable of dealing with it satisfactorily.

As regards residence in a malarial country of a person who has suffered severely, the general condition has to be considered, as well as the completeness of the recovery. There is no reason why return should not be allowed if these points are satisfactory, as there is no increased liability to reinfection. On the contrary, there is a variable amount of partial immunity.

Nursing.—In an ordinary attack of malaria skilled nursing is hardly required except for comfort. The patient, moreover, is often irritable, or may be slightly delirious, and no unwelcome attentions should be persisted in except such as may be absolutely necessary. He should be protected from noise, bright light, and above all from draughts.
Blankets and clothing require changing after the sweating stage, and both must be kept thoroughly dry and warm.

Warm sponging after the sweating stage is comforting and cleanly.

During the stage of rigor hot bottles are appreciated, but are not necessary. Some protection to the bed is necessary, as the perspiration is frequently sufficient to soak through the blanket, and mattresses thus acquire a peculiar, unpleasant, musty smell.

To protect the bed fine native grass mats placed under the blanket are serviceable; they are usually cheap and can be washed and sunned. In hot weather these mats will be found very cool and pleasant to lie on. Waterproof sheets, such as are used in England, perish rapidly in the Tropics and are expensive.

If there is much vomiting sinapisms should be applied to the epigastrium. Drinks should then be given hot, or iced, and in small quantities at a time.

In the severe forms of fever more attention is required. Any tendency to a lethargic condition must be noted, as this often precedes coma or hyperpyrexia; and the temperature must be taken at once, and every half hour afterwards, if this tendency is observed, till the symptoms subside, even if the temperature is very little above normal.

If coma supervenes, hot packs are by many considered to be of great value. These may be given on the bed, but the packs are more readily and rapidly changed if the bedding and patient are placed on the floor. Either a blanket or sheet may be used. The blanket retains the heat longer, but the sheet is more readily arranged. The sheet or blanket must be placed in water of a temperature ten degrees higher than the pack is meant to be applied. This is the safest rule, but in emergencies, or when an exceedingly hot pack is required, it is better to use nearly boiling water and wait until, as tested by the elbow, the temperature is such that it can just be borne. This will be about \(108^\circ\) to \(112^\circ\) F.
Great care must be taken to thoroughly wring the blanket, especially at the ends; retention of hot water in these places frequently leads to blistering of the patient. The patient should be turned on to his side, the blanket is well wrung out and folded lengthwise, the edges must be close to the back of the patient towards the middle of the bed. He is then rolled on his back on to the under half of the damp, hot blanket, which is folded round him from head to foot, and covered with other and dry blankets. If profuse perspiration does not occur, or the temperature rises, the pack should be repeated. After the pack is removed, wrap the patient in a warm, dry blanket and rub him with warm dry towels. These packs must be hot, and in desperate cases and with a patient deeply comatose a certain amount of blistering may result. This is usually due, not to the excessive heat, but to imperfect wringing of the pack. When the temperature is so high that hyperpyrexia is feared cold or even iced baths may be required. The patient should be lowered in a sheet into the bath at a temperature of 85° F., an assistant supporting the head. Cold water is gradually added and well mixed, or ice, if available, may be added. The temperature of the patient must be taken frequently, every five minutes, per rectum, as when once it begins to fall, and has fallen below a point of danger, 102° F., it will continue to fall after removal of patient from the bath, and dangerous or even fatal collapse may occur if the temperature has been too much reduced. Stimulants are practically always required. When a bath is not available cold or iced packing is sometimes employed. A half pack is very useful, and can be managed single-handed. The patient, stripped to the hips, is placed on his back on a waterproof sheet or native mat, and large towels wrung out of cold water are placed on his chest or abdomen, completely covering them, and tucked in at the sides. These towels are to be repeatedly changed and renewed from a bucket of cold water placed at the bedside. This
water may be further cooled with ice, or a block of smooth ice may be rubbed up and down over the wet towel as it lies on the patient, so as to keep it constantly cold—"ice planing." Cold applications, ice-bags, &c., to the head should also be used.

Administration of Quinine.—This, when given by the mouth, may cause vomiting. The ordinary precautions should be taken, but if the vomiting is uncontrollable hypodermic injections of morphia, $\frac{1}{4}$ gr., should be given, preferably over the epigastrium. It is absolutely necessary that quinine should be absorbed, and if it cannot be readily retained by the stomach it must be administered in some other manner. In giving quinine by the rectum the nozzle of the syringe and the long tube used must be warm, or a funnel and tube may be used. The injection should be given well above the anus, and must be made very slowly.

The patient is to be kept perfectly still and the buttocks should be pressed together in order to counteract any slight efforts at straining. In children the nurse must maintain this pressure for half an hour, otherwise the injection will not be retained sufficiently long for absorption to take place.

Superficial hypodermic injections of quinine must not be given as they are painful and often followed by abscesses. If administered by injection the quinine must be introduced into one of the larger muscles, such as the gluteus maximus. Injections into the forearm, or amongst any mass of small muscles, cause a good deal of pain and swelling, and if injected into or close to a nerve trunk may cause permanent paralysis. This accident occurs most frequently if the injections be given in the forearm. The most important point to be remembered about these injections is their liability to cause tetanus or abscesses. Such accidents appear to be due to the injury inflicted by the quinine upon the tissues with which it came in contact, thus facilitating the growth of any organism introduced with it, or, as
Semple has shown, already present in the patient. The risk does not occur where strict antiseptic precautions are taken. The skin at the point of injection must be cleaned and thoroughly washed with antiseptics, alcohol and ether, and 1 in 20 carbolic acid, 2 per cent. lysol, or acetone, followed by $2\frac{1}{2}$ per cent. solution of tinct. of iodine, which is the best. The syringe must be sterilized by boiling, and the solution of quinine must be sterilized in the same way immediately before use. It is sometimes objected that it is the adult and more than half-grown parasites which cause the change in the corpuscles, and that these parasites are not amenable to the action of quinine. No doubt this is so to some extent; but it must be remembered that quinine has an action on parasites enclosed in red corpuscles; and secondly, that as the parasites sporulate that portion of the block due to that corpuscle gives way, so that unless the corpuscles causing the stasis are continually reinforced by fresh corpuscles containing more or less half-grown parasites the circulation will be restored. In practice, by giving large doses of quinine repeatedly the mortality is not very large, often three or four cases will be treated in the same ward without any deaths. Cases do die, but usually within two to four hours of admission. If they live more than four hours deaths are exceptional.

Synthetic antipyretics, such as antipyrin and phenacetin, give relief, but should only be used on patients who are in bed and in mild cases. They may, in severe cases, be the cause of fatal collapse. On the whole their use is to be deprecated. In comatose cases, in addition to the free use of quinine, alcoholic stimulants are required. The use of a cardiac stimulant which acts also as a vasomotor dilator, such as alcohol, is far better than strychnine or digitalis.

Hot packs in adults and hot baths, with a little mustard in them, in children are of great value in the comatose or convulsive cases.

Food.—Little food can be taken during a sharp pyrexial
attack, and there is no object in forcing any on the patient during this period. Thirst is a common symptom, and there is no reason why abundant fluid should not be taken, provided that small quantities only are taken at a time, otherwise vomiting may be provoked. Any fluid taken should be hot; hot tea is a favourite drink, but must be freshly prepared and not too strong, as tannate of quinine may be formed in the stomach and is very slightly soluble.

Many of the native remedies, such as lemon-grass tea, are comforting and aid in diaphoresis. In subtertian malaria the fever is long continued and careful feeding is important. Milk, and milk and barley water or other light food is usually retained and digested.

During convalescence, protection from chill is of great importance. Good food is also required; it should be light, nutritious and varied, as the appetite is frequently capricious.

Few men can be persuaded to remain long in bed even after a severe attack of fever, but a minimum of three days should be insisted on.

Special Cases.—In pregnant women the frequency of abortion with or without quinine must be kept in mind. Unless the fever is controlled,-abortion will take place in many cases, but quinine, the only reliable drug, undoubtedly has a similar tendency.

Before treating a case of malaria in a woman, careful inquiries should be made in order to find out if she is pregnant. If so, quinine must be given, but in very small doses, gradually increased till the fever is controlled. The large heroic doses advocated in an ordinary case must only be given in pregnancy if there is urgent danger to life. A pregnant woman should be kept in bed for at least one day before the quinine is given. Drastic purgatives must be avoided, but a fair action of the bowels must be obtained, and the quinine given after the laxative has ceased to act. During the whole course of the treatment the patient must be kept quiet in bed.
If premature birth occurs, the child is frequently still-born. If born alive it is not infected with the malarial parasites at birth in the great majority of cases, but exceptions occur, and even in England the child of a person suffering from malaria, though born in England, may be found to have malaria, which must have been acquired from the mother.

A patient who has had blackwater fever must be given quinine very cautiously. Unless there is danger to life, the doses must be very small, commencing with $\frac{1}{4}$ gr. and gradually increased till the minimum effective dose is reached.

*Malarial Cachexia.*—The term has been and is much abused and used to cover many mistakes in diagnosis. Conditions such as kala-azar, ankylostomiasis, chronic dyspepsia and its results are so frequently mistaken for it that some authorities are tempted to abandon the term.

A real cachexia does follow repeated attacks of malaria, and is still more marked in the chronic malarial condition where parasites are present in small numbers in the blood, but are rarely sufficiently numerous to cause sharp febrile attacks, and may not cause any rise of temperature at all. The condition does not necessarily occur in all cases of chronic malaria, badly or irregularly treated, or even if not treated at all, and there are many degrees of it and varying complications.

The usual condition is one of anaemia with some discolouration of the skin and associated with an obviously enlarged spleen and sometimes liver.

The anaemia may be very marked and the red corpuscles reduced to 2,000,000 per cubic millimetre. Such cases are not common; more frequently the reduction in the number of corpuscles is moderate, say to three and a half or four and a half millions, but many of the corpuscles show signs of degeneration—polychromatic corpuscles, corpuscles with basophilic granules, poikilocytes—and great variation in size and colour of the individual corpuscles (Plate II., i to 9). The average haemoglobin value of the corpuscles is usually maintained.
As the bronzing of the skin often masks the anaemia, the conjunctival and mucous surfaces must be examined or the anaemia may be overlooked. The spleen if enlarged is hard, and as a rule slightly tender on deep pressure. It may be painful. The degree of enlargement does not correspond to the anaemia. The liver is enlarged in some cases and tender. This tenderness may be so extreme as to give rise to suspicion of hepatic abscess. Associated with these conditions are anorexia, dyspepsia and muscular weakness. Insomnia, mental depression and neuralgias are common concomitants and may be the most prominent symptoms. In the more advanced cases there is œdema of the legs and rarely albuminuria, though in persons suffering from any form of Bright's disease the symptoms of that disease will be aggravated.

Any latent disease present is likely to recur or be aggravated, and this is specially the case with syphilis.

Amongst the rarer complications are various ocular disturbances. Optic atrophy or retinitis may occur, and various forms of conjunctivitis. The possibility of a malarial complication must always be considered in any ocular disturbances in the Tropics. Diagnosis may be very difficult. Careful blood examination will often enable the diagnosis to be made. Prolonged examination may reveal the presence of an occasional malarial parasite, sometimes of a crescent, sometimes of a ring form. Failing this, the differential count may show a relative increase in the large mononuclear leucocytes, and if this be not present it is improbable that the case is one of malaria.

In cases of doubt the patient should be kept in bed, alimentary disturbances attended to, and quinine given in moderate amounts, either by intramuscular injection of 10 gr. on alternate days, or in solution by the mouth, 5 gr. three times a day. Food should be light and nutritious, and in a case of malarial cachexia rapid improvement will take place. When convalescence has
commenced the patient need not be confined to bed or even to the house, but quinine must be continued for many months. Under such treatment the anæmic condition rapidly improves, but can be expedited by administration of small doses of arsenic or of iron and arsenic by the mouth, or, better, by intramuscular injection. Such mixtures as Easton’s syrup in 1-dr. doses will often be found useful. Cold “bracing” climates should be avoided at first, the warmer “relaxing” climates are more suitable. Later, dry bracing climates, such as the Swiss winter resorts, or Harrogate in the summer, are distinctly beneficial.

If the weather be suitable when convalescence is well established, as much time as possible should be spent in the open air, and exercise, not of a violent character and always short of fatigue, should be encouraged.

The enlargement of the spleen at first subsides rapidly, but some enlargement will persist for many months. Soamin, in 5-gr. doses intramuscularly, is advocated by some. Pierpont and Acton give full doses on six alternate days, and claim excellent results. It is important to be certain of the diagnosis; some of the milder cases of supposed malarial cachexia are the result of too prolonged unnecessary administration of quinine, and the symptoms will rapidly cease when quinine is discontinued.

Ill-effects of prolonged use of quinine are not uncommon. The ordinary effects of quinine—buzzing in the ears, dizziness, and so on—are not usually met with in persons who habitually take quinine. The main effects are chronic, atonic dyspepsia and its sequelæ, and nervous depression or irritability. Too large doses may cause permanent deafness, but this is rare; more commonly gradual but complete recovery takes place.

Amblyopia may occur. The onset is usually sudden, and both eyes are affected. The pupils are dilated and do not react to light. The disc is pale, there is a white haze over the fundus, and the vessels are constricted. Vision is lost completely for a time, but as a rule there
is complete recovery. The condition is quite different from the still rarer optic neuritis due to malaria, as in that condition the pupils react to light, the fundus is congested, sometimes there are hæmorrhages, and the disc is swollen.

Sequela.—One result of successful prevention and treatment of malaria is a diminished death-rate from all causes, though no direct relation between some of these diseases and malaria can always be traced.

Tuberculosis and dysentery are specially prone to attack persons who are much reduced by malarial diseases.

Boils and other skin affections are very common, though no special type of skin disease can be said to be a sequela. In individual instances there is no proof of lowered resistance to other diseases, but taken in mass the evidence is strongly in favour of malaria inducing a condition in a proportion of the cases of increased susceptibility to bacterial invasions.
CHAPTER VI.

PROPHYLAXIS.

Etiology.—It is not necessary to do more than allude to the older hypotheses as to the causation of malaria. These were mainly founded on the belief that emanations from decomposing vegetables or from soil or rocks such as granite caused the fever. These emanations were known as "miasmata," and were believed to rise only a short distance from the ground during the night and to be dissipated by the sun. It is from this hypothesis that the term for the disease, malaria, is derived. These observations as to the occurrence of malaria are in many cases more readily explained now that it is known that the disease is carried by mosquitoes.

We now know that malaria is a parasitic disease, and that the parasites are conveyed from man to man by certain species of mosquitoes.

As far as we know these parasites can only exist in man and mosquitoes. Seasonal variations occur in most places, due (1) to the variations in the meteorological conditions affecting the multiplication, breeding, and prevalence of suitable mosquitoes; and (2) to the temperature being suitable for the development of the malaria parasites in these cold-blooded definitive hosts. Local variations are often due to the prevalence and proximity of suitable warm-blooded hosts—human beings—the intermediate hosts of the malaria parasites. Native children and bodies of new-comers from non-malarial countries are the most important carriers, or reservoirs, of the parasites to consider.

Malaria can be propagated from man to man by trans-
fusion or by the injection of the blood of a malarial patient into another person, but this method of transmission can play no part in the natural dissemination of the disease. Ross records fifty-one successful inoculations by many observers with blood, either intravenously or by subcutaneous injection. The natural method, and, as far as we know, the only method under ordinary conditions, is by certain mosquitoes.

The proofs of the mosquito malaria hypotheses are as follows:—

(1) The development day by day of the parasites can be followed in a batch of mosquitoes fed on a person in whose blood gametocytes are found. This is so definite that, knowing the time that has elapsed since the mosquito was fed, the appearances of the malarial parasite in it can be predicted with certainty. No such bodies are found in other mosquitoes bred from larvae. When these parasites have reached a certain stage of development the sporozoites are found in the salivary glands of these mosquitoes, and if such mosquitoes be allowed to bite any susceptible person he will, after a period of incubation, develop malaria of the same type as that of the man on whom the mosquito fed. This period of incubation is not constant, and differs with the species of malaria, and also from that found by direct inoculation of blood. Ross contrasts these from records he has collected as follows:—

<table>
<thead>
<tr>
<th>Species</th>
<th>Average Period in Days before Symptoms</th>
<th>Shortest period after mosquito inoculation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blood inoculation</td>
<td>Mosquito inoculation</td>
</tr>
<tr>
<td>P. malariae</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>P. vivax</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>P. falciparum</td>
<td>8</td>
<td>11</td>
</tr>
</tbody>
</table>

If quinine is being taken the incubation period is prolonged, and if taken regularly in small doses may be prolonged by weeks or months, and symptoms not appear till two or three weeks after the quinine is discontinued.

(2) Mosquitoes were allowed to feed on a patient with
malaria in Italy, and transported to London. These fed on two uninfected persons there and these persons then developed malaria.

(3) It has been further shown that people can live in malarial, swampy country, such as the Campagna, and that so long as they are protected from bites of mosquitoes they will be free from malaria, though other inhabitants suffer.

(4) Certain islands in the Tropics are free from malaria, though neighbouring islands in sight are intensely malarious, e.g., Barbados is free from malaria, whilst in St. Vincent it is abundant. It is found that in the malaria-free island no mosquitoes capable of carrying malaria exist, whilst in others they are common. Fiji may be quoted as an exception as there is no malaria there, and amongst the many mosquitoes sent from that country one wing of an anopheline was found. No other specimens have been found, though they have been looked for.

(5) The success of anti-malarial operations which diminish the liability to be bitten by malaria-carrying mosquitoes by diminishing the number of those mosquitoes is an additional proof of the correctness of the hypothesis. In places, such as Ismailia and Kwala Klang, where the reduction in the number of these anophelines was great, the cases of malaria diminished to one-tenth or less. In many other places where the reduction in the number of these mosquitoes was less, there was still a decided diminution in the amount of malaria.

(6) In many parts of Africa the liability to malarial infection in the settlements is very closely related to the actual number of mosquitoes capable of being malaria-bearing.

It is often urged that although this is one way in which malaria is caused, there may be others. It is possible that in other blood-sucking insects a similar development of the parasites might take place, but there is no evidence
in favour of such a view, and it is exceptional for protozoa to be equally capable of similar development in widely separated groups of arthropoda.

The success of prophylactic measures used on the hypothesis that certain mosquitoes are the carriers of malaria shows that this at any rate is the important method of the propagation of malaria. If, when the possibility of this method of conveyance is removed, malaria still continued to exist in any place, special inquiry would be required, but no such instances are known at present. For prophylactic work, therefore, the known method in which the disease is carried is the only one now to be considered.

Some knowledge of insects in general, and of mosquitoes in particular, is essential to advise as to economic prophylactic measures, and an outline of the classification of insects, and the principles on which the mosquitoes are classified, is given in a separate chapter as an appendix.

All known carriers of malaria belong to the division of the mosquitoes known as *Anophelinae*. The different species of anophelines do not serve equally well as carriers of malaria. Some species are readily infected, others only with difficulty, and some not at all. The dangerous species are those which are both numerous and readily convey the disease.

For economic and efficient prophylaxis a knowledge of the habits of each species is required, and it is found that the different species vary greatly in their habits, life-history, and breeding-places.

In any place or country the species of anophelines must be determined; those that are good carriers of malaria must be found out experimentally, and the breeding-places and habits of these must be studied in great detail.

The anophelines, which include all the known carriers of human malaria, are easily distinguished from other mosquitoes, which have a straight, penetrating proboscis.

(1) The palps in both male and female are practically
FIG. 22.—1, Culicine male; 2, Culicine female; 3, Anopheline male; 4, Anopheline female.
Fig. 23.—Various Forms of Wing-scales (Theobald). 1, Scales on veins and on costa in *Anopheles*; 2, scales on veins in *Cyclolepteron*; 3, scales on veins and on costa in *Janthinosoma*; 4, scales on veins in *Mansonia*; 5, scales on veins in *Stegomyia*; 6, scales on veins in *Eretrmapodites*; 7, scales on veins and on costa in *Culèx*; 8, scales on veins in *Mucidus*; 9, scales on veins and on costa of *Psorophora*. 
the same length as the proboscis, and in the male are clubbed (fig. 22).

(2) The scutellum, which is more or less trilobed in other mosquitoes, shows no sign of such lobing in the anophelines.

(3) The scales on the veins of the wings are lanceolate in the anophelines, whilst they vary greatly in the other Culicidae (fig. 23).

(4) The proboscis is nearly in the long axis of the head, thorax and abdomen, so that the mosquito almost forms a straight line. When at rest, as the proboscis points towards the surface on which the mosquito rests, the abdomen points away from it (fig. 24).

(5) The larvae have no respiratory syphon; they lie flat on the surface of the water when at rest, and after their first moult have compound "palmate" tufts along each side of the abdomen on the latero-dorsal aspect.

(6) The eggs are more or less boat-shaped, and have lateral air-floats; they are laid singly and not formed into rafts.

For the propagation of malaria all that is required is:—

(1) That suitable anophelines should feed on a person in whose blood sexually mature parasites—gametocytes—are present; (2) that these mosquitoes should be kept at a proper temperature for a period varying according to the temperature, from about eight to some sixteen days or more; and (3) should then bite a person susceptible to malaria. In about ten to fourteen days such a person will develop malarial fever. As far as is known man is the only animal that ever acts as the intermediate host for the species of parasites which cause malarial fever in man, and therefore mosquitoes, the definitive hosts, derive the parasite from man only, and transmit it to man only. Any break in the sequence will result in the destruction of the parasites, and it is with this in view that all attempts at prophylaxis must be conducted.

1. The parasites in man can be attacked by the use of quinine in all infected persons, so that the chances of the
Fig. 24.—A, Lateral view of Anopheline; B, lateral view of Culicine; C, Anopheline viewed from above; D, Culicine viewed from above; E, head of Corethia; F, head of Megarhinina.
mosquitoes becoming infected are much diminished. Persons may be rendered insusceptible by the free use of quinine, so that even if infected mosquitoes bite, the parasites do not develop. This affords protection to the individual, but either of these measures to be successful requires practically universal dosing with quinine.

II. Increased protection from mosquito bites by mosquito nets, clothing better adapted for protection against mosquitoes, mosquito-proof houses and the more general and intelligent use of mosquito nets, are all measures that may alone under exceptional circumstances prevent infection, and in any case are of great value in diminishing the opportunities for infection either of man or of the mosquito.

III. Avoiding places where mosquitoes are probably infected, in travelling by land, and sleeping in the native huts or in the same clearing as the native village should be avoided. It is safer to make the encampment in the jungle, a mile or so from the native settlements. Rest-houses and bungalows should not be built in or near to a native settlement; if they are in such situations they should be avoided.

Mosquitoes acquire the malarial parasite only from man, and there is no reason to suppose that it can be conveyed to the mosquitoes from any other source. Experiments have been made, and it has been attempted to infect the lower animals with human malaria; but they have all failed. Anophelines may be present in a place in large numbers, and yet there may be no malaria; if, however, they bite men already infected with malaria they will spread the disease and that place will then become very malarious. It is therefore important that the human sources of infection should be known. In this connection it is important to determine where men get infected, and where the mosquitoes which infected him become infected. The place where the infected person spent the nights ten to fourteen days before he got fever—preferably twelve days before—is the probable
place where he was bitten by an infective anopheline. That mosquito must have fed on a person in whose blood gametocytes were present some ten days before. It must always be remembered that the gametocytes are present in a person convalescent from a malarial attack, especially from subtertian malaria.

In a country where malaria is prevalent, those liable to attack may be divided into two main classes, both consisting of persons who have not acquired immunity by previous attacks of malaria:

(1) Children, native and European, will be liable to harbour the parasites, as there is no hereditary immunity. There may be some hereditary tolerance. Adults who have lived for a long time in the country will have acquired some immunity and therefore will not commonly harbour parasites.

(2) Susceptible adults, European and native, are those who have lived long in a non-malarial country, and are therefore not immune. Either of these classes in a malarial country may serve as the starting-point of fresh cases by infecting the mosquitoes.

The first class are of most importance in fixed settlements and also in infecting travellers passing through a country.

The second class are of special importance in opening up uninhabited country; in mines, plantations, and road or railway construction.

With large bodies of men outbreaks may originate from infection acquired from native children, or may be imported by some of the adults joining such a force, as these may harbour the parasites. When malaria is once introduced amongst such a body of men, each case serves to infect the mosquitoes, and these in turn infect other men till all susceptible members of the gang are attacked.

In travelling through a malarial country an endeavour should be made to avoid being bitten by mosquitoes by the free use of mosquito netting, by avoidance of places, particularly for camps, where the mosquitoes are likely
PREVENTION OF MALARIAL FEVER

to be infected, and by the use of quinine. The common practice in travelling by river of tying up for the night near a native village should be discontinued. In a town, settlement, or permanent camp, more radical measures should be instituted.

The policy of isolation cannot be carried out fully by missionaries, or by persons in charge of labour on extensive works; and in countries where native races are civilized it does not tend to improve or aim at improving the sanitary condition of the place, nor at reducing the heavy infantile mortality always met with in native races in a badly malarial country.

Universal administration of quinine to all persons in whose blood there is evidence of malarial infection and to all new-comers, and visitors to a community must be similarly treated before they are allowed to reside; it is expensive and, except with persons under strict control, impracticable. With troops, gangs of European workmen, and school children, it can be carried out successfully, sometimes also in small villages or settlements.

The methods by medicinal means, adopted or advocated, for the prevention or extermination of an infection of the people in a settlement fall into two groups: (1) The regular daily administration of quinine, and (2) the regular administration of larger doses at longer intervals. The writer favours the first and advocates the administration of 5 gr. of the hydrochloride every day. The object is not to get rapid absorption, as is required for treatment of the acute condition, but to get slow and complete absorption. If taken as an uncoated tabloid during a meal in any person with a healthy digestion it will be in the stomach during the time when the contents are acid and absorption is most rapid. In persons liable to insomnia breakfast or the first heavy meal is the best meal with which to take it. Few people can take more than 5 gr. for prolonged periods without ill effects, but it is admitted that it does not prevent infection though it reduces the parasites well below the number required
to cause symptoms. Many persons will take this dose daily during their whole residence of one year in Africa and have no fever at all, but if they discontinue it on the way home, or on arrival in England, within two or three weeks after they have ceased to take it they get fever, showing that this dose had not prevented infection. It also has little effect in reducing the number of crescents already formed. In children quinine tannate, 1 or 2 gr., made up with chocolate is effective and is readily taken.

Of the methods of administration at longer periods there are many variations: 10 or 15 gr. once or twice a week is advocated by some; 10 or 15 gr. on the ninth and tenth, twentieth and twenty-first, and last two days of each month is preferred by others. Thomson advocates the daily use of 20 gr. for a period of three weeks four times a year. This dose, he contends, kills off both the sexual and asexual forms, and would free the population from the parasites. In isolated places, where the plan could be adopted simultaneously for the whole population, the method is well worth a trial.

With large stations the most satisfactory results are obtained by diminishing the number of the definitive hosts, anophelines. The most vulnerable period in the life-history of these insects is in their larval stage. This is always passed in water. A somewhat detailed knowledge of the class of breeding-place for the species that carry malaria in each place is required for effective and economical work in this direction. As these places differ for each species of mosquito, without detailed knowledge money will be wasted and the results cause disappointment.

It is important to have both the coolie lines and the European quarters at some distance from each other, so that infected anophelines cannot readily pass from one to the other, and that both should be well in the cultivated, cleared and drained area where the number of anophelines has been reduced.

Wet methods of cultivation, such as that required for rice growing or such cultivation as requires an extensive
system of artificial irrigation, are not permissible in the vicinity of a station.

In all procedures for the reduction in the amount of malaria it must be remembered that partial measures are of value and will result in a diminution in the amount of malaria, but that the more complete the methods are the more successful they will be. The exact measures adopted require an exact knowledge of the local conditions and of the normal and exceptional breeding-places of the local dangerous species of anophelines.

The exact method or combination of methods best suited for each set of conditions will vary according to circumstances, and it may be cheaper to use all measures partially than to carry out thoroughly any single one, and the combination may be fairly effective.

Estimation of the prevalence of malaria in any place is important, as on the variations in this prevalence the test of the success or otherwise of anti-malarial measures must be judged, and the justification for the cost of the works and the advisability of European occupation determined.

There are few diseases which affect the working strength of labour gangs so much as malaria. Attacks of the disease in persons once infected are frequent, debility results, and much sick leave is required, so much so that a double staff of Europeans has to be provided. The mortality is high, though relatively not so high as the morbidity. Amongst natives, the infantile mortality is very high in any place where malaria is prevalent.

The usual term used to indicate the prevalence of malaria is endemic index. No satisfactory single word has been devised. The determination of the endemic index may be made in many ways:—

(A) Determination of the proportion of the inhabitants infected with the parasites.

This requires the division into age groups, as in malaria immunity is slowly acquired by repeated attacks. Examination of the blood of adults, therefore, in a
very badly malarial place would show no parasites, i.e., if examination were confined to adults the endemic index would appear to be nil.

Examination of the children who have, when born, no immunity will show a higher index. In a very badly malarial place some children in the first six months of life will be found to be infected; in the second six months the proportion with parasites rapidly rises, and in the second to fourth years the great majority, over 80 per cent., may show evidences on blood examination of malarial infection. After the fifth year the proportion showing such evidences rapidly diminishes, so that

![Diagram](image)

**FIG. 25.** ——Negroes (native Africans).—Hausa and Yomba Children, 320; Hausa Adults, 100. Compiled from Official Report, Lagos, of W. H. G. H. Best.

in a very malarial place the majority may acquire immunity by the sixth year or even earlier, and practically all before the tenth year. In a less malarial place the proportion free from evidence of malaria in the first five years of life will be higher, and in the second five years lower, and in places where the amount of malaria is not great, or where infection does not occur during part of the year, as in temperate climates, a large proportion of the population may never acquire immunity.

A common method for determining the endemic index
is to determine the proportion of children aged 10 years or less in whose blood evidence of malaria is found. This age is rather high, and the results differ if a large proportion are over or under 5 years of age. In the same country the results would therefore appear to vary greatly according to the ages of the children examined (fig. 25).

The best method would be to determine the age at which the largest proportion of children are found to be infected. Thus, if the largest proportion of infected children were under 2 years old, it would indicate a higher endemic index than if the maximum proportion was at 5, and still more if the maximum was in children aged 10. A low rate in persons over 10 years of age in a place where malaria is known to occur suggests a high endemic index.

(B) Prevalence of enlarged spleen. This test has fallen undeservedly into disuse on account of the manner in which it was at one time abused in India by the laity as well as by medical men. With limitations it is of considerable value. The limitations are: (1) That other
diseases, such as kala-azar, trypanosomiasis, &c., are also causes of enlargement of the spleen, and that therefore where these diseases are prevalent the value of the test is greatly reduced; and (2) that the examinations should be limited to children, as in adults of many races, Indians, &c., chronic enlargement of the spleen, whether as a result of early infection of malaria or not, persists throughout adult life, and may even increase.

With negro races the results obtained by the spleen test are of high value. With other races only the examinations made of children up to 15 are valuable (fig. 26). The advantages of the method of spleen examination are that: (1) There is less opposition to palpation of the abdomen in children than to blood examination; (2) that the examinations can be made more quickly than the examination of blood for parasites, and far more quickly than differential leucocyte counts; (3) that with little training moderately reliable results may be obtained by trustworthy men with no medical education; (4) that the condition of the spleen does not vary so rapidly as the number of parasites in the blood. Thus a spell of cold or wet weather will often result in an increase in the proportion of persons in whose blood the parasites are sufficiently numerous to be readily found, whilst the probabilities of a new infection are not affected by such meteorological changes. The size of the spleen is affected by such changes to a very slight extent.

(C) The period of residence or exposure required in the average European or other susceptible person before an attack of malaria develops is a very fair measure of the endemic index. Most Europeans are able to give fairly definitely the period that elapsed between their arrival in the country and the onset of their first attack of fever. The first attack of fever is usually a marked one, and comparatively few errors in diagnosis are made with this attack in a malarious country. The shorter the period of average residence required, the higher the endemic index.
The period mentioned includes the period of incubation, usually ten to fourteen days. The first attack of fever is usually a severe one, but it must be remembered that many Europeans are inclined in a malarial country to call any illness from which they suffer "fever." This reduces to a small extent the value of the method.

(D) The proportion of bodies showing past or present evidence of malaria in the shape of malarial pigment deposits is only of value in places where post-mortem examinations can be made (fig. 27).

![Graph showing percentage of bodies showing past or present evidence of malaria](image)

**Fig. 27.**—Negroes (native Africans), compiled from post-mortem examinations in British Guiana, 1893-1895. The line commences at one month, no pigmentation being found earlier. The next point is "under six months."

(E) The number of anophelines, especially of those belonging to species known to carry malaria, is of great importance. A large number indicates the possibility of a high endemic index in the place, if sufficient opportunities for the infection of these mosquitoes exist. If the proportion of the anophelines found to be infected is large it indicates a high endemic index; but the absence of infected mosquitoes, even when a large number are examined, especially of the mosquitoes caught in European houses, is quite compatible with a high endemic index. In fact this test is a better
indication of the present danger in a certain house than of a high malarial index in a village or country. It also applies only to the time at which the examination was made, for if susceptible mosquitoes are present in abundance the introduction of one or two persons in whose blood gametocytes are present may lead to the infection of a large number of anophelines and transform a place from one with a low to one with a high endemic index.

Much careful work is yet required to ensure uniform results in carrying out prophylactic measures cheaply. Enquiries must include (1) the determination of the dangerous and harmless species of anophelines present; (2) their breeding-places; (3) the endemic index of malaria as determined by various methods, and with a sufficient number of observations to diminish the mean probability of statistical error.

Ross uses a modification of Poisson's formula by Professor Karl Pearson, and illustrates the use by determination of the percentage error in the application of the spleen test in a village as follows:—

Let $N$ be the total number of children, $n$ the number examined, and $x$ the number with enlarged spleens. \( \frac{x}{n} \times 100 \) will be the percentage proportion with enlarged spleens of those examined = the spleen rate.

We cannot conclude that the same rate will hold for the entire number $N$. Let $e$ denote the probable percentage error:—

\[
e\% = \frac{200}{n} \sqrt{\frac{2 \times (n-x)}{n}} \sqrt{1 - \frac{n-1}{N-1}}
\]

In the instance Ross gives ("Report on the Prevention of Malaria in Mauritius") 200 out of 800 children in a village were examined, and the probable error was \( \pm 8.65 \), so that, as regards merely the statistical error, the rate, if half the children examined were found to have enlarged spleens, would be for the whole infantile population between 58.65 and 41.35, i.e., 50 \( \pm 8.65 \).
For a full discussion of the problems involved the reader is advised to consult "The Prevention of Malaria," by Sir Ronald Ross, published by John Murray, Albermarle Street, W., 1911.

NOTABLE DATES.

CHAPTER VII.
BLACKWATER FEVER.

THROUGHOUT Tropical Africa, hæmoglobinuric fever, or blackwater fever, is one of the most important of the diseases met with and an important cause of the excessive mortality amongst Europeans. In the numerous enquiries made into the causation of this disease by various observers the possibility of the active causal agent being a piroplasma, or other specific organism, has been fully considered. No piroplasmata have been found, and as competent observers have made the examinations, if it is due to such a parasite it must be to one so small that it has escaped detection. Various observers have found other organisms, but in most instances the bodies described are not admitted to be specific organisms. The distribution of the African Ixodidæ does not support the hypothesis that it is a disease carried by ticks, as it probably would be if it were a piroplasmosis.

Blackwater Fever (Endemic Hæmoglobinuria).—This disease is essentially an acute hæmolysis, usually of short duration, terminating in recovery, unless complications, such as suppression of urine, occur. Death also occurs from the intensity of the anæmia induced, and more rarely from hyperpyrexia. The causation is not definitely known.

Geographical Distribution.—It is a common disease throughout the whole of tropical Africa and occurs in subtropical South Africa. It occurs frequently in Assam and some of the Indian terais; isolated cases occur in South America, and it is common in Panama; in Malay it is now fairly common, and in the islands in the Indian
Ocean and the Solomon Islands. In these places it is more common now than formerly. It also occurs in Cyprus, and outbreaks, sometimes called epidemics, have occurred in Greece, Sardinia, &c.

The main types are: (1) slight or ambulant cases; (2) severe attacks; (3) relapsing forms in which the attacks, whether mild or severe, recur with a short interval—intermittent form—or without any interval, where the urine is free from hæmoglobin—remittent form.

The clinical course of the severe simple type of the disease varies, but the course can be conveniently divided into five stages:

(1) Prodromal stage, usually febrile.
(2) Onset of more characteristic symptoms—hæmoglobinuria and jaundice.
(3) Continuance and disappearance of the hæmoglobinuria.
(4) Secondary pyrexia.
(5) Convalescence.

(1) The prodromal stage is usually taken for an ordinary attack of malaria, and in cases where blood examination has been made in this stage malaria parasites—subtertian in most instances—have been found. The fever need not be severe, in fact the patient is often able to travel and walk about, and is rarely so ill as to be rigidly confined to bed. Sometimes yawning, pallor, and pains in the limbs precede the attack. Occasionally, but very rarely, no symptoms at all are observed, and the prodromal stage may then appear to be absent.

(2) The actual onset appears to be sudden and is frequently marked by a severe rigor and high temperature, and pain usually in the region of the liver, but sometimes in the loins. This pain may be very severe, or may be little more than discomfort; in the majority of instances it is transient. The patient is seized with an urgent desire to micturate, and finds his urine to be of a deep black colour, but when shaken up in a bottle the
froth is pink, and the spectroscope shows the hæmoglobin bands. Sometimes it is of a deep brown, methæmoglobin in that case, and not hæmoglobin, being passed.

The urine when passed is a valuable guide to the duration of the acute disease. If methæmoglobin alone is passed the attack is only slight, but may be followed by a more serious relapse. If much dilution is required to render the urine transparent, a severe attack may be anticipated.

An examination of the second urine passed should be made. If the first only be examined, confusion might occur, as this is diluted by the urine that had previously accumulated in the bladder. From the examination of this second urine a fair estimate of the duration of the hæmoglobinuric period can usually be made.

(3) After the onset of the hæmoglobinuria urine is secreted in much larger quantities than is normal, and if abundant water be supplied either by the mouth, if there be little or no vomiting, or by the rectum or subcutaneously, the rate of secretion continues high as long as the hæmoglobinuria lasts.

The frequency of micturition at first is only increased in proportion to the amount of urine secreted, the bladder being emptied only when distended, but later the urine is passed more frequently, and in small quantities only at times, as the urine appears to act as an irritant to the bladder. Occasionally there is marked irritability of the bladder and penis, and in rare cases retention of urine.

Jaundice, or rather a yellow staining of the skin and conjunctivæ, rapidly develops, and increases during the continuance of the hæmoglobinuria. There is no bile in the urine, and the stools are very dark, so that the jaundice is not obstructive, and is probably hæmatogenous. There is a marked increase in the amount of urobilin in the faeces. This indicates that the products of the blood destruction are discharged by the rectum as well as with the urine. Constipation is usual, but is
easily relieved by enemata if necessary. These must be used with great caution, and purgatives, in the opinion of the writer, should not be given during this stage. Some authorities advocate free purgation with calomel or other drastic purgatives.

The temperature remains high, and there may be hyperpyrexia, but it falls as the hæmoglobinuria diminishes. There may be only the initial rigor, but frequently there is more than one, and sometimes there are several each day. There is always nausea, and frequently vomiting. This may be so severe that the smallest amounts of food or fluid are returned as soon as they are taken. Very rarely there is hæmatemesis; commonly there may be streaks of blood if the vomiting be violent (figs. 28 and 29).

Hiccough is common, and may be so incessant that it becomes a source of danger from the exhaustion induced. The prognosis is unfavourable if there is much hiccough. When only occasional it has no prognostic value. There is usually no pain after the onset, not even headache, but sometimes there is aching pain in the loins, and the abdominal or hepatic pain present at the onset already mentioned may recur and become continuous.

The rapid development of extreme anæmia is most important. The red blood corpuscles in the course of three days may be reduced to 1,000,000, or even less, per cubic millimetre. The remaining blood corpuscles may be much changed, many being mere shadows devoid of hæmoglobin, or appear fairly normal and above the average tonicity. Associated with this anæmia is extreme debility, and violent palpitations on the slightest exertion. Death from syncope may occur during attempts at defæcation or even micturition.

The duration of this stage of hæmoglobinuria varies greatly; it may last only two or three hours, but usually, in a moderately severe case, from two to three days. If it lasts more than two days the prognosis is very grave, unless the prolongation is due to the occurrence of relapses. A series of relapses, in each of which the
haemolysis is slight, and in which the urine clears, or nearly clears, every twenty-four hours or less, may extend over a week or more without such profound anaemia as occurs in a continuous three-day attack (fig. 30).

Fig. 28.—Blackwater Fever, mild attack: haemoglobinuria less than twenty-four hours.

Fig. 29.—Blackwater Fever, severe attack; haemoglobinuria, two and a-half days.

There is usually much mental anxiety, partly on account of the reputation of the disease, but still more because of the large amount of blood-like urine that is being passed. The mental faculties are quite clear, and beyond the debility there is little actual distress. The amount of haemoglobin passed steadily diminishes, though still sufficient to render the urine opaque. The
Fig. 30.—Relapsing Case of Blackwater Fever. After Wakelin Barratt and Warrington Yorke (modified).
last urine passed in this stage often contains no oxyhaemoglobin, but methaemoglobin only, the urine changing from a red-black to a dark brown colour. As the urine clears the temperature falls to normal or subnormal. Profuse sweating may occur several times in one day. The change from the haemoglobinuric period to the non-haemoglobinuric is less abrupt than would be judged by mere superficial examination of the urine. The haemolytic process has ceased, and the waste products are being rapidly eliminated. As the haemoglobin disappears the diuresis diminishes, so that even when abundant fluid is supplied the rate of secretion of urine may fall to much below normal. This is probably merely the result of the over-stimulation of the renal cells, so that secretion becomes slow. If any urine at all is passed, a fall in the rate of secretion to less than half the normal is to be expected and should cause no alarm, though fluid must still be supplied freely.

The rate of secretion in a favourable case soon increases. The urine is clear and of normal colour, but contains a small amount of albumin and some casts. The patient remains in an extremely weak condition, and the anaemia may show a slight increase, though the appearance of the blood corpuscles is more natural. The temperature may remain normal or commence to rise. After a day or two the temperature rises, usually above normal, and for several days there may be irregular pyrexia, secondary fever. This varies a great deal in severity. In some cases it is very slight, the temperature rising in the evening to 100° F. or even less (figs. 28 and 29). More frequently the nocturnal rises are to 101° and 102° F., the temperature falling nearly to normal in the morning. In other cases it is much more severe, and occasionally there is fatal hyperpyrexia in this stage without any recurrence of haemoglobinuria. The usual duration of this stage is three to four days, and it may be protracted to two or three weeks. The urine in this stage remains free from haemoglobin and usually from albumin. No
further blood destruction is taking place, and the red corpuscles and haemoglobin are rapidly increasing at a rate sometimes of 400,000 or 500,000 corpuscles per c.mm. per week. Sometimes the pyrexia is due to malaria, as proved by the examination of the blood.

This secondary fever is probably associated with the metabolic changes due to the absorption and assimilation of some of the waste products of the haemolysis, which have been stored up in various organs. The icterus rapidly disappears, the urine remains clear and pale though casts will be present. After this secondary fever has subsided, convalescence is rapid and usually uninterrupted. It is exceptional for anyone who has had blackwater fever to have any malaria attacks for a prolonged period; probably the corpuscles containing parasites are amongst the first to be destroyed, and so a "cure" of the malaria results. Sometimes, as in a few cases in England, an attack of malaria may occur shortly after the blackwater fever, though a new infection has not occurred. In these cases, in England, where malaria occurs during convalescence, the parasites are usually those of benign tertian malaria, less commonly of subtertian fever. There are few sequelae, but the debility and anaemia persist to some extent for several weeks, and fatal cardiac failure has occurred during convalescence.

If fluid is not freely supplied the history is very different. The urine, while still loaded with haemoglobin, diminishes in amount, and vomiting becomes incessant. The amount of urine continues to diminish so that only an ounce or less is passed per diem. This urine may become free from haemoglobin and even from albumin, the temperature becomes normal, the anaemia diminishes, but unless the flow of urine is rapidly restored death is certain. This usually occurs in four or five days, or less, but life may be protracted up to ten days. There is no delirium, no convulsions, the mind is clear, and beyond headache, which is not necessarily severe, there are none of the ordinary symptoms
associated with renal disease or uræmia; vomiting is persistent. In rare cases, although the urine clears and is even abundant, the patient does not improve. In these the urine is of low specific gravity, 1,001 or 1,002, and with the exception of the water the kidneys are practically not excreting. These cases are fatal, and there will be found extensive blocking of the tubules. The condition more closely resembles that due to blockage of the ureters.

This is the commonest cause of death, and if it can be avoided the mortality from blackwater fever is low.

**Diagnosis.**—The diagnosis is made on the character of the urine. This is dark red, practically black. If diluted the red colour appears and the urine is clear and transparent. On shaking the urine the froth that forms on the surface is red. If allowed to stand a thick deposit soon forms, but this is not present in abundance when the urine has been recently passed. The deposit in the quite fresh urine is scanty. Casts are easily found, and later in the course of the disease are even more abundant; some may still be found weeks after the urine is free from albumin. These casts are usually granular and contain bright yellow granules, not uric acid, similar to those found in the organs; blood cells are rarely found; bladder epithelium may be moderately abundant after the first day. When the urine is kept much deposit is formed; this is composed usually of casts, coagulum and altered hæmoglobin.

The urine in paroxysmal hæmoglobinuria is similar, and that disease would certainly be diagnosed as blackwater fever if a case occurred in a blackwater district.

If methaemoglobin only be passed the difficulty in diagnosis is much greater, as the brown urine is not very unlike some high coloured normal urine, and may be mistaken for bile-stained urine; fortunately the cases where this occurs early are mild. In all cases if the urine be boiled the albumin coagulated will be a dark brown colour.
The best test to apply is the spectroscopic one, the urine being first diluted with water to render it transparent; both the haemoglobin and methaemoglobin can be recognized at once and with certainty by the use of any of the simplest and cheapest direct vision spectrosopes. The addition of ammonia in cases of methaemoglobinuria will cause the colour to change so that it becomes red, something like the colour of haemoglobin. (Spectra 4 and 5, fig. 31).

The absence or great rarity of blood corpuscles readily distinguishes this disease from any of the forms of haematuria. Without microscopic examination the transparency of the diluted urine in blackwater fever distinguishes it from the smoky opalescent urine of haematuria cases.

Prognosis.—If suppression of urine is averted the prognosis is good. Constant vomiting and hiccup are of unfavourable import, and great care has to be exercised in order to prevent syncope or cardiac failure.

Recurrences of the haemoglobinuric attacks sometimes occur at short intervals, sometimes only of a few hours, and in others they follow each other so closely that the urine is never quite clear. Such a relapse may take place within twenty-four hours of a serious attack, or be delayed for three or four days; it is rare after longer periods, though the interval may be one or two weeks. As each attack runs its own course, a fatal degree of anaemia may be induced, and in each attack there is the same liability to suppression of urine.

Susceptibility.—A person who has once had blackwater fever appears to be specially liable to it, and, if he remains in or returns to a country where the disease exists, will probably have other attacks. These are usually of a similar character to his first attack, so that, if his first attack was a mild one, subsequent attacks will probably be of the same nature. Cases are known of twelve, or even more, such attacks in one person. If, however, the first attack is severe, so will subsequent attacks be, and few persons will survive the third or fourth attack.
Fig. 31.—1, Oxyhaemoglobin; 2, reduced haemoglobin; 3, CO. haemoglobin; 4, methaemoglobin; 5, methaemoglobin (after addition of alkali); 6, alkaline haematin; 7, acid haematin (etherial solution); 8, haematozporphyrin (acid); 9, haematozporphyrin (alkaline); 10, bilirubin.
Pathological Anatomy.—No specific organism has been discovered. Malarial parasites are present when the blood is examined before the onset of the disease; they disappear in these cases very shortly after the onset of the haemoglobinuria. In the great majority of cases of blackwater fever, those examined only after the onset of the disease, no parasites are found.

In fatal cases, on microscopical examination of the liver and spleen, finely divided intracellular black pigment will be found as in recent malaria. Frequently it is not abundant enough to be seen on inspection with the naked eye. No parasites are found in the organs, but sometimes pigmented leucocytes are present. The blood examination shows an increase in the large mononuclear elements, such as is found in malaria, but this also occurs in other protozoal diseases. No piroplasmata have been found, and the blood and organs are sterile as regards bacteria. The organs show all the usual evidences of blood destruction. In the hepatic cells, in the convoluted tubules of the kidneys, and in the spleen, are abundant deposits of haemosiderin, and other granules, not pigmented, are present which give the reaction of iron in inorganic combination. This evidence of blood destruction occurs to a less marked extent in some cases of malaria and in other diseases attended with haemolysis; it is marked in the piroplasmosis of cattle. A further evidence of blood destruction is the great increase in the amount of urobilin in the faeces.

The kidneys in all cases show casts in the tubules (figs. 32 and 33). When death has occurred from suppression these casts are very numerous. They usually show evidence of the presence of iron in inorganic combination.

The renal cells, except for the presence of haemosiderin, are singularly little affected. The epithelium is neither detached nor necrotic, but usually shows cloudy swelling and sometimes fatty degeneration. The spleen may be
enlarged or not. The liver, beyond the evidence of haemolysis and a certain amount of cloudy swelling, is normal in appearance and structure. Subserous hæmorrhages and hæmorrhages into either solid or hollow viscera are exceptional. Hepatitis and even hepatic abscess may occur.
Treatment.—No drugs have any specific action. The depth of colour of the urine passed early in the attack enables a fairly accurate estimate of the duration of the

![Diagram of a renal tubule](image)

**Fig. 33.**—Diagrammatic representation of a renal tubule. (A) Normal. (B) Commencing deposit in haemoglobinuria. (C) Sufficient deposit to be washed on and cause obstruction of tubules in the pyramid. (After J. O. Wakelin Barratt and Warrington Yorke.)—(From the "Annals of Tropical Medicine and Hygiene," Liverpool University, by permission.)

haemolysis to be made, and this is not shortened by treatment with quinine or any other drug which may be used. Though we cannot deal with the essential cause, as this is unknown, much may be done to avoid the
main dangers of the disease. The failure to recognize these essential features has caused the adoption of injurious measures from time to time.

The disease is not a haemorrhagic one; it is a haemolytic one. The actual disease occurs in the blood-vessels, and the red corpuscles, once broken up, set free the haemoglobin in the plasma, and there it is injurious and has to be disposed of. The liver and other organs can absorb it in part only, but the capacity of these organs is limited and the greater proportion is discharged with the urine. This discharge must not be checked, but aided by the free supply of water. If considered as haemorrhage it would be natural to attempt to diminish this discharge. The patients themselves notice that they fill chamber-pot after chamber-pot with what looks like almost pure blood, and are anxious that the loss should be diminished, as they fear that they are bleeding to death. The medical attendant requires a firm faith in the soundness of his pathological views, and his action should be to maintain, and if possible increase, the total amount of the bloody urine discharged. The dilution of the urine makes no obvious difference in its appearance, and, from the point of view of the patient and his friends, the measures that should be taken will only increase the loss.

Free administration of water is necessary to maintain this flow, otherwise there is danger of such extensive blocking of the renal tubules that suppression will occur; the coagula and débris formed in the convoluted tubules may remain there, but usually are carried along and block the tubules in the pyramids, so that extensive areas of the kidneys are unable to discharge their secretion. This process commences with the onset of haemoglobinuria, and probably always, even in the mild cases, some of the tubules in the pyramids are blocked. It is essential that the treatment, by encouraging the flow of urine by a free supply of water, should start as soon as the disease occurs. The drugs used have belonged to many classes. Haemostatics, such as ergotin, have been extensively used, but
can have no good effect. Water has been withheld in order to stop the loss, and this practice is responsible for much of the mortality. Stimulating diuretics, such as turpentine, have been employed, but the haemoglobin in itself acts as so powerful a diuretic that it is unnecessary to employ any additional one. Large doses of calomel are recommended by some authorities on the assumption that the disease is in some way due to some toxin absorbed from the bowel. This method of treatment is not recommended. Quinine should not be given unless parasites of malaria are found, and even then must be given very cautiously. Quinine in large doses usually has no effect at all. Patients may recover whilst taking 60 gr. a day, but it does not shorten the duration of the disease. In these doses it may increase the tendency to vomiting, and as in some cases it actually causes further haemoglobinuria it should not be given.

Good results are claimed for the frequent administration of boracic acid in solution, and of carbonate of soda in moderate doses, with perchloride of mercury in minute doses frequently repeated. They all have the advantage of increasing the amount of fluid taken by the patient, and the mixture of perchloride of mercury and carbonate of soda, given as in yellow fever, seems to check the vomiting and also acts in the late stages as a bland diuretic. This treatment has been practised by Hearsey with excellent results.

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| Carbonate of soda      | 5 gr.
| Perchloride of mercury | 1/60 gr.
| Water                  | 2 oz.
| This dose should be given every hour till the urine clears.

The most uniformly successful treatment consists in giving frequent rectal enemata, 6 to 8 oz. at a time, of normal saline solution; water alone is not retained. These must be repeated every hour, or every half-hour, according to the severity of the case, till the haemoglobinuria ceases. The injection of large quantities of sterilized normal saline into loose cellular spaces such
as the axilla is preferred by some. This cannot be repeated so often as the rectal injections, but must be employed in cases where there are both vomiting and rectal irritability. The great point is to commence the treatment early. If this is done from the onset, fluid by the mouth only will suffice, as the vomiting is to a great extent due to the renal obstruction, and if the latter can be prevented, or only a few tubules are blocked, the vomiting can be controlled.

If suppression has set in, recovery does not take place, but there is just the possibility that the free supply of fluids may enable a sufficient flushing to take place to dislodge some of the casts and so restore the functional activity of a part of the kidneys. In some cases where a free discharge of urine of very low specific gravity is induced there is no improvement in the condition. Alcoholic stimulants are required in all severe cases, but their use should not be commenced too early; strychnine also should be given.

The patient is usually constipated; but active purga-
tion is probably injurious, as it diverts into the intestine the fluid that we wish to pass through the kidneys.

During convalescence good, easily digested food must be given. The digestive powers are usually good. The bowels should be kept freely open with salines.

Iron and arsenic may be taken with benefit in the later stages, but there is no advantage in giving them early, as all the actively metabolic organs are at that time overloaded with iron.

For the secondary fever free purgation seems to be the most effective. Quinine has no beneficial action and may provoke a relapse. Phenacetin and other anti-pyretics are to be avoided; their action is temporary and the danger of cardiac failure is great. In hyperpyrexia during this stage hot packs, cold packs, or cold baths may be resorted to, but the prognosis is most unfavourable.

Relapses must be treated in the same way as the primary attack.
In the exceptional cases where an attack of malaria follows blackwater fever, quinine should be given in small but gradually increasing doses, commencing with $\frac{1}{2}$ gr. doses.

**Nursing.**—During the first day of the illness the main precaution to be taken is to administer fluid frequently, so that a considerable quantity, at least equal to that of the urine passed, is taken. Ten ounces every hour by the mouth, or 5 to 6 oz. *per rectum* every hour are usually sufficient. As there is always a tendency to vomiting, water must be given in small quantities, 1 to 2 oz. at a time. Though there is thirst, the amount of water that must be taken is in excess of that which the patient desires. The urine should be measured after each act of micturition, as it is of the utmost importance to obtain information as to any diminution in the rate of secretion. As nearly as possible secretion at the rate of at least 4 oz. every hour is the result desired. Any drop to a lower rate than this calls for rectal or subcutaneous administration of fluid or of both. Tepid sponging after the perspirations is required, and great care must be taken to avoid a chill.

This treatment must be continued throughout the attack, but after the first day, though the muscular strength may be considerable, the patient must not be allowed to leave his bed or even raise himself in it without assistance. Any necessary movement must be made very slowly. These precautions become more and more necessary, not only whilst the blackwater persists, but for several days after. The vomiting must be checked; if not restrained by sinapisms or hot applications to the epigastrium, hypodermic injections of morphia should be administered and all fluid given in teaspoonfuls if necessary. Painting the skin over the course of the pneumogastric nerves in the neck with blistering fluid sometimes succeeds when other methods have failed.

Patients must never be worried to pass urine; they all
know the danger of suppression, and any concern shown by the attendant as to this will still further increase their anxiety. The danger is suppression, and if no urine is in the bladder it can do no good for the patient to attempt to micturate. Retention does occur occasionally, so that if there is undue delay in micturition the abdomen above the pubes should be examined to make sure that the bladder is not distended.

If the vomiting cannot be checked, or sufficient water cannot be administered by the mouth, rectal injections of normal saline solution, 0.87 per cent., should be given hourly.

As the frequent administration of such enemata leads to an irritable condition of the rectum, great care is required. The enemata should be given very slowly and should be at blood heat.

The blankets and clothing must be replaced by warm, dry clothing as often as is required. If the tendency to syncope becomes marked, the lower end of the bed must be raised, hot-water bottles applied to the axilla, and the legs bandaged from the feet upwards, and stimulants given freely by the mouth, rectum, or by hypodermic injections. Transfusion into the veins has not been successful.

Hyperpyrexia may occur either whilst haemoglobinuria is present or afterwards during the secondary fever. The temperature should be taken frequently, hourly, or even half-hourly, when it is above 103° F. The hyperpyrexia after the urine has cleared is the more dangerous.

When the patient is so situated that there is no skilled nursing available, the danger is greatly increased. Attention to the general principles will be of service, and if the patient has to leave the bed his movements must be as slow as possible and the head held low. He must crawl, not walk, and never hold himself upright under any circumstances. Any expressions of despondency must be discouraged. It is useless to attempt to minimize the danger, but the patient's courage must be sustained as much as possible.
Under these circumstances the advisability of removing the patient to a place where he can receive skilled care has often to be considered. If moved at all, he should be moved early, in the first day of the disease. Later the risk of collapse is enormously increased by any journey, and after the first day should not be undertaken. Even on the first day, the risks, on the whole, of moving the patient are at least as great as the advantages resulting from the more careful attention would be.

If moved, the patient must be carried in a recumbent position. A hammock is as good a method as any. He must be well wrapped up and receive water frequently whilst on the road, and food in addition if the journey be a long one.

Food must be fluid and nutritious: it is well digested.

During convalescence great care must still be exercised both to prevent chill and exposure, for fear of relapses, and to avoid over-exertion or anything that may throw any strain on the heart, as fatal syncope may occur during this period.

Constipation during the early stages is not of importance, and should not be relieved till the urine is clear; later the bowels must be kept open, preferably by mild saline aperients.

Etiology.—The true cause of blackwater fever is unknown. It occurs in both sexes, but is not known in early childhood. It does occur in negroes, but not in the native negroes in an area where the disease is endemic. In proportion to their numbers it is more common amongst Europeans than amongst Asiatics. In Europeans it rarely occurs during the first six months of residence in an endemic area, but after that period becomes more common, and is most common in the second and third year of residence. In Panama the incidence appears to be rather different, as the number of cases in the first two years of residence is nearly equal, and in the first three months the incidence is at the same rate as for the first two years. First attacks are very rare
after ten years' residence. A person who has not had blackwater fever in an area in which the disease is endemic may have his first attack after leaving that area, sometimes up to six months or more after leaving it.

Generally speaking, in Africa, it is most prevalent where malaria is most prevalent, and by many persons malaria is considered to be essential for the development of the disease. As the disease is not known in some countries where malaria is prevalent, it has either to be assumed that there is a special variety of the malarial parasite implicated, or that there is some special condition under which this extreme haemolysis takes place. So far all experiments that have resulted in a decrease in the amount of malaria have been associated with a reduction in the number of cases of blackwater fever. This seems to hold whether the reduction is due to attacking the carriers of malaria, anophelines, or to steady administration of quinine.

No morphological differences have been observed in the malarial parasites in a malarious country where blackwater fever is endemic and in malarious countries where it does not occur. The carriers differ in the different countries, and in Africa Myzomyia funesta is the commonest carrier in places where blackwater fever is prevalent.

The special condition that has been considered to be the immediate exciting cause is quinine poisoning. The advocates of this hypothesis contend that in some individuals, after they have been exposed to the endemic influences, the blood is so altered that quinine produces haemolysis. There are cases in which a dose of quinine, even a small one, may bring on an attack of haemoglobinuria; this has been proved in many instances. There are reasons for considering that this, though an occasional cause of blackwater fever, is not an essential or even the common cause. In many countries where large doses of quinine are given, after and during fever, no such effects take place. In analysing the cases in an endemic area there is no close relation, either as
regards dose of quinine or interval between taking quinine and the onset of hæmoglobinuria, as might have been anticipated if the quinine acted as the determining cause. In a few instances quinine has not been taken. In many the dose taken is no larger than, or not as large as, the person was in the habit of taking, and after the onset of hæmoglobinuria further administration even of large doses of quinine does not, usually, cause fresh hæmolysis. In cases in England the usual history is that whilst in Africa regular prophylactic doses of quinine were taken, in England the patients either discontinued the drug or took it irregularly, or only when they felt seedy or had fever. Irregularity in the use of quinine appears to be the important factor in many cases, and blackwater fever is rare in those who take 5 gr. of a salt of quinine quite regularly. By some the sulphate is believed to be the salt which is most likely to precipitate or induce an attack of blackwater fever, as sulphates cause a decrease in the organic salts in the blood and may upset osmotic equilibrium. But attacks occur in persons who only use the hydrochloride. Exposure to cold and wet seems to often act as the determining cause, but a few of the cases occur amongst persons who have no chance of such exposure.

Various hypotheses have been formulated in the attempt to explain why a disease which appears to be closely connected with malaria is not directly due to the malarial parasite. A want of balance between the production of hæmolysins and antihæmolysins, dependent partly on the parasites and partly on blood changes in the host as a result of the formation of antibodies, appears to be the most promising, or it may be considered as a phenomenon of anaphylaxis.

Sequela. In the majority of cases recovery is complete, and there are no persistent ill-effects beyond a liability to subsequent attacks. Sometimes a malarial attack will occur, but as a rule there is freedom from such attacks. In rare cases there may be persistent
albuminuria. Parotiditis has been known to occur, and hepatic abscess may follow an attack of blackwater fever. Retinal haemorrhages or haemorrhages into the vitreous may lead to impaired vision, but in such cases complete recovery of sight is usual.

Piroplasma.—Piroplasmata have been frequently looked for but never found, as has been already mentioned. There is no relation known between the distribution of any species of tick and blackwater fever, but more work in this direction is required. The distribution of Ornithodorus moubata does not correspond with that of blackwater fever. Leishman has described bodies, which he suggests may be parasites, of the nature of Chlamydozoa in the leucocytes; but it is doubtful if the bodies he describes are not inclusion forms of remnants of broken-down blood-cells, as similar appearances are seen in the blood in cases of other diseases having no connection with blackwater fever.

Prophylaxis.—The close relationship in Africa between the distribution of blackwater fever and of great liability to malarial infection points to the desirability of dealing with the malaria.

Persons in whom quinine produces hæmoglobinuria are unsuited for residence in a malarial country. In such persons it is sometimes possible to treat the malaria with quinine, if small doses of quinine, very gradually increased, are employed. Persons who have never had blackwater fever in Africa are still liable to an attack for some months after their arrival in England. It is therefore advisable that the regular prophylactic use of quinine should be continued, not only on the voyage home, but for two or three months after arrival in England. Such persons must also avoid exposure to chill, over-fatigue, or any depressing influences.

A previous attack of blackwater fever appears to predispose to other attacks. A single severe attack or two milder attacks should be considered as disqualifying that person for residence in an endemic area.
CHAPTER VIII.

PIROPLASMOSIS.

*Piroplasmosis.*—"Malaria" of cattle, horses, dogs, &c. Piroplasmosis is the term sometimes applied to the affection caused by certain sporozoal blood parasites (Plate II, 24-27) which, being commonly pear-shaped, are called piroplasmata. The piroplasmata differ from the hæmamœbæ in that (1) they do not form pigment; (2) division is usually into two, sometimes into four, and the young forms are not immediately set free, but continue to grow in the red corpuscle in which they live. Ultimately they escape from these red corpuscles. It is probable that a large proportion of their nutriment is derived by osmosis from the blood plasma and less from the hæmoglobin than in the hæmamœbe. The free parasites may be found in the plasma, actively motile, before they enter other corpuscles; (3) they are conveyed in all known instances by ticks of various genera. The diseases are transmitted not by the tick that feeds on the infected animal, but by the second and sometimes the third generation of these ticks, as the parasites are transmitted to the eggs and develop in the young ticks.

The piroplasmata in the early stage have no definite vesicular nucleus, though a clear non-stained space or vacuole is present. The chromatin is frequently in two equal or unequal masses, and though it divides to some extent the complete fragmentation and diffusion observed in the malarial parasite does not occur.

Division is more by a process of budding than of breaking up into spores. The pear-shaped body, after escaping from a red corpuscle, enters another and then becomes a rounded amœboid mass. In this stage it does not escape from the red corpuscle. After a time two
processes or buds are formed at the periphery of this rounded body, and these gradually increase in size, the chromatin divides, and half enters each of these buds. The increase in size in the buds is by absorption of the original protoplasmic mass, which is reduced to a mere thread connecting the two bodies, and this finally is absorbed and the two pear-shaped bodies lie free in the red corpuscle. They may remain in the red corpuscle for some time, and when they escape enter in turn other red corpuscles, before they again become amœboid and divide and so repeat the cycle.

Piroplasmata occur in most of the domesticated animals, and cause serious disease, and frequently death, in cattle, sheep, horses and dogs. They have been described in man, but their occurrence is very doubtful.

By some observers Leishman-Donovan bodies, now known to be a resting stage of a flagellate, were considered as piroplasmata. In all the diseases of domesticated animals pyrexia occurs, not showing definite periodicity. A common character is haemoglobinuria, so much so that the popular name of the disease in cattle is "redwater fever," in sheep "heart fever." In dogs the disease they cause is called epidemic jaundice, on account of the hæmatogenous colouring of the conjunctiva from the hæmolysis. Although hæmolysis is a common result of piroplasma infection, haemoglobinuria is by no means always a prominent symptom. Redwater does not occur, for example, in Rhodesian or East Coast cattle fever, and although piroplasmosis is common in cattle throughout the East, yet hæmoglobinuria is rarely met with except in animals suffering from serious intercurrent disease, such as rinderpest, or among those imported from countries where piroplasmata do not occur.

An infection with piroplasma in cattle appears to last during the whole life of the animal, but the clinical evidence of the presence of the parasites disappears, and though the animals harbour the parasites in small numbers they seem to have acquired a degree of toler-
ance that enables them to prevent the multiplication of the parasites and to resist the effects of their presence. Such animals, however, though in good health themselves, are able to infect ticks. The non-recognition of the practically universal infection of native cattle has in several instances led directly to the destruction of imported animals, as in the process of immunizing against rinderpest virulent blood has been injected into newly imported animals, which have then died from "red-water."

**Human Piroplasmosis.**—Several observers have described piroplasmata in human blood; so far, however, without confirmation.

A very fatal form of fever, occurring in the Rocky Mountains and called locally spotted fever, was attributed to the presence of a piroplasma in the blood, and infection was thought to be due to a tick (*Dermocentor reticulatus*). Subsequent observers have failed to find the piroplasma, but confirm the opinion that it is a disease carried by ticks which can be communicated to lower animals. The disease occurs chiefly in the spring and affects white races only; it is more common in persons under than over 40, and in males than females.

The incubation is short, symptoms commencing two to five days after the bite of a tick. The onset is gradual and the general symptoms resemble those of typhus fever, but are more severe, and a rash appears on the second to the fifth day. The rash appears first on the ankles or back, but soon becomes general. It is at first vesicular, but later petechial, jaundice is usual and desquamation occurs in patients who survive.

The mortality is very high, between 70 and 80 per cent. of the patients dying, usually between the sixth and eleventh days. In patients who survive recovery is gradual, and commences about the end of the second week. Quinine is said to be the only drug which does good, and the avoidance of tick-bites is suggested as a preventive.
Post-mortem examination shows a considerable enlargement of the spleen and acute parenchymatous degeneration of other abdominal organs. There is no ulceration of the intestine. By many the disease is believed to be typhus.

The term "human piroplasmosis" has sometimes been applied in India to cases of kala-azar, but it will be seen that this disease is due to a parasite of a different nature.

Piroplasmata have also been described in the blood of a cowherd suffering from fever during the presence of Texas fever amongst cattle in India. This observation also lacks confirmation.

Bodies resembling piroplasmata, but easily distinguishable upon careful examination, have been described by Cropper working in Palestine, and by Smith working in America, as occurring in the blood of persons suffering from severe forms of malaria. The bodies have a rotary but no amœboid movement; their nature is unknown. They do not stain with basic stains. The edges, probably the edges of the hæmoglobin, are sometimes stained irregularly. Similar bodies have been found by Nuttall in the blood of dogs. They are probably not parasites.
CHAPTER IX.

YELLOW FEVER.

The parasitology of this disease is unknown. It is in no way connected with malaria, but as it has been proved to be carried by a mosquito, *Stegomyia fasciata* (*S. calopus*), and as there is further proof that time has to elapse after the infection of the mosquito before it in turn becomes infective, development must take place in the mosquito. On these grounds the disease is here included with the probably protozoal diseases.

Yellow Fever in its severer form is characterized by fever, intense headache, jaundice, and albuminuria increasing steadily in amount; by tendency to haemorrhages from mucous and sometimes from cutaneous surfaces, and by haematemesis—"black vomit." In fatal cases there is frequently suppression of the urine. In the milder form there is fever for two or three days, gastric disturbance, and epigastric pain.

It is conveyed from man to man by mosquitoes belonging to the genus *Stegomyia*.

Geographical Distribution.—It is best known as a disease of the New World, and occurs endemically, or as epidemics, in the West Indies and along the Atlantic coast from New York down to Rio de Janeiro. It was at one time common in the West Coast of Africa, and recent outbreaks have occurred. In South Europe, on the Atlantic coast, it is an imported disease, and on board ship. It has spread to a small extent even in English ports in the vicinity of infected ships, during summer months.

It is usually limited to the larger settlements on the coast in the Tropics. Ship epidemics were common in the past, but are now rare.
Clinical Course: Severer Type.—The onset of the disease is sudden, but not invariably with a rigor. The temperature rises rapidly, there is violent headache, most intense over the frontal region. The eyes are much injected and often described as ferrety. Jaundice soon appears, but not as early as in blackwater fever; the conjunctiva and skin are at first lemon-coloured, but soon deepen to a bright yellow colour. Vomiting is a prominent symptom; at first, merely of food, then watery, then “acid vomit,” and later almost black—“black vomit.”

The act of emesis is performed with little or no effort, and the amount ejected is surprising. The vomit seems rather to gush out than to be forcibly expressed. There is a feeling of marked and decided relief after each evacuation of the stomach.

Epigastric pain and tenderness occur early and are intensified by pressure. There is usually an intensely acid or bitter taste in the mouth.

The course of the disease is best considered divided into three stages as described by Blair. During the first stage the temperature is high and the pulse quick and bounding. The headache and epigastric pains are severe, and the vomit is free from blood till towards the close of this period. The urine contains albumin about the second day, and the jaundice appears and progressively deepens. The duration of this stage is from three to four days.

The passage into the second stage is rapid, though not exactly by crisis. The temperature falls to normal or subnormal, the pulse-rate is much reduced, and the rate may be 40 or even less per minute, the restlessness, pain, and delirium disappear, and the patient feels much relieved, and often quite well. The general appearance of well-being in the second stage is deceptive, and death may occur in such a patient, and he, even while he is sinking, may feel quite well.

In some cases—the mild ones (yellow fever simplex)—this remission is the end of the disease and the patient steadily continues to improve, and passes into the stage of convalescence without secondary fever (fig. 34).
These very mild cases may form the greater number in an outbreak, and unless severe cases are also found the epidemic may be overlooked. The mild cases by themselves are very difficult to diagnose, but they are of special importance as they are the "reservoirs" of the disease; and from them the mosquitoes derive their infection and may spread it either in the mild or severe form. These mild cases are believed by some to be the usual type in coloured persons and in young children, and in these there may be no single symptom diagnostic of the disease.

![Graph of temperature changes](image)

**Fig. 34.**

In other cases, after a short apyrexial period or period with a moderate temperature, the temperature again rises (fig. 35)—secondary fever—but the pulse-rate remains low, the vomiting recurs, and the vomit if not previously mixed with blood is so now (yellow fever gravior). The urine becomes more and more loaded with albumin, and diminished in amount, and the distressing symptoms again recur. This is the most dangerous stage and may last for about a week or more. In cases progressing favourably the symptoms gradually subside, the temperature gradually falls and the amount of urine
increases whilst the albumin decreases and convalescence is established.

**Diagnosis.**—The diagnosis of an epidemic of yellow fever is not difficult. If severe or fatal cases occur the fever, severe headache, increasing albuminuria and jaundice, with the occurrence in a proportion of the cases of "black vomit," render the diagnosis certain. In fatal cases, even when there has been no black vomit, at the autopsy, the contents of the stomach and duodenum will be black from effused blood.

![Fig. 35.—Yellow Fever. Severe attack.](image)

The limitation of the disease to certain quarters, or even streets of a town, and the dependence of one case on preceding cases are all aids in this diagnosis. The diagnosis of isolated cases is more difficult. Acute yellow atrophy of the liver may closely simulate the severe forms of the disease and malaria with jaundice, and Weil's disease have each many points of resemblance.

There are certain points of resemblance between yellow fever and blackwater fever that have in the past led to a confusion between the two diseases, so much so that both have been considered to be manifestations of malaria, and are still often mistaken for "bilious remittent fever" with jaundice.

The points of similarity are the jaundice, liability to
suppression of urine, and vomiting; the temperature charts are not unlike in the two diseases, as in both there is a remission in the pyrexia between the primary and secondary fever. Clinically there are important differences. Hæmatemesis may occur, but is very rare in blackwater fever, and common in yellow fever. Hæmoglobinuria or methæmoglobinuria is invariable in blackwater fever and very rare in yellow fever, though there may be hæmaturia. In neither disease are malarial parasites found in the blood, during the attack, and in yellow fever the increase in the relative number of the large mononuclear leucocytes is not found. The intense headache in the early stages of yellow fever is not present in blackwater fever, and the repeated rigors so common in blackwater fever are usually absent in yellow fever. Icterus appears later in yellow fever than in blackwater fever, and it is only in yellow fever that the pulse-rate does not increase as the temperature rises.

Treatment.—A preliminary purge seems to be of great importance, and calomel is frequently used for this purpose. Many drugs have been employed, and a treatment for which great success was claimed, by Blair, was by large doses of calomel and quinine, 20 gr. of each being given. All later work shows that quinine has no effect on the disease.

Carbolic acid, in drop doses every hour, and other intestinal antiseptics have also enjoyed a great reputation. There does not appear to be any drug with a specific action. The present treatment is that introduced by Sternberg, well diluted bichloride of mercury and carbonate of soda being given frequently in small doses. It is on this treatment that Hearsey's treatment of blackwater fever is founded. Some hold that any administration of food by the mouth in the early stages of the disease is injurious and may lead to the conversion of an attack of the mild type into one of the more severe. When suppression of urine threatens, rectal injections of salt and water or injections of fluid into the subcutaneous areolar tissues are indicated as in blackwater fever.
Nursing.—Careful nursing is of great importance. The room must be kept very quiet and dark, as there is great intolerance of light. Vomiting must be checked if possible, and opium is contra-indicated. All food, drinks, and medicines must be given in small quantities at a time, and well iced.

Ice-bags or cold compresses to the abdomen give more relief in most cases than hot applications.

Protection from the bites of mosquitoes must be very carefully attended to in order to prevent the spread of the disease and the infection of the mosquitoes, and through them of the occupants of the house. This is of the greatest importance during the first stage of the disease. The danger is present both day and night, as the freshly emerged mosquitoes feed both during the day and night. Mosquitoes which have once fed become feeders at night only. The bed must be always screened off in a mosquito net sufficiently large for the attendant also to be inside it, and any mosquitoes that obtain entrance to the net must be caught and killed, as otherwise they may become infective in ten days. The netting must not be too coarse, as the S. fasciata can pass through a mesh of 15 to the square inch. All the evidence is opposed to the belief that any discharges from the patient are infective.

Mosquito larvae in the room should be destroyed, and no breeding-places—flower-vases, water-jugs, &c.—allowed to remain in the room.

Pathology and Morbid Anatomy.—The organism that causes yellow fever has not been isolated. It is present in the blood of the patient during the first three days of the disease, and is so minute that blood serum of such a patient retains its infectivity after passage through a Berkefeld filter. This serum if injected into a non-immune subject will cause an attack of the disease, not merely a toxæmia, as the blood of this person is infective, showing that he also harbours the parasite. The morbid changes due to the action of this unknown organism
result in liability to hæmorrhages, congestion of viscera, and extreme fatty degeneration of the cells in the liver, kidneys and elsewhere. The fatty degeneration in the liver is most marked at the periphery of the lobules. The changes somewhat resemble those in phosphorus poisoning and are less like those in acute yellow atrophy. This fatty degeneration is so marked that the liver and kidneys are pale yellow in colour, almost like boxwood, and extremely friable. The tubules of the kidneys may become blocked as the epithelium is detached and there is a coagulable exudate. Suppression is from mechanical obstruction of the tubules by this epithelium and exudate. There will be no malarial pigment unless there have been previous attacks of malaria. The stomach is always congested, submucous hæmorrhages are common, and the contents of the stomach and alimentary canal are black and tarry, even when there has been no black vomit. Subserous hæmorrhages are always present, and the serous membranes are stained with bile.

All attempts at isolating an organism that can be regarded as the cause of the disease have failed. From time to time organisms have been described, and the one that for some years attracted considerable attention was a bacillus described by Sanarelli. This organism, one of the coli group, has been shown to be that of hog-cholera. Seidelin describes bodies that he found in the blood, in cases of yellow fever, as protozoal organisms. These bodies are either in red corpuscles or free in the plasma. They consist of a chromatin nodule either alone or surrounded by a variable amount of cytoplasm. Seidelin finds them not only during the first three days of the disease but later, and names them *Paraplasnia flavigenum*. The protozoal or parasitic nature of these bodies is not universally admitted, and it is difficult to state to what group of protozoa they belong, if they are protozoa. Some absolute method of diagnosis in the mild forms of yellow fever is much to be desired, as some observers consider ailments to be yellow fever which others consider to be mere trivial digestive disturbances.
Though the cause has not been discovered, it is now known, as the result of the experimental work of Reed and Caroll, fully confirmed by numerous observers, that the infective agent is imbibed with the blood of patients by certain mosquitoes, and that such mosquitoes, after a definite period of ten to twelve days, are in turn capable of infecting non-immunes. These experiments have shown:—

(1) That neither in the vomit, black or otherwise, in the faeces, or sweat, or other discharges from the patients is any infective agent contained, but that it is contained in the blood during the first three days of the attack.

(2) That mosquitoes (*Stegomyia fasciata*) can convey the disease, and that the other common and domestic mosquitoes do not so carry the disease.

The condition necessary for the conveyance of the disease by these mosquitoes are:—

(a) That the mosquito must have fed on the blood of a yellow fever patient during the early stage, first, second or third day of the disease.

(b) That the mosquito must have lived for ten days or more after this feeding.

(c) That the person bitten in the second instance must be susceptible.

This series of events shows that the parasite of yellow fever requires development in the mosquito before it can be injected into man, and that it is not simply a transference of the organisms from one man to another.

Marchoux and Simond claim that the mosquitoes may transmit the organism to their offspring, though the more extensive observations of Rosenau and Goldberger have failed to confirm these results, and the method in which yellow fever is spread is in more accordance with the transmission by the adults than in this manner.

The period of incubation of yellow fever after the bite of an infective mosquito varies little and is usually from three to four days, very rarely over five. In persons partially immune a longer period of incubation may be
The early cases in an epidemic are twelve to fifteen days after a case is introduced, as the mosquitoes have to be infected and become infective, which takes ten days, and then the person infected by them will not develop the disease for two, three or four days. The incubation period for an epidemic is therefore about two weeks. Most of the etiological factors connected with yellow fever are closely related to the conditions favourable for the life and multiplication of S. fasciata, but this insect is more widely spread than yellow fever, and is only of importance, in this connection, when persons with yellow fever are present or are imported, or where the disease is endemic in a mild or severe form.

Prophylaxis.—The carrier of yellow fever is known, and for effective prophylaxis thorough knowledge of the habits of this insect is required, and the means of identification. It is possible that other members of the same group may carry yellow fever.

The point of special importance is the class of persons who harbour the parasites and serve as a reservoir of the disease from which these mosquitoes become infected. The general recognition of the presence during an epidemic period of numerous cases of illness, characterized by brief fever and gastric disturbance, with occasionally jaundice, some at least of which are probably yellow fever, has broadened the scope of inquiry.

Such cases, as well as the more marked cases of yellow fever, serve as "reservoirs" of the disease and mosquitoes become infected from them and in turn infect other persons.

As the mild cases are the usual forms of the disease in children, and the immunity conferred by a previous attack, whether mild or severe, is rather immunity against a severe attack than against reinfection with the disease, it is held by some that in tropical countries, where the mosquito S. fasciata is common, such constant reinfection occurs amongst the native children and the partially immune adolescents and adults that the disease persists
in an endemic mild form, and that highly susceptible new-comers may acquire the disease in a virulent form from the mosquitoes infected from the resident population. Such virulent cases would be the only ones to attract attention and would be considered as sporadic cases. The commoner mild cases would either be overlooked altogether or grouped with bilious remittent fever. Such virulent cases would be the only ones to attract attention and would be considered as sporadic cases. The commoner mild cases would either be overlooked altogether or grouped with bilious remittent fever.

Simond, Aubert, and Noe consider that in Martinique the epidemics which occur from time to time are acute manifestations of the endemic disorder. The variations in the severity of yellow fever they explain either as the result of an exceptionally large dose inoculated by the mosquito, or—and this is more probable—that the virulence of the organism is increased by passage through a series of susceptible adults and diminished by passage through a series of partially immune adults or children, such as must be present in a country where the disease is endemic. This would explain why when yellow fever occurs on board a ship manned by Europeans or amongst the members of a European regiment crowded in barracks, where the infection after a time will usually be derived from another susceptible person, the mortality is very high, 50 per cent. or more, whilst in the later epidemics, as in that described by Blair in 1843, in British Guiana, the mortality was only 13.3 per cent. in the whole epidemic and nil in the mild form then first described. In the first general outbreak throughout the West Indies the mortality amongst all races was very high during the first year of the invasion, one to two-thirds of the cases died, though later a larger proportion recovered.

Manson suggests a further hypothesis, that possibly man is not the only reservoir, and that some of the lower animals may receive and carry on the infection in a mild form. We know that anthropoid apes are susceptible, but as regards other animals, if susceptible, the disease does not appear to affect their health. If a lower animal serves as the reservoir that animal would probably be a rat, as the early distribution of the cases is in the
crowded business quarters of a town, usually near wharves and the shipping. The possibility of the disease being carried in an attenuated form through several generations of mosquitoes cannot be excluded.

Till a parasite which can be detected at all stages of the disease or in infected mosquitoes has been discovered, the subject is a fruitful one for the proposal of hypotheses, but the method of prophylaxis to the extent of eradicating the disease is more difficult. Whatever hypothesis may be adopted as regards the reservoir, natives, rats or other animals, there is no doubt that S. fasciata is the carrier and the success in Cuba and Panama of measures based on the destruction of this mosquito have been strikingly successful, whether or not this will convert a partially immune resident population into a highly susceptible population depends on whether the disease is carried on in the reservoirs in an attenuated form or is reintroduced.

We are not yet in a position to relax any quarantine regulations. The introduction in the past of cases of yellow fever in a virulent form has been followed by outbreaks of the virulent form of the disease; and by quarantine alone, even without the isolation of cases, many of the West Indian Islands and British Guiana were free from virulent cases for from ten to twenty years without any reduction in the number of Stegomyia.

In case of an outbreak, protection from mosquitoes, both day and night, of all infected cases, protection at night of all susceptible persons, destruction by fumigation of all house mosquitoes, and of the larvæ and breeding-places of S. fasciata, would render the outbreak easily controllable.

There is no risk of spread of yellow fever in a town where S. fasciata has been exterminated, nor in a house where there are no breeding-places for this mosquito near.

In a town not so protected, or only partially protected so that some mosquitoes of the species S. fasciata are present, the introduction of a patient with yellow fever
is a source of danger to the whole community. This
danger can, by energetic measures, be reduced to a
minimum.

(1) All cases of fever must be at once reported and
inquired into. Any that are yellow fever must be at
once isolated. In a port where yellow fever is likely to
be introduced, the machinery for the registration, identi-
fication, and isolation of cases must be kept in working
order, and form a department or bureau that is at all
times available.

(2) If there is a case of yellow fever the patient must
be removed to another room and placed inside a mos-
quitos net, and kept there night and day till convalescent,
as the young mosquitoes feed both during the day and
night, and may become infected therefore at any time.

(3) The room from which the patient has been re-
moved must be at once closed and all places where
mosquitoes can escape blocked. The room must then
be fumigated with burning sulphur 1/2 lb., or pyrethrum
2 lb., to each 1,000 cu. ft. As soon as possible after the
fumigation the floor must be swept and the sweepings
at once burnt, as mosquitoes may revive after such a
fumigation. The attendants, those engaged in fumigation
or mosquito destruction, and any persons having business
in the house, must be protected by suitable clothing from
mosquitoes.

(4) In adjoining houses every effort should be made
to destroy the mosquitoes, as some may have escaped
to them. If the case of yellow fever is detected early,
when these precautions are adopted there is frequently
no spread of the disease, because the mosquitoes, as in
malaria, are not capable of infecting human beings in
less than ten days after biting the patient.

Where the first case is not detected early, and the
disease has spread, each case as it is reported must be
treated in the same manner as an original case. The
success of the measures depends on each case being
reported early, and a thoroughly efficient central bureau
is therefore essential.
When an outbreak does occur measures for the destruction of the larvæ must be most energetically pushed.

For the success that has attended such prophylactic measures the reader is referred to the reports as to the sanitation of Havana, New Orleans, and the Panama Canal Works.

Importation of disease is usually by ship. Either infected mosquitoes are introduced or infected persons. Infected mosquitoes may be brought in with the cargo or in private baggage, and in that case the focus of the epidemic is the place where the baggage is opened.

Ship Epidemics.—S. fasciata can thrive on board ship, and can be transported for long distances by sea as eggs, larvæ, or adults. The adult mosquitoes may be infected in one port, and only become infective after reaching a second port, and then may give rise to an epidemic in the vicinity of the wharves. It is quite possible in a voyage of a week or less that the crew of the ship might escape infection, and the source of infection of the port would not then be known. It is different in cases where the mosquitoes become infective whilst at sea. In such a case a large proportion of the susceptible crew may acquire yellow fever.

The mosquitoes need not be numerous, but every attempt must be made by fumigation of one part of the ship after the other to destroy any mosquitoes, and the sweepings, as on land, must be burnt at once. S. fasciata become torpid with cold, and consequently such epidemics subside four or five days after reaching colder latitudes, but in summer may continue active and develop as far north as England, and may spread in the vicinity of the wharves as the mosquitoes escape from the ship. In some cases the infection has remained in the ship for several months, even when it has not been occupied for this period. In a sheltered warm part of a ship these mosquitoes may live for that period.

The history of yellow fever deserves special notice, as so
many problems are involved. It is not proposed to give an exhaustive history of the occurrence of the disease. Till recently there has been so much confusion between yellow fever and malaria, particularly the clinical variety of it known in the West Indies as bilious remittent fever, subtertian malaria, and possibly Weil's disease, that many of the records are of doubtful value. A fatal fever was first recorded in San Domingo amongst the followers of Columbus in 1493, fourteen months after the discovery of America, and ten years before the first shipment of slaves to America. This outbreak, if, as seems probable, it was yellow fever, would prove that the disease was one of the New World and not of African importation.

Though various outbreaks occurred in some of the West Indies in the sixteenth and seventeenth centuries, it was not till the big outbreak which swept all through the West Indies and to South America in 1793 that it became of general occurrence, and in each island or country it appears to have been considered as a new disease. Since then outbreaks have occurred in most places every twelve to twenty years on the average.

In West Africa and the West African islands the disease, or a similar fatal fever, was early noted, the first outbreak being in 1510, though there had been an epidemic in the Canaries in 1494. In West Africa, the Canaries, and Madeira there were outbreaks every twelve years in the sixteenth century, three times in the seventeenth, ten times in the eighteenth, and eleven times in the nineteenth century.

The intervals when places were believed to be free varied from short intervals of one to five years, to longer ones twenty, fifty, or in one instance sixty years.

In Bermuda the first record of an epidemic is in 1699, but since then there have been frequent outbreaks, some local and some widespread.

Several authorities, including Blair, point out that great variations in the severity and characters of epidemics occur. And Blair in his description of the disease divides
the cases into simplex, mitior and gravior. The first group he states may occur at any time in an epidemic, but cases are more prevalent towards the close. This form was first recognized in 1841, and previously had been known as ephemeral fever, and in that form the mortality was nil. In the mitior and gravior the mortality was from 20 to 25 per cent., and the total mortality amongst all recognized cases was 13·3 per cent. The epidemic ceased, but was followed by widespread influenza, and amongst sailors cases continued to occur presenting some of the yellow fever symptoms grafted on intermittent fever. That at this period the very mild form of some cases was clearly recognized is shown by the application of the remark that it varied in intensity from a "flea-bite to the plague."

He, like all the older authorities, contended that the cases of the disease amongst the negroes were milder, not, as so many subsequent writers have stated, that the negro was immune.

In the next outbreak in 1853 he also subdivides the cases according to race:

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Deaths</th>
<th>Per cent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seamen</td>
<td>1,242</td>
<td>328</td>
<td>27</td>
</tr>
<tr>
<td>E. Indians (natives of India)</td>
<td>42</td>
<td>11</td>
<td>26</td>
</tr>
<tr>
<td>Madeira (Portuguese)</td>
<td>698</td>
<td>246</td>
<td>35</td>
</tr>
<tr>
<td>Creoles</td>
<td>17</td>
<td>2</td>
<td>11</td>
</tr>
</tbody>
</table>

The actual case mortality not only varies in different outbreaks, but is to a great extent dependent on the recognition of the mild form—simplex—as those cases, which in some outbreaks are numerous, have no mortality, and consequently, unless they are included, the mortality will appear higher than it really is.

Clarke gives an account of the 1793 epidemic as it affected the inhabitants of Dominica. The mortality was high, especially among the immigrants, irrespective of race, and he gives an instance of twenty-four negroes from West Africa who were all attacked, and of whom one-third died, indicating that at that time the West
African native was not immune: Creole negroes usually escaped.

The series of outbreaks in Bermuda are of interest as showing how in a place much visited epidemics were frequent. Records of epidemics date from 1699, followed by others in 1779, 1796, 1812, 1818, 1819, 1837, 1843, 1853, 1856, and 1864. The mortality in these outbreaks was usually comparatively low; fatal cases occurred amongst the blacks, but only in small proportion—e.g., in 1864 there were only three deaths amongst 1,469 cases in the coloured natives, 0.2 per cent., whilst 49 per thousand of the white people attacked died.

There can be little doubt that after an epidemic, and probably before it, mild cases occur and keep the epidemic alive. The epidemics in Bermuda of 1818 and 1819, and again of 1837 and 1843, represent two epidemics only. Whether the disease can remain restricted to cases of the mild type, and the infection remain alive with no manifestation of cases of the severer forms for periods of ten, twenty, or fifty years, is a different question, and for each country must be decided on the evidence in that country and not on general principles. In the meantime, even where the evidence that the disease is endemic is fairly strong, quarantine regulations against places where the disease exists in a virulent form should be enforced.

Yellow fever is the most important member of a group of diseases believed to be caused by protozoa, though the parasites have not been found. The virus exists in the blood plasma, is ultra microscopic, and the diseases are carried by insects. A period elapses before the insect which has imbibed the blood is capable of transmitting the infection. Dengue fever is carried by Culex fatigans and Stegomyia fasciata, and Phlebotomus fever is carried by Phlebotomus papataci; there are other known members of this group. They are described in Part III.
CHAPTER X.

HUMAN TRYPANOSOMIASIS.

(Sleeping Sickness.)

Diseases due to the presence in the blood of trypanosomes. The best known—the African forms—manifest themselves as long-continued fevers, at first of a severe type, but later low forms of hectic fever, or periodic attacks of fever, and associated with enlargement of the lymphatic glands, especially the cervical; evanescent rashes, and often splenic enlargement. They usually terminate fatally with cerebral symptoms, those of the form long known as sleeping sickness being the most usual, or death occurs earlier from intercurrent diseases or from cardiac failure.

Geographical Distribution of Sleeping Sickness.—The disease is only known in Tropical Africa as an indigenous disease, but many cases have been reported in Europe, all in persons who had resided in Africa within the last few years. As judged by the distribution of its terminal phase—sleeping sickness—the disease has within recent years been spreading rapidly across Africa. There are differences in the parasites in Rhodesia from those in Uganda and the Congo, and the former is the more severe type, but, clinically, they resemble each other and are considered here together. It was unknown on the Zambesi and south of it till recently, and is now known in the neighbourhood of Lake Nyasa, and to the west of this lake. It is prevalent throughout the Congo, but is rare on the Gold Coast, in Lagos, and in Southern Nigeria. It has been introduced into the neighbourhood of Victoria Nyanza within the last twenty years, and now extends throughout that district and down the Nile some
200 miles. There is every probability that it will become more widely diffused in Africa, though it is less prevalent in some places, such as Liberia, where at one time it was common. The intermediate hosts belong to the genus

![Diagram](image-url)

**Fig. 36.**—Chart I, 1909. Onset of disease and marked temporary effect of soamin in the second week.

![Diagram](image-url)

**Fig. 37.**—Chart II, 1909. Third and fifth weeks. Imperfect control of temperature by soamin and atoxyl in large doses.

_Glossina_, and the species implicated are _Glossina palpalis_ and possibly _G. fusca_, and for the form known as _Trypanosoma rhodesiense_, _G. morsitans_. _Glossinae_ are only found in Africa and Arabia, and suitable species to
act as alternate hosts are not present in South Africa and South America, and though the disease has been introduced there it has not spread. The South American

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**Fig. 38.**—Chart III, 1910. Two other periods some three months later, showing absence of any marked beneficial effect from these drugs. Trypanosomes were usually to be found.

**Fig. 39.**—Chart IV, 1910. Marked temporary effect of intravenous injections of tartar emetic. The trypanosomes, which before the injection were 3 to 200 leucocytes, were not found for three days, but became as numerous as before in six days. The severity of the reaction is indicated by the temperature.

disease due to a *trypanosoma* will be considered separately.

*Clinical History.*—Little is known as regards the onset
TARTAR EMETIC GIVEN INTRAVENOUSLY EVERY FIFTH DAY, BUT NO ATOXYL, FOR SOME TIME SEEMED TO BE A SUCCESS; AS THE TEMPERATURE, EXCEPT FOR THE RISES WHICH FOLLOWED THE INJECTIONS, WAS NORMAL, AND NO TRYpanosomes WERE FOUND. ULTIMATELY THE TEMPERATURE BEGAN TO RISE ON THE FIFTH, AND TRYpanosomes WERE SOMETIMES FOUND ON THAT DAY.

Later condition. Under atoxyl the temperature remains about normal for eight to twelve days and no trypanosomes are found. Then there is a rise of temperature, and, as a rule, trypanosomes can be found. An intravenous injection of tartar emetic is followed by a severe reaction, indicated by the dotted line in the temperature chart, and the temperature then falls and trypanosomes cannot be found for another period. The use of atoxyl now seems to have lengthened the period of well-being from four or five to eight to twelve days.
of the disease in man. The period of incubation in monkeys is about fourteen days. In some cases in man it is even shorter. The onset in man appears to be often confounded with malaria, but in some cases there is high and continued fever as in typhoid, whilst in other cases there is no marked fever. At this stage there appear to be no characteristic symptoms, but sometimes trypanosomes are found abundantly in the blood.

The temperature after this early stage may fall to normal, and remain so, but even in these cases the diurnal variation is usually increased, so that when the temperature is taken frequently, though it may rarely exceed 99° F., there may be a variation at different times of the day of as much as 2° F. More frequently there is slight irregular fever, the temperature rising to 100° or 101° F. every day. At times, in such cases, there will be definite pyrexia, the temperature rising to 103° or 104° F., or even more, for several days, falling gradually to normal or a little above it.

Some of the lymphatic glands are soon found to be enlarged and are soft to the touch. They are not acutely painful, but are tender on pressure. The glands at the base of the neck are those most commonly enlarged, but any glands may be affected.

In Europeans a rash is usually present. It is evanescent, but appears as erythematous rings surrounding an area sometimes slightly discoloured by blood pigments. This discoloration may amount to an actual bruised appearance. The rings are not raised to the touch. The chest, abdomen and covered portions of the body are the usual sites for this eruption, but it may occur on any other part of the body, such as the forehead and face. Swellings of various parts of the body, and particularly fugitive swellings under the eyelids, are sometimes seen. There is progressive muscular weakness, some loss of flesh, and anaemia, which may be profound. Even in the early stages a slight blow may cause prolonged
muscular pain—Kerandel's symptom. In other cases the slightest pressure on the muscles is acutely painful, and putting a muscle on the stretch may cause so much pain that the patient is unable to stand or walk. The cardiac action is very rapid and unduly subject to irregularities as a result of slight exertions. A fine muscular tremor is often perceptible in the hands in late stages. The appetite is good, and unless there is much pyrexia the tongue is moderately clean and the bowels regular.

Fig. 42.—Child with trypanosomiasis showing oedematous swellings of the eyelids.

The disease runs a very chronic course in most cases, but in some death may occur early from the severity of the disease, or from cardiac failure before the period arrives when the temperature becomes nearly normal or cerebral symptoms supervene. Intercurrent diseases, particularly pneumonia, are often fatal, and with the subsidence of the fever the general condition shows some improvement, and the patient may be able to go about
his work and believes that he is recovering. This condition may last for two or three years. During this period trypanosomes will only be found in the blood after prolonged search: they may be more abundant during a pyrexial period in those cases in which definite attacks of fever recur. They are much more readily found in the soft enlarged glands, but in old hard glands, though they be still enlarged, the trypanosomes may not be more numerous than in the peripheral blood.

Orchitis occurs in some cases both from the Congo and, more commonly, from Rhodesia, one or both testicles may be affected, or alternately one and the other.

Hæmorrhages from the nose or gums may occur and may be repeated.

Iritis, keratitis or retinal changes may occur in untreated cases, and in cases treated by arsenic cataract, optic atrophy, and other changes considered to be due to that treatment, are common. Keratitis in the lower animals resembles the interstitial keratitis of syphilis, and the lesions are similar on microscopical examination.

Injections of considerable amounts, 2 c.c. or more, of the blood of such patients into monkeys or other susceptible animals will result in the infection of such animals, and the trypanosomes can be found in number in their blood, and the animals will die shortly after. Rats may be infected in this way, but the results are uncertain, and the period of incubation may be prolonged to months.

Sooner or later in a patient who may have been free from fever, and in whom the presence of parasites may only be shown by the infection of animals with the patient's blood, terminal cerebral symptoms supervene.

The cerebral symptoms vary in character; they may take the form of a rapidly fatal coma or of a series of epileptiform convulsions, or of the progressive lethargic condition known as sleeping sickness or negro lethargy, in some of its aspects, and in the pathological lesions not unlike general paralysis of the insane.
In this condition, which is the most common termination of the disease, the patient passes into a peculiarly lethargic state, so that while the total amount of sleep obtained may be little above normal he is always drowsy, and frequently falls asleep even at meals or when in the act of performing some ordinary occupation. Before the onset of these symptoms there is usually marked fine tremor and dull headache. The temper is frequently uncertain, and there may be mental irritability. This irritability, as the disease progresses, becomes more marked and mental deficiency occurs. There is a general aspect of misery about the patient and he is apt to be neglectful of his person, and dirty and careless in his habits.

Muscular weakness is extreme, and unless the patient is regularly fed he rapidly emaciates and dies, partly of starvation. Even when well fed and carefully nursed there is rapidly progressive emaciation. The termination of the disease may be associated with diarrhoea, or the patient may die comatose.

Varieties.—The disease, as it appears in Rhodesia, runs a more rapid and severe course. All known cases have been fatal. The parasite in man appears to be morphologically identical, but in rats a varying proportion of distorted forms, in which the nucleus is more posterior than in the ordinary forms and may even be posterior to the micro-nucleus, are found. The trypanosomes are more virulent and more readily infective to experimental animals. Stephens and Fantham describe this trypanosome as a distinct species under the name of *T. rhodesiense*. Whether the difference is specific, or whether it is a virulent strain modified by passage through different mammalian hosts, and with a different species of Glossina, *G. morsitans*, as a carrier, is not conclusively proved. A further difficulty is that in some strains isolated from cattle similar irregular forms are found, and Bruce contends that *T. rhodesiense* is really *T. brucei*, the cause of Nagana. As in other strains no such forms have been found, others consider that in some parts of Africa two
trypanosomes are causes of disease in cattle, *T. brucei* and *T. rhodesiense*. No symptoms or changes have been described in man in infections with this Rhodesian form that have not been described in infections from the Congo and Uganda. Anaemia is more frequent, orchitis occurs in a larger proportion of cases, and death from cardiac failure before the onset of cerebral symptoms is more common.

*Diagnosis.*—The disease may be mistaken in the early stages for malaria and typhoid fever and possibly pellagra. In the later with any of the chronic forms of intermittent, remittent, or "low fever," such as kala-azar.

As the disease is confined to Tropical Africa, suspicion may be excluded in patients who have not resided in that country. The presence of enlarged glands and the fugitive circinate eruptions are of great value in the diagnosis.

Certainty can only be obtained by finding trypanosomes in the blood or fluid obtained by hypodermic puncture of one of the enlarged glands, or by the results of the injection of the blood into monkeys or other susceptible animals, but with some of these, such as rats, the period of incubation may be indefinitely prolonged.

In the terminal stage the epileptiform convulsions and the comatose condition might readily be mistaken for other diseases. When this stage shows the peculiar lethargy of sleeping sickness mistakes could hardly occur. When cerebrospinal symptoms have set in trypanosomes may not be found in the blood, but only in the cerebrospinal fluid. This should be drawn off by lumbar puncture, and centrifugalized, as the parasites are usually scanty. Lumbar puncture can usually be readily performed with the aid of a local anaesthetic, though it is easier when chloroform is given. The patient should lie on his side with the thighs flexed, and the back arched as much as possible, to increase the space between the vertebrae. The space to be selected is between the third and fourth lumbar vertebrae, and the needle
should be inserted half an inch from the middle line and steadily pushed inwards and slightly upwards, till it is felt to pass through the tough membrane. If it strikes the bone the needle should be partly withdrawn, and then directed slightly more downwards. The escape of clear fluid will render it certain that the point of the needle is in the canal.

Prognosis.—The terminal stage, sleeping sickness, is invariably fatal. The earlier stages of the disease, when there is merely a trypanosome infection of the blood and lymphatic system, are often amenable to treatment, and there is good reason to believe that complete and permanent recovery may ensue.

The disease is a serious one, and the prognosis, even when all the symptoms have disappeared and the parasites cannot be found in either glands or blood, must be guarded, as cerebrospinal symptoms may occur years after the original infection. The prognosis is worse in the Rhodesian variety and in all cases that do not yield readily to moderate doses of atoxyl.

Pathological Anatomy.—Little is known of the pathological anatomy of the early stages of the disease in man. In monkeys and the lower animals the condition is mainly one of visceral congestion, but enlargement of the spleen and intense congestion, sometimes hæmorrhagic, of the lymphatic glands and extreme congestion of the brain are also met with. Similar changes occur in the liver.

In sleeping sickness there is formation of round cells in the perivascular spaces of the cerebral capillaries, closely resembling that found in general paralysis of the insane.

Treatment.—The drugs most distinctly useful in malaria, quinine and methylene blue, have no effect in this disease, and do not alleviate the symptoms or reduce the number of trypanosomes. Arsenic long had some reputation in the treatment of the early stages of sleeping sickness, and experiments with various trypanosome infections in lower animals showed that this drug had a decided controlling effect, and that the number of parasites could
be reduced, and life much prolonged by its administration. The effects were not permanent; if the arsenic were pushed the animals died from arsenical poisoning, whilst if given in smaller amounts the trypanosomes became tolerant of the drug and the animals died of trypanosomiasis.

In human trypanosomiasis it was soon found that only a few persons could tolerate arsenic given by the mouth in sufficient quantities for the parasites to be affected, and one case so treated is still in good health eleven years after the treatment was commenced. Various forms of injection of the drug were tried, cacodylates and the like, but arsenic in the form of atoxyl or soamin appears to be both the safest and most promising. In the lower animals very large doses seemed to effectively control the disease without producing arsenical poisoning. In man smaller doses have to be used or arsenical poisoning will result. The most successful method is to use a freshly made 10 per cent. solution of atoxyl in normal saline. The solution must be sterilized before use and injected whilst still warm into one of the large muscles, such as the gluteus maximus: 20 ml every alternate day can always be borne, and the dose should be gradually increased and given more frequently till a decided effect is produced, 2½ to 3 gr. of atoxyl will usually suffice for each dose; in some persons symptoms of poisoning are produced by 25 ml, but a larger dose is better and in most cases can be taken. In some 70 ml or more may be well borne; 30 ml every other day appears to be an effective dose, the parasites diminish in number and ultimately cannot be found. The glands become small and hard, the temperature normal, and the eruption ceases to appear. The general health also is completely restored. Relapses occur, particularly if there be any intercurrent disease. The atoxyl treatment should be continued for at least two years after the symptoms have disappeared. Sufficient time has not yet elapsed for certainty as to the completeness and permanency of the
recovery, and particularly whether all possibility of the recurrence of the cerebral symptoms or of sleeping sickness has been obviated.

It is somewhat unfortunate that a different line of treatment has been adopted on a large scale. This plan, introduced by Koch, was to use large doses and repeat them a fortnight later. The immediate effects were good, so much so that the method was widely advertised, and has been extensively employed. Further experience has shown that the effects are temporary, relapses the rule, and optic atrophy common. These results have to some extent discredited the use of atoxyl.

The attempt to treat diseases by a few heroic doses of a specific has often been tried and failed. As instances: if syphilis be treated with a few large doses of mercury, or malaria similarly by quinine, the temporary results may be good, but relapses are usual and the disease recurs. The same drugs in moderate doses continued for a long time have a permanent beneficial effect, and the same appears to hold good with atoxyl in trypanosomiasis. Alternate treatment with atoxyl and mercury has been advocated, but the results, in man, have been no better than with atoxyl alone.

Injections of preparations of antimony have a more powerful effect on the trypanosomes than atoxyl or any other arsenical preparations, but the antimony preparations used cause much pain and local tissue necrosis unless very dilute—and even then do so in some persons. Finely divided metallic antimony suspended in Lambkin's medium usually causes less necrosis, and is as effective. Intravenous injection of a solution of tartar emetic, 1 to 2 gr. in 10 c.c. of sterilized normal saline, is the most effective method. If the vein be irrigated with a little normal saline before the tartar emetic solution is injected, and after the injection of that solution, there will be no local trouble. A rigor and sharp reaction will occur in most cases. The immediate effects are striking even in cases which do not yield to atoxyl. In some cases, such in-
j ections given every alternate day for two weeks, and after an interval of one week a second two weeks' course, have been permanently effective. In others the trypanosomes have returned, but yield readily to atoxyl. A combination of this form of treatment with intramuscular injections of atoxyl appears to give the best results. Even the Rhodesian form of the disease can be controlled by this treatment, but no permanent good result has yet been obtained.

*Nursing.*—No special precautions are required. The disease is a chronic one and good feeding is necessary. On account of the cardiac condition sudden movements or exertion on the part of the patient must be discouraged. When the general condition of the patient permits it he should be allowed to live an ordinary healthy life. But over-fatigue and any risk of intercurrent disease must be carefully guarded against.

When taking atoxyl or any other preparation of arsenic, any digestive disturbance, such as nausea, vomiting, or abdominal pains must be carefully noted. Any complaint of dryness of the mouth, and pain or irritation of the eyes, must also be reported.

Increasing muscular tremor, headache, and disturbed sleep are premonitory signs of the onset of sleeping sickness. When this supervenes, all that can be done is to feed the patient at regular intervals, and to keep him clean, warm, and comfortable. There is no object in endeavouring to prevent him from sleeping.

*Etiology.*—There are certain points of analogy between trypanosomiasis and some cases of syphilis. In both there is a latent period followed by a more or less marked febrile stage, and associated with glandular enlargement and cutaneous eruptions and terminating in the formation of diffuse lymphoid growths around the cerebral vessels.

In some cases of trypanosome infection there is a definite scar, the result of a bite from an insect, which was painful for some time, and this may be considered
as the primary sore. In the Congo, and where infection is through \textit{G. palpalis}, this scar is usually on the legs. In Rhodesia, where the higher flying \textit{G. morsitans} is the carrier, on the neck. It may not be present.

The mode of propagation of one of the trypanosome diseases in the horse is by sexual intercourse. With human trypanosomiasis there is no evidence that the disease is spread in this manner. Direct inoculation of the blood of an infected animal into another will transmit the disease, and even an abraded surface is sufficient, but, as far as is known, in nature it is transmitted by the bites of certain flies belonging to the genus \textit{Glossina}.

From the distribution of the disease, and the corresponding distribution of the flies, \textit{G. palpalis} is believed to be the important carrier, whilst \textit{G. fusca} and possibly \textit{G. tachinoides} may also be carriers. The commonest of the tsetse-flies, \textit{G. morsitans}, though it carries the trypanosome of nagana, is probably not a carrier of \textit{T. gambiense} in Uganda or on the Congo, but is the carrier in Rhodesia and on the Zambesi of \textit{T. rhodesiense}.

The Glossinae are a genus limited to Africa and the shores of the Arabian Gulf, and are easily distinguished from other biting flies.

They are dipterous insects, and closely resemble many of the Muscidae, but are distinguished by the long, straight proboscis, by the arista or spine which arises from the third joint of the antennae being plumose on the one side only, by the palps being the same length as the proboscis and grooved on the inner side, so that together the two palpi form a sheath for the proboscis. There are hairs only on the convex side of the arista and these are compound. The wings are crossed, so that when at rest their tips overlap each other—"scissor" wings—and project beyond the abdomen. The fourth longitudinal vein is bent twice, once to meet the transverse vein, and a second time to approximate to the third longitudinal.

Glossinæ are nearly pupiparous; the larvae attain their
full growth in the ovary, and after being passed do not
feed but pass into the ground and become pupae. As the
larvae are still motile and only ready to pupate, the flies
are rather larviferous than pupiparous.

G. palpalis can be easily distinguished from other
common Glossinæ, as the last four joints of the hind legs
are entirely black. Two other species have this character,
G. pallicera and G. maculata, whilst in G. tachinoides the
last four joints, though black, are not entirely so. The
commoner species, G. morsitans, has only the last two
joints of the hind legs black.

Without going into detail, then, Glossinæ are flies which,
when alive, are readily recognized by the straight, long
proboscis projecting out in front of the head, and by the
crossed position of the wings of the insect when at rest.
These wings are always longer than the abdomen, and
projecting beyond it give the insect the appearance of
being longer than it really is (fig. 43).

Glossinæ bite mainly in the daytime, though some species
also bite at night. The bite is painful at the time, feeling
more like a sharp sting, but not producing any subsequent local effects unless infected. Then they may produce a swelling and sometimes an ulcer. They will bite a man or other animal while he is in motion, and seem to bite almost as soon as they alight on him. *G. palpalis* is often found in boats and canoes, sheltering under the thwarts. Very frequently it will crawl out and bite the legs, and in other cases, as they often fly low, will alight on the legs and bite, whereas the higher flying *G. morsitans* more frequently attacks the upper part of the body, the head or neck.

They are usually found in narrow belts near water on the edge of forest land, and may in such situations be present in large numbers for a few hours, whilst at other times few or none may be found. They are also found in well-wooded country, in forest clearings, and near forests. The larvaæ are deposited in the neighbourhood of rotting vegetation, and particularly near the roots of certain plants, such as bananas, as well as many other plants and trees. The pupæ are usually found in banks covered with trees near open water, lakes, or streams. Extensive clearings, therefore, form an important part of prophylaxis.

By the formation of such clearings and the burning off of refuse vegetation in the vicinity of settlements, the actual habitations may be kept clear of these flies. It has been suggested that keeping and breeding fowls, or the importation of jungle fowls from India, might aid in the destruction of such larvaæ. It is doubtful, however, whether such fowls would have any chance of continued existence at any distance from human habitations, as the larvaæ also are deposited away from the cleared tracts or in plantations.

More hope of the destruction of the flies in their adult form may be entertained by the introduction or cultivation of insectivorous insects and other animals, such as dragon-flies. Koch believed that their most important source of food is the crocodile, and advocates the
extermination of that reptile. Protection from the bites of flies is very difficult, not only must fly-proof houses be made, but fly-proof clothing must be worn when outside such houses. Such measures should be taken when living in an endemic area close to native settlements where sleeping sickness is prevalent.

Biting flies belonging to other families are not to be altogether ignored, as the trypanosomes of Asia are carried by some of these, such as Stomoxys. Attention in Africa has been almost entirely directed to Glossinae.

Experimentally Glossinae convey trypanosomiasis in two ways. There is direct evidence that occasionally they convey the parasites by feeding first on an infected animal and very shortly afterwards feeding on another susceptible animal. Such transmission is direct. Usually attempts at transmission in this manner fail, but possibly this mode of spread of the disease from man to man does take place at times. Kleine has shown that flies again become infective eighteen days and more after they have fed on infected animals, and remain infective for an indefinite time.

Attempts to demonstrate a definite cycle of development of trypanosomes in the Glossinae are difficult because flagellates are so common in the alimentary canal of flies. Bruce and others have shown that laboratory-bred flies do not harbour intestinal flagellates. If such flies be fed on a person or animal with trypanosomes changes occur. In many of the flies the trypanosomes disappear. In a minority the trypanosomes multiply in the intestine, but are long and narrow, or short and stumpy, and not like the forms found in the blood. In these, about the twenty-eighth day (according to Bruce the commonest time for the flies to become infective), trypanosomes are found in the salivary glands, and these trypanosomes are similar in appearance to those found in the human blood.

In mammals they multiply asexually by longitudinal division (fig. 44). Small resting forms, according to
some observers, may be produced. Unfortunately man is not the only animal capable of being infected, and in Rhodesia many of the wild game harbour the human trypanosomes and serve as the "reservoir" from which the flies derive their infection and in turn infect man.

Even in Uganda, months and years after the population had been removed from the shores of Victoria Nyanza, the flies there were still infective.

Prophylaxis amongst Europeans is comparatively simple. Districts where sleeping sickness is prevalent should be avoided as much as possible. European habitations should not be near water nor placed where
G. palpalis is plentiful. The houses should be fly-proof, and as far as possible from native settlements.

When travelling fly-proof clothing should be worn and boots after the style of mosquito boots; veils also should be worn and loose gloves.

Prophylaxis for natives is very difficult. (1) Segregation of the infected; (2) deportation of the non-infected to a fly-free area; (3) destruction of the fly along ordinary routes of travel; (4) treatment of infected persons to reduce the number of trypanosomes where it is impossible to isolate them in a fly-free country, are the most promising measures.

(1) Segregation of the infected is not likely to be thorough, as the symptoms are for a long time indefinite and the prolonged search of the blood necessary to find trypanosomes is impracticable for a large collection of persons.

Examination for enlarged glands is not conclusive, as glandular enlargement is so common from other causes. A combination, however, of the examination for enlarged glands and microscopic examination of the fluid obtained by gland puncture is of value in preventing the introduction of diseased persons into a community. The segregation camps must be in a district free from the fly or they may form a focus for the spread of infection.

(2) Deportation of the whole of the uninfected population to a fly-free area is the most satisfactory of the present methods. The old station must be burnt, the gardens destroyed, and patrols established, or some of the people will return and may become infected.

(3) Destruction of the fly along known trade routes is important. The points of special danger are ferries, fords and watering-places, as at such places many travellers pass and the fly is often present.

Extensive clearing of the jungle along the banks of the rivers for 100 yards from the edge of the water and on each side of the path in the vicinity of water will greatly reduce the number of flies present.
(4) Treatment with atoxyl will greatly reduce the number of trypanosomes present in the blood and thereby diminish the probability of infection of the fly, even in cases where the course of the disease is little affected.

For the trypanosomiasis of Rhodesia different methods will be required as *G. morsitans* is more widely distributed and follows game, man, and cattle farther from water. Extermination of the game in broad belts of country may check the spread into districts now believed to be free. An efficient and sufficient resident medical service, with a central laboratory to decide which districts are free, and to supervise the destruction of game and the spread of the disease, would be necessary.

In South America a chronic febrile disease is due to a blood parasite first described as *T. cruzi*. A fair number of cases have been observed, and the disease produced is a chronic type of irregular fever associated with a progressive anaemia and enlargement of the spleen, liver, and lymphatic glands. It is most common in children, and death usually occurs from an intercurrent disease, commonly dysentery or diarrhoea. There is no terminal cerebral stage.

The parasite, though it resembles the other blood trypanosomes, differs in the method of multiplication. It does not divide longitudinally in the peripheral blood, but in the lungs it divides into eight bodies within a limiting capsule. This method of division led to its being described by Chagas as a *Schizotrypanum*.

The carrier is not a biting fly but a blood-sucking hemipterous insect, one of the Reduviidæ, *Conorrhinus sanguisuga*. After this bug has fed on an infected person it is not infective for eight days or more, but after that, for an indefinite period, it is capable of infecting man or other susceptible animals.
CHAPTER XI.

KALA-AZAR. KALA-DUKH. DUM-DUM FEVER. TROPICAL SPLENOMEGALY.

Definition.—A chronic infective febrile disease due to a flagellate protozoal organism found in its resting, non-flagellate form in the spleen, liver, intestines, superficial lymphatic glands, and other organs. The disease is characterized by long-continued fever, enlargement of the spleen and liver, wasting, debility, and anaemia, and by a very high mortality. It occurs both endemically and in epidemics.

Geographical Distribution.—The principal seat of kala-azar is Assam, in parts of which it has long been prevalent, though it was first mentioned in 1882. Its name, signifying the "black disease," refers either to the terrible mortality attending the epidemics which for many years devastated district after district of Assam, or to the darkening of the skin observed in many of those suffering from it.

Epidemics have occurred in Lower Bengal, where the disease is also endemic, and the name "Dum-dum fever" was given to attacks of it contracted at this station by British soldiers, many of whom have died of it in England.

Kala-azar also occurs in Madras, and sporadic cases have been met with in Bombay and other parts of India, also in Burmah and Ceylon. Cases of this or a similar disease, occurring in children on the Mediterranean coast and in some of the islands in the Mediterranean, have also been described. The disease has been reported in
China, the Straits Settlements, the Philippines, Panama, Northern Africa, and the Soudan.

The population of some of the places named is drawn from so many sources that it is not possible to say at present whether the disease is endemic in them or not, but in most instances it appears to be endemic.

Clinical Course.—The clinical picture of a case of kala-azar of some months' duration is very striking. The patient, even if up and about, is obviously ill. He is a wretchedly thin, tired-looking man, with a big abdomen and shrunken limbs, and complains of having had fever off and on for months, and that in spite of quinine and various other medicines he has become gradually thinner and weaker, while his abdomen has got bigger and bigger.

A very slight examination of the patient's distended abdomen will show that his spleen is enormously enlarged, that his liver is also increased in size, and perhaps that there is a little ascites present; possibly the superficial abdominal veins will be noticeably prominent, and if attention be turned to the feet some oedema of the ankles and dorsum will be found. Besides being thin, the patient is also anaemic, and his skin, especially that of the face, is darkened or pigmented. His hair is dry and lustreless and may fall out in quantities, leaving him almost bald. He is very easily tired and any little exertion causes breathlessness. His intellect is generally clear, and he may make little complaint except of his gradually increasing weakness and wasting; he may or may not complain of present fever, but even in its absence may say that he is disturbed at nights by violent sweats, but for which he probably sleeps well.

Not infrequently, however, patients at this stage of the disease suffer from attacks of epistaxis, or of bleeding from the gums or from other mucous surfaces. Sometimes, too, petechiae appear, more commonly in the axillae than elsewhere. Attacks of bronchitis or sore throat are not uncommon. Less common symptoms, but of sufficient frequency to require mention, are
jaundice, rheumatic pains in the joints, and ulcers on the skin.

The tongue is singularly clean and the bowels are inclined to be constipated. There is usually an undue degree of thirst. Later on, however, diarrhoea or dysentery sets in, the latter being the most common immediate cause of death. Less commonly the patient dies, after several months of illness, of asthenia; or some intercurrent disease, such as pneumonia, carries him off.

In places where the disease is epidemic, patients will not infrequently be met with who say that several of their relations have died of a similar disease within the previous year or two.

The incubation period of kala-azar is not definitely known, though it is probably long, some months having elapsed in many instances between the departure of patients from infected places and the onset of symptoms. In experimental inoculation of the similar parasite in Delhi boil the period may be five months or even longer. Considerable difficulty in determining the incubation period arises from the circumstance that sometimes the onset of the disease is very insidious, while in many cases the earliest symptoms are mistaken for those of malarial fever, or of typhoid fever.

Three stages of the disease are commonly recognized: those of the initial fever, of the secondary low fever, and of cachexia.

These stages are not sharply marked off from one another, for the acute pyrexial attacks of the initial period become gradually less severe, until they merge into the chronic irregular fever of the secondary period, and after this has persisted for some months the cachectic condition is established. There is a gradual loss of ground throughout the course of the disease, though periods of temporary improvement may occur.

The initial fever may resemble typhoid fever (fig. 45), or in other cases malarial remittent fever, commencing with chills, or less commonly with a rigor, mounting to a
considerable height, and after several hours falling several degrees, the fall being accompanied by profuse perspirations. These febrile attacks recur daily. At first the type is remittent, but may soon become intermittent, the daily range of temperature being considerable, varying between 97° and 103° F. (fig. 46).

![Fig. 45.—Kala-azar. Simulating typhoid.](image)

![Fig. 46.—Kala-azar. Later showing intermittent type.](image)

The rise of temperature usually occurs in the evening, but not uncommonly there is a double or, even a treble rise and fall in the twenty-four hours. Sometimes there are short periods of apyrexia, followed by further outbursts of fever.

After the fever has lasted a short time, the spleen becomes enlarged and tender; enlargement and tenderness of the liver also occur, but are less marked.
Wasting, anaemia, and debility are early symptoms of the
disease, and sometimes darkening of the skin is observed
at this stage.

Headache sometimes accompanies the fever, but there
is very little, if any, digestive disturbance; the tongue
remains clean, and the appetite good, except in cases
where high fever has persisted for some time. The first
stage usually lasts about a month, but the duration may
vary from ten days to two months.

It is followed, either directly or after an interval of
apparent health, by a stage in which low fever persists
for weeks or, more frequently, for months. Sometimes

![Figure 47: Kala-azar. Undulating type.](image)

the course of this secondary fever is very irregular. It is
rarely high, though there may be occasional attacks of
high fever, lasting for some days, while, on the other
hand, there may be days or weeks of apyrexia (fig. 47).
In some cases the course of the fever may be remarkably
regular, the temperature rising and falling to exactly similar
points at the same hours day after day for weeks. Fre-
quently also the course of the temperature chart shows
a double daily rise and fall. The fever at this stage often
causes but little discomfort, and but for profuse sweating
the patient may be unaware that he has any. Sweating,
especially at night, may, however, occur without any rise
in the temperature.
The liver and spleen continue to enlarge, the latter often attaining enormous dimensions. Emaciation, anaemia and debility are progressive until the condition already described is attained, and the stage of cachexia supervenes.

As the end approaches the patient's condition is wretched in the extreme. He is terribly emaciated, and so weak that he can hardly move, he suffers from diarrhoea or dysentery, though his appetite may be ravenous to within a day or two of death. By this time the fever may have given place to subnormal temperature, and the spleen and liver, though still considerably enlarged, may be smaller than formerly. Death is most commonly due to dysentery, which appears to be an integral feature of the last stage of the disease, rather than an added complication. As already stated, however, patients sometimes die from mere asthenia, while not uncommonly death is due to some intercurrent disease, of which lobar pneumonia, phthisis, and cancrum oris are those most frequently met with.

The duration of the disease varies from three or four months to two years, but is most commonly a year or eighteen months. Of this period the stage of initial fever lasts a month or two, and that of low fever six months to a year.

While the description given above applies to most cases of kala-azar, variations from this type of the disease are met with. In some instances the period of initial fever seems to be absent, the patient gradually becoming weak and ill without any definite symptoms beyond loss of flesh and enlargement of the liver and spleen. In other cases the onset may be very acute, and the patient may be carried off by fever or dysentery before the development of cachexia.

For so serious a disease the symptoms other than those mentioned are remarkably slight. Besides headache, those referable to the nervous system are chiefly a diminution of nervous energy and occasional muscular tremors, resulting, for example, in educated patients, in inability to write.
Cases are said to be met with in the endemic area in which the symptoms throughout are of a mild nature.

The symptoms referable to the circulatory system are chiefly dependent upon anæmia. In the early stage the pulse is less rapid than might be anticipated from the height of fever present, while later, owing to the anæmia, its frequency is out of proportion to the temperature, and is full, though very soft. Pulsation of the carotids is often noticeable, and hæmic murmurs are common, as also is palpitation on slight exertion.

Anæmia is a constant symptom of kala-azar. Its degree varies in different cases and at different periods of the disease, but is usually considerable, though not extreme. It commences early in the disease and there is a progressive reduction in numbers of both red corpuscles and leucocytes. Instead of the usual 5,000,000 red corpuscles to the cubic millimetre, only half that number may be present, though 3,000,000 or 3,500,000 are more common counts. The hæmoglobin value of the red corpuscles is only slightly reduced. The diminution in the number of the leucocytes is much more marked than that of the red corpuscles, their numbers varying from 3,000 down to 1,000, or even to only 500 to the cubic millimetre. This marked leucopenia is, according to Rogers, diagnostic of kala-azar.

The decrease chiefly affects the polymorphonuclear leucocytes, while the mononuclear elements show a considerable relative increase. The results of differential blood counts are commonly as follows, the figures given representing percentages: Polymorphonuclears, 40 to 60; lymphocytes, 20 to 30; large mononuclears, 13 to 16.

Although the specific parasite may be met with in the peripheral blood, it occurs so sparingly, especially in the early stages of the disease, that the diagnosis can rarely be made by blood examination. It occurs in the polymorphonuclear and in the large mononuclear leucocytes, and the method which affords the best chance of finding it is to centrifugalize 2 or 3 c.c. of blood, and
after separating the red corpuscles to again centrifugalize the remainder and prepare films from it. Another method is to make blood films terminating in a thick edge; leucocytes accumulate at this edge, and search for the organism is thus facilitated. By this method a skilled observer may be able to make his diagnosis certain by examination of the peripheral blood alone. Unless the case is complicated by malaria, no malarial parasites or pigment will be present in the blood.

Among the results of the blood changes are the hæmorrhages from mucous surfaces already mentioned. Of these epistaxis is the most common form, and is sometimes profuse and difficult to control; in other cases slight but persistent oozing of blood from the nasal mucous membrane occurs; bleeding of the gums is not uncommon, and sometimes intestinal hæmorrhages occur, quite apart from those met with during the dysenteric attacks of the final stage. Hæmaturia is occasionally observed.

Mention may here be made of the occasional presence of slight general anasarca; this and the transitory œdemas sometimes met with are probably due to the condition of the blood. The anasarca may be most marked in the face, and may mask the emaciation.

Digestive System.—There is little to add to what has already been said of symptoms referable to the digestive system. During the early stages they are slight or absent, this being in contrast to the condition usually met with in malaria.

While diarrhœa or dysentery are usually symptoms of the final stage, attacks may appear at any period of the disease. In some instances, indeed, soldiers have been invalided from India to England for dysentery, and the symptoms of kala-azar have supervened.

The enlargement of the liver and spleen is usually painless, though these organs are often tender, especially in the early stage of the disease. Sometimes, however, there is considerable pain in the liver, which has led to the
mistaken diagnosis of hepatic abscess, and exploratory punctures, while the microscopic examination has shown the presence of the characteristic parasites of kala-azar in the fluid abstracted. While the enlargement is usually progressive until towards the end, variations in the size of the liver and spleen sometimes occur, diminution being usually coincident with temporary general improvement in the patient's condition. The slight degree of ascites not infrequently met with is probably due, at least partly, to the obstruction to the circulation caused by the enlargement of the liver and spleen.

The urine is normal in most cases of kala-azar, though towards the end it may contain a little albumin. Hæmaturia is a rare complication.

**Respiratory System.**—A liability to congestion of the respiratory passages, as evidenced by sore throat or by slight bronchitis, is common in patients suffering from kala-azar, and there seems to be a special liability to pneumonia during the later stages of the disease; the pneumonia is of the ordinary lobar type. True tubercular phthisis is one of the causes of death in kala-azar. The parasites may occur in the lungs, and in that case nodules resembling tubercles will be present. The cases of this description, described by Darling in Panama, are associated with parasites with a thicker capsule, and in which the two chromatin masses are not always present. He called the parasite *Histoplasma*. Some authorities consider them more allied to yeasts than to the parasites of kala-azar.

**Cutaneous System.**—Darkening or pigmentation of the skin is sometimes very marked, especially among dark-skinned patients. The skin of Europeans suffering from this disease often has a dull, dirty appearance. Except for occasional petechiae, there are no special skin eruptions in kala-azar.

Cancrum oris is frequently met with in the last stages of kala-azar, especially in children. Although nearly always fatal, cases have been recorded in which its appearance
has been followed by great improvement in the general symptoms and even in subsequent recovery.

Diagnosis.—With regard to the diagnosis of kala-azar, it may at once be said that this cannot be made with certainty except by the demonstration of the specific parasite. In Assam, where the disease was first recognized, medical practitioners who have been familiar with it for many years admit that in the early stages kala-azar cannot be readily distinguished clinically from malaria, or sometimes from enteric, and that even in the later stages a consideration of the history of the patient is necessary before any conclusion can be arrived at. Should the patient be from an infected house or village, and should the development of his cachexia have been more rapid than is usual in malaria, he is considered to be suffering from kala-azar, otherwise the diagnosis of his disease is likely to be malarial cachexia. In Madras, too, all of the patients in whom the earliest discovery of the parasite had been made during life had been considered to be suffering from malarial cachexia, and this in spite of the fact that no malarial parasites could be discovered by repeated examination of their blood. Of the early investigators of the disease, one believed that it was ankylostomiasis, others that it was a special epidemic form of malaria, while yet another believed it to be undulant (Malta) fever.

An important feature for the clinical differentiation of kala-azar from malaria is the resistance of the former disease to quinine, and should this resistance be definitely proved, the latter may be excluded. It is important to note, however, that the two diseases may co-exist, and that therefore the demonstration of malarial parasites in the blood and their disappearance following the administration of quinine cannot be considered as definitely excluding in suspicious cases the diagnosis of kala-azar. In such cases, should the temperature show a double or triple daily curve, and should there be little or no digestive disturbance, the likelihood of their being kala-azar
KALA-AZAR

is considerably increased. It is only in the early stages that kala-azar is likely to be mistaken for enteric fever, from which the points just mentioned should serve to distinguish it.

The examination of the blood is an essential preliminary step in the diagnosis of kala-azar. The combination of marked leucopenia with relative increase in the number of mononuclear leucocytes at once differentiates it from a number of diseases which at some stage or other resemble it in some respects, but in which this condition is absent. Such are enteric fever and undulant fever among acute diseases, and splenic anæmia (Banti's disease) and spleno-medullary leucocytæmia among chronic diseases, in all of which the spleen may be considerably enlarged, and a varying degree of anæmia present, but in which the number of leucocytes is increased—in the chronic anæmias very greatly so. In patients suffering from tropical abscess of the liver there is usually leucocytosis. This may not be marked in some cases, but there is no leucopenia. A blood count would differentiate the two diseases, the total number of leucocytes being in excess in hepatic abscess and diminished in kala-azar.

The diseases other than kala-azar in which leucopenia is combined with a relative mononuclear increase are malaria and trypanosomiasis. In malaria, however, leucopenia is less marked than in kala-azar, the relative proportion of white and red corpuscles remaining the same as in normal blood, about 1 to 750. In kala-azar, on the contrary, the diminution of white corpuscles is much greater than that of the red, the proportion falling as low as 1 to 1,500, or even as 1 to 3,000.

In ankylostomiasis there is leucocytosis at the onset of the disease with marked eosinophilia.

Examination of the blood alone should not, however, unless the specific parasites of these diseases are recognized, be relied upon to differentiate them from kala-azar.

To place the diagnosis beyond doubt the demonstration of the parasite of kala-azar is necessary. The parasite is
most readily obtained by puncture of the liver or spleen. The risk of haemorrhage following puncture of the spleen may be great in kala-azar and has been fatal. It is preferable to puncture the liver. The method of puncture is as follows:

The syringe and needle must be sterilized dry, as any admixture with water may cause a breaking up of the parasite. The skin over the site selected for puncture must be thoroughly sterilized and the needle plunged deep into the liver with a slight rotatory movement. When well in the liver the syringe will move with the respiratory movements. The needle should be kept in position for about a minute and slightly withdrawn before gentle aspiration is attempted. The less blood that is present the more satisfactory is the operation, as the parasites are not in the blood, and any blood present only serves to dilute the fluid and render it more difficult to find the parasite.

The fluid withdrawn should be blown out on to a series of slides, making as thin films as possible. These films when dry may be stained with Leishman's method, or, after fixation, with dilute, 1 in 4, freshly filtered carbol-fuchsin. The parasites may be numerous in such films, or scanty, and several films should be examined before a negative diagnosis is given. They can be recognized by the presence of two chromatin masses, one small, rod-like and deeply staining, the other larger, oval, and staining less deeply. Cochran has shown that in cases in China the parasites may be readily found in the superficial lymphatic glands even when they are very scanty in the liver and spleen.

**Prognosis.**—The mortality of kala-azar is very high. In Assam the mortality was estimated at 96 per cent., but it is most likely that the remaining 4 per cent. of the patients were suffering from malarial cachexia, the difficulty in the differentiation of which from kala-azar by clinical methods alone has already been mentioned. In Madras the case mortality is recorded as 98 per cent.
One recovery has been known of a patient invalided to England in whom the diagnosis was fully confirmed by liver puncture, and in whom parasites were also found in leucocytes in the peripheral blood. Rogers, however, believes that a fair proportion of the cases recover if properly treated.

Pathological Anatomy.—The most noticeable feature in the morbid anatomy of kala-azar, apart from the great emaciation, is the enlargement of the spleen and liver. Besides this, inflammation and ulceration of the large intestine, and some degree of ascites or oedema are common. The spleen is almost invariably very greatly enlarged, sometimes weighing over 80 oz.; it is of firm consistency, retaining its shape on removal. There is usually no thickening or inflammation of the capsule. On section the surface is dark red, and the spleen substance is firm and friable; should, however, the examination have been delayed, especially in warm weather, the spleen substance will be found to be soft. There is no malarial pigmentation, and there are no infarcts. Microscopical examination reveals great dilatation and enlargement of the splenic capillaries, with reduction in the lymphoid elements. Scattered irregularly throughout the organ are enormous numbers of parasites, the Leishman bodies. These are contained chiefly in the cells lining the lymph spaces and in the endothelial cells of the capillaries. They also occur in the spleen cells themselves, and in leucocytes, chiefly in the mononuclear, but also in some of the polymorphonuclear cells. They are not met with in the Malpighian corpuscles or lymphatic follicles.

The enlargement of the liver is usually less than that of the spleen in proportion to the relative sizes of the organs. Like the spleen, the liver is of firm consistency and friable. It is usually rather paler than normal and presents a nutmeg appearance, this being due partly to the growth of mononuclear cells, chiefly in the centre of the lobules, and partly to fatty degeneration of the liver cells. Parasites are numerous in the endothelial
cells of the capillaries and lymphatics, and are also met with in free mononuclear cells, but do not occur in the liver cells themselves. Hæmosiderin is present both in the hepatic cells and in the spleen pulp.

Next to the spleen and liver the bone-marrow and lymphatic glands are the principal seats of the parasites, which occur chiefly in the large mononuclear cells; the marrow appears to be increased in amount and is redder than normal.

Should death have been brought about by dysentery, as is so commonly the case, the large intestine will be found thickened and inflamed, the descending colon and sigmoid flexure being chiefly affected. The inflammation sometimes affects the whole length of the large intestine, and may involve the lower part of the small intestine. There is great inflammatory infiltration of all the coats of the bowel, and frequently there are ulcers extending from the mucous to the serous coat, or even causing perforation; sometimes the mucous membrane is covered with a tough film of exudation.

The inflammation of the intestine does not appear to be directly due to the Leishman body, for but few of these organisms are usually found in its coat; they occur chiefly in the endothelial cells of the capillaries.

In uncomplicated cases the other organs of the body appear to be healthy, but even in this case parasites may be found, though sparingly, in the endothelial cells of the capillaries and lymph spaces of various organs, e.g., lungs, kidneys, suprarenal capsules, and lymphatic glands. Sometimes the mesenteric glands are enlarged, and contain the specific parasites in large numbers. In spite of the wide distribution of the parasite in the body it has never been found in any of the secretions or excretions during life. The difficulty of finding the organism in the blood has already been alluded to.

In fresh unstained preparations the parasites of kala-azar are difficult to see. They appear as rather refractile, motionless bodies of indefinite outline, almost colourless
or of a light greenish tinge, and may then be mistaken for blood platelets.

The organisms are best seen when stained by one of the modifications of Romanowski's method. So stained, they appear as sharply defined, round or oval bodies, between 2 μ and 3 μ in diameter, of a faint blue colour, and containing two masses of chromatin; one large, round, of a light violet colour, the other small and rod-shaped, and staining a deep red, almost black. The two chromatin masses are usually situated in the shorter diameter of the oval-shaped parasites, the larger at one pole, the rod at the other, with its length directed at the larger mass across the body of the parasite. The rod is usually sharply defined, but is sometimes reduced to a mere dot of deeply staining chromatin. The organisms are remarkably uniform both in size and appearance; they appear to possess a strong cell wall which resists distortion, and the relative size and position of the chromatin masses are very constant. The cytoplasm of the parasite shows little or no structure, but sometimes
vacuoles are seen in it. The parasites can also be stained by many of the basic aniline dyes, weak carbol-fuchsin and carbol-thionine perhaps giving the best results.

In smears obtained from the liver and spleen during life the parasites may either be free or contained in cells or embedded in a matrix. The matrix is not seen in smears made from organs after death, nor in sections in which the parasites always appear to be intracellular. In the great majority of cases the cells containing the parasites appear to be endothelial cells of capillaries and lymph spaces, either unaltered or of large size and irregular shape, constituting macrophages. The macrophages often contain large numbers of parasites, upon which they appear to exert no phagocytic action. On the contrary, under the influence of the parasites the macrophages undergo gradual disintegration, and in all probability furnish the matrix seen in ante-mortem smears, and the parasites are alive and capable of developing into flagellate forms.

Next to the endothelial cells the large mononuclear leucocytes most frequently harbour the parasites, and a few are found in the polymorphonuclear leucocytes; they also occur in the myelocytes of bone-marrow, but are not met with in parenchymatous cells.

When obtained post mortem, and especially if several hours have elapsed since the death of the patient, many of the parasites show changes indicative of development. They are larger, 3 μ to 5 μ in diameter, the chromatin masses show signs of division and may even be reduplicated, and commencing cleavage of the cytoplasm is seen, each half containing a large and a small chromatin mass.

In sections, owing to shrinkage, the parasites appear much smaller than in smears; the chromatin masses are closer to each other and the smaller has frequently lost its rod-shaped appearance.

Etiology.—The etiology of kala-azar is of special interest, both because of the repeated failures which have
attended the investigations undertaken for its elucidation, and because of the remarkable series of observations which have resulted in the discovery of the cause of the disease and the nature of the specific parasite, and probably of its mode of transmission and prophylaxis.

The great mortality caused by epidemics of kala-azar in Assam, during the last two decades of the nineteenth century, prompted the Government of India to send one medical officer after another to investigate the disease, and if possible to discover its cause and devise methods for its prevention. All the investigations so undertaken, although carried out with great care, failed in their object. One observer, influenced by the anaemia of the patients and by the discovery that many of them harboured ankylostomes, considered that the disease was essentially ankylostomiasis. Another came to the conclusion that kala-azar was malarial fever, in an intense and communicable form; and a third investigator, while noticing the absence of malarial parasites in the blood and of melanin pigment, thought that it was a form of malaria with marked incidence on the liver and spleen, and with a mortality enhanced by the concurrence of ankylostomiasis or of dysentery; another believed it to be undulant fever (Malta fever). The subject stood thus when, in May, 1903, Leishman published in the British Medical Journal a short note entitled “On the Possibility of the Occurrence of Trypanosomiasis in India.” A few years previously, in 1900, he had noticed in smears made from the spleen of a soldier, who had died at Netley of tropical cachexia and dysentery, contracted near Calcutta, enormous numbers of the small, round, oval bodies, with the two characteristic chromatin masses already described. As to the meaning of these bodies Leishman was at a loss. In 1903, however, he found almost exactly similar bodies in the spleen of a white rat, which forty-eight hours previously had died of infection with the trypanosome of nagana. Up to the time of its death the blood of this rat was swarming with trypanosomes, and experiments
proved that it was possible to trace every step in the degenerative changes which had led to the formation of the small rounded bodies, the two chromatin masses, one of which represented without doubt the macro- the other the micro-nucleus of the trypanosomes from which they had been formed (fig. 49). This second observation gave a clue to the explanation of the first, and Leishman felt himself justified in suggesting not only that the soldier had suffered from trypanosomiasis, but that “some of these severe tropical cachexias, such as Dum-dum fever, as well as kala-azar and sleeping sickness, might be due to trypanosomiasis. These suggestions have been justified to the extent that the parasites have been proved to develop flagella, and therefore belong to the flagellates.

In July, 1903, Donovan announced that some months previously he had seen the bodies described by Leishman in the spleens of several patients, who had died at Madras of what was considered to be chronic malaria, but he was not aware of their nature until he had seen Leishman's paper, and that he had since found identical bodies in the blood, obtained by puncture, of the spleen during the life of a patient suffering from irregular pyrexia, and in whose blood no malarial parasites could be found. In the following January, Bentley discovered similar bodies in spleen smears from living patients suffering from kala-azar in Assam, and since then numerous similar observations have been made as regards cases presenting similar symptoms, where the disease was contracted in or near Calcutta, and in certain other places in India and elsewhere. It may, however, be noted here that the parasite has not been discovered in patients suffering from “malarial cachexia and enlarged spleen” in the Punjab where organisms morphologically similar have been shown to occur in Delhi boils.

A further stage in the etiology of the disease was reached in November, 1904, when Rogers announced that he had observed the development from the parasite of flagella, leaving, as he said, “but little room for doubt
that the human parasite belongs to the flagellates." Rogers's observations have been confirmed by others, including Leishman (fig. 49).

The flagellate organism into which the Leishman body develops differs from a true trypanosome in that it does not possess an undulating membrane, and that its flagellum and micronucleus are situated at the blunter, posterior end of the parasite. It thus resembles a herpetomonas. Similar forms have, however, been observed in the so-called cultivations of true trypanosomes, and Rogers noticed forms in his cultures similar to those described by Bradford and Plimmer as occurring in the lungs of animals artificially infected with *Trypanosoma brucei*.

Mention may be made of the opinion expressed by Laveran and Mesnil that the Leishman body is a piroplasma, and of Ross's suggestion that it belongs to a new genus which he named *Leishmania*, calling the parasite *Leishmania donovani*. Both these opinions, however, were expressed before the development into flagellate forms had been observed. Rogers found that when the blood obtained by spleen puncture of patients suffering from kala-azar was mixed with sterile sodium citrate solution, and kept at a temperature of 22° C. for a few days, developmental forms occurred. The cytoplasm of

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**Fig. 49.**—*a*, Trypanosomes and the altered forms found in culture; *b*, Leishman-Donovan bodies and the altered forms found in culture.
the parasites increased in size, became granular, and the body became elongated, the macronucleus enlarged and the micronucleus migrated to the thicker end of the organism from which a flagellum arose. The protrusion of the flagellum was preceded by the formation in the cytoplasm surrounding the micronucleus of a rounded mass which stained with eosin, the rest of the cytoplasm staining blue with Leishman's stain.

In one instance long, flagellate forms were developed within twenty-four hours, these chiefly occurring in pairs. In later experiments (1905) Rogers has found that the development of flagellated forms from kala-azar parasites takes place more freely and with greater regularity in an acid than an alkaline medium, and that sterility of the medium is essential. This has led him to suggest that the intermediate host of the parasite might be the bed-bug, the intestinal contents of which he found supplied these conditions. Working on this hypothesis, Patton has announced that he has been able to trace the complete cycle of the parasites up to completely developed flagellates in certain tropical bed-bugs, and that in his opinion there is no doubt that the Indian bed-bug, *Cimex rotundatus*, transmits the disease.

The rarity of the occurrence of the parasites in the peripheral blood has been advanced as an argument against this method of infection. Donovan has, however, shown that they occur in the peripheral blood in the leucocytes intermittently in all cases of kala-azar, and at times may be fairly numerous. It must also be remembered that trypanosomiasis can often be transmitted by the injection of blood, the microscopical examination of which fails to reveal any parasites.

In the Assam epidemics kala-azar spread slowly from village to village along the lines of communication. Isolated villages, or those to which persons from outside were not admitted, remained free from attack, and the common history of infected villages was that some person had arrived there suffering from the disease; after a short
time the members of his household were attacked and the disease gradually spread from house to house. Rogers reports that he has observed a similar house or family incidence among his hospital cases of kala-azar at Calcutta.

All these facts, as well as the success which has attended attempts to stamp out epidemics of kala-azar in Assam by the isolation of patients, coupled with the burning of infected huts, is in favour of the view that the disease is transmitted by some house-infesting parasite, such as a bug.

A suggestion, based upon the consideration of the low temperature at which the flagellate forms are developed in vitro from the oval forms obtained from the spleen, is that the parasites escape in the feces and undergo a stage of development in some cold-blooded animal, a fish or mollusc, and that they obtain entrance into the human body by the ingestion of such alternative hosts, either direct or through the water supply. There is, however, no experimental evidence in support of this suggestion, and the circumstances that the parasites cannot be found in the feces, and that a sterile medium is required for the development of flagellate forms, are opposed to it.

The seasonal prevalence of kala-azar, as shown by the number of fresh attacks, is greatest in the cold weather months, November to April, in Assam and Lower Bengal. The "cold weather" temperature in this area ranges between 60° and 75° F., and Rogers points out that it is only within these limits that developmental forms of the parasite are obtainable in vitro. He suggests that epidemics of kala-azar have been due to a succession of periods of prolonged cold weathers, which have extended the conditions favourable to the extra-corporeal development of the parasite. He further suggests that the more severe cold weather of North-west India accounts for the absence of kala-azar there.

As has been seen, kala-azar when epidemic may carry off entire households, persons of either sex and all ages
being liable to attack. Rogers states that males and females are attacked in equal proportion, and that infants and old people are less liable than others to the disease, while it is commonest among children and young adults.

As to race, kala-azar is comparatively rare among Europeans in India, and occurs chiefly among the poor, whose domestic hygiene in places like Calcutta resembles that of natives. In Assam it has been noticed that infection of Europeans is often traceable to cohabitation with natives, or to occur in missionaries and others whose duties bring them into close contact with natives. Rogers has pointed out that, in contrast to the case of enteric fever, kala-azar occurs more commonly among Europeans who have lived some years in India than in newcomers.

 Treatment.—Once kala-azar has become well developed no treatment seems to have any effect upon the course of the disease. It is claimed by some that quinine in very large doses may arrest the disease at a very early stage, but it is possible that cases responding to quinine are malarial. Besides quinine a very great number of drugs have been tried—arsenic, the salicylates, and also bone-marrow—but with little effect. More recently atoxyl has been given, but the results are not rapid, though in one case so treated, that of which the charts are given, recovery has taken place. Salvarsan has been tried, and in infections with similar parasites in the lower animals with highly satisfactory results.

 In man it is worth an extensive trial, but the results so far recorded are conflicting.

 It is possible that careful attention to the general health of the patient, coupled, in the case of Europeans, with residence in a temperate climate, and living as much as possible in the open air, may prolong life a little, and it is important that such measures should not be neglected, for they at any rate add greatly to the patient's comfort, and throughout the disease treatment must be symptomatic.
The marked improvement in the condition of kala-azar patients who have recovered from an intercurrent attack of some inflammatory affection suggests the trial of measures for inducing leucocytosis.

The diet should be liberal, but it is important to avoid overfeeding and foods difficult of digestion, for, as has been seen, the voracious appetite of kala-azar patients, if unchecked, frequently results in digestive troubles.

**Prevention.**—In view of the part played in all probability by the Eastern bed-bug, *Cimex rotundatus*, in the transmission of kala-azar, cleanliness, domestic and personal, is the best safeguard against the disease. In countries where the disease prevails, every effort should be made to rid houses of these parasites. Old bug-infested houses should be abandoned and burnt, as it is very difficult, if not impossible, to free such houses from bugs by milder measures. In other circumstances, should the disease appear, the patients should be isolated, the infected houses thoroughly fumigated with sulphur or pyrethrum, all beds and furniture likely to harbour bugs soaked in boiling carbolic solution or similar disinfectant, and all clothes and bedding similarly disinfected. Segregation of patients and the burning of infected huts have proved successful in dealing with outbreaks of kala-azar in Assam.

**Varieties.**—The specimens of the parasites obtained by Darling in Panama present certain differences, in that the parasites are larger and the ectoplasm more definite and thicker. In this form the lungs are more frequently attacked. It may be a different species.

**Infantile Kala-azar, Leishmania Anæmia.**—Splenomegaly, ponos, is a disease which occurs on the Mediterranean shores and in many of the islands, such as Malta, Cyprus, &c.

It is mainly a disease of early life, but each year more records of cases in adult life are reported. The main symptoms are irregular fever, splenic enlargement, and steady emaciation.
Clinical Course.—In many cases the first symptom noted is diarrhoea, sometimes accompanied by vomiting. Later there is irregular fever and steadily increasing anaemia. There is loss of spirits, steady emaciation, and sometimes attacks of epistaxis, bleeding from the gums or elsewhere. As the anaemia becomes more marked oedema of the feet becomes noticeable, and enlargement of the abdomen from the increase in size of the spleen. The pallor of the skin is of a peculiar yellowish white tint, not like that of an equal degree of anaemia from other causes. Though diarrhoea or other digestive disturbances are common, the appetite, as a rule, is not affected. In uncontrolled cases the prognosis is unfavourable, though it is rarely fatal in less than six months, and may last for years. Spontaneous recovery does take place.

Pathology.—The spleen and, to a smaller extent, the liver, are enlarged, and the parasites, apparently morphologically identical with those of kala-azar, are found in numbers. The lymphatic glands are not enlarged. The blood shows great reduction in the number of red corpuscles, which may be as low as 1,000,000 per cubic millimetre, and there is a diminution in the amount of haemoglobin, not, as a rule, to the same extent as that of the number of corpuscles. There is leucopenia in many cases, but not to as extreme an extent as in Indian kala-azar. The mononuclear elements are usually in increased proportion. In many cases the increase is in the large mononuclear elements.

Treatment.—Spontaneous recovery takes place in a small proportion of cases, and recoveries have taken place after injection of salvarsan, though in other cases the results have not been satisfactory.

Etiology.—Nicolle, to whose work our knowledge of this disease is largely due, discovered that in the districts where this disease is endemic a certain proportion of dogs are naturally infected with a similar parasite. Injection, either of the juices from the tissues or of cultures of the organisms from them, are followed by infection of
the dogs. These observations have been fully confirmed by other investigators.

**Canine Leishmania.**—The course of the disease is comparatively mild, though there may be a certain amount of pyrexia and emaciation. The parasites may be found in large numbers in the liver, in the spleen, and in the bone-marrow. A considerable proportion of dogs have been found infected naturally, though the proportion varies both according to district and according to season.

Whether the disease in man is derived from dogs is at present unknown. It is possible that they form the reservoir, and some experiments show that *Pulex serraticeps*, which will occasionally feed on man, can serve as a carrier of the disease, as parasites develop in these fleas. Attempts to infect dogs with the parasites of kala-azar in India have failed.
CHAPTER XII.

ORIENTAL SORE.

ALEPPO EVIL, AURANGZEBE, BOUTON DE BAGHDAD, CLOU DE BISKRA, DATE SORE, DELHI BOIL, FRONTIER SORE, ORIENT BUELE, YEMEN ULCER.

The various names mentioned above, and many others, are given to ulcers occurring in Algeria, Egypt, Asia Minor, the Levant, Cyprus, Arabia, Persia, Northern India, the Sudan, and South America and Panama, and other subtropical countries. Possibly these are different forms due to parasites which morphologically are indistinguishable. These ulcers are characterized by the thick crusts which form on their surface, and by their great chronicity. There are several distinct types, some scaly and not ulcerating.

(1) A non-ulcerating form, the usual one in the Sudan, but not rare in India.

(2) Superficial flat ulcer, the usual form of frontier sore.

(3) Deep ulcer with overhanging raised edges, the common form in Arabia, India, and South America.

The affection begins as a small red, itching papule, resembling the effect of a mosquito bite. This soon increases in size, becomes shiny and transparent, and surrounded by a red areola. In the non-ulcerating form this simply gets larger, lasts for some months and slowly subsides. Later in the ulcerating forms there is a serous discharge which, together with desquamated epithelial scales, form a crust which is often studded with small yellow points. Underneath the crust ulceration takes place, until the crust giving way, an indolent ulcer is
Fig. 50.—A case of Leishmaniasis from South America.
(Photograph by R. McKay.)
(From the *Journal of the London School of Tropical Medicine.*)
exposed, which slowly spreads. The surface of the ulcer is studded with flabby red granulations, which bleed readily on pressure; its base is freely movable over the subjacent tissues, and its edges are raised, irregular and slightly indurated. There is always a considerable amount of thin, serous or purulent discharge which coagulates, forming dirty yellow crusts. The degree of pain varies; often there is little or none, but sometimes, especially if irritated, or if the discharge be pent up by thick scabs, the ulcer is very painful and the edges acutely tender.

The ulcer slowly spreads in an irregular manner for some time, often for several months, and either of itself or by coalescing with similar ulcers forms a large open sore an inch or two in diameter. After a time the ulcer ceases to spread and slowly heals, the healing process being often interrupted by the retention of the discharge beneath the crusts. Depressed, pitted, and pigmented but superficial scars are left which may be mistaken for those of syphilis. These ulcers are most common on exposed parts of the body, especially on the face, neck, wrists, and on the back of the hands and dorsum of the feet. They may be single, but are more commonly multiple, and are irregularly distributed. There is usually no enlargement of the lymphatic glands. As a rule, there is no constitutional disturbance, but if numerous and severe the ulcers lead to gradual impairment of the health.

The South American form (Plate III, fig. 50) is sometimes known as "Forest Yaws." It has no connection with yaws, *Frambésia tropica* (figs. 57 and 58).

The Sudan type (Plates IV and V, figs. 51 and 52) is one of the non-ulcerating forms. The growths commence as small, pink, circular points raised above the skin, which gradually increase in size, and round them other similar papules form. These coalesce with the primary tumour, and an irregular mass is formed, pink in colour and with a smooth shining surface. They are soft to the feel and
freely movable over the deeper tissues. They do not break down, ulcerate or caseate, but may last for years. A somewhat similar non-ulcerating form occurs in Egypt. There are no constitutional symptoms.

**Pathological Anatomy.**—Oriental sore is essentially an infective granuloma. The proper elements of the skin and its accessories, the hair and sebaceous follicles, and the sweat glands, are invaded and destroyed by granulation tissue, which extends deeply into the corium and necroses superficially, thus producing an ulcer. In the early stage, before an ulcer is formed, there is proliferation of the cuticular cells leading to the formation of papules; later this proliferation extends a little in advance of the edges of the ulcer. The cells composing the granulation tissue are almost exclusively of the mononuclear type. They are large rounded cells with prominent nuclei, and are apparently of endothelial origin. The appearance is thus very different from that of simple ulceration of the skin, in which polymorphonuclear cells predominate. A few of these cells also occur in Oriental sore, but giant cells, such as those seen in tubercular and some syphilitic affections of the skin, are not met with.

Scattered throughout the granulation tissue, but chiefly contained in the large mononuclear cells, are vast numbers of parasitic organisms, very similar to those occurring in kala-azar. These bodies were first described as occurring in Oriental sore by Wright, of Boston, in 1903. He discovered them in an ulcer contracted in Armenia some months previously. The discovery was confirmed, as regards similar sores contracted at Delhi, Lahore, Quetta, and other places in Northern and Western India, by James in 1904, and as regards Egypt by Billot, and by Darling and others in the South American form. The parasites, *Leishmania tropica*, are indistinguishable morphologically from those of kala-azar, a description of which will be found on p. 165. James described the occurrence in some of the parasites of a third chromatin mass—a rod tapering towards the micronucleus and at right angles
FIG. 51.—Growth on face, neck, and left arm.
to it. He believed it not to occur in the organism of kala-azar, but it has since been shown to do so sometimes. In artificial cultures some of the parasites develop a flagellum, just as the parasites of kala-azar do, and, as a rule, the development in suitable media is more rapid and the flagellates are larger. Men and monkeys have been successfully inoculated and a local lesion results sometimes six months or more later. With the appearance of the local lesion there may be fever and constitutional disturbance. In dogs these results vary, as either a local lesion may result or a general disease of a mild type.

Etiology.—From the great abundance throughout the cells composing the granulation tissue of Oriental sore of the binucleated organisms described by Wright and James, it seems highly probable that these are the cause of the disease. How they enter the body is unknown, but long before their discovery the malady was considered to be of a parasitic nature, and various parasitic bodies were described as occurring in the affected tissues. Among these mention should be made of the bodies described in 1885 by Cunningham, and considered by him to be monadina. From his description and figures there can be little doubt that the bodies he considered to be parasites were the large endothelial cells containing the organisms described by Wright and James, the magnification and staining methods at his command not admitting of more precise differentiation. It may be added that Cunningham’s description of the histological appearances of the sores is in close agreement with those of Wright and James.

While many of the earlier observers agreed that water was in some way responsible for these sores, some attributed them to its chemical contents, and others to its containing parasites which were ingested or entered through abrasions in the skin. Other suppositions are that these sores are the result of bites of mosquitoes or of sandflies or other biting flies, or that the parasites exist in the soil
and are directly inoculated by accidental abrasions. It is at least possible that infection may be carried directly from an Oriental sore to simple ulcers or wounds by flies so common in places where the disease is prevalent. The circumstance that these sores are most common on parts of the body not protected by clothes, and especially on the face and neck which are not particularly liable to abrasions, is in favour of the view that the parasite is introduced by some biting insect, the nature of the organism favouring this view.

It has been suggested that true Oriental sore only occurs in countries in which camels are in common use, and that infection is in some way derived from camels. The disease, however, is more prevalent among town-dwellers than among those who have especially to do with camels or who usually lead a nomadic life.

It has been shown that Oriental sore can be directly inoculated in man, and there is a strong popular belief that recovery is followed by immunity, so much so that in certain places it is the practice to inoculate children on unexposed parts of their bodies with matter taken from such sores, with the object of avoiding disfigurement of the face. Attempts have been made to inoculate dogs with pus from Oriental sore, with a certain amount of success, but some monkeys are susceptible to inoculations. Sores occurring in dogs at Delhi, and locally believed to be of the same nature as Delhi boils in man, were shown by James to contain numerous spirilla, but no Leishman bodies. After inoculation with the parasites dogs appear to be in good health and may not develop sores, but the parasites may be found in large numbers in their liver and spleen. Possibly dogs serve as the reservoir and man acquires his infection from them. No general infection of dogs is found in places where Leishmania tropica occurs as is found where infantile Leishmania anaemia occurs.

In places where Oriental sore is very prevalent children are the principal sufferers, and newcomers are specially
Fig. 52.—Neck growth from same case as fig. 51 (twice natural size).
liable to attack. Where less common, persons between 15 and 30 are most affected. Otherwise, age, sex and race appear to be without influence. The seasonal prevalence varies in different places, but the attacks appear to be most common at the beginning and end of the hot weather.

Diagnosis.—The description given above should be a sufficient guide to the nature of the affection, and the diagnosis can be established by the discovery of the specific parasite. Syphilis is the disease for which Oriental sore is most likely to be mistaken. The absence of the other symptoms of syphilis and the failure of antisyphilitic treatment should enable a correct diagnosis to be made.

Treatment.—The treatment of Oriental sore, unless thoroughly carried out, is very unsatisfactory. Medication by the mouth has no effect, but Nicolle and Mauceaux had excellent results from salvarsan, a simple 0·6 gr. dose being followed by the healing of the ulcers in three weeks. If protected from irritation the sores heal very slowly, but with slight scarring. Of local applications, copper sulphate solution, 1 to 4 per cent., sometimes gives good results. Cardamatis' ointment, composed of methylene blue and lanolin, has been used with apparent benefit in some cases, whilst Row has recorded cases of cure from inoculation with killed cultures of the organisms. If the diseased tissues are completely destroyed healing is more rapid but the scar may be greater. In the early stage complete excision may be possible, but failing this, the surface and edges of the ulcer should be thoroughly scraped and ordinary antiseptic dressings applied. Should scraping be considered inadvisable some caustic application, preferably strong carbolic acid, may be applied. Others use caustic alkalies, such as potassa fusa. Change of air is often of great benefit in obstinate cases.

Prevention.—In the present state of knowledge concerning the manner in which Oriental sore is contracted it is
not possible to give precise directions for its avoidance. The proved inoculability of the ulcers suggests the importance of measures to avoid direct contagion, these including, besides personal cleanliness, the covering of the sores with some antiseptic application. Until it has been shown that the water of places in which the disease prevails is innocuous, it would be well to boil it before use, either for drinking or washing. Similarly, the bites of insects and contamination by flies are to be avoided.

It is well not to allow dogs in the houses and to discourage any close contact with these animals.
CHAPTER XIII.

RELAPSING FEVER.

Famine Fever; Spirillum Fever; Fièvre à Rechutes; Rückfallsfieber.

An acute infective fever characterized by the presence of spirilla in the blood and by the common occurrence of relapses. Relapsing fever was formerly common in the British Isles, especially in Ireland, where the association of its attacks with famine gave it the name of "famine fever." Epidemics, also associated with scarcity, have occurred in several countries of Northern Europe, most commonly in Russia, where there have been recent outbreaks. There was also an outbreak in Austria in 1903. In its epidemic form the disease is now most common in India, more particularly in the Bombay Presidency. Outbreaks have also occurred in recent years in Northern China and in Egypt, and cases have been met with in various parts of the world, including Mexico, New York, Cuba, London, Northern Africa, the Sudan, Palestine, Hong Kong, and the Philippines.

The disease is probably much more common than is supposed, for without systematic examination of the blood isolated cases are almost certain to escape recognition. With such examination it would probably be recognized at any large seaport among the crews of vessels arriving from the Tropics.

Incubation.—The most common duration of the incubation period of relapsing fever is two to five days. The extremes which have been noted are twelve hours and eight days.

The course of an attack of relapsing fever is commonly as follows:—
Clinical Course.—After a few hours of malaise the patient is suddenly seized with chills, and in two or three hours he is suffering from high fever, with a hot, dry skin, with rapid pulse, severe frontal headache, and great pain in the back and limbs. Bilious vomiting sets in, accompanied by much thirst and by pain and tenderness of the upper part of the abdomen. Considerable prostration ensues, and by the second day of his illness, if not earlier, the patient takes to his bed. Here he lies for about a week, his tongue becomes dry and coated, his bowels constipated, and his liver and spleen enlarged and tender. Jaundice may supervene, and slight bronchitis is common at this stage.

The patient is troubled with sleeplessness (the insomnia resembling that of a patient with delirium tremens), or he may be delirious. His aspect is weary, his face livid, and his condition appears to be very serious. On or about the seventh day, however, a crisis occurs. Following a brief increase in the severity of the symptoms, copious perspiration sets in, the temperature falls very rapidly, and symptoms of collapse may follow, not infrequently accompanied by diarrhoea or even dysentery. In a favourable case, however, the collapse is not serious: the patient falls asleep and wakes after a few hours, apparently convalescent. After about a week of this seeming convalescence the patient is subjected to another attack of fever commencing almost as suddenly as the first.

The symptoms of the relapse are similar to those of the initial attack, but milder, though the fever may be higher and the debility more pronounced. The duration is, however, shorter. A second crisis occurs on or about the fifth day, and is usually followed, after a short convalescence, by complete recovery. Sometimes, however, a second, and in decreasing frequency a third, fourth, or fifth relapse may occur. On the other hand, there may be no relapse. Some cases are cut short by death in the first attack.

The suddenness of the rise and fall of temperature is a
startling feature of relapsing fever. Within a few hours
the temperature in the axilla reaches 103°F. or beyond.
While usually showing a diurnal variation of about 2°F.,
being lowest in the morning, the temperature remains at
a high level throughout the initial attack, with an upward
tendency as the crisis is approached. At the acme of the
fever a temperature of 105°F., 106°F., or even higher, is
not uncommon, but as it is not long maintained is of less
serious import in this than in most other acute fevers.
The crisis, while usually occurring on the seventh day of
the primary attack, may often be accelerated or delayed

![Graph](https://via.placeholder.com/150)

**Fig. 53.—Relapsing Fever. Indian.**

a day. Rarely the crisis occurs on the ninth day, or
still more rarely on the fourth. Whenever it occurs the
critical fall of temperature is usually very sudden, reach-
ing the normal point or, more commonly, a degree or
two below it within twelve hours.

The temperature remains subnormal for two or three
days, then rises to the normal point, where it remains
until a relapse occurs. The course of the fever in relapses
is similar to that of the initial attack, tending, however,
to be less abrupt in its onset, to show greater daily
oscillations and to be of shorter duration. In fact, all
the symptoms of a relapse are less typical than those
of the initial attack. The interval between each suc-
cessive relapse also tends to be longer. Thus, while the
ordinary duration of the initial attack is seven days, and
of the first apyrexial interval also seven days, the first relapse usually lasts five days and the second only two or three days, while the interval between them is commonly nine days. It will be evident that an attack of relapsing fever with only one relapse lasts nearly three weeks.

Considerable variations may occur in the temperature of relapsing fever. Instead of by crisis, for example, the fever may subside by lysis, and in some cases a secondary rise may abruptly succeed the critical fall.

The pulse during relapsing fever follows the course of the temperature, though with a tendency, more marked with each successive relapse, to lag behind. It rapidly increases in frequency with the onset of the fever and continues to rise, though more slowly, as the crisis is approached. Its rate commonly reaches 120 per minute during the first day of the disease—rather more than that in women and children—and by the third or fourth day of fever it may be 130 or even 140 per minute. With the crisis the pulse-rate falls, though less rapidly than the temperature. It may be unusually slow for a day or two following the crisis, after which it returns to normal until the relapse sets in.

Although at first bounding, the pulse of relapsing fever soon becomes soft and compressible, these features (which are almost invariable) becoming more marked in proportion to the duration of the disease.

Corresponding with the condition of the pulse, the heart almost invariably shows signs of weakness. The impulse soon becomes weak and the first sound prolonged and booming. In rare instances, and these almost always met with during the acme of the initial attack, sudden heart failure occurs, causing fatal syncope.

Respiration in an uncomplicated case of relapsing fever corresponds with the pulse. There is commonly slight bronchial congestion evidenced by cough and frothy expectoration. With no further complications than this, the breathing may be very rapid and the patient may suffer from acute dyspnœa at the acme of the fever,
which, however, is quickly relieved with the fall of temperature.

A frequent and serious complication of relapsing fever is pneumonia, which may be either of the lobar type or more commonly lobular.

The relation of the two conditions is liable to be overlooked, for while on the one hand the indications of serious pulmonary inflammation may be so slight as to be only discovered after death, on the other hand pneumonia may be the most prominent feature of the illness and may modify the crisis or obscure the onset of a relapse. The onset of pneumonia is most common towards the end of the initial attack, but may be earlier, or not until the commencement of a relapse. It may sometimes be indicated by a diminution in the severity of the general symptoms shortly before the crisis is due. The temperature and pulse-rate fall, breathing becoming more frequent, and working of the alæ nasi may be observed. The headache and bodily pains diminish and there is less epigastric discomfort. Examination of the chest will reveal the ordinary physical signs of pneumonia. There is, however, less tendency to involvement of the bases of the lungs than in primary pneumonia. It is always accompanied by pleurisy.

Reference has been made to the thirst, vomiting, and epigastric discomfort of relapsing fever. The severity of the thirst is often a striking symptom. It is associated with a dry tongue, which quickly becomes coated with brown fur, except at the tips and edges. Following the crisis the tongue soon becomes clean and the thirst diminishes.

Vomiting is a variable symptom. It is usually not serious, but the irritability of the stomach may render feeding difficult and aggravate the thirst.

The vomited matter is usually greenish, a mixture of bile and mucus, occasionally containing streaks of blood. In rare instances "black vomit" has been observed.

The epigastric discomfort which is so common a
symptom is due to catarrhal inflammation of the stomach, partly also to active congestion of the liver and spleen.

While the constipation of the early period of relapsing fever is constant enough to be of some diagnostic value, severe diarrhoea not infrequently occurs at the crisis, the stools sometimes containing blood.

Occasionally there is actual dysentery, depending probably upon previous infection.

Pain and tenderness of the liver and spleen are early symptoms. Both organs are enlarged, the spleen especially, and both rapidly diminish in size after the crisis.

Frequently associated with enlargement and tenderness of the liver is jaundice, though this symptom is more common in some epidemics than in others. It usually commences about the fifth day of the initial attack, disappearing a few days after the crisis. Its intensity varies greatly, but while usually slight and transient it may sometimes be very intense.

The urine is dark and scanty during the febrile stages of relapsing fever, and also during the early part of the apyrexial period. It is of rather low specific gravity (1010 to 1015), and contains an excess of urea. A small amount of albumin may occur, and granular casts may be found; blood is uncommon. When jaundice is present the urine contains biliary pigments.

Mention has been made of the hot, dry skin of the febrile stage and of the sweating at the crisis of relapsing fever. The skin, though dry, does not feel as hot as might be expected from the bodily temperature, thus differing from the condition observed in certain other acute febrile diseases, pneumonia for example.

The critical sweats are usually very profuse, even more so than in malaria, and may saturate the clothes and bedding.

Night sweats sometimes occur after the crisis, and during relapses the skin may often be moist.

While there is usually no rash in relapsing fever, facial
herpes is not uncommon. In certain cases small rose-coloured spots, something like those of enteric fever, but smaller, are met with. They come out in crops, which, commencing near the crisis of fever, may continue into the apyrexial period. These papules are most common on the front and sides of the chest and abdomen. They are never very numerous, last only a few days, and disappear on pressure without leaving a stain.

Sudamina are common, and in rare cases petechiae are met with.

Desquamation, except in the form of minute branny scales following sudamina, is uncommon.

Complications.—The more important complications of relapsing fever are pneumonia, severe diarrhoea, or dysentery, and have already been dealt with.

Mention may here be made of the liability of a small proportion of cases to haemorrhages. Epistaxis at the acme of fever is the most common example. Haematemesis may also occur, and more rarely cerebral haemorrhage, always fatal, has been observed.

Swelling and inflammation of the parotid gland and of lymphatic glands, most commonly those of the inguinal regions, have been observed occasionally. This is of importance in connection with the differentiation of the disease from plague.

Inflammatory affections of the eye and ear sometimes occur, but are rarely serious in the Indian variety.

Inflammation of serous membranes are rare, but slight painful swelling of some of the joints, most commonly those of the upper limb, are not uncommon.

Pregnant women always abort; the abortion is generally followed by recovery.

The co-existence of relapsing fever, with malaria, smallpox, measles, plague, and diphtheria has been noticed, and in certain epidemics, following famines, with scurvy.

There are no special sequelae of relapsing fever, though mental and bodily weakness frequently persist for some time. A certain degree of immunity is conferred by an
attack of relapsing fever, but only lasts a short time, as two or even three attacks may occur in the same person.

**Prognosis.**—The prognosis of an uncomplicated case of relapsing fever is good. The mortality varies in different epidemics, probably depending upon the condition of the infected population. When the disease prevailed in Great Britain the mortality was estimated at about 4 per cent. A similar rate is said to be common in Russia. In Bombay, however, Vandyke Carter found that the mortality was 18 per cent. His statistics were, however, based upon hospital experience. The death-rate amongst cases treated in the municipal hospital in Bombay during the last ten years has been much higher than this, something like 30 to 40 per cent., and Choksy records 2,832 deaths out of 9,275 cases, from 1898-1907, an average mortality of 30.6; but in the northern parts of India the mortality is not high, nor is it in the form in which it occurs in North America, nor in that found in Egypt.

Death is most likely to occur during the acme of the initial attack and may be due to collapse or to heart failure, or may occur during collapse following the crisis. The risk is greater in the first attack. As might be expected, extremes of age are unfavourable.

The case mortality is slightly higher among women than among men, though abortion is usually followed by recovery.

In cases complicated by pneumonia the prognosis is unfavourable, recovery being rare.

Severe jaundice also renders the prognosis unfavourable, and, as has been seen, cerebral haemorrhage is always fatal.

**Diagnosis.**—While a typical case of relapsing fever is easily recognized, instances occur in which it is impossible to arrive at a correct diagnosis by means of the clinical signs alone, and the real nature of the disease may quite easily be overlooked, even at the autopsy. It can be understood, also, that a patient seen for the first time at
the acme of the fever or at the crisis might be thought to be suffering from malaria, while, but for the occurrence of the crisis, the diagnosis in severe cases might well be that of septicemic plague, especially should death ensue. It may be added that the pneumonic form of plague may resemble that of relapsing fever, though it is usually much more severe, and the very abundant blood-stained sputum, seen in pneumonic plague, is characteristic when it occurs.

It is quite possible that cases of relapsing fever accompanied by severe jaundice and bloody vomiting, occurring in countries in which yellow fever prevails, might easily be mistaken for that disease. The discovery of the *Spirillum obermeieri* in the blood is therefore sometimes the only means by which a positive diagnosis can be arrived at.

It is essential, therefore, that in all cases in which the diagnosis of relapsing fever is doubtful the blood should be carefully examined for this parasite. Moreover, in view of the differences which have been described in the spirilla of relapsing fever cases occurring in different parts of the world, and of the discovery of a similar parasite in the blood of persons suffering from African tick fever, the examination of the blood in cases in which the clinical diagnosis has been well established is of great interest and importance. It should be remembered that the spirillum can usually be found in the blood only during the febrile period, as it disappears at the crisis and reappears only with the onset of a relapse. This statement is not absolute, however, for cases are not infrequent in which spirilla have been discovered, though in greatly diminished numbers, in the blood of patients during the early part of the apyrexial period. For the discovery of the spirilla, either fresh, unstained, or dry, stained films may be used. In either case the search may be easy or difficult, depending upon the number of parasites present, this varying greatly. In some cases they may be so numerous as to make the whole of the field of the microscope seem in active motion, while in others careful
search of stained films is necessary to discover any. In examining fresh films it is an advantage to use dark-ground illumination.

The best staining method is probably Leishman's or other modifications of Romanowsky's stain. Failing this, gentian violet or carbol-fuchsin may be used. The spirillum is described under the heading of Etiology, p. 193. The blood of patients suffering from relapsing fever shows a condition of leucocytosis. The number of both polymorphonuclear and mononuclear leucocytes is increased. Sometimes this is very marked, and as there is also a diminution in the number of red corpuscles the excess of these over the leucocytes is greatly reduced.

The spirillum has not been demonstrated in any of the patient's secretions or excretions.

**MORBID ANATOMY.**

The bodies of patients dying of uncomplicated relapsing fever do not show any very characteristic gross changes. The condition is that of a general septicæmia with enlargement of the spleen and liver and catarrhal inflammation of the stomach—often also of the intestines and of the bronchi. Subserous hæmorrhages under the peritoneum, pericardium, and pleura are common. The enlargement of the spleen is usually very considerable, its weight sometimes reaching 5 lb., and its size exceeding the normal by five or six times.

The splenic capsule is distended and smooth, and the whole organ is rounded. The spleen substance shortly after death is firm and dark and mottled with small white spots, which are the enlarged Malpighian corpuscles; these may sometimes be breaking down into minute abscesses. Large wedge-shaped infarcts are common, usually having their base at the capsule, though they may be met with throughout the organ. When recently formed they are of a dark red colour, but later they become pale and may be found breaking down into pus.
Microscopically the hypertrophy of the spleen is found to be due both to proliferation of its cellular elements—especially of the Malpighian corpuscles—and to vascular engorgement. Spirilla may be found in the spleen both free and in polymorphonuclear cells, often in great profusion.

The enlargement of the liver is often marked and the weight may be as much as 5 lb. Though sometimes dark and congested, it is more commonly pale and mottled. Its substance is soft and the lobules are indistinct. There is cloudy swelling of the cells.

Besides the conditions mentioned, the heart is usually found to be pale and soft, the muscular fibres showing signs of cloudy swelling and sometimes fatty degeneration. The kidneys and other abdominal organs are also in the condition of cloudy swelling. The inflammation of the intestinal tract is often considerable. The stomach is the part most commonly affected and there are usually numerous small hæmorrhages beneath the mucous membrane. In cases complicated by diarrhoea or dysentery there is intense congestion of the ileum and colon, which may even be superficially ulcerated.

A certain amount of bronchial catarrh is usually found, but in uncomplicated cases the lungs are pale.

Two forms of pneumonic consolidation may be met with. The more common form is that in which patches of consolidation, often of considerable size, are scattered through both lungs; they may be met with in any part of the lobes and are not more common at the bases than elsewhere. The other form of consolidation is similar to that of ordinary croupous pneumonia.

While inflammation of the brain or its meninges is rare in relapsing fever, passive congestion as shown by venous engorgement and serous exudation is not uncommon.

Etiology.—Relapsing fever is remarkable in being the first disease shown to be due to a micro-organism. During an epidemic in Berlin, in 1868, Obermeier discovered in the blood of patients suffering from relapsing fever a spirillum, which since the publication of the
discovery in 1873 has been accepted as the cause of the disease. These spirilla are now commonly termed spirochætæ.

The *Spirillum obermeieri* or *Spirochæta recurrentis* is a delicate wavy thread measuring between 15 μ and 40 μ in length by about .25 μ in breadth at its widest part. The number of spirals varies greatly, as also does their contour. A common number of spirals is eight, but often two spirilla are joined together, giving the appearance of one long form with sixteen spirals. Sometimes the spirals may be short, giving a corkscrew appearance, or they may be only slight undulations. In thick films the spirilla may be in bold curves or figures of eight, with few or no undulations (fig. 54).

No details of structure can be made out except that it has tapering pointed ends, and that, especially when stained by Romanowsky’s method, slight differences in the degree of staining of different parts can be noted, the
central part staining least. Some observers have described a delicate terminal flagellum; the presence of flagella is denied by most authorities. A striking feature of the organism is its extraordinary motility, which is progressive as well as rotary and lateral. It is best stained by aniline dyes, especially by some modification of Romanowsky's stain, and also by carbol-fuchsin and gentian violet. It is decolorized by Gram's method.

When faintly stained by Romanowsky's method the parasite is blue, if the staining is prolonged it becomes red. All attempts to cultivate it have failed, but it can be kept alive in citrated blood outside the body for several days. Tictin found the spirillum in bugs fed upon patients suffering from relapsing fever and showed that they could survive in them for seventy-seven hours. He also succeeded in infecting monkeys with the fluids of such bugs crushed immediately after feeding, but when bugs had been killed forty-eight hours after feeding their fluids were not infective, although the S. obermeieri could be found in stained preparations. Karlinsky, in infected houses, found the spirillum in bugs, and that the spirilla could live in these for thirty-nine days. Nuttall has recorded the infection of one mouse from another through the medium of a bug which was fed first on the infected animal and then allowed to bite the uninfected mouse.

Blood containing the spirillum has been frequently inoculated into man, both deliberately and by accident, and has caused relapsing fever. Various kinds of monkeys have also been successfully inoculated. Until recently man and monkeys were considered to be the only susceptible animals, but Novy and Knapp have recorded the successful inoculation of white mice in which relapses occurred, and of white rats after a preliminary passage through a monkey.

The incubation period following inoculation in man is usually between thirty and thirty-six hours.

There has been a good deal of speculation as to the
interdependence between the presence of spirochaetes and the different phases of relapsing fever. An early view was that the fever resulting from the presence of the parasite in the blood caused its destruction and that relapses were due to the development of further generations of spirilla from spores. The existence of spores of *S. obermeieri* has, however, not been demonstrated. The blood of a patient during the apyrexial intervals will still infect monkeys if injected into them. Another view attributed the disappearance of spirilla to the formation in the blood of some bactericidal agent at the crisis, while a more modern view is that the spirilla are destroyed by phagocytosis, this destruction occurring chiefly in the spleen. The lengthening periods of interruption and the mildness of relapses is by others attributed to the acquirement by the patient of increasing degrees of immunity. This view is consistent with the probable protozoal nature of the parasite. The spirillum or *S. obermeieri* is one of a class of organisms of which many pathogenic species are known. These mentioned in the order of their discovery include *S. anserini*, the cause of septicaemia of geese; *S. theileri*, affecting cattle in South Africa; *S. gallinarum*, causing fever in fowls in Brazil, the Sudan, and elsewhere, and *S. duttoni*, the cause of African tick fever. These organisms resemble each other in their general morphology and active motility. They all occur free in the circulating blood during the febrile paroxysm and are no longer found after the temperature has fallen. In the intervals between the attacks of fever small actively motile bodies containing chromatin are found in some of the red cells.

It has furthermore been demonstrated that certain of them are conveyed by the bite of certain ticks; thus, *S. gallinarum* is transmitted by *Argas persicus*, *S. theileri* by *Boophilus decoloratus*, and *S. duttoni* by *Ornithodoros moubata*. No such demonstration has been made in the case of Indian and European relapsing fever, but a tick
very similar to *O. moubata—O. savignyi*—has been shown to occur in India.

In parts of Persia *Argas persicus*, the "miana bug," has long been believed to cause severe fever, and similar consequences are thought to follow bites of *A. turcata* in Mexico and Central America.

Mackie reports an epidemic of relapsing fever in a school in India, in which he believed the transmitting agent was *Pediculus vestimentorum* (fig. 55). The disease was much more prevalent in the boys who were infected with pediculi than in the girls who were less so. Fourteen per cent. of the lice from the boys were infected, and 2.7 per cent. from the girls. Spirochætes were found in the secretion expressed from the mouths of the infected pediculi.

Mention may be made of certain other spirochætes, such as *S. vincenti*, found in certain forms of gangrenous inflammation; *S. pallida*, described by Schaudinn in syphilitic lesions and believed to be the cause of this disease; *S. pertenuis* found by Castellani in yaws, and
others found in the mouth, in smegma, in tropical ulcers, and in certain tumours in mice. Whether the last two have any pathological significance is not known. Spirochaetes may be found in large numbers in the faeces in some cases of diarrhoea and in the expectoration in some forms of bronchitis.

The question as to whether spirochaetes are protozoa or bacteria cannot be fully discussed here. Formerly they were considered to be bacteria. As long ago, however, as 1888, Tamilensky suggested that the S. obermeieri might be only a stage of a haemocytozoan, and since 1904, when Schaudinn suggested that spirochaetes should be considered as protozoa, this view has been generally accepted. More recently (1906) Novy and Knapp have disputed Schaudinn’s conclusions, asserting that he was mistaken in his observations, and reclassifying the spirochaetes as bacteria.

The question must for the present, therefore, be considered an open one, but it is of interest to note that the known pathogenic species have certain features strikingly resembling those of organisms concerning the inclusion of which among the protozoa there can be no dispute. These features are the constancy and intensity of the blood infection, and, in the case of some at least, the transmission by alternative hosts.

A remarkable feature in the etiology of relapsing fever is the fact that although its local infectivity is very marked it does not spread widely except among populations living under uncleanly conditions. Thus, when outbreaks occurred in English towns, they were almost entirely confined to the Irish, and in the Bombay epidemics described by Vandyke Carter, the disease only affected overcrowded localities. It may, however, spread to other patients in a moderately well arranged institution or hospital in the Tropics.

At one time famine was considered to play such an important part in the etiology of this disease as to give it the name of “famine fever.” While, however, famine-
stricken individuals may offer less resistance to infection, it has not infrequently been found that attacks have occurred in the absence of any such conditions, as, for example, among bodies of workmen in receipt of good pay but living in dirty and overcrowded quarters.

The liability to attack of attendants on the sick has long been recognized. Doctors, nurses, students and hospital servants are frequent sufferers; laundry hands come under the same category.

Instances of place infection are common, successive occupants of a house, room, or ship being attacked, and the introduction of cases into a hospital has led to cases among other patients. An interesting example of ship-infection is furnished by the s.s. "Caledonia," in which cases of relapsing fever occurred in London in October, 1905, and again in June, 1906, these being the only cases known in this port during those years.

Treatment.—Till recently there was no specific treatment for relapsing fever. Quinine, eucalyptus, the salicylates, arsenic, iodide of potassium, and a variety of drugs have been tried with the object of cutting short the disease, but without effect. Salvarsan, whether given intravenously or by intramuscular injection, both cuts short the attack and prevents the relapses. Neosalvarsan will no doubt have the same beneficial effects. Treatment with the serum of hyperimmunized animals is promising.

As in all specific fevers, the patient should be confined to his bed in a well-ventilated room, and his strength should be maintained by careful feeding.

A point calling for special mention is the necessity for prompt and liberal stimulation on the earliest indication of heart failure or collapse. The early use of alcohol in moderate doses is advisable, and may be combined with strychnine. The collapse of the crisis is best met by hot drinks, e.g., hot brandy or whisky and water, and by hot blankets and hot-water bottles.

High temperature, per se, does not usually call for special treatment in relapsing fever. Antipyretic drugs
exert little effect upon it, and should be avoided on account of their depressing action upon the heart. Tepid or cold sponging may, however, be beneficial, the choice depending upon the height of the fever.

Thirst and vomiting may both be relieved by the frequent administration of small quantities of cold but not iced water. It is further important to let the patient have plenty of water or other cooling drinks, provided that they do not cause vomiting. The vomiting may require the application of a mustard plaster or other counter-irritant to the epigastrium, this also relieving the tenderness of the liver and spleen.

In view of the tendency to relapse, and thus to considerable duration of the disease, it is very necessary to see that the patient is properly fed. During the febrile period fluids only should be given. The best is milk diluted with soda-water, or with lime or barley water. During the apyrexial period, should there be no intestinal complications, easily digestible solid food may be given.

The constipation of the early stage is best treated by a mild aperient, but in view of the tendency to diarrhoea at the crisis, it is important to avoid violent measures. For the headache and insomnia, cold applications to the head and small doses of bromide and chloral are the best remedies. The treatment of other symptoms and of complications should be conducted on general principles and does not call for special remedies.

Preventive Treatment.—From what has been said with regard to the etiology of relapsing fever it would appear that cleanliness of the persons' clothes and dwelling and the destruction of vermin are the best safeguards against the disease. From an administrative point of view the condition to be prevented or overcome is that of overcrowding, for it is only under this condition, whether it be in city or camp, that epidemics occur. Should it be impossible to avoid overcrowding, it is important, in view of the probability of the transmission of infection by means of pediculi, bugs or similar
blood-sucking parasites, to see that the houses of the poor are kept free from dry dust, which harbours such parasites. Should outbreaks occur the patients should be isolated, and the clothing, bedding, furniture and dwellings of the patients and their associates should be disinfected. In the disinfection of furniture and dwellings, it is important to ensure that the disinfectant penetrates all cracks and crevices and destroys the insects and other parasites and their larvae which harbour in such places. Infected native huts should be burnt when it is possible.

Before a patient is admitted to the wards of a hospital his person and clothes should be freed from external parasites. In view of the possible transmission of infection otherwise than by external parasites, it is wise not to admit relapsing fever patients to the general ward of a hospital, and though active spirochaetes have not been discovered in any of the secretions or excretions, it is wise to adopt the same precautions in dealing with them as in the case of other infective diseases.

It is important to keep the patient either in hospital or under observation for at least fourteen days after the cessation of fever. This is in order to avoid any danger of his again becoming a source of infection should a relapse occur.
CHAPTER XIV.

TICK FEVER.

AFRICAN RELAPSING FEVER.

An acute specific fever closely resembling relapsing fever both in its symptoms and in being associated with the presence of spirochætes in the blood. Infection is transmitted by the bite of a tick.

Tick fever occurs throughout the greater part of Tropical Africa. Livingstone and other early travellers in Central Africa had recorded the occurrence of a fever attributed by natives to the bites of a certain tick, *Ornithodorus moubata*. The disease was well known to the Portuguese and other European inhabitants of the upper reaches of the Zambesi and in Central Africa, but it was not till 1903 that Philip Ross and Hodges, working in Uganda, discovered in the blood, first of an Indian, and later of Africans and of one European, suffering from symptoms similar to those of relapsing fever, a spirillum which they considered was probably identical with *Spirochæta obermeieri*. Following up this discovery, Philip Ross in 1904 demonstrated the presence of a spirillum in the blood of several natives of Uganda suffering from an illness which the patients themselves ascribed to the bites of ticks. Independently, but somewhat earlier, Nabarro had made the same discovery, but his researches were not published for some years.

In 1904 Dutton and Todd, working in the Congo Free State, also met with cases of tick fever, and showed that it was due to a spirillum which they also thought was probably identical with *S. obermeieri*. They were further able to reproduce the disease in monkeys by
submitting them to the bite of the ticks which had been caught in native houses, or which had been reared from the eggs of such ticks. These ticks were also identified as *O. moubata*. Dutton and Todd also gave the disease to monkeys, guinea-pigs and rats by injection of infected blood.

They were not able to find spirochætes in the ticks which transmitted the fever to monkeys, but Koch shortly afterwards, in German East Africa, demonstrated that not only the infected ticks were infective, but also that their eggs must be infected, as the second and third generations were capable of infecting susceptible animals.

Koch also successfully infected mice and rats by the bites of infective ticks and their offspring.

Breinl and Kinghorn, working at Liverpool with ticks infected in the Congo Free State, have been able to infect a number of laboratory animals with the spirochæte. While they were unable to separate this spirochæte from the *S. obermeieri* by any morphological differences, they showed that each spirochæte conferred immunity against itself but not against the others.

They therefore considered the spirochætes to be distinct species and named that causing tick fever *S. duttoni*. Attempts to transmit these infections by bed bugs failed. The symptoms produced in animals by inoculation of these two different species of spirochætes are very similar, but there are slight differences. Inoculation of *S. duttoni* produced a much more serious illness than that caused by *S. obermeieri*, often causing death, while no animals died of infection with the latter parasite. In monkeys inoculated with *S. duttoni*, the incubation period was usually shorter, the pyrexial attacks longer and the relapses more frequent than in those inoculated with *S. obermeieri*.

The symptoms of tick fever in man resemble very closely those of relapsing fever, so much so that Dutton and Todd, from their experience of it in the Congo Free State, expressed the opinion that the two diseases were
clinically identical. The sudden access of high fever, the headache, pains in the back and limbs, prostration, thirst, and vomiting are as characteristic of tick fever as of relapsing fever, as also the sudden crisis with profuse sweating, followed by an apyrexial period, and this again by one or more relapses. Enlargement and tenderness of the liver and spleen are symptoms common to both diseases, and herpes and epistaxis are frequently met with in both. Tick fever differs from relapsing fever chiefly in that the duration of attack is usually shorter, four days or less instead of seven, with comparatively longer apyrexial intervals and more frequent relapses. Diarrhoea is the rule in tick fever, while constipation is almost always a marked symptom of the early stage of relapsing fever. Jaundice is rarer and iritis commoner than in Indian relapsing fever.

A slight degree of bronchitis is common and pneumonia is also met with. As in relapsing fever, spirochaetes are usually found in the blood of patients suffering from tick fever only during the pyrexial period. Of the two diseases tick fever is the less severe, and death is rare among persons who were in good health previous to attack. It is said to be more severe in Europeans than negroes, this probably depending upon partial immunity, or tolerance, resulting from previous attacks in the latter. Facial paralysis is not uncommon after an attack.

The incubation period of tick fever is commonly about five days, but may be shorter or longer, the duration perhaps depending upon the severity of infection.

Diagnosis.—Before the discovery of the spirochæta in the blood many cases of tick fever were considered to be suffering from malaria, pneumonia, or other diseases. As in the case of relapsing fever, a correct diagnosis is often impossible without the demonstration of the spirochæta in the blood. From what has been said of the symptoms of the disease, as well as of the morphology of the parasites, it is obvious that the differentiation of tick fever or relapsing fever may sometimes be impossible without resort to experimental inoculation of animals.
In the autopsy of the fatal case which Dutton and Todd met with, the liver and spleen were enlarged, the heart muscle showed slightly fatty change, the lungs were pale but otherwise normal and the kidneys were enlarged and showed fatty degeneration. The other organs examined appeared normal, but there was some blood-stained fluid in the abdomen. The blood was fluid and resembled blood-stained water. Spirochætes were found in it at the time of the autopsy.

In animals dying of tick fever the *post-mortem* appearances are similar to those observed in relapsing fever in man. Thus, in *post mortems* on monkeys, Breinl and Kinghorn found the spleen to be greatly enlarged, deeply congested and very soft. It often contained hæmorrhagic infarcts and necrotic areas; similar changes were found in the liver; the lungs were œdematous and contained infarcts and the heart muscle was much degenerated. The lymphatic glands were frequently hæmorrhagic and all organs showed signs of congestion. Spirochætes were found in the spleen and bone-marrow and also in other organs.

The etiology of tick fever is indicated by its names, *i.e.*, tick fever and African relapsing fever. As the parasite can be cultivated outside the body in special media such as mouse broth, with mouse blood and yolk of egg, all of Koch's requirements for proving that the disease is due to the *S. duttoni* have been fulfilled. Previously, in view of the fact that infection can be transmitted by the offspring of ticks which have fed upon patients, even this condition was practically complied with. The subcultures retain their virulence.

That infection is ordinarily transmitted by ticks—the *O. moubata*—admits of little or no doubt. It is, however, of some interest to mention that although negroes have long persisted in attributing this rôle to the ticks, European medical men were unable to demonstrate it as a fact until quite recently. It has been seen that infection can also be conveyed by direct inoculation of blood
containing the spirochete. So far no other means of infection is known, and it has already been mentioned that attempts to transmit the disease by other parasites than ticks, namely bugs, have been unsuccessful.

Infected ticks can transmit the disease either immediately or by means of their progeny after an interval of weeks and months; the limit of the infectivity of such ticks is at present unknown. Chromatin bodies have been found by Leishman in the ova of these ticks, probably a stage in the development of the spirochaetes.

There are certain further points of importance in connection with the propagation of tick fever. These are that ticks may transmit infection from animals which they bite during apyrexial periods, when no spirochaetes can be discovered in the blood; that the blood which has been passed through a Berkefeld filter remains infective; and that a period of immunity follows infection.

The first two of these facts indicate that infection may be conveyed by some other—possibly a developmental—form of the spirochete, while these last may explain the transmission of the disease from an apparently healthy person. Experiments have been made with a view to obtaining preventive and curative sera for tick fever. All that can be said at present is that attempts to produce a curative serum have failed, while a serum has been produced by the hyperimmunization of a horse, by means of which the incubation period is lengthened and the attack rendered milder in laboratory animals, though relapses have not been prevented.

Treatment.—As in the case of relapsing fever, there is no specific for tick fever and the treatment must therefore be symptomatic. It should be on the same lines as that indicated for relapsing fever. Atoxyl and mercury have been tried for tick fever, but without much effect. Salvarsan, as in all diseases due to spirochaetes, has a markedly beneficial effect.

Prophylaxis.—As far as we know the disease is spread only by the Ornithodorus moubata in nature (fig. 56).
FIG. 56.—*Ornithodoros moubata*. a, Ventral aspect; b, dorsal aspect; c, lateral aspect between second and third pair of legs.
These ticks belong to the division *Argasina*, and these differ from the ordinary cattle and dog ticks, *Ixodina*, in that the mouth is on the under or ventral surface of the body, that there are no dorsal or ventral chitinous plates or shields either in the male or female, that the last joint of the palpi is quite distinct and that the palpi are not grooved nor do they form a sheath for the rostrum. The young also have four pairs of legs when they emerge from the egg. In habits also they differ, as they do not remain firmly attached to their host, but after feeding leave him and may feed on many individuals, as they live for months or years. They feed at night mainly. They inhabit houses, living in the dry dust so abundant in houses with mud floors, or in thatch or reeds of which the roof and walls are composed. The ticks which feed on infected persons do not themselves necessarily become infective, as the infection is transmitted to the progeny, and therefore if a tick feeds on an infected person it may be many months before the progeny of these ticks can infect a susceptible person. Another point is that from an infected tick many infective ticks may be derived.

The problem differs therefore in many important respects from prophylaxis against malaria. Destruction of these ticks may be attempted but is difficult to carry out, as in a country like Africa, where termites (white ants) are so destructive, wooden floors and walls are impracticable. Mud floors, reed and thatched walls and roofs cannot be thoroughly cleansed. Even in European houses as little woodwork as possible should be used, but with cement floor, brick walls and galvanized iron roofs there is little danger of the *O. moubata* being present.

Prophylaxis for Europeans is fairly easy. In travelling, native huts should be avoided, even if they have not been occupied for many months. The *O. moubata* cannot climb up a smooth vertical surface, so that even in a native hut if a camp bedstead be used and no part of the bedding be in contact with the walls little risk is run.
The servants must be instructed not to place the bedding on the floor, or the ticks may enter it. Bedding in a district where the tick is common should always be carried in a tin box. These ticks do not readily feed by day and do not attach themselves to persons in movement, therefore there is little risk even in a native hut in the day time, or at night whilst the hut is well lighted and the occupant is awake.

In the event of a European house or the servants’ quarters becoming infected, careful search should be made for the ticks, and the floors and walls abundantly flushed with some disinfectant solution, such as 1 in 2,000 perchloride of mercury solution, or, and better in the case of a native-built house, it should be pulled down and burned.

**Varieties.**

Some authorities consider that there are four distinct varieties of relapsing fever.

*Varieties of Relapsing Fever Contrasted.*—European and American relapsing fever show some differences and may also be due to different species of spirochaetes. The more important differences are shown in this table:

<table>
<thead>
<tr>
<th></th>
<th>Indian</th>
<th>African</th>
<th>European</th>
<th>American</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incubation period...</td>
<td>7 days</td>
<td>5—7 days...</td>
<td>5—7 days...</td>
<td>5—7 days...</td>
</tr>
<tr>
<td>Duration of first</td>
<td>5—7 days...</td>
<td>3 days, rarely up to 5</td>
<td>3—6 days...</td>
<td>5—6 days...</td>
</tr>
<tr>
<td>attack</td>
<td></td>
<td>1—8 days, or more</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of apy-</td>
<td>5—13 days</td>
<td>3—5, or more</td>
<td>7—10 days</td>
<td>7—10 days</td>
</tr>
<tr>
<td>rexia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of relapses...</td>
<td>1 in 40 per cent., more than 1 in 10 per cent.</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Relapses absent in...</td>
<td>50 per cent.</td>
<td>Infrequent</td>
<td>Mild, except in grave cases</td>
<td>Mild, except in grave cases</td>
</tr>
<tr>
<td>Jaundice ...</td>
<td>70—80 per cent.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye affections ...</td>
<td>1 per cent.</td>
<td>Very common</td>
<td>Mentioned Under 5 per cent.</td>
<td>Mentioned. 2—4 percent.</td>
</tr>
<tr>
<td>Mortality ...</td>
<td>20—40 per cent.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Whilst it seems clear that the African relapsing fever is even clinically a distinct disease the differences between the three other forms are less marked. As regards the parasites, Mackie proposes to call that in Asiatic relapsing fever S. carteri, and in the American S. novyi. S. obermeier i is the name used for the parasite in European relapsing fever—S. recurrens is more correct—and S. duttoni in the African. The differences in the parasites are shown in the following table:

<table>
<thead>
<tr>
<th></th>
<th>S. carteri</th>
<th>S. duttoni</th>
<th>S. obermeier i</th>
<th>S. novyi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum length</td>
<td>12 μ ...</td>
<td>13 μ ...</td>
<td>12 μ ...</td>
<td>7—9 μ. Regularly</td>
</tr>
<tr>
<td>Shape</td>
<td>Open flexures</td>
<td>Open flexures</td>
<td>Spiral ...</td>
<td>spiral.</td>
</tr>
<tr>
<td>Animals susceptible</td>
<td>Monkeys; small rodents with difficulty</td>
<td>Small rodents easily</td>
<td>Small rodents only after passage through monkeys</td>
<td>Small rodents easily.</td>
</tr>
<tr>
<td>Course in animals</td>
<td>Very mild</td>
<td>Very severe</td>
<td>Mild</td>
<td>Severe.</td>
</tr>
<tr>
<td>Serum reaction: Immune serum no effect on</td>
<td>S. novyi</td>
<td>S. novyi or S. obermeier i</td>
<td>S. novyi and S. duttoni</td>
<td>S. obermeier i, S. duttoni, or S. carteri.</td>
</tr>
</tbody>
</table>

The form of relapsing fever occurring in Algeria, Egypt and the Sudan is not the African species S. duttoni. Possibly it is a new species and is considered to be so by Balfour.
CHAPTER XV.

DISEASES ASSOCIATED WITH SPIROCHÆTÆ IN THE TISSUES.

Syphilis is a fairly common disease in most tropical countries, both amongst the Europeans and the natives. In some countries, as in Central Africa and some of the Pacific Islands, it is not met with amongst the natives.

Neither race nor warm climate alone have any influence on the manifestations of the disease. It is indigenous in the more highly civilized countries, such as India and China, and has been carried to other countries chiefly by Arabs and other traders, including Europeans. Travellers are apt to mistake all kinds of ulceration for syphilis, and there can be no doubt that much exaggeration as to the frequency and violence of the disease in native races is due to such inaccuracies.

Circumcised races, both Mahommedans and others, are quite frequently attacked, but in them a considerable proportion of the chancres are urethral. The primary sores are not so often seen in natives as in Europeans. These are frequently extra-genital or within the rectum or anus as the result of sodomy, or on the abdomen or pubes or scalp, from the custom among certain natives of shaving these parts, barbers being employed; occasionally also syphilitic infection follows tattooing, saliva being largely used to mix the pigments.

Syphilitic ulceration among native races in the Tropics is apt to be severe, or even phagedænic at all stages of the disease, owing to neglect of both cleanliness and treatment. This is less common amongst prostitutes, who are careful as to personal cleanliness, e.g., Japanese, than amongst those who are less so, e.g., Cantonese.
Secondary symptoms are often overlooked. Macular eruptions are not easily seen on dark skins, and as there is no discomfort attention is not directed to them. Papular eruptions can be seen more readily. The throat conditions if severe will be recognized, but are not often seen.

There is a prevalent belief, especially among soldiers, that syphilis contracted from natives is unusually severe. This, however, is not borne out by Indian experience, where the disease among Europeans, except in persons debilitated by other causes, appears, if anything, milder than at home. Among the native army in India the known incidence of syphilis is much less than among the British troops.

Typical tertiary lesions are observed and include those of bone and gummata of the brain and abdominal viscera, which are fairly often seen in post-mortem examinations.

On the whole the disease is less severe in the Tropics than it is amongst the poorer classes in England, where the treatment has been neglected. The Chinese, of course, have used mercury from time immemorial, but other races, unless treated by Europeans, are practically untreated.

In tropical countries where yaws is uncommon there is no tendency for the syphilitic eruptions to be framboesial, and in countries where yaws is common the common manifestations of secondary and tertiary syphilis also occur.

Atheroma and lesions of the vessels are fairly common in the Tropics, but less so amongst Indians than amongst the negroes. The atheroma is frequently in patches and often leads to aneurism.

It must be remembered that a chronic irregular fever occurs in some cases of secondary and tertiary syphilis and may be mistaken for the similar fevers that occur in tropical diseases such as kala-azar or malaria. A course of antisyphilitic treatment may speedily cure a fever of this kind.
DISEASES ASSOCIATED WITH SPIROCHÆTÆ

The diseases believed to be remotely due to syphilis in England are practically unknown in the Tropics amongst the natives; these are the parasyphilitides—general paralysis of the insane, and tabes dorsalis.

In the treatment of syphilis amongst natives it must be remembered that mercury is not well borne by anaemic persons and that pyorrhœa alveolaris, so common in native races, is often increased by mercury, and must therefore be treated independently. In dealing with large bodies of men intramuscular injections are specially valuable, as a weekly injection insures sufficient treatment.

The method in use in the Army is essentially that introduced by Colonel Lambkin. A cream is made of metallic mercury in lanolin:

\[
\begin{align*}
\text{Hydrargyri} & \quad \ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \frac{3}{i}
\text{Adipis lanæ} & \quad \ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \frac{5}{iv}
\text{Paraffin liquidi (with 2 per cent. carbolic acid)} & \quad \text{ad} & \ldots & \frac{5}{x}
\end{align*}
\]

The mercury and lanolin are by weight, the liquid paraffin by volume. Great care must be taken to obtain a thorough mixture of the mercury. It should be stored in small quantities, as if kept in bulk the mercury will settle at the bottom. Ten minims of the mixture contain 1 grain of mercury. Injections must be made into a muscle, preferably the gluteus maximus, and never into the subcutaneous cellular tissue. The skin must be carefully sterilized before the injection. An all-glass syringe should be used; this may be sterilized by drawing up olive oil at a temperature of 160° F. Between the injections the point of the needle should be dipped into the heated oil, and the needle should be wiped with a sterilized cloth so that none of the mercury cream is left along the track of the needle.

It is important that the patient should not take any violent exercise for some hours after the injection, and care must be taken that no injection is given in a place where there is any induration as a result of previous injections. The advantages of the method are: (1) An attendance once a week only is required; (2) there is no
uncertainty as to whether the mercury is regularly taken; 
(3) though the rate of absorption varies, still the mercury 
is certainly absorbed. The disadvantage is that the 
injection is slightly painful, that a certain amount of 
induration and tenderness may be left, and that, rarely, 
abscesses may form. Much depends on the confidence 
the natives have in their medical officer.

Salvarsan, or neosalvarsan, especially when injected 
intravenously, have a rapid effect even when mercury 
has had little effect. The early hopes that one or two 
injections would result in a permanent "cure" have not 
been realized, and it is advisable after treatment with 
salvarsan to continue the use of mercury for at least three 
months even if a negative Wassermann reaction is 
obtained.

Congenital syphilis is not common, but it is probable 
that syphilis is an important factor in the causation of the 
large number of abortions and stillbirths, and is respons-
ible for much of the sterility of the native. It must be 
remembered that the negro is fertile earlier in life, when 
the effects of the virus are most marked, but ceases to be 
fertile in many cases at an earlier age than the European, 
and therefore has few children at ages when the most 
fatal effects of the disease are less likely to occur.

Prophylaxis.—Prophylactic measures are similar to 
those required in England. The local labour supply 
is usually insufficient for the large plantations, mines and 
other enterprises of Europeans. Large numbers of men 
are therefore imported from other districts and countries 
or attracted by the superior rate of pay. Men as a rule 
come in great excess of women, who are of less value 
as labourers, and many of these women are or become 
prostitutes. With such gangs of men, whether soldiers 
or labourers on plantations, it is often possible to find 
the infecting agent or agents. A certain proportion of 
women should always be imported with the men, and 
this is arranged for in Indian immigration ordinances. 
Every encouragement should be given to men bringing
their wives, and labour of a suitable kind should be provided for women as well as men, even if it is not directly remunerative to the employer. Under any circumstances the immigrant system usually results in a larger or smaller proportion of the men becoming infected, and these, having earned a considerable supply of money, often disseminate the disease on their return to their native villages. The disease is then propagated in the same manner, and unless the human carriers of the disease are isolated or segregated reliance is only to be placed on personal prophylaxis.

Regular inspection of men as well as women, and detention and treatment until the most infective stage is passed, will greatly reduce the prevalence of the disease. Legislation and increased powers in dealing with such cases are much to be desired.

A warning is necessary to missionaries and others as to interference with native customs too quickly. Amongst most natives, women are jealously guarded and their movements restricted in many ways. This condition is sometimes considered by Europeans as "slavery." An unfortunate result of too speedy liberation from their accustomed restraints is a great increase in the amount of promiscuous intercourse and the rapid spread of syphilis and other venereal diseases.

OTHER GRANULOMATA.

Amongst the large class of diseases known as infective granulomata, two of the purely tropical ones are associated with the presence of spirochæta, yaws and granuloma pudendi. But similar organisms have been found in many forms of ulcers.

YAWS.

Yaws (Frambæsia tropica). Native names: Puru (Malay), Coko (Fijian), Paranghi (Ceylon), &c. This disease is characterized by the appearance of successive crops of raised granulomatous nodules covered with thin
or thick sulphur-yellow crusts and subsiding without deep ulceration or the formation of any but superficial scars. The usual duration of the disease is two or three years, but on the parts of the body where the epidermis is thick, such as the soles of the feet, it may persist for much longer. Destructive ulceration of the mucous surface and a lupoid eruption on the face are by some considered to be sequelæ, and onychia may also occur.

**Geographical Distribution.**—As an indigenous disease it was probably limited to the West Coast of Africa, to the aborigines of the Malay Peninsula, possibly Ceylon, and to the Pacific Islands. Introduced by the slaves into the West Indies and South America, it has been firmly established there for over a century. An outbreak has also occurred in Assam, probably introduced by labourers returning from Fiji or the West Indies. Cases are occasionally seen in many tropical ports, and to a limited extent it has spread amongst the inhabitants of such ports. It does not occur on the East Coast of Africa and is very rare in the central plateau. Outside the Tropics it does not seem to spread.

**Clinical Course.**—Experimental inoculations have shown that there is a period of incubation of about twenty-eight days. In such experiments there need be no primary sore; a primary yaw is, however, common in accidental inoculation. It may appear at the edge of an ulcer or in a clean-cut wound, but is more common at or near the junction of the skin and mucous membranes, such as the angle of the mouth. When there is a primary sore it is a raised granulomatous mass similar to the subsequent eruptions. The generalized eruption may appear in any part of the body and is associated with febrile symptoms. Sometimes the temperature is 103° or 104° F. There are aching pains in the limbs, and particularly in the back and loins, sometimes severe enough to raise the suspicion of small-pox. The eruption may be abundant, but in other cases there may only be a few yaws limited to the lower part of the face, the chest,
or the genitals (fig. 57). When there are few yaws they are more common near mucous orifices; when abundant the whole body and limbs may be involved (fig. 58). On the extensor surfaces the eruption tends to be more abundant. The scalp and axillae are rarely involved, and the palms and soles only in the later eruptions. The actual duration of each yaw is three or four weeks, and fresh yaws may appear before the subsidence of the earlier ones.

On moist surfaces, as in the perineum and at the angles of the mouth, little or no crust is formed on the yaw, but in drier parts the peculiarly yellow scab is always present. This scab is detached with difficulty, and a slightly milky fluid is found beneath it. The exposed surface bleeds very readily. The glands are not enlarged unless the yaw is injured or secondarily ulcerated. Ulceration may take place in parts exposed to much movement or to friction, and secondary deeper ulceration sometimes, but rarely, occurs.

The eruption may recur for two or three years, but the later crops are usually scanty, and in this stage are frequently under thick, hardened epidermis, such as the sole of the foot (fig. 59).

The granulomata in such situations cannot grow to any great size, and are compressed by the thickened epidermis and very painful. These painful granulomata on the soles of the feet may persist for years after all other manifestations of the disease have ceased—"crab yaws."

Sequelae attributed to yaws are numerous, but the evidence that they are related to that disease is inadequate. A destructive ulceration of the mucous membrane of the mouth, palate, pharynx, and nares is common in Fiji, and occurs in other countries where yaws is common. It is a disease which occurs usually in early adult life, many years after the last definite manifestation of yaws. It occurs in persons who have not had syphilis, and if not a sequela of yaws is probably a separate and distinct
disease and will be described separately. Associated with this disease is sometimes a lupoid ulceration of the skin of the face, extending by continuity from the ulceration of the nares. Periostitis, and chronic ulcers of the legs and elsewhere have been described as sequelæ of yaws. If they are results of this disease they are very rare ones. Gummata probably do not occur.

Diagnosis.—At the onset of the general eruption, and whilst the granulomata are still small, in cases where the muscular and back pains are severe and the temperature is high, the disease has been mistaken for small-pox; such errors are very rare. The disease in the majority of cases has to be diagnosed from syphilis and other skin diseases. In a single case the diagnosis from a framboesial syphilide may be impossible; from any other syphilide it is easy. The absence of ulceration, the raised granulomatous tumour and the sulphur crust with the milky fluid underneath it differentiate the disease from rupia or similar tertiary syphilitic lesions. Where the case is under observation the close similarity of the successive eruptions is unlike that in syphilis. The exposure to contagion, the occurrence of other cases, and the absence of any other signs of syphilis all aid in the diagnosis.

Prognosis.—Death may occur in children under one year, or in debilitated persons, but even in such cases a fatal termination is exceptional. Good feeding, cleanliness, and protection from irritation of the yaws diminish the liability to ulceration but do not shorten the course of the disease.

Pathological Anatomy.—The lesions are limited to the skin and subcutaneous tissues. Essentially the growth is a vascular granuloma, and there is no tendency to caseation, necrosis, or suppuration. The epidermis is softened, and the distinction between the various layers is lost. Pigment is either not formed or irregularly distributed in the deeper layers or subcutaneous tissue. Keratinization is imperfect, and the superficial layers of
The epidermis are cast off, and form the scab covering the granuloma. The cause of the peculiar yellow colour is unknown. In moist situations in the neighbourhood of the genitals or mouth there is little or no scab formation, and superficial ulceration is common.

Treatment.—Salvarsan has an extraordinary effect in reducing the duration of the disease. Mercury and arsenic in their inorganic combination certainly do not. Potassium iodide is uncertain in its action. The eruptions will sometimes disappear rapidly when iodides are given, but even in such cases when the use of the drug is continued fresh eruptions appear. The value of iodides is therefore limited, but salvarsan causes a rapid disappearance of the lesions. Local applications that merely serve to keep the granuloma clean are valuable, but escharotics and irritants, though they may destroy the yaws, are likely to cause the formation of scars. The painful granulomata on the feet are best destroyed by the action of nitric acid, acid nitrate of mercury, or silver nitrate.

Etiology.—Most observers who have had extensive experience of the disease known as yaws consider it to be a clinical entity. Some eminent authorities, and especially Hutchinson, believe it to be syphilis, and that the differences from the common manifestations of that protean disease as seen in temperate regions are due to the effect of climate, race and heredity in the Tropics. The similarity of the two diseases will be admitted by all. In both there is a rather prolonged period of incubation with a primary sore, rarely absent in syphilis, commonly absent in yaws, and a series of cutaneous eruptions lasting for months or years, with later manifestations usually of a destructive character, which are common in untreated syphilis, and also in yaws if the lupoid diseases of the mucous membrane are correctly attributed to the antecedent yaws. The parasitic cause of syphilis is now generally believed to be a spirochæte, Spirochæta pallida, and a spirochæte morphologically indistinguishable
from *S. pallida* has been found by Castellani in yaws, *S. pertenues*. That the diseases belong to the same class is clear; that they are identical is a different matter, and is open to serious question.

The manifestations of yaws for at least the first three years of the disease are all of the same character, the primary sore and each successive eruption differing slightly in moist parts, or when under thickened epidermis. Syphilitic cutaneous manifestations are polymorphic. Yaws may be universal in a population, but if uninfected newcomers of any race—Europeans, Portuguese, Chinese, Negro, Malays, Indians—are introduced into such a community and are infected, the disease they acquire is yaws, and resembles in all its characters the disease in the native population. From a single source of infection in a negro the disease has been acquired in the same form in a whole family of Portuguese, and in an Indian servant. Yaws therefore breeds true.

Syphilis, when acquired by members of the same races, presents the usual characters of that disease. Syphilis is little modified in persons resident in the Tropics. The formation of gummata and the extensive and destructive bone lesions do not occur in yaws. It is sometimes urged by those with little experience of some of the native races, amongst whom the disease is common, that the overcrowding and filth of the native houses favour the wide diffusion of the disease, and that therefore the fact that all the children have "yaws" is no argument against the disease being syphilis. A closer study of these races will convince anyone that as regards personal cleanliness and absence of overcrowding and morals they compare very favourably with the lower classes of Europeans, amongst whom syphilis does not become universal in the children.

Yaws does not protect from syphilis nor syphilis from yaws. The relationship between yaws and syphilis, in the sense of both diseases being due to organisms of the same genera, is admitted and was predicted, but the
relationship is like that between variola and varicella, not that between variola and vaccinia.

Prophylaxis.—Infection can be carried from man to man by direct contact, and the virus is contained in the discharges from the granulomata. The frequency of the early yaw in the neighbourhood of the mouth suggests that food is a frequent source of infection. The commonest ages for infection, 3 to 5 years, are ages at which children frequently exchange partially eaten pieces of food. Probably flies are also direct carriers of infected material, and the frequency with which ulcers and wounds become infected is probably explicable in this manner. The chigoe (Sarcopsylla penetrans) is by some believed to be an important carrier. There is no evidence that the virus can enter through the unbroken skin, but cracks about the mouth, small ulcers as a result of insect-bites, or other sources of irritation are so common in the Tropics that possibilities of infection are numerous.

There is little risk to well-clad Europeans, even if stopping in the same house as persons with the disease, but amongst European and half-caste children who play about with native children cases of infection are common. It is well to carefully cover up even superficial wounds, and to prevent, if possible, children from having access to natives in a country where yaws is endemic, and to take sufficient precautions to prevent the interchange of partly eaten articles of food with native children.

"Guam" disease in most respects corresponds to the description given of the destructive ulcerations about the naso-pharynx so common in Fiji, and there considered to be tertiary frambœsia. Those who consider it a separate disease call it granuloma gangrenosa. It is said to be most common in places where yaws is rare, and to be very rare in some places where yaws is very common. Probably it is the same condition as the Fijian "kanailoma."
GRANULOMA OF THE PUDENDA.

SERPIGINOUS ULCERATION OF THE GENITALIA (MCLEOD); ULCERATING GRANULOMA OF THE PUDENDA; SCLEROSING GRANULOMA OF THE PUDENDA.—The disease manifests itself as a chronic indurated superficial growth on or near the genitalia, male or female. It is slow growing and extends along moist surfaces, whilst the older and deeper portions of the growth are converted into a dense fibrous mass of tissue. It is very vascular.

Geographical Distribution.—It occurs in many islands of the West Indies, in Tropical South America, on the West Coast of Africa, and either it or a similar disease occurs in India, Northern Australia, and many of the Pacific Islands.

Clinical Course.—This differs to some extent in different races, and in the two sexes. It usually commences in the male on the penis, and extends in the neighbourhood of that organ; if situated on the skin it is very slow growing, but is more rapid when the glans is attacked, and the granulations may then be very large and coarse; it extends for a fraction of an inch up the urethra, and causes very serious stricture. It rarely extends by direct continuity down the penis; more often the inguinal folds or other places with which the penis may rest in contact become infected (fig. 61), and from such a point extension by continuity along the fold of the groin (fig. 62), and backwards on the inguino-scrotal fold, takes place, and from that directly backwards on the perineum surrounding the anus, and extending up it into the lower part of the rectum (fig. 63). Sometimes both groins are affected. Frequently the penis and scrotum become slightly elephantoid, probably from compression of the lymphatics by the indurated subjacent tissue.

In the female the early growth is on the inner surface of the labia majora or nymphae, which may become elephantoid, and the growth extends upwards into the vagina, and rarely into the bladder. It also extends over
the labia majora, and backwards along the perineum, surrounding and extending up the anus. In such cases, where both the vagina and rectum are involved, incurable recto-vaginal fistulae are common. The growth may continue for many years, and the general health of the patient is not affected. The lymphatic glands are not enlarged, though there is evidence of lymphatic obstruction. There is always a considerable formation of hard fibrous tissue beneath the growth, and when healing occurs naturally the growth is entirely converted into dense fibrous tissue. Very rarely complete cicatrization takes place; more frequently it is partial and extension of the growth at the edges takes place. Spontaneous healing of the mucous surfaces does not take place.

The diagnosis has to be made from other diseases of the same part. On the penis it is frequently mistaken for epithelioma. In the groin it may be mistaken for any form of ulceration, syphilitic or otherwise. In the vagina it is usually mistaken for chronic gonorrhœa. The chronicity of the growth, the dense fibrous base, and the absence of glandular enlargement are important points in the diagnosis. In cases of doubt, microscopic examination will exclude epithelioma.

Prognosis as regards life is good. The growth is not malignant. Natural cure is highly exceptional, and it is only when complete removal of the growth can be effected that recovery is probable.

The most troublesome complications are stricture of the meatus of the urethra, which can only be treated effectually by amputation of the glans penis; recto-vaginal fistulae, which are not suited for operations, as the tissue between the rectum and vagina is mainly composed of the growth; and stricture of the anus with ulceration of the lower part of the rectum. If the growth does not extend too high, excision of the rectum gives good results in the last complication.

Pathological Anatomy.—The growth is a vascular granuloma. The cells are round cells with a single
rounded nucleus. There are no giant cells. There is no tendency to caseation, necrosis, or suppuration, and the epithelium is usually present over the growth, though softened and thickened.

_Treatment._—Mercury and potassium iodide in the majority of cases have no effect. In a few, where the tendency to natural cure is strong, large doses of iodides seem to aid this tendency.

Cleanliness and antiseptic dressing favour rather than retard the growth. Escharotics, such as chloride of zinc, nitrate of mercury, and salicylic acid, are rarely effective; complete excision of the growth where that is possible is highly satisfactory, but the dense fibrous tissue should be excised as well. The raw surface left is always more extensive than the growth removed. Where excision is impossible, scraping and the use of escharotics may give satisfactory results.

Good results have been obtained by the use of the Röntgen rays. In Dr. McLeod's case the use of these rays converted the granulomatous tissue into a cheesy mass, which was readily scraped away, and healing then took place rapidly.

_Etiology._—The occurrence on the genitalia and the different situations in the two sexes are strongly in favour of the view that the disease is conveyed by venereal intercourse; it does not seem to be highly contagious, as there are cases where the husband only is infected and the wife escapes.

Spirochætes resembling _S. pallida_ and _S. refringens_ have been described by Wise as occurring in these granulomata. Oval bodies have been described in the deeper layers of the granuloma, but their exact nature is unknown, and it is doubtful if they have any causal relation to the disease.
PLATE IX.

Fig 53.
CHAPTER XVI.

INTESTINAL PROTOZOA, &C.

Many protozoa are found in the intestines, and may be discharged with the faeces. In coccidia infections, either of the liver or intestinal mucosa, the fertilized macrogametocytes are discharged in this manner.

The more important of the human intestinal protozoa are those associated with diarrhœa and dysentery. These diseases are so often due to bacterial infections, and the prevention of such diseases is so closely connected with the disposal of sewage and the provision of a good water supply, that they are best considered at the same time as the diseases similar clinically, but due to vegetable organisms in Part III. Only a brief reference to these parasites and the diseases they cause will be given here.

The protozoal organisms described as concerned in the production of intestinal diseases are Sarcodina, such as the Amœba coli; Flagellata, as Trichomonas hominis, Lamblia intestinalis and various spirochaetae; and Infusoria (Ciliata), as the Balantidium coli (fig. 64). Of these the most important is the Amœba coli—Entamœba histolytica (E. tetragena, Schaudinn).

Other protozoa, especially Balantidium coli, which invades the tissues, may cause ulceration and all the symptoms of dysentery.

Balantidium dysentery often commences as an occasional attack of diarrhœa. In the more severe attacks there will be persistent but remittent diarrhœa. The parasites are found during the periods when there is diarrhœa. Blood and mucus are present in all the more severe cases and may be considerable in amount.
Peritonitis with or without perforation may occur, and the parasites are found not only in the mucosa and in the walls and floor of the ulcers, but in the submucosa and in the blood-vessels. In fatal cases there may be extensive ulceration, but it is most severe near the rectum and diminishes towards the caecum. No specific treatment is known.  

*Lamblia intestinalis* is probably pathogenic. It does not invade the tissues, but lies closely applied by its sucker-like aspect to the mucosa, in the small intestine, and is associated with chronic enteritis of a catarrhal character. It is easily recognized by the paired nucleus and the six pairs of flagella. The two terminal are the largest and work in a longitudinal groove. Where there is no diarrhoea the cysts will be found. In these the two nuclei are situated near one end, but there are no flagella.

The symptoms are of a chronic recurrent diarrhoea, with abundant discharge of mucus, often bile-stained, and sometimes there is also blood. When there is diarrhoea the parasite may be found in abundance; at other times the encysted forms only will be found. These are easily recognized by their oval shape and the pair of nuclei situated near one extremity. The treatment is not very satisfactory. Free purgation to remove the mucus, followed by intestinal antiseptics such as kerol, seems the most promising line of treatment. Enemata are used by some, but as the main infection is in the small intestine it is difficult to explain the satisfactory action claimed. Methylene blue in one or two grain doses in some cases has a satisfactory effect. Liquid paraffin in tablespoonful doses twice or three times a day may be used alone or with methylene blue.

The distribution of the parasite is extensive, but as from some parts of India so many cases seem to come it is one of the possible causes of the local forms of diarrhoea, such as Poona diarrhoea.

*The Amæbina.*—An order belonging to the Rhizopoda
or Sarcodina. The members of this order are either naked masses of protoplasm or enclosed in a simple shell, either secreted by the organism or formed from some foreign substance. They have blunt, lobulated or finger-shaped pseudopodia and a single nucleus. Many of them live in fresh or salt water, and are abundant where there is moist decaying vegetation; some are parasitic. In the genus *Amoeba* the body is always naked, and usually there

![Balantidium coli](image)

**Fig. 64.—Balantidium coli.**

is a marked distinction between the outer part, ectosarc, and the interior, endosarc. The former is clear and transparent but viscid, whilst the latter is more liquid and granular, and frequently contains foreign bodies taken in as food. The compact nucleus and a contractile vesicle are contained in the endosarc.

When active the amoebae are constantly changing shape, and throw out blunt processes or pseudopodia. The number and shape of these are points to consider in the differentiation of species. When motionless or dead the
amœbæ assume a spherical form, and are difficult to distinguish from other mononuclear cells. Propagation takes place by budding, division, or segmentation. Where there is no diarrhoea the actively moving amœbæ are not found, as a rule, though they may be present in mucus passed before, or after, or with a motion. Artificially induced purgation, as by the use of saline aperients, will usually result in the passage of active moving amœbæ.

Amœba coli.—This is a large amœba, frequently 0.05 mm. in diameter, though smaller forms are common. The

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**Fig. 65.—Scheme of Development of Amœba.** Multiplication in encysted forms (autogamous). Sexual multiplication. The early stages of division of the nucleus (a–d) and conjugation of the divided nuclei in pairs (e), followed by further division of these products of conjugation, first into two and then into four each (f–i). The thick wall of the cyst in the later stages indicates the hardening of the cyst wall during the stages when the cysts are outside the body.
ectosarc can be readily seen when pseudopodia are thrown out, but it is difficult to see in the resting animal. The pseudopodia are very broad and only one or two are protruded at a time. The nucleus in unstained specimens can be readily seen near the centre of the cell. Movement is active at or near blood-heat, but is retarded or stopped at lower temperatures. Multiplication of the amœba may take place by simple division; the nucleus divides, and the protoplasm then divides, so that two equal individuals are produced. This is the asexual method of reproduction, and takes place readily where the conditions for existence are favourable. The second method may be considered as a rudimentary sexual process, though the conjugation is by fusion of two chromatin masses derived from one nucleus and not of two separate cells.

If considered as a sexual process it would be an instance of *autogamy*. In this method the amœba becomes encysted. The nucleus divides into two, and each of these nuclei after extruding polar bodies again divides into two. The four nuclei thus produced conjugate in pairs, so that the number of nuclei is again reduced to two. These two nuclei each divide into two and then again divide so that there are eight nuclei, and these with the protoplasm segmented round them form eight young amœbæ which are still contained in the cyst (fig. 65). These quasi-sexual encysted forms are resistant, and it is probably this form only that is capable in the parasitic amœbæ of retaining vitality in a free form under ordinary meteorological conditions.

These encysted forms are therefore the important ones, as the infective agents in amœbic infection. In some of the parasitic amœbæ in the lower animals the active amœbæ are only found in the small intestine. The changes described take place in the large intestine. The amœbæ passed in the faeces are all encysted. In such animals, if the intestinal contents were passed rapidly through the alimentary canal, as after purgatives or in diarrhœa, active amœbæ would be passed with the stool.
In man encysted amœbæ may be found in apparently healthy stools, but the hosts from time to time have attacks of diarrhœa or dysentery and then the active amœbæ are present in the stools. The diagnosis therefore of the encysted forms is important both for diagnosis and treatment.

Some amœbæ can be cultivated from stools, but it is doubtful if these are obligatory parasites, and these may be merely encysted forms of non-parasitic amœbæ which have been swallowed and passed through the intestinal canal.

Amœbæ parasitic in the internal organs of man are sometimes called Entamœbæ. Morphologically there is no real difference between these and other amœbæ beyond the absence of a contractile vesicle.

The problem is to a large extent one of species, as it is only the pathogenic amœbæ that are of importance to us. The others can be cultivated outside the intestine.

Morphological characters are only adequate when the characters during the whole life-cycle are considered. The characters in the encysted stage are the most constant.

There are said to be several species, one occurring in the mouth, A. buccalis, in some persons with dental disease, and two at least in the large intestine (vide Table). Of these, the A. coli, or Entamœba coli, is not found in other parts of the body and the life-cycle is as described by Schaudinn. According to the same author it is distinguishable by its appearance as the ecosarc or ectoplasm is not visible as a distinct layer, and the nucleus is large and rich in chromatin, so that it stains deeply in stained preparations. This amœba is not considered to cause disease. It may be present in the small intestines as an active motile amœba, and only the encysted forms found in the stools unless there is diarrhœa.

The other intestinal amœeba, Entamœba tetragena (? histolytica), has a more distinct ectoplasm and the pseudopodia are entirely formed by it at first, so that
We may tabulate some of the various characteristics said to be diagnostic of the parasitic Entamoeba.

<table>
<thead>
<tr>
<th>Species</th>
<th>Size</th>
<th>Ectoplasm and Endoplasm</th>
<th>Nucleus</th>
<th>Multiplication</th>
<th>Reproduction</th>
<th>Pathogenicity</th>
<th>Culturability</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli</em></td>
<td>12—25µ but variable</td>
<td>No distinct ectoplasm, except at beginning of pseudopodia formation</td>
<td>Round, vesicular, sub-central, with a karyosome; visible in life</td>
<td>Binary fission; schizogony—8 merozoites</td>
<td>Encystment total, endogenous, 8 spores in cyst</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><em>E. histolytica</em></td>
<td>25—30µ</td>
<td>Distinct; endoplasm ingests red blood corpuscles; burrowing pseudopodia</td>
<td>Small, eccentric, poor in chromatin; invisible in life</td>
<td>Binary fission; budding</td>
<td>Small exogenous spores</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><em>E. tetragena</em></td>
<td>20—30µ</td>
<td>Ectoplasm distinct when pseudopodia formed; endoplasm ingests red blood corpuscles</td>
<td>Round; visible when fresh</td>
<td>Binary fission</td>
<td>Encystment total, endogenous; cysts contain 4 “spores” of which the nuclei are readily seen.</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><em>E. tropicalis</em></td>
<td></td>
<td>Distinct</td>
<td>Round, rich in chromatin</td>
<td>Binary and multiple fission (?)</td>
<td>Encystment total, endogenous, numerous small spores in small cyst</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><em>E. hominis</em></td>
<td>6—15µ</td>
<td>Ectoplasm apparent only in the pseudopodia; single contractile vacuole present</td>
<td>Round ... ... ...</td>
<td>“By division and by sporulation”</td>
<td>Cysts 4’6—7’7 µ</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><em>E. phagocytoides</em></td>
<td>2—15µ</td>
<td>Ectoplasm well developed; active; phagocytic</td>
<td>... ... ...</td>
<td>Binary fission; schizogony</td>
<td>... ... ...</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><em>E. minuta</em></td>
<td>14µ</td>
<td>Not distinct</td>
<td>Round, rich in chromatin; invisible in life</td>
<td>Schizogony — 4 merozoites</td>
<td>Encystment total, endogenous; cysts with 4 “spores”</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><em>E. nipponica</em></td>
<td>15—30µ</td>
<td>Distinct</td>
<td>Round, rich in chromatin; visible when fresh</td>
<td>Binary fission; schizogony—6 to 8 merozoites</td>
<td>Encystment total; incompletely known (?))</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td><em>E. undulans</em></td>
<td></td>
<td>Single, long, narrow pseudopodium and an undulating membrane</td>
<td>... ... ...</td>
<td>... ... ...</td>
<td>Develops spores in a cyst which are set free as small flagellates</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note.—E. histolytica* differs from all the others in that its encystment is exogenous, not total and endogenous as in the other cases where the sporogony is known. From this table it will be seen at once how slight are many of the differences between the so-called species of *Entamoeba* in the human intestine.
they are tougher and stronger than those of the *A. coli*. The nucleus is not readily visible and is poor in chromatin, and therefore does not stain deeply in stained preparations. Schaudinn describes the multiplication as different from the *E. coli*.

The whole cell does not form a cyst, but a series of buds are formed externally, each of which becomes a latent encysted form. These observations have not been confirmed, and (by many) the distinctions between *E. coli* and *E. histolytica* are doubted. Many consider that this parasitic amoeba is *E. tetragena*. In the encysted forms there are never more than four nuclei. It is highly pathogenic to cats and may in them cause liver abscesses. In the active moving forms it is indistinguishable from *E. histolytica*. Probably *E. histolytica* and *E. tetragena* are the same, and possibly *E. minuta*.

*E. histolytica* or *tetragena* may enter the subcutaneous tissues and be carried to various parts of the body, such as the liver, spleen, and kidneys, and there may cause the formation of abscesses. These abscesses are slowly formed and may attain enormous size, containing many pints of pus. They are usually single, but two or three are not rare. The pus in such abscesses is white, yellow, or may be chocolate in colour. It is a very thick, slimy pus. The walls of the abscess are rugged, and as a rule there is little formation of fibrous tissue around, though there is an area of intense congestion. In the pus from such an abscess no bacteria are found, either on examination or by culture, in the majority of cases. In others, the minority, there are bacteria, but these are not of any uniform species. These facts are taken to show that the amoebae are pyogenic, and that for the formation of pus no bacterial aid is necessary. Others particularly state that in early abscesses bacteria are to be found, but admit the possibility that they have been carried by the amoebae, and that in the large sterile abscesses these bacteria have died out.

The amoebae are very scanty in the pus in the abscess,
so that they are rarely to be found. In the walls of the abscess, in scrapings from the walls, and in the pus discharged a few days after the abscess is opened, they are usually present in very large numbers. An abscess may become quiescent and encapsuled or be reduced to a putty-like mass. More commonly they continue to increase in size, and bursting through the liver may extend in the cellular spaces almost anywhere. Frequently they burst into the lungs or intestines and a natural cure results.

![Graph](image)

**Fig. 66.**—Hepatic Abscess with Irregular Pyrexia.

The hepatic abscess or tropical liver abscess is usually single, but two or more may be found. The onset is often insidious, and it may be preceded by a more general hepatitis, but as a rule the general hepatitis is not followed by abscess formation.

The symptoms, once attention is directed to the liver, are usually marked. The liver is enlarged often upwards, so that the upper limit of hepatic dulness is convex. The edge of the liver is usually, but not always, pushed down so that it can be felt below the ribs. The liver is tender, often extremely so, but in other cases firm pressure is required to elicit any signs of pain. The rectus and other abdominal muscles are more rigid on the right side, and pain in a shoulder, usually the right, is a very frequent symptom. The blood usually shows a moderate leucocytosis, and the proportion of polymorphonuclear
leucocytes is increased. The dysenteric symptoms at or before the hepatic troubles may be very slight and even escape the notice of the patient. In fatal cases ulceration of the colon is nearly always present. Even when there are no symptoms of dysentery encysted amœbæ, E. tetragena, may often be found in the stools. Ipecacuanha is again coming into favour in cases of amœbic hepatitis when there is no evidence of the formation of pus.

The parasitic amœbæ die if left in the fæces as soon as putrefaction occurs. Reproduction takes place by simple
division, whilst they are parasitic, but transference from one host to another is believed to be by the encysted forms. In these the organism becomes spherical, is covered with a thickened cyst wall, and the contents are divided into four or eight.

Sometimes localized œdema may be found and more frequently local tenderness. Either of these are valuable localizing symptoms of the abscess. If an abscess has formed it must be localized by exploratory punctures with an exploring needle and freely opened and drained. If no abscess is found the symptoms may be due to hepatitis, and if that be due to amœbic infection a course of ipecacuanha or a series of intramuscular injections of emetin hydrochloride $\frac{1}{6}$ to $\frac{1}{2}$ a grain daily will bring down the temperature and relieve the symptoms.

![Fig. 67.—Pyrexia due to Entamoeba. X indicates when Ipecacuana was administered.](image-url)
Amoebic dysentery will be fully considered later, with other forms of intestinal disease. Here it is sufficient to state that the disease may be acute, and rapidly fatal perforation in the most severe cases of this form is not uncommon.

In the common form the onset may be sudden, but more frequently is insidious; sometimes the patient is not even laid up. It runs a very protracted course: attacks of diarrhoea with the passage of a little mucus and blood, alternating with periods of constipation, when the hard faeces are sometimes coated with blood or mucus, or the stool may be apparently normal. This relapsing, or rather remittent, type of dysentery, for the stools are rarely normal, is usually associated with the amoeba indistinguishable from *A. coli* or *E. histolytica*. Associated with this type of dysentery is hepatic abscess, and rarely abscesses in other organs, such as the spleen. These abscesses are usually sterile as regards bacterial growth, but in the walls of the abscesses the amoebae will be found in abundance. The possibility of this condition must always be considered in any person who has had chronic dysentery, however mild, and in any person from the Tropics with a chronic irregular fever (fig. 66). There is nothing characteristic about the temperature and there may be periods of apyrexia. The liver is enlarged and often tender, but the enlargement is not always marked. Leucocytosis occurs, but may be slight, and is often only to the extent of 12,000 to 15,000 leucocytes. The polymorphonuclear cells form 75 to 80 per cent. of the total, as a rule.

Solitary hepatic abscess may occur in England, and in the Tropics, and may be due to other causes, *e.g.*, *Ascaris lumbricoides* and *Clonorchis sinensis*. When due to amoebae the associated dysentery may be very mild and in many cases no history of dysentery can be obtained, but in these either amoebae are found in the stools or ulceration of the caecum is found at the *post-mortem* examination.
In some countries where hepatic abscess is said to be rare, as in the West Indies, at *post-mortem* examinations it is found to be common; clinically, the condition is often overlooked.

Without either hepatitis, liver abscess, or definite dysentery the Entamoeba may give rise to irregular fever. The cysts may be found in the stools and the fever yield to a course of ipecacuanha or emetin (fig. 67).
CHAPTER XVII.

Prophylaxis in Protozoal Diseases: Résumé.

(I) General Prophylaxis.—Few of the protozoa are known to be carried under natural conditions directly from man to man. As a rule an intermediate development of the parasite has to take place before it can again re-enter man. In many cases this development only takes place in a suitable alternative host—mosquito, biting fly, bug, or tick; in others, the further development can take place on the ground or in water.

Where an alternate host is required prophylactic measures must be directed not only against the pathogenic parasite but also against the intermediate host, so that detailed knowledge of the life-history of these hosts is required.

As a general rule, where the parasites are found in the blood or where the blood is infective a blood-sucking intermediate host is required. Where the parasite exists in the intestinal canal or in the skin no such host is necessary. For each disease, therefore, there will be differences in detail as to the prophylactic measures required.

(II) Special Prophylaxis.—With the intestinal diseases prophylaxis depends (1) on the success of the methods adopted for the disposal and destruction of excreta, and (2) preservation of the water supply from all possible sources of contamination and the uniform use of thorough boiling or efficient filtration to destroy any of these infective forms in water and milk.
### Table indicating briefly mode of transmission of the more important protozoal diseases:

<table>
<thead>
<tr>
<th>Disease</th>
<th>Parasite</th>
<th>Reservoir</th>
<th>Leaves mammalian, Host: man</th>
<th>Life outside</th>
<th>Re-enters man</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria—Benign tertian</td>
<td><em>Plasmodium vivax</em></td>
<td>Susceptible persons—Convalescents from primary attacks and for weeks after convalescence from many attacks</td>
<td>With blood drawn by blood-sucking insects</td>
<td>Sexual stages in some species of anophelines</td>
<td>By injection with saliva of mosquito.</td>
</tr>
<tr>
<td>Quartan</td>
<td><em>Plasmodium malariae</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtertian (malignant tertian)</td>
<td><em>Plasmodium falciparum</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blackwater fever</td>
<td>?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yellow fever</td>
<td>?</td>
<td>In blood in early stages of mild or severe attacks</td>
<td>With blood</td>
<td>In a mosquito—<em>Stegomyia fasciata</em></td>
<td>Injected by mosquito 10 days after feeding on infected persons, when the mosquitoes have become infective.</td>
</tr>
<tr>
<td>Dengue fever</td>
<td>?</td>
<td>As in yellow fever</td>
<td>&quot;</td>
<td>&quot;</td>
<td>Injected by mosquito.</td>
</tr>
<tr>
<td>Plebotomus or papataci fever</td>
<td>?</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>Injected by phlebotomus.</td>
</tr>
<tr>
<td>Trypanosomiasis (sleeping sickness)</td>
<td>(1) <em>Trypanosoma gambiensis</em></td>
<td>Man usually, sometimes other mammals</td>
<td>&quot;</td>
<td>&quot;</td>
<td>18 days or more after the fly has fed on an infected person it becomes infective, and injects with saliva trypanosomes into the person on whom it feeds. By bites of these infected bugs.</td>
</tr>
<tr>
<td></td>
<td>(2) <em>Trypanosoma rhodesiense</em></td>
<td>Usually wild game</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Kala azar ...</td>
<td>Leishman-Donovan bodies</td>
<td>Man probably</td>
<td>In leucocytes with the blood ?</td>
<td>In bed bugs, <em>Cimex rotundatus</em> ?</td>
<td></td>
</tr>
<tr>
<td>Oriental sore</td>
<td>&quot;</td>
<td>Man, and probably, in some varieties, dogs</td>
<td>In blood plasma</td>
<td>In blood and in saliva</td>
<td>By bites.</td>
</tr>
<tr>
<td>Relapsing fever</td>
<td><em>Spirocheta recurrentis</em></td>
<td>In man usually</td>
<td>In blood plasma</td>
<td>In <em>Pediculus proboscis</em> probably</td>
<td></td>
</tr>
<tr>
<td>African tick fever</td>
<td><em>Spirocheta duttoni</em></td>
<td>Man or progeny of infected ticks</td>
<td>In blood and in saliva</td>
<td>In <em>Ornithodoros monticola</em></td>
<td></td>
</tr>
</tbody>
</table>
## Table—continued.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Parasite</th>
<th>Reservoir</th>
<th>Leaves mammalian. Host: man</th>
<th>Life outside</th>
<th>Re-enters man</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spirochetal diseases—Yaws, syphilis, and some ulcers</td>
<td><em>Spirocheta pertenius</em></td>
<td>Man ...</td>
<td>Discharges</td>
<td>No development</td>
<td>Contact usually with abraded surface.</td>
</tr>
<tr>
<td></td>
<td><em>Spirocheta pallida</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoebic dysentery</td>
<td><em>Entamoeba tetragena</em>, and possibly other entamoeba</td>
<td>Convalescent cases or persons during intervals in the acute stages. Possibly cuts</td>
<td>With the feces in the encysted form, capable of surviving when stools are formed</td>
<td>Further development whilst encysted in water, earth, or dust</td>
<td>By the mouth in water, food, or milk contaminated by the encysted entamoeba.</td>
</tr>
<tr>
<td>Balantidium dysentery</td>
<td><em>Balantidium coli</em></td>
<td>Pigs ...</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lambia diarrhoea</td>
<td><em>Lambia intestinalis</em></td>
<td>Other infected persons or convalescents</td>
<td>Leaves man in encysted form</td>
<td>Further development whilst encysted</td>
<td>By the mouth as in amoebic dysentery.</td>
</tr>
</tbody>
</table>

With the other diseases prophylactic methods depend on (1) measures to prevent the parasites leaving man or other mammalian hosts, (2) the prevention of the infection of the special alternative hosts in which further development takes place, (3) preventing the access of possibly infective intermediate hosts to susceptible persons, and, where possible (4) rendering such susceptible persons immune to infection or tolerant of the results if they should be infected.

Parasites can in some cases be destroyed in man, as in malaria by the regular use of quinine, in trypanosomiasis by use of atoxyl, and in the spirochetal infections by the use of salvarsan. In these, as well as other cases, protection by the use of mosquito nets or suitable clothing or covering may prevent the parasites being abstracted by mosquitoes or other suitable host; but these measures should be in addition to the main line of defence, which should be the extermination as far as possible, in any locality, of insect carriers of disease.
For this purpose, some knowledge of insects in general, and mosquitoes in particular, is essential in order to advise as to economic prophylactic measures, and an outline of the classification of insects, and the principles on which insects are classified, are here given briefly.

Classification of Diptera.

Suborder I. Orthorrhapha.—The adult imago escapes from the pupal case through a longitudinal anterior or posterior \( T \)-shaped slit. As there is no ptilinum, there is, in the imago, no frontal lunule. Antennæ usually project in front of the head.

They are divided into Nematocera (thread-like antennæ) and Brachycera (short antennæ).

Nematocera.—Antennæ have many joints—always more than six; the segments, except the one at the base, are similar to each other; palps, usually four or five joints.

Nematocera vera.—Joints of the antennæ are long, and frequently have whorls of hairs, legs long and slender, abdomen usually long, e.g., Culicidæ (mosquitoes).

Nematocera anomalæ.—Antennæ composed of many segments; but these are all short, and, as a rule, without whorls of hair. The abdomen is usually stout, and the legs are shorter and thicker than in \( N. \) vera, e.g., Simulidæ, or sand-flies.

Brachycera.—The number of true joints in the antennæ is less than six; palps, one or two joints.

Brachycera vera.—Third joint of antenna is not ringed, and usually terminates in a bristle or style, e.g., Asilidæ, or robber-flies.

Brachycera anomalæ—Terminal joint of antenna composed of several short segments fused
together. These fused segments appear as rings, e.g., Tabanidæ.

Suborder II. — Cyclorrhapha. — A circular cap is pushed off the pupal case by the bladder-like protrusion, ptilinum, which forms on the anterior part of the head of the imago and this imago escapes through the circular opening thus made.

In the imago a curved scar is left when the ptilinum contracts. This scar is the lunule, and the presence of this scar shows that the insect belongs to the Cyclorrhapha. Antennæ are short, usually three-jointed, and more or less flattened against the head or dependent. The third segment has at the base a bristle or style, arista.

(1) Aschiza. — The extremities of the lunule are not continued as sutures on each side of the face, e.g., Syrphidæ, or hover-flies.

(2) Schizophora. — The extremities of the lunule are continued as lines on each side of the face, so as to separate off the antennæ and mouth-parts from the rest of the face. These lines form the frontal suture, e.g., Muscids, Glossinæ, Stomoxys.

Suborder III. Pupipara. — Larva nourished within the parent and changed into a pupa without feeding. Some are wingless, in others the wing venation is imperfect. Antennæ are small rounded masses showing no division into joints, with one or more stiff hairs; the claws are powerful and much curved, e.g., Hippoboscidæ and sheep-ticks.

Suborder IV. Siphonaptera, or fleas, are by some con- sidered to be wingless diptera; but, if so, they are so much modified that they are best considered separately, and will be considered in Part III. in connection with plague.
Subdivision of the more important groups of the Diptera.

The *diptera* include carriers of disease and are characterized by having a single pair of membranous wings, the posterior pair being reduced to two knob-like processes, the balancers or *halteres*. They may be blood-sucking or not according to the structure of the mouth parts.

Of the groups into which the Diptera are divided the *Nematocera vera* and the *Cyclorrhapha schizophora* are of the most importance to us, as some of them are proved to be carriers of important diseases. *Nematocera anomala* has among its groups *Simulidæ* or sand-flies, and Sambon considers that the topographical evidence is in favour of a Simulium being the vector of pellagra. The wing venation of the group is simple; they are virulent blood-suckers, though the popular name "sand-flies" includes many species belonging to other groups than Simulium.

Many of the others are blood-suckers, others are important as mechanical carriers of bacillary diseases, and others, both of the dipterous and other insects, are important as destroyers of both larvae and adults of dangerous species and in many cases do much injury to growing crops, to fruit, grain, &c.

*Nematocera vera* are sub-divided mainly according to their wing venation. This venation varies greatly in the members of the group, and the family known as the Culicidæ are characterized by having scales on the veins of the wings and by the forking of the 2nd, 4th and 5th longitudinal veins. These characters of the wings separate the Culicidæ from all other *Nematocera vera*. The subdivision of the Culicidæ is made on variations of the mouth-parts into subfamilies, and at this point various difficulties arise and other schemes have been proposed, some based on larval characters and others on those of the eggs. Each of these methods would lead in some cases to quite a different grouping and in others would
make very little difference. It must always be borne in mind that any grouping founded on a single character is unsatisfactory, the larger the number of the characteristics that show a marked difference the sounder is that classification.

The important subdivisions of the Culicidæ are:

**Corethrinae.**—Proboscis adapted for suction and not for penetration.


![Fig. 68.—Neuration of wing characteristic of Culicidæ (Theobald).](image)

**Anophelina.**—Proboscis straight. Palps same length as the proboscis in both sexes, clubbed in male. Scutellum not lobed. Scales on veins of wings usually lanceolate. Scales on thorax and abdomen rarely abundant. Larvae asiphonate. Eggs with lateral air-floats.

**Culicina.**—Proboscis straight. Palps short in female, in male as long or longer than the proboscis. Wing scales variable. Scales on thorax and abdomen abundant. Scutellum trilobed. Larvae always siphonate; the siphon may be long or short. Eggs variable; may be in rafts or thick-shelled eggs deposited singly.

**Ædina.**—Proboscis straight. Palps short, often very
short in both sexes. Scutellum trilobed. In some genera hairs on scutellum and metanotum.

Malaria.—The known carriers of malaria all belong to the division of the mosquitoes known as *Anophelinae*. All anophelines do not serve equally well as carriers of malaria. Some species are readily infected, others only with difficulty, and some not at all. The dangerous species are those which are numerous and readily convey the disease.

For economic and efficient prophylaxis a knowledge of the habits of each species is required, and it is found that the different species vary greatly in their habits, life-history, and breeding-places.

In any place or country the species of anophelines must be determined; those that are good carriers of malaria must be found out experimentally or must be found infected and the breeding places and habits of these must be studied in great detail.

The anophelines, which include all the known carriers of human malaria, are easily distinguished from other mosquitoes, which have a straight, penetrating proboscis.

1. The palps in both male and female are practically the same length as the proboscis, and in the male are clubbed.

2. The scutellum, which is more or less trilobed in other mosquitoes, shows no sign of such lobing in the anophelines.

3. The scales on the veins of the wings are lanceolate in the anophelines, whilst they vary greatly in the other *Culicidae*.

4. The proboscis is nearly in the long axis of the head, thorax and abdomen, so that the mosquito almost forms a straight line. When at rest, as the proboscis points towards the surface on which the mosquito rests the abdomen points away from it.

5. The larvae have no respiratory siphon; they lie flat on the surface of the water and after their first moult have curious palmate tufts on the latero-dorsal surface of the abdomen on each side.
The knowledge of the habits and breeding places of the dangerous species in each place will determine the practicability of dealing with malaria by the extermination or diminution of these definitive hosts.

With large stations the most satisfactory results are obtained by diminishing the number of the definitive hosts, anophelines. The most vulnerable period in the life-history of these insects is in their larval stage. This is always passed in water. A somewhat detailed knowledge of the class of breeding-place for the species that carry malaria in each place is required for effective and economical work in this direction. As these places differ for each species of mosquito, without detailed knowledge money will be wasted and the results cause disappointment.

Measures that would be well adapted in places where the malaria is carried by *Pyretophorus costalis* would be unnecessary, useless and extravagant, say in Malaya, as they would only result in the destruction of the harmless *Myzomyia rossi*, and would be insufficient and unsuitable in places where the carrier was *M. funesta* or *M. culicifacies*.

*M. funesta*, *Anopheles maculipennis*, *P. costalis* and *Cellia argyrotarsis* or *albimanus*, are the important carriers of malaria in Southern Europe, Tropical West Africa, and Tropical America, respectively. In Asia, *Nyssorhynchus willmori*, *M. culicifacies*, *N. fuliginosus*, and *N. stephensi*, are proved carriers, but many others, such as *C. kochi*, *A. aitkeni*, &c., are probably important carriers. Of these there is some similarity in the habits of *A. maculipennis*, *P. costalis* and *C. argyrotarsus*, and also *C. kochi*, a suspected carrier. They all breed in roadside pools, small collections of water, in stagnant water, sometimes very foul, and occasionally in collections of water in artificial receptacles. *N. stephensi* is usually found in disused or partially used wells, as well as artificial receptacles such as tubs and tanks.

Their favourite breeding places vary. In Asia the anopheline that is mainly found in such situations is
M. rossii, which practically does not carry malaria. Asiatic towns, therefore, are relatively free from malaria, whilst in African and South American towns a much more complete drainage would be required to have any material effect on the amount of malaria.

N. willmori, M. culicifacies, and N. kartwari, all stream breeders in open country, are good carriers.

M. funesta in Africa and many of the important Asiatic malaria-carrying mosquitoes (e.g., M. culicifacies) are only found in clear water which is usually in motion, and in grass-grown edges of springs, streams and rivers. They cannot thrive in stagnant waters. They may be found in marshes, but only when the water is kept fresh by springs, or streams, and during seasons when there is a heavy rainfall.

The problems to be dealt with will vary according to the breeding-places of the dangerous mosquitoes. Where, as in a settlement, there is artificial interference with the natural drainage, as in making roads, fords and bridges, the problem is more complicated. In such places frequently hollows have been left in house building or road making, and there are trenches at the roadsides or for local drainage which must also be dealt with. In the East such places are of little importance in the towns, whilst in Africa they are of vital importance.

As a general principle, superficial drainage must be so complete that even during the rains the shallow pools formed only last for a day or two, or at any rate not for more than a week, and drains must be so graded that with heavy rains they are well flushed and no pools are left of any depth in the intervals.

In all places where there is a hill at the back of a settlement a well-devised intercepting drain must be arranged along the base of the hill so that flooding from the hill sides will be avoided. This hill water is the main cause of the constant high level of subsoil water; the rain actually falling on the area of the settlement is comparatively unimportant. In low-lying land, as in many
of the flat lands, rich alluvial soil on the coast or near the mouths of the river where the water is tidal, banks and intercepting trenches, draining by self-acting sluice-gates during low tides will also be required.

Such drainage is necessary for many agricultural purposes, and the drainage required for rubber growing or sugar plantations, as long as the drains are kept clear, is
ample to render such places healthy, if care is taken that
he drains themselves are not suitable for breeding places. Where the malaria-carrying anopheles are mainly breeders in such drains, it is more effective to use pipe drains, or other forms of curved drains, and though more expensive at first, as they require less constant supervision and a smaller gradient, in the long run they are more economical as well as more effective.

The history of plantations in the past is instructive. In the early history there is a serious amount of malaria before the drainage is complete; whilst the estate is flourishing and kept in good order no malaria or very little; but when the estates are abandoned or neglected, and the drains are sedge grown, blocked or partly broken down, they become intensely malarial for any remaining inhabitants.

The class of drains employed in any place is mainly dependent upon the amount of money that can be devoted to the purpose. Earth drains suffice, but require much continued expenditure in upkeep and repairs, whilst constant supervision is required. Wherever there is much flushing or scouring, brick or cement open drains are absolutely essential.

All open drains should be V-shaped in section, so that a small amount of water will suffice to flush them and little water can accumulate in the narrow bottom of the drains. The large drains should be similar in section, but the bottoms may be flat or, better, rounded. Half pipes or stone pipe inverts make excellent bottoms for such drains.

It is always advisable to keep a settlement or village clear of jungle and undergrowth. Such growth gives shelter to mosquitoes in the daytime, prevents the drying of the surface, and often leads to blockage of drains and interference with natural drainage.

As temporary methods the destruction of larvac by larvicides is of great use, but should not be relied on for permanent purposes. Crude petroleum or other oils
rapidly destroy larvae, as the films formed on the surface prevent the larvae getting air through their respiratory syphons. Unfortunately it also kills off fish and many forms of life, and the water becomes putrid and offensive. Something may be hoped for from some of the native fish poisons. These usually belong to one or other of the species of *Derris*. The roots are crushed and thrown into the water, and the milky fluid from the fresh roots, even in minute quantities and much diluted, will destroy the larvae, and for small collections of fluid, cesspits, &c., is highly effective, and though killing off most forms of animal life does not render the water as putrid or offensive as the use of oils. Where fish are present these would be destroyed, and therefore this method is not advisable in larger collections of water. Many fish feed on mosquito larvae, and are one of the important enemies of mosquitoes. Amongst these the *Cyprinodontidae* are of special importance. The small fish known locally as “millions” in Barbados belong to this family, either *Pecilia* or *Gambusia*, and are by some believed to be the reason for the absence of anophelines from that island. In India, species of *Chela*, *Haplochilus* and *Therapon* are effective, the last in brackish waters. Even worse enemies are the larvae of some of the Dragon-flies (*Agrionidae*); these breed in similar places to mosquito larvae, and live on them to a large extent.

In countries where the dangerous mosquitoes are stream and river breeders, drainage is of little value and the use of larvicides impracticable. Much can be done by removing sedges, reeds, and grasses growing into the streams, keeping the banks clear, and removing obstructions in the river bed or sides, so that fish can get at the larvae and so that a uniform flow of water is maintained in the part of the stream in the vicinity of the settlement, and the larvae are washed further down stream.

The selection of the site for a settlement is a most important matter. In the case of small stations on unsuitable
sites, it will often be found better to abandon the station than to attempt to render it healthy. A suitable site is one in which there is natural drainage or in which there is sufficient slope to allow of easy drainage. Small streams and springs are sources of danger. If a settlement be made on a river the side selected should be that where there are no shallow shoaling edges; these are much more liable to be overgrown and the current is slacker. In the selection of sites for settlements, marshes or low-lying ground must be avoided and any site in proximity to such places. The effect of cultivation is twofold. In the first place, the clearing of the ground and the removal of dense jungle renders the air drier and admits much more sunlight. Clearing alone will suffice for the extirpation of some mosquitoes: those that frequent jungle, which are mainly *Aedina*, but in a few instances dangerous *Anophelina*. Clearing, if thorough as regards the low jungle, will cause a great diminution in the number of these jungle mosquitoes or their complete disappearance, even if the tall trees are left. On the other hand, if suitable breeding-places are left, such as sedgy streams, other mosquitoes may become much more abundant, and these may include dangerous anophelines, such as *M. willmori*, *N. christophersi* and *M. culicifacies* in Asia, or *M. fumesta* in Africa, or *C. argyrotarsus* in America. Clearing without drainage, therefore, may substitute one dangerous mosquito for another, though, on the whole, it is beneficial, as the exposed ground dries more readily in dry weather and is more likely to be thoroughly flushed in heavy rains than uncleared ground. If combined with drainage, and if the drains are kept clear, or even moderately clear and free from sedges, it is usually effective. The better the drainage required for the special form of cultivation, the more will the healthiness of the district be improved. Rubber plantations require deep drainage, and the only breeding places possible in such a plantation are in the drains or in the areas beyond the plantation into which the water may be discharged.
Sugar-cane is also satisfactory, for though the drainage required is not so deep, the surface of the ground is so thoroughly worked up that water soaks into the soil and no pools are left for more than a short period, even during a rainy season. Maize also, for similar reasons, is a satisfactory crop. Rice, on the other hand, is an unsuitable crop in a malarious tropical country, as during the early stages of cultivation the earth is covered with water. Wet rice cultivation should not be allowed within one mile of any settlement, as many anophelines, some harmless and others good carriers of malaria, may breed in the paddy fields.

In many forms of cultivation irrigation is employed, either as in the paddy fields where the ground is flooded and remains flooded, which is very dangerous, or by conveying water through a series of superficial trenches to keep the subsoil moist. In this form of irrigation, which is used for gardens, vegetables, &c., the risk is slight if the irrigation be intermittent, and the drains kept clear and so graded that water does not remain in any part of the trench for more than one or two days. It sometimes happens, however, that the water is drawn from a mosquito-breeding place, and then pupae may be conveyed by the water to the gardens in or close to a settlement and hatch out in the irrigation trenches. No system of irrigation is safe unless well looked after and in which the supply of water is not so under control that it can be rendered intermittent. Care also must be taken that the overflow is conveyed into a definite channel, natural or artificial, and not allowed to spread over the surface of adjoining land, as though the cultivated area may be free from anophelines the surrounding district may be made worse. And the adult mosquitoes can readily travel with the prevailing wind for at least a quarter of a mile, and much more if there is scrub or long grass to give them shelter.

The anophelines usually considered to be carriers of malaria are as follows:
In Europe:

*Anopheles bifurcatus* breeds in slowly running water and roadside ditches. In Britain the larvæ live all through the winter.

*A. maculipennis* breeds in roadside ditches. Adults hibernate in houses during the winter and the larvæ die.

*A. pseudopictus.*—? the same as *A. sinensis*, a carrier in some localities.

In Asia:


*A. sinensis*, in Japan and North Borneo, not in the Malay States.

*A. stephensi*, Bombay.

In Africa:

*A. funestus*, a stream and river breeder. Feeds in the shade in the daytime as well as at night. Believed by Alcock to be the same as *A. culicifacies*.

*A. costalis*, breeds in roadside ditches, pools and in stagnant and even putrid water.

*A. mauritianus, A. paludis*, proof insufficient.

*A. pharaonis, A. squamosus*, and *A. nili* are probable carriers.

In Australia:

*A. annulipes (?)* *A. bancrofti*.

In America:

*A. maculipennis, A. bifurcatus, A. lutzii, A. argyrotarsus, A. albimanus*.

In some of these the evidence is incomplete. Experimental cultivation of the parasites in some of these is difficult, and in other species such as *Anopheles kochii* and *A. aitkeni*, which from their topographical distribution are probable carriers, is almost impossible, as the mosquitoes soon die and will not feed in captivity.

Alcock's simplified classification is adopted in the
above list. He does not recognize the subdivision of the anophelines into subgenera, but groups them all under Anopheles. Culicines may also be carriers of protozoal diseases. It was in Culex fatigans that Ross first demonstrated the complete life-cycle of Proteosoma, a bird parasite very similar to the human malaria parasites.

**The Distinction of Culicines into Groups.**

Theobald considers that the character of the scales on the veins of the wings, head and scutellum are of great importance. These differ from those in anophelines and in different culicines so markedly that Theobald bases his division into sub-genera on the character of the scales. Yellow fever has been proved to be carried by a culicine belonging to the subdivision Stegomyia.

In the group "Stegomyia," in addition to the upright fork scales on the head, there are also curved tile-like scales and similar tile-like scales on the scutellum. They are small mosquitoes and usually black with brilliant silver-white markings. These markings, especially those on the thorax, serve to distinguish the different species, and in S. fasciata there is a faint central, narrow silver line on the dorsum, and on each side of this a more conspicuous curved line.

The S. fasciata (S. calopus) is commonly known as the "tiger mosquito," because of the brilliant striping of the legs and abdomen.

The breeding-places and habits of the Stegomyia in general, and of S. fasciata in particular, differ greatly from those of the Anophelines, and the prophylactic measures must be varied accordingly. Stegomyia eggs are laid singly, and have no lateral air-floats. They are covered with a thick shell. They float for a time on the surface of the water, but ultimately sink and lie at the bottom of the water in which they were deposited. These eggs are not killed by immersion in water, nor are they destroyed by prolonged desiccation.

This extraordinary vitality of the eggs is the cause of
the great variety of breeding-places, and of the wide dissemination of this mosquito.

In the first place eggs are often deposited in quite small receptacles, shallow pools, gutters of houses, old tins used for preserved foods, broken bottles, empty cocoanut shells, &c., and it is immaterial if this deposition takes place at the end of a spell of wet weather, as the eggs will remain alive even if the water dries completely. With the next rain, either there will be sufficient water to moisten the eggs, or there will be an excessive amount, so that these receptacles overflow. In the first case the eggs will hatch where they were laid; in the second, they will be washed away into some larger and perhaps more permanent collection of water.

Eggs that have fallen to the bottom of a pond remain alive, and if in taking water, as on board a ship, the bottom is at all disturbed, the eggs will be taken with the water, and hatch out and develop in the water-barrels. Old wooden barrels in which water has been kept, if not well cleansed, will often be found full of larvae within twenty-four hours or less if refilled with water. Such barrels are often used for storage of water on a small scale and for catching roof water, and whether kept indoors or out of doors are most prolific breeding-places. With the onset of the wet season these species of mosquitoes very rapidly become abundant. The mature eggs are present in old beds of dried puddles, and in every receptacle that will hold even a few drops of water, and these hatch out with the first rain, and if rain continues the pupæ will form in a week, and a day or two later the imagines emerge. Light is not necessary for the development of these larvae, so that cisterns and tanks are suitable breeding grounds.

The larvae have a respiratory syphon or tube attached to the eighth abdominal segment. This syphon is present in all the Culicinae, but varies greatly in length. In the Stegomyia it is a short, broad, stumpy syphon, shorter than in most of the commoner Culicinae. The
mouth-parts are simple, the clumps of hairs, the brushes situated on each side of the mouth are short, stiff, and not very abundant. The mandibles and maxillae are powerful. These larvæ feed at the bottoms or sides of the water in which they live, and mainly on lower forms of animal and vegetable life. They require abundant food and serve to keep down algæ. They can remain under water for a long time, and often escape notice in that way. When breathing or resting they hang with their heads down from the surface of the water, and in butts and barrels are often numerous enough to blacken the surface of the water. Any slight disturbance appears to alarm them, as the whole lot will then immediately dive to the bottom of the barrel, and may remain there for some time, and the surface of the water be free from larvæ. The larvæ are very hardy, active in their movements, and less readily killed by desiccation than most larvæ. The larvæ live well on board ship. They require a fairly high temperature and are killed when frozen. They do not occur outside tropical and sub-tropical regions.

The adults—imagines—are hardy mosquitoes, and most species feed readily on man. Some jungle species bite by day only, many feed both at night and by day, but S. fasciata at first will feed by day or night, but after once feeding continue to feed at night only. Many species are jungle mosquitoes, but some of these, as S. scutellaris, are much more numerous in settlements in the vicinity of jungle, and readily become domesticated. S. fasciata is far more abundant on the sea-coast, and in many countries, such as the Guianas and the Malay Peninsula, is rarely met with except in coast settlements and towns. Though strong, active mosquitoes, they do not take extensive flights, or go far from their breeding-places. It follows that when these mosquitoes are numerous, the breeding-places are close at hand. As a rule, the breeding-places of the mosquitoes are in the immediate surroundings of a house and destruction of these
breeding-places will result in the freedom of that house from these mosquitoes.

The places to look for breeding-places of S. fasciata are:

(1) The back of servants' quarters, as behind these empty tins, bottles, and broken crockery of all kinds are allowed to accumulate. If there is long grass these receptacles are hidden by it, and thus, sheltered from the sun, retain water for a long time.

(2) Tanks, barrels, water-butts, used for collecting or storing water. The largest as well as the smallest are common breeding-places. Wooden receptacles are perhaps the most likely to harbour the larvæ. The warning that any incautious movement is to be avoided in examining such places must be remembered, as the larve, if they are not on the surface, cannot be seen. Badly graded gutters are also fertile breeding-places. The ordinary roof-gutter is apt to sag, and even if properly graded is liable to be blocked by leaves and other débris, so that pools, permanent in the wet season, are formed. Moreover, eggs deposited on their extensive surface are carried down into the water-tanks and there develop. Some authorities condemn roof-gutters for these reasons, but there is no reason why roof-gutters should not be properly graded and kept clean, and it is of little importance that eggs are washed down if the mosquitoes that develop in the tank cannot escape from it. More frequent openings in such gutters are advisable.

(3) In houses, bath-tubs, vessels for holding flowers, flower-pots, even filters, such as the drip stone filters, water-coolers, and every receptacle for water will serve as a breeding-place. These are frequently found in unoccupied rooms. As these mosquitoes can breed in foul water, they may be present in the receptacles for kitchen refuse, and even cesspits. Stable cesspits, stable buckets and drains are often the breeding-places of these mosquitoes.
In preventing the spread of yellow fever, a knowledge of their breeding-places is essential. In any country into which yellow fever may be introduced the extermination of these mosquitoes will render the spread of the disease impossible; and in all countries their extirpation will greatly increase comfort. In a scattered settlement it is an easy and inexpensive matter to render a house free from this species of mosquito, but constant care is required. The important point is that in such a place the breeding-places are in the immediate surroundings of the house. The occupier breeds his own mosquitoes. In a more crowded settlement continued efforts are required, and it should be made compulsory for each occupier to free his own property from breeding-places; or the whole work may be done by the municipality at the common expense. A combination of these methods is most effective. It should be compulsory on the occupier to free the actual premises from breeding-places, and to have his water-tanks so protected that mosquitoes cannot escape from them, and to see that no accumulation of empty tins and bottles is present in his compound. The municipality should remove such bottles, and inspect and report on the condition of drains, gutters, tanks, and stable surroundings as to their freedom from larvæ, and should make recommendations to the occupier and enforce the carrying out of such recommendations. The gutters must be well graded and kept clean. The pipes supplying water to the tanks must be long enough to reach the bottoms of such tanks, otherwise the mosquitoes as they hatch out will escape through this pipe. The manhole must be kept covered, and it is better to have a double covering, an inside one of gauze, and the ordinary solid one over it. It is useless to attempt to render the supply pipe impervious to mosquitoes by placing a gauze diaphragm in any part of it, as the meshes soon become clogged and the water will not pass through. An inspection and collection of any portable breeding-places, *e.g.*, bottles, &c.,
should be made twice a week, and any foul drains, or cesspits should be treated with crude petroleum, or better, some such poison as tuba root (*Derris elliptica*).

With a good organization, with the active support of the intelligent section of the community, and stringent regulations well enforced, the cost of extirpation of this mosquito is not prohibitive.

Roof water forms the best available supply of drinking water in many places, so that measures that prevent its infection cannot be overlooked.

Dengue fever is conveyed mainly by *Culex fatigans* and *Stegomyia fasciata*, but it also occurs in places where the latter mosquito is not found. *Stegomyia scutellaris*, easily distinguished by the broad median white band down the thorax, is also a carrier. *S. scutellaris* also breeds in foul water, and is common in similar conditions to those in which *S. fasciata* is found, but occurs in jungle, and more on the outskirts of settlements than in the larger crowded townships.

*Culex fatigans*, which, as well as the Stegomyia, is implicated in the conveyance of dengue fever and is the common carrier and intermediate host of *Filaria bancrofti*, breeds in roadside ditches and in almost any collection of still water. It is a domestic mosquito and is found in houses, often in large numbers, but, unlike *Stegomyia fasciata*, the breeding-places are often a long way from the houses it frequents as an imago. The extirpation of *C. fatigans* from a settlement requires combined effort, practically municipal control, whilst the freedom of a house from Stegomyia mainly depends on the individual care of the occupant of a house. Houses on the top of a hill are often much frequented by *C. fatigans*; these mosquitoes are strong fliers and are often carried, partly by the wind, for considerable distances, they seek shelter in the houses and will remain in such houses resting and quiescent in the day time, but active at night. Under artificial conditions they may live for three months or more, and under natural conditions will hibernate all through the cold season.
Papataci or phlebotomus fever is carried, not by a mosquito, but by one of the biting psychodidæ. The species implicated is known as *Phlebotomus papatasii*, but probably other species are carriers. Those insects are not sandflies, *Simulidæ*, and are recognized by the peculiarly pointed tips to the wings and the thick covering of the

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*a, Shape of wing and venation in Phlebotomus minutus denuded of hairs.*

*b, Side view (only one side shown) of claspers, &c., of Phlebotomus papatasii.*

*Fig. 70.*
wings, thorax, abdomen, and legs with long hairs. They have no ocelli. The larvae breed in caves, crevices, in walls, amongst stones, in any dark moist place where the air is still and there is protection from light. Decaying nitrogenous refuse is favourable to their development. They are slower in their development than mosquitoes, the eggs take about a week to hatch, the larvae some eight weeks before pupation, and the pupal stage about two weeks. These periods are shorter in hot weather and may be indefinitely prolonged in very cold weather. The flies, therefore, are most abundant during hot weather.

The infective agent is present in the blood only during the first twenty-four hours of the attack and an interval of six days is required before the phlebotomus is capable of infecting man.

*Trypanosomiasis* is carried by Glossina of several species. The larvae live in the abdomen of the female till ready for pupation and then burrow into loose earth and become pupae. The vulnerable periods then are limited to the pupal stage and the imago, and in the case of a pupa in loose earth, decayed leaves, and crevices there is little chance of its destruction. Protection of infected persons and animals from a day-biting fly is difficult, and so far the most successful results have attended the abandonment of places where the fly is prevalent. Systematic prophylactic treatment with atoxyl is a more serious matter than systematic treatment with quinine, and has not been adopted on a large scale. Suitable clothing, selection of places for rest, neither in boat nor near water in forest country, diminishes the risks.

*Kala-azar.*—The general belief is that a species of Cimex, *C. rotundatus*, is the carrier. This insect is a breeder in places similar to the European bed bug, *Cimex lectularius*. It is not conclusively proved that this bug is a carrier. Donovan suggests that *Conorhinus rubrofasciatus* may be a carrier, possibly acquiring the infection second-hand from the bed bugs on which it is believed to feed.
African tick fever is carried by one of the Argasine ticks, *Ornithodorus moubata*. It bites mainly at night and only persons who are at rest; and so the usual time of infection is during the hours of sleep. In a bed well raised from the ground and not in contact with the walls, there is little probability of infection unless these ticks are present in the bedding. All bedding should be carried in a tin box and not deposited on the ground of a rest house or native hut at any time, and the ticks will not gain access to the bedding. As the ticks of the second and third generation are infective, it is well to act as if all the ticks of this species were infective.

Dry dust is the preferential haunt of these ticks. In a well-kept, well-built European house they should not be present.

Indian relapsing fever is probably carried by Pediculi. Cleanliness of body, hair and clothing is the best preventive.

Prophylaxis as regards intestinal protozoa requires suitable measures for the destruction and disposal of excreta, good uncontaminated water supply and protection of the collecting area, roof or otherwise, from dust. Food, milk, &c., must also be protected from dust, even after it has been cooked or boiled.
APPENDIX.

I.—Notable Dates.

Malaria.—Discovery of the parasites, Laveran, November 6, 1880.—Differentiation of species and asexual life-cycle, Golgi and others, autumn of 1885, and onwards.—Conjugation of sexual forms, McCallum, 1897-8.—Sexual cycle, Ross, 1897-8.

Redwater Fever.—Piroplasma discovered by Babes in 1888.—Mode of transmission, Smith and Kilburne, 1893.

Yellow Fever.—Mode of transmission of yellow fever, Reed and Carroll, U.S. Army Commission, 1900-1.—Mild form recognized, 1841.

Trypanosomes.—In fish, Valentine, 1841.—In frogs, Gruby, 1843.—In rats, Lewis, 1878. As a cause of disease (surra), Evans, 1880.—As a cause of disease (nagana), Bruce, 1894.—In man Nepveu described a trypanosome, 1890, but the description was not conclusive.—In man Ford discovered and Dutton described T. gambiense, 1901.—In man, in sleeping-sickness, Castellani discovered the same trypanosome in the cerebrospinal fluid, 1902.—1908, Kleine showed that after Glossina have fed on an infected man in fifteen days or more the fly is infective.

*Spirocheta obermeieri* or *Spirocheta recurrentis*, discovered by Obermeier, 1873, named *S. recurrentis*, 1874, and *S. obermeieri*, 1875.

*Spirocheta duttoni*.—P. Ross, 1904.—Nabarro had previously reported this discovery, but report was not published till after Ross’s.


Leishman-Donovan Bodies.—Leishman and Donovan independently in kala-azar, 1903.—In Delhi boil, Wright, 1903.—Rogers proved their flagellate stage, 1904.
Amebae coli first found in stool by Lambl, 1860, and recognized as the cause of dysentery by Losch, 1875.—Trichomonas, Donne, 1836.—Lamblia intestinalis, Lambl, 1859.—Balantidium coli, Malmsten, 1857, recognized as a cause of dysentery by Strong and Musgrave, 1902.

This list, though giving the names of the actual discoverers and the dates, does not necessarily imply that the only or even the main credit is due to the actual discoverers.

Most discoveries are founded on antecedent ones; the part played by mosquitoes in carrying malaria is based on the previous observations of Manson on the transmission of Filaria.

Improvement in methods of technique leads directly to further discoveries, and the introduction of a simple rapid method of staining for chromatin by Leishman led to the discovery of the Leishman-Donovan bodies and their relationship to flagellates. In other cases, discoveries have been made independently by two or more workers nearly at the same time. The Spirochata duttoni was discovered independently by Dutton and Todd very shortly after P. Ross.

In trypanosomiasis, though Castellani discovered the parasite in cases of sleeping-sickness, the fuller confirmation of the causal connection and the mode of transmission is mainly due to Bruce and others. It is rare to find that the credit of any discovery is due to one man only.

Nor can the influence of the English Tropical Schools, founded in 1899, be ignored, nor their founders, including Sir Patrick Manson, Mr. J. Chamberlain and Sir Alfred Jones.

II.—Important Measurements.

1 μ (micron) ... = 0.001 millimetre or \( \frac{1}{39000} \) of an inch, nearly.

1 millimetre ... = 0.04 or \( \frac{1}{25} \) inch.

25 millimetres ... = 1 inch.

1 centimetre ... = 0.39 of an inch.

1 gramme ... = 15.432 grains.

28 grammes ... = 1 ounce, nearly.

1 cubic centimetre = 16.23 minims, and weighs at 4° C. 1 gramme.

28 cubic centimetres = 1 ounce, nearly.

1 litre ... = 1 1/4 pints or 35 ounces, nearly.
Normal blood: Weight about \( \frac{1}{13} \) of the body weight, say, 9 pints or 5,000 cubic centimetres.

Red corpuscles: About 5,000,000 per cubic millimetre.

Leucocytes: 6,000 to 8,000 per cubic millimetre.

Of these 65 to 75 per cent. are polymorphonuclear leucocytes.

" 5 " 10 " " large mononuclear.

" 15 " 25 " " lymphocytes, but number varies according to the stage of digestion.

" 1 " 3 " " eosinophiles.

Malaria. Diameter of "spores" or merozoites:

Benign tertian ... ... \( 1.5 \mu \).

Quartan ... ... \( 1.75 \mu \).

Subtertian ... ... \( 0.7 \mu \).

Full-grown parasite, sporocyte or schizont:

Benign tertian ... ... \( 8.5 \mu \).

Quartan ... ... \( 6 \mu \).

Subtertian ... ... \( 4.5 \mu \).

Full-grown zygote ... ... = 50 to 60 \( \mu \).

Sporozoite ... ... = 14 \( \mu \).

Leishman-Donovan body ... = 2.5 to 3.5 \( \mu \times 1.5 \) to 2 \( \mu \).

*Ameba coli* ... ... = Up to 50 \( \mu \).

Encysted form ... ... = 15 to 20 \( \mu \).

*Lambdia intestinalis* ... ... = Up to 15 \( \mu \) in length.

Encysted form ... ... = 13 \( \mu \times 7 \mu \).

*Trichomonas hominis* ... ... = 3 \( \mu \) to 20 \( \mu \).

Encysted form ... ... = Up to 15 \( \mu \).

III.—Ticks.

Blood-sucking Arthropods are found also amongst the Arachnidæ, which in the adult stage are readily distinguished from the insects, even from the wingless insects, by the presence of four pairs of legs and the absence of antennæ, whilst the orifice of the mouth is a small slit.

The blood-sucking groups are the Ixodidæ.

Ixodidæ have either a hard and chitinous or thick, leathery skin. The mouth-parts consist of a central hypostome armed with teeth projecting backwards, and on each side a powerful chelicera, also armed with teeth projecting backwards, *chelicera*,
enclosed in a sheath. There are a pair of four-jointed palps or pedipalps.

The opening of the genitalia is on the under aspect near the head, and respiration is conducted by a pair of sieve-like openings in the respiratory areas, situated close to the bases of the fourth pair of legs.

There are two great groups of the Ixodidae, Ixodinae and Argasinae.
Ixodinæ.—The rostrum projects from the anterior extremity of the body. The palps are deeply grooved on their inner aspects and act as a sheath to the rostrum. The last joint of the palps is a small projection from the third. The second joint is long in one division, Ixodinæ (fig. 71), and shorter, as broad as long, in another: Rhipicephalæ (fig. 72). On the dorsal aspect is a hard chitinous plate, dorsal shield, covering the entire dorsum in the male but only the anterior part in the female. The Ixodinae are important as the carriers of piroplasma in the lower animals. They are not proved to carry any disease to or from man.

Fig. 73.—Mouth-parts of Argasina.

Argasinae differ from Ixodinæ in that (1) the rostrum is on the under surface of the body; (2) the palps do not form a sheath for the rostrum (fig. 73); (3) they have no dorsal shields, but a thick leathery covering ornamented with knobs or bosses, making a regular pattern.

There are two genera:—

Argas.—Body with sharp edges. The pattern of the marking close to the edge differs from that on the rest of the dorsum. Species of this genus carry the avian spirochaetes.

Ornithodorus.—Body with rounded edges. No difference in the pattern of the marking on the edge from that of the rest of the dorsum.

Ornithodorus moubata carries Spirochæta duttoni, the cause of the African form of relapsing fever.
INDEX.

ABDOMEN, distension of in kala-azar, 152
Abortion in malarial fever, 48, 64
— in relapsing fever, 180, 190
Abscess following injections of quinine, 56, 62
Abscesses due to Entamoeba histolytica, 232
Edina, 243
Africa, blackwater fever in, 108
—, trypanosomiasis in, 131, 150
—, West Coast, yaws in, 216
African relapsing fever. See Tick fever
Ague fever. See Malaria
Albuminuria in malaria, 47, 66
— in yellow fever, 117
Alcohol in relapsing fever, 199
Alcoholism and malaria, 46, 49, 51
Aleppo evil. See Oriental sore
Alkaloid, percentages of, in salts of quinine, 53
Amoeba buccalis, 230
— coli, 225
— —, autogamy in, 229
— —, discovery of, 263
— —, encysted forms, 229
— —, scheme of development, 228
Amobina, 226
Anaemia, extreme, in blackwater fever, 91, 99
— in kala-azar, 157
— in malaria, 50, 65
Anasarca in kala-azar, 158
Animals, domestic, piroplasmosis in, 111-113
—, inoculation of Oriental sore in, 180
—, tick fever, post-mortem appearances in, 205
—, trypanosomiasis in, 144
Ankylostomes, 1
Anophelines, 32, 243
— carriers of malaria, 244
—, characteristics of, 72-76
Anophelines, breeding places of, 246
—, list of malaria carriers, 252
—, relation to malaria, 14, 85
Antipyretics in malaria, 63
Apes, anthropoid, yellow fever in, 124
Argas persicus, 196
— turcata, 197
Argasina, 208, 266
Arsenic in malaria, 53
— in sleeping sickness, 140
Arthropods, 264
Aschiza, 241
Assam, kala-azar in, 151, 160, 162, 167
Atheroma in the Tropics, 212
Atoxyl in sleeping sickness, 132, 141
Babesia, 9
Bacteria, insect carriers of, 8
Balantidium coli, 225
— —, discovery of, 263
Balantidium dysentery, 225
Beri-beri complicating malaria, 46, 51
Bermuda, epidemic yellow fever at, 128, 130
Black vomit in relapsing fever, 187
— — in yellow fever, 115, 119
Blackwater fever association with malaria, 108
— —, blood examination in, 99
— —, complications of, 90
— —, diagnosis of, 96
— —, diuretics in, 102
— —, etiology of, 107
— —, geographical distribution of, 88
— —, mistaken for yellow fever, 118
— —, nursing in, 105
— —, pathological anatomy of, 99
— —, prognosis of, 97
— —, prophylaxis against, 110
— —, quinine in, 65
— —, quinine poisoning theory, 108
— —, relapses in, 91, 93
— —, renal conditions in, 96, 99
— —, sequelae of, 109
— —, susceptibility to, 97
— —, treatment of, 101
Blood changes in kala-azar, 157-158, 161
— corpuscles, red, malaria parasites in, 17
— examination in blackwater fever, 91, 99
— — in malaria, 50, 65
— — in relapsing fever, 191
— films, preparation of, 15
— —, stained by Leishman’s method, 27
—, peripheral, gametocytes in, 24
Blood serum of yellow fever, infectivity of, 120
— stasis in malaria, 44, 48
Blood-pressure in malaria, 47
Boophilus decoloratus, 196
Brachycera, 240
“Brassy bodies” in red corpuscles, 18
Bronchitis in kala-azar and tick fever, 152, 155, 204
Bugs, spirillum found in, 195
Cachexia in kala-azar, 152, 155
—, malarial, ’65-67
Calomel in yellow fever, 119
Cancrum oris in kala-azar, 156, 159
Capillaries, malaria parasites in, 46, 52
Cardamatis’ointment in Oriental sore, 181
Cattle, piroplasmosis in, 111-113
Cerebrospinal fluid, trypanosomes in, 139
Chigoe, carrier of yaws, 221
Children, effects of malaria on, 44
— —, kala-azar in, 173
Chromatin masses in kala-azar parasites, 165, 167
— — in ticks, 206
Ciliata, 3
Cimex rotundatus, 260
Cisterns, cleansing of, in prophylaxis, 236
Clothing, disinfection of, 201
Coccidia, 11
— —, development of, 4
Coko. See Yaws
Cold bath in malarial hyperpyrexia, 61
Congo, sleeping sickness in, 131
Conorrhinus rubrofasciatus, 260
— sanguisuga, 150
Convulsions in subtertian malarial fever, 45
Corethrinae, 243
Crops, cultivation of, 251
Culex, 74
— fatigans, 130
—, dengue fever conveyed by, 258
—, pulps of, 72
Culicidae, 242
Culicina, 243
Culicines, distinction of, into groups, 253
Cyclolepteron, 74
Cyclorrhapha, 241, 242
Cyprinodontidae, destruction of mosquito larvae by, 249
DATE sore. See Oriental sore
Delhi boil. See Oriental sore
Dengue fever, 258
Dermocentor reticularis, 113
Derris, 249
Diagnosis table of Entamoebeæ, 231
Diarrhoea due to Lamblia intestinalis, 226
— in kala-azar, 156, 158
Diptera, classification of, 240
— subdivision of groups of, 242
Disinfection methods, 126, 201
Diuretics in blackwater fever, 102
Dogs, leishmaniasis in, 175
Donovan's confirmation of Leishman's discovery, 168
Dragon-flies, destruction of mosquito larvae by, 249
Drainage, defective, breeding of mosquitoes due to, 246
Drains, sections of, 247
Dum-dum fever. See Kala-azar.
Dysentery, 10
—, amoebic, 235
—, balantidium, 225
Entamœbeæ, 231
—, diagnosis table of, 231
Entamœbe histolytica, 225, 230
— tetragena, 232
Epithelioma, granuloma mistaken for, 223
Eretmapodites, 74
Europeans, blackwater fever amongst, 107
—, endemic index of malaria in, 81-87
Eye affections in malaria, 66-67
— in sleeping sickness, 137
Famine fever. See Relapsing fever
Fijian "kanailoma," 221
Fish, killed by larvicides, 249
—, mosquito larvae destroyed by, 249
Flagellata, 3, 225
—, Rogers's observations on, 168
Flies, bacteria conveyed by, 8
—, bites of, effects of, 146
"Forest yaws," 177
Framboesia tropica. See Yaws
Frontier sore. See Oriental sore
Gametocytes, 21
— of subtertian malaria, 24
Genitals, serpiginous ulceration of, 222-224
Geographical distribution of blackwater fever, 88
— of granuloma of pudenda, 222
— of kala-azar, 151
— of mosquitoes, 71
— of relapsing fever, 183, 190
— of sleeping sickness, 131
— of yaws, 216
— of yellow fever, 115, 124, 128
Glands, enlarged in trypanosomiasis, 135, 139
Glossina morsitans, 138, 145, 150
— palpalis, 144
Glossinæ, characteristics of, 145
— , hosts for trypanosomes, 132
— , trypanosomiasis carried by, 144, 260
Granuloma, infective, of Oriental sore, 178
— gangrenosa, 221
— of pudenda, clinical course of, 222
— , diagnosis of, 223
— , etiology of, 224
— , pathological anatomy of, 223
— , prognosis of, 223
— , spirochætes found in, 224
— , treatment of, 224
Granulomata, 215
— , treatment of, 219
Gregarinida, 9
— , reproduction of, 11
“Guam” disease, 221

Hæmamæba, 9, 11
Hæmoglobinuria, endemic. See Blackwater fever
— , prognosis of, 91
Hæmogregarinida, 9, 12
Hæmolysis in malaria, 49
Hæmorhages in malaria, 47, 52
— in yellow fever, 121
Hæmosiderin, deposits of, 99
Hæmosporidia, 9, 12
— , diseases caused by, 14
Headache in kala-azar, 153, 155
Hearsey’s treatment of yellow fever, 119
Heart, effect of malaria on, 46, 51
“Heart fever,” 112
Hereditary tolerance of malaria, 78
Herpes, facial, in relapsing fever, 189
Herpes, labial, in malaria, 44
Hiccough in blackwater fever, 91
Histoplasma in lungs, 159
Historical dates in tropical diseases, 262
Hosts, description of, 6
— , distribution of, 1
— , invertebrate, 7
Hot packs in malaria, 60
Hyperpyrexia in malaria, 43, 61
Hypodermic injections of quinine in malaria, 62

“ICE planing” in hyperpyrexia, 62
Immunity from malaria, 81
India, kala-azar in, 151, 160
— , syphilis in, 212
Infusoria, 3, 9
Insects carriers of bacteria, 8
— , infection of, by parasites, 7
Intermittent fever. See Malaria
Intestines, congestion of in malaria, 45, 47
— , inflammation of in kala-azar, 164
— , protozoa found in, 225-232
Intramuscular injections of metallic mercury cream in syphilis, 213
— of quinine, 56
Intravenous injections of quinine in malaria, 57
Irrigation systems, 251
Ixodixæ, 208, 264

Janthinosoma, 74
Jaundice in blackwater fever, 90, 95
— , in relapsing fever, 188
KALA-AZAR, anaemia in, 157
— , blood changes in, 157, 161
— , carriers of, 260
— , clinical course, 152, 155, 174
Kala-azar, cutaneous disorders in, 159
—, diagnosis of, 160
—, digestive disorders in, 158
—, etiology of, 166
—, geographical distribution, 151
—, incubation period of, 153
—, infantile, 173
—, intestinal conditions in, 164
—, malaria differentiated from, 160
—, mortality of, 162, 167
—, parasites in liver in, 162, 164
—, of flagellated forms from, 170
—, of, staining of, 165
—, pathology of, 174
—, prevention of, 173
—, prognosis of, 162
—, respiratory disorders in, 159
—, simulating typhoid, 154
—, stages of, 153
—, treatment of, 174
—, types of, 154
Kerandel’s symptom in trypanosomiasis, 136
Keratitis in sleeping sickness, 137
Kidney, effects of blackwater fever on, 96, 99, 101

*Lamblia intestinalis*, 225
—, —, diarrhoea due to, 226
—, —, discovery of, 263
Larvae, destruction of, 248
Leishman-Donovan bodies, 112, 164
—, —, discovery of, 167-169, 262
Leishmania anemia, 173, 180
—, canine, 175
—, *donovani*, 169
—, *tropica*, 178
Leishman’s stain, 16
—, method in blood films, 27
Leucocytes, mononuclear, increase in malaria, 50

Leucocytosis in kala-azar, 161
Leucopenia in kala-azar, 157, 161
—, in other diseases, 161
Liver abscess with irregular pyrexia, 233
—, enlargement of in kala-azar, 152, 156, 158, 163
—, in relapsing fever, 188
—, parasites in, in kala-azar, 162, 164
—, puncture of, diagnostic, 162
Lungs, condition of, in relapsing fever, 103
—, congestion of, in malaria, 45
—, parasites in, in kala-azar, 159

MACROGAMETES, 5, 21, 26
Macrophages, containing parasites, 166
Malaria, anaemia in, 65
—, anopheline carriers of, 244, 252
—, association with blackwater fever, 108
—, blood examinations in, 50
—, cachexia in, 65
—, carriers of, 244, 252
—, cerebral, 35, 45
—, clinical varieties of, 33
—, complications of, 47-49, 51, 64
—, conditions favourable to development of, 1
—, diagnosis of, 49
—, effects of toxins in, 49
—, endemic index of, 81-87
—, enlargement of spleen in, 52, 83, 85
—, etiology of, 69-76
—, food during, 63
—, geographical distribution of, 32
—, *hæmosporidia*, causing, 14
—, hyperpyrexia in, 43
—, immunity from, 81
INDEX

Malaria in cattle, &c. See Piroplasmosis
—, incubation periods in, 70
—, kala-azar differentiated from, 160
—, list of anopheline carriers, 252
—, localities free from, 70-71
—, management of, 59
—, mortality in, 51
—, mosquito hypothesis concerning, 70, 244
—, nursing in, 59
—, parasites causing, 10
— — of, date of discovery, 262
— —, development of, 27
— —, species of, 14
— —, toxic effects of, 31
—, pathological anatomy of, 51
—, pernicious manifestations of, 44
—, pigmentation in, 52
—, pregnancy in, 48, 64
—, prevention of, 77
—, prognosis of, 51
—, propagation of, 75
—, prophylaxis against, 69-81
—, Quartan. See under Quartan fever
—, quinine treatment of, 53-58, 62, 79
—, sequelæ in, 48, 51, 68
—, sources of infection, 77
—, subtertian, 22, 40-48
—, table of differences between parasites of, 23
—, tertian. See under Tertian
—, topographical distribution of, 33
—, treatment of, 53-64
Malpighian capsules enlarged in relapsing fever, 192
Mansonia, 74
Marsh fever. See Malaria
Mastigophora, 3, 9
Measurements, important, 263

Megarhinina, 243
Mental conditions in tertian fever, 35
Mercury cream injections in syphilis, 213
Merozoites, 20
Metazoa, 7, 9
Methaemoglobinuria, 97
“Miana bug,” 197
Miasmata, 69
Microgametes, 21
Micturition, frequency of in blackwater fever, 90
Mosquito malaria hypotheses, 70
Mosquitoes, breeding-places of, 80
—, carriers of malaria, 70, 244
—, geographical distribution of, 71
—, larvae of, destruction in water, 249
—, parasites conveyed by, 32
—, wing - scales of various forms, 74
—, yellow fever conveyed by, 122, 125
Mouth, ulceration of, in yaws, 217
Mucidus, 74
Myxosporidia, 9, 13
Myzomyia, species of carriers of malaria, 245

NAGANA, cause of, 138
Natives, phrophylaxis against sleeping sickness, 149
Negroes, endemic index of malaria in, 81-87
Nematocera, 240, 242
Neosalvarsan in syphilis, 214
Neosporidia, 13
Nervous complications in malaria, 47, 49
Neuritis in malaria, 47, 49
Nose, ulceration of in yaws, 217
Nursing during blackwater fever, 105
— during malaria, 59
— in yellow fever, 120

Oöcyst, 26
Oökinet, 26
Orchitis in trypanosomiasis, 137
Oriental sore, diagnosis of, 181
— —, etiology of, 179
— —, inoculation experiments with, 180
— —, mistaken for syphilis, 181
— —, parasitic organisms of, 178
— —, pathological anatomy, 178
— —, prevention of, 181
— —, treatment of, 181
— —, types of, 176

Ornithodorus moubata, 110, 196, 202, 207, 261
— —, tick fever transmitted by, 205, 208
— savignyi, 197

Ortthorrapha, 240

Paludism. See Malaria

Pancreas, parasites in capillaries of, 46
Papataci, 259
Paranghi. See Yaws

Paraplasma flavicenum, 121
Parasites, conditions favourable to development of, 1
— —, conveyed by mosquitoes, 32
— —, dates of discovery of, 262
— —, in capillaries, 46
— —, in liver in kala-azar, 162, 164
— —, malarial, 17
— —, sexual development of, 18, 21, 27
— —, table of differences between, 23
— —, toxic effects of, 31
— —, mode of infection by, 7

Parasites, origin of, 8
— —, table of groups of, 9
Parasitic protozoa, 3
Parasypilides, 213
Parotid swelling in relapsing fever, 189

Pediculus vestimentorum, 197

Penis, granuloma of, 222-223
Pharynx, ulceration of in yaws, 217
Phlebotomus minutus, 259
— papataci, 130, 259
Pigmentation in malaria, 52

Piroplasmat, 9, 11, 110
Piroplasmosis in domestic animals, 111-113
— —, human, 113
— —, mortality of, 113
— —, post-mortem examination in, 114

Plasmodium falciparum, 23, 32
— malax, 17, 23
— vivax, 17, 19, 23
Pneumonia complicating relapsing fever, 187

Pregnancy complicating malaria, 48, 64
— —, relapsing complicating, 189, 190
Prophylaxis in protozoal diseases, 237-261

Protista, 2, 9
Protozoa, description of, 2
— —, groups of, 3
— —, intestinal, 225-232
— —, prophylaxis in diseases due to, 237-261
— —, transmission of diseases due to, 238

Psorophora, 74
Pudenda, granuloma of, 222-224

Pupipara, 241
Puru. See Yaws

Quartan fever, clinical course of, 36
— —, parasites of, 17, 23
Quartan fever, pathology of, 37
— —, toxic symptoms of, 38
— —, treatment of, 39
— —. See also Malaria
Quinine, administration of,
forms of, 55, 62, 79
— in malaria, dosage of, 57, 79
— —, effects in stomach, 54
— —, hypodermic injections, 62
— —, by intravenous injections, 57
— —, methods of administration of, 55, 62, 79
— —, by mouth, 55, 62
— —, precautions in, 64
— —, preventive doses, 79
— —, prolonged effects of, 67
— —, by rectum, 55
— —, salts of, 53
— poisoning in blackwater fever, 109
— in quartan fever, 39
— —, resistance to in kala-azar, 160

RECTAL enemata in blackwater fever, 103
Rectum, administration of quinine by, 55, 57
"Redwater fever," 112
— —, date of discovery, 262
Relapsing fever, blood examination in, 191
— —, clinical course, 184
— —, complications in, 186, 188
— —, crisis in, 184
— —, diagnosis of, 190
— —, disinfection urgent in, 201
— —, enlargement of liver and spleen in, 188
— —, etiology of, 193
— —, geographical distribution, 183, 190
— —, herpes in, 189
— —, incubation of, 183

Relapsing fever, infectivity of, 199
— —, jaundice in, 188
— —, morbid anatomy of, 192
— —, mortality of, 190
— —, overcrowding favourable to, 198, 200
— —, pregnancy in, 189, 190
— —, preventive treatment of, 200
— —, prognosis of, 190
— —, pulse and temperature in, 184, 186
— —, sequelæ of, 189
— —, sweating in, 188
— —, treatment of, 199
— —, urine in, 188
— —, varieties of contrasted, 209
— —. See also Tick fever
Rhinosporidia, 9, 13
Rhizophycalus, 265
Rhodesia, trypanosomiasis in, 131, 137
Rogers's observations on flagellata, 168
Romanowsky's stain, 16
Röntgen-rays in granuloma, 224
Salvarsan treatment of syphilis, 214
— — of yaws, 219
Sand-flies, 242
Sarcodina, 3, 9, 225
Sarcopsylla penetrans, carrier of yaws, 221
Sarcosporidia, 9, 13
Schizogony, 20
Schizonts, 4, 20
Schizophora, 241, 242
Schizotrypanum, 150
Seamen, epidemic yellow fever amongst, 129
Serpiginous ulceration of genitilia, 222-224
Settlements, mosquito extirpation in, 246, 250
Settlements, sites for, 249
Sexual development of malarial parasites, 20
Ships, infectivity of, in relapsing fever, 199
—, Stegomyia fasciata on, 127
—, yellow fever on, 115, 124, 127
Simulidae, 242
Siphonaptera, 241
Skin manifestations in kalaazar, 152, 159
—, in trypanosomiasis, 135
Sleeping sickness, biting flies causing, 147
—, cerebral symptoms in, 137
—, clinical history of, 133
—, complications of, 137
—, diagnosis of, 139
—, etiology of, 143
—, geographical distribution, 131
—, nursing in, 143
—, pathological anatomy, 140
—, prognosis of, 140
—, prophylaxis against, 149
—, rash in, 135
—, treatment of, 132, 140, 150
—. See also Trypanosomes
Soamin in sleeping sickness, 132
Spirillum anserini, 196
— carteri, 210
— duttoni. See Spirochæta duttoni
— gallinarum, 196
— novyi, 210
— obermeieri, 191, 196, 210
—, discovery of, 262
— recurrentis, 210
— theileri, 196
Spirillum fever. See Relapsing fever

Spirochæta duttoni, 210
— obermeieri, 202
— pallida, 197
—, causal organism of syphilis, 219
—, date of discovery, 262
— pertenueis, 197
—, association with yaws, 220
—, date of discovery, 262
— recurrentis, 194
—, discovery of, 262
— vincenti, 197
—. See also Granuloma, Syphilis, Yaws
Spirochætes, classed as protozoa, 198
— found in granuloma, 224
— in tissues, diseases associated with, 211
Spleen, enlargement in kalaazar, 152, 154, 156, 158, 163
— in malaria, 52, 83, 85
—, in relapsing fever, 188, 192
Splenomegaly. See Kala-azar
Sporogony, 20, 26
Sporozoa, 3, 9
—, classification of, 10
—, development and life-history, 4
Sporozoites, 4, 6
Sporulation, 20
Spotted fever, 113
Stegomyia, 74
— fasciata, 122, 130
—, breeding places and habits of, 253, 256
— on board ship, 127
—, yellow fever absent after extermination of, 125
— scutellaris, 258
Stomach, effects of quinine on, 54
Subtertian malarial fever, 40-47
—, parasites of, 22, 26
<table>
<thead>
<tr>
<th>Index Terms</th>
<th>Page Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtertian malarial fever, tertian periodicity in</td>
<td>41-43</td>
</tr>
<tr>
<td>— — —. See also Malaria</td>
<td></td>
</tr>
<tr>
<td>Sudan type of Oriental sore</td>
<td>177</td>
</tr>
<tr>
<td>Sulphur fumigation after yellow fever</td>
<td>126</td>
</tr>
<tr>
<td>Sweating in relapsing fever</td>
<td>188</td>
</tr>
<tr>
<td>Syphilis, analogy between trypanosomiasis and</td>
<td>144</td>
</tr>
<tr>
<td>—, congenital</td>
<td>214</td>
</tr>
<tr>
<td>—, diagnosis from yaws</td>
<td>218, 220</td>
</tr>
<tr>
<td>—, eruptions of</td>
<td>212</td>
</tr>
<tr>
<td>—, extra-genital</td>
<td>211</td>
</tr>
<tr>
<td>—, irregular fever in</td>
<td>212</td>
</tr>
<tr>
<td>—, less severe in Tropics</td>
<td>212</td>
</tr>
<tr>
<td>—, mercury cream injections in</td>
<td>213</td>
</tr>
<tr>
<td>—, Oriental sore mistaken for</td>
<td>181</td>
</tr>
<tr>
<td>—, prophylaxis against</td>
<td>214</td>
</tr>
<tr>
<td>—, salvarsan treatment of</td>
<td>214</td>
</tr>
<tr>
<td>—, secondary and tertiary</td>
<td>212</td>
</tr>
<tr>
<td>—, treatment of</td>
<td>213</td>
</tr>
<tr>
<td>Tanks, hatching place for eggs of Stegomyia</td>
<td>256</td>
</tr>
<tr>
<td>Tartar emetic in sleeping sickness</td>
<td>134</td>
</tr>
<tr>
<td>Telosporidia, 0</td>
<td></td>
</tr>
<tr>
<td>Tertian, benign, clinical course of</td>
<td>23</td>
</tr>
<tr>
<td>—, geographical distribution of</td>
<td>33</td>
</tr>
<tr>
<td>—, parasites of</td>
<td>17, 23</td>
</tr>
<tr>
<td>—, temperature charts of</td>
<td>34, 35</td>
</tr>
<tr>
<td>—, fever, malignant. See Subtertian malarial fever</td>
<td></td>
</tr>
<tr>
<td>— periodicity in subtertian malaria</td>
<td>41-43</td>
</tr>
<tr>
<td>—. See also Malaria</td>
<td></td>
</tr>
<tr>
<td>Tetanus complicating malaria</td>
<td>56, 62</td>
</tr>
<tr>
<td>Thirst in relapsing fever</td>
<td>187</td>
</tr>
<tr>
<td>Tick fever, bronchitis and pneumonia in</td>
<td>204</td>
</tr>
<tr>
<td>— — carried by Ornithodorus moubata</td>
<td>205, 261</td>
</tr>
<tr>
<td>— —, diagnosis of</td>
<td>204</td>
</tr>
<tr>
<td>— —, etiology of</td>
<td>205</td>
</tr>
<tr>
<td>— —, historical account of</td>
<td>202</td>
</tr>
<tr>
<td>— —, post-mortem appearances in animals</td>
<td>205</td>
</tr>
<tr>
<td>— —, propagation of</td>
<td>206</td>
</tr>
<tr>
<td>— —, prophylaxis of</td>
<td>206</td>
</tr>
<tr>
<td>— —, resemblance to relapsing fever</td>
<td>204</td>
</tr>
<tr>
<td>— —, Spirocheta duttoni causal organism of</td>
<td>203</td>
</tr>
<tr>
<td>— —, symptoms of</td>
<td>203</td>
</tr>
<tr>
<td>— —, transmitted by Ornithodorus moubata</td>
<td>205, 208</td>
</tr>
<tr>
<td>— —, treatment of</td>
<td>206</td>
</tr>
<tr>
<td>— —, varieties of, contrasted</td>
<td>200</td>
</tr>
<tr>
<td>Ticks, 110, 113, 196, 208</td>
<td></td>
</tr>
<tr>
<td>— as hosts, 7</td>
<td></td>
</tr>
<tr>
<td>—, bloodsucking groups, 264</td>
<td></td>
</tr>
<tr>
<td>—, transmission of infection by</td>
<td>208</td>
</tr>
<tr>
<td>Toxins, effects of in malaria</td>
<td>48</td>
</tr>
<tr>
<td>Treponema pallidum</td>
<td>262</td>
</tr>
<tr>
<td>Trichomonas, 263</td>
<td></td>
</tr>
<tr>
<td>— hominis</td>
<td>225</td>
</tr>
<tr>
<td>Tropical diseases, distribution of</td>
<td>1</td>
</tr>
<tr>
<td>— fever, 40</td>
<td></td>
</tr>
<tr>
<td>— schools, English, founding of</td>
<td>263</td>
</tr>
<tr>
<td>— splenomegaly. See Kala-azar</td>
<td></td>
</tr>
<tr>
<td>Tropics, syphilis less severe in</td>
<td>212</td>
</tr>
<tr>
<td>Trypanosoma brucei, 138</td>
<td></td>
</tr>
<tr>
<td>— cruzi, 150</td>
<td></td>
</tr>
<tr>
<td>— rhodesiense, 138</td>
<td></td>
</tr>
<tr>
<td>Trypanosomes, 167</td>
<td></td>
</tr>
<tr>
<td>—, development of</td>
<td>147</td>
</tr>
<tr>
<td>—, date of discovery</td>
<td>262</td>
</tr>
<tr>
<td>—, effect of arsenic on</td>
<td>142</td>
</tr>
<tr>
<td>—, Glossina, hosts for</td>
<td>132</td>
</tr>
</tbody>
</table>
Trypanosomes in the blood, 139
Trypanosomiasis, 10
—, analogy between syphilis and, 143
— carried by Glossina, 260
—, geographical distribution of, 131, 137
—, human. See Sleeping sickness
— in animals, 144
—, possible occurrence in India, 167
—, varieties of, 138
Typhoid fever, kala-azar simulating, 154

ULCER, Oriental sore, 176, 182
Ulceration, serpiginous, of genitalia, 222-224
Ulcerations in yaws, 217
Unicellular organisms, 2, 9
Urethra, structure of due to granuloma, 223
Urine, condition of in relapsing fever, 188
— contents in blackwater fever, 92-94, 96
—, examination of in blackwater fever, 90
— haemoglobin in, in blackwater fever, 94
—, spectroscopy of, 97
Urobilin in faeces in blackwater fever, 99

VOMITING in blackwater fever, 91, 103, 105
— in relapsing fever, 187

WATER-BARRELS, hatching place of eggs of Stegomyia, 254

Women, native, and syphilis, 214

YAWS breeds true, 220
—, chigoe as carrier, 221
—, clinical course of, 216
—, diagnosis from syphilis, 218, 220
—, etiology of, 219
—, geographical distribution of, 216
—, granulomata of, 216-217
—, pathological anatomy of, 218
—, prognosis of, 218
—, prophylaxis against, 221
—, salvarsan in, 219
—, sequelae of, 217
—, treatment of, 219
—, ulcerations in, 217

Yellow fever, clinical course, 116
—, diagnosis of, 118
—, epidemics of, 124, 127, 129
—, geographical distribution, 115, 124, 128
—, incubation period in, 122
— mistaken for blackwater fever, 118
—, morbid anatomy of, 121
—, mortality of, 124, 129
—, mosquito transmission of, 122, 125
—, pathology of, 120
—, prevention of spread of, 257
—, prophylaxis against, 123
—, severer type, 116, 118
—, symptoms of, 115
—, transmission of, 262
—, treatment of, 119

Yemen ulcer. See Oriental sore

ZYGOTE, 26
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