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BLACKWATER FEVER



L. J. B. BÉRENGER FÉRAUD

(1832–1900)

Médecin général

du

Service de Santé de la Marine

Author of

De la fièvre bilieuse mélanurique

(1874)

BLACKWATER FEVER

A Historical Survey and Summary of Observations made over a Century

By

J. W. W. STEPHENS, M.D., F.R.S.

Professor Emeritus of Tropical Medicine,
University of Liverpool



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TO THE MEMORY

OF

A. A. KANTHACK

(1863–1898)

Sometime Professor of Pathology
in the
University of Cambridge

FOREWORD

With great care and thoroughness Professor Stephens has collected in the present volume all that is really known about blackwater fever. His book thus forms an invaluable, indeed necessary, guide to all who have to deal with this disease, whether medical men who are interested chiefly in the symptomatology, pathology and treatment, or the research worker more intent on the nature of its causation. Whatever has been written will be found exhaustively, yet clearly and concisely recorded.

Blackwater fever is a difficult disease to write about. The difficulty arises from the fact that practically nothing is known of the ultimate causes concerned in the bringing about of the destruction of red cells to which the disease owes almost all its features. It is true that it is now generally conceded that blackwater fever is in some way a result of preceding malaria, but how malaria brings about the sudden access of blood destruction is entirely unknown. Seemingly also quinine enters into the picture but to what extent and how far as an essential factor and in what way it acts is again completely a matter of hypothesis. Unlike most important diseases there is no specific organism to describe, no causative chemical basis to discuss, scarcely any really relevant investigations on the nature of the disease to set forth. As a consequence there is no rational basis on which treatment, other than empirical or purely palliative, can be placed. Even the symptomatology is largely a description of various secondary effects following upon and produced by the blood cell destruction. Nevertheless blackwater fever is perhaps the most important disease, medically and economically, affecting Europeans in the more malarious regions of the tropics. It is the mechanism by which

malaria under such conditions most usually kills. Further, no more serious responsibility rests on the medical man practising in countries where blackwater fever occurs, than to decide what is best to be done for the cases he may be called upon to treat of this dramatic and so often fatal disease, where the chances of life and death appear so closely balanced. To add to his difficulties there are few diseases so largely but diffusely written about, so that in his endeavour to ascertain what is known about it, the ordinary medical man may well become lost in the fog of the literature. Even those whose work is directed to the more scientific investigation of tropical diseases are hampered by the multitudinous but inconclusive literature, and it is a thought that must often have passed through the mind of one who has made a serious study of the subject, that the putting forward of theories as to the causation of blackwater fever is a function inversely proportionate to knowledge of the facts which are really known about the disease.

With the present volume in his hand, two thoughts will probably be uppermost in the reader's mind, first, what a mass of facts of a sort have been accumulated, *e.g.* in the symptomatology so fully set out by the author, and secondly, what a need there is of a really adequate investigation of this disease on modern lines. If Professor Stephens' book has done nothing else, it has given a sort of platform of so far recorded data from which both the medical man and the pure investigator can start square, the first with a means of easily ascertaining what clinical and pathological observations have been made and what treatments described, and the latter with the jungle of past literature mapped, abstracted and systematised.

An attempt to ascertain whether blackwater fever was known before quinine began to be used in the treatment of tropical fevers, has led the author to make a close study of the history of the introduction of quinine to Europe and its use in the tropics, and the account given, relegated among other indirectly relevant matters to a series of appendices,

can scarcely be read without interest and profit. In fact the information given on the early history both of blackwater fever and the "suspect" drug quinine forms an unusually interesting contribution to medical history. Who first described the condition now known as blackwater fever (apparently not with certainty, as is often stated, Hippocrates), who first gave it this name and the names it is known by in other countries, what was the real story of the "Countess" and many other facts of general interest will be gathered from the book besides more prosaic details as to distribution, aetiology, pathology and treatment of the disease so precisely and accurately documented.

S. R. CHRISTOPHERS.

1937.

PREFACE

I HAVE attempted in the following pages to give an account of blackwater fever since its first recognition as a distinct condition about a century ago.

The extracts given are necessarily brief, and though separated from their context will, I think, suffice to illustrate the development and present state of our knowledge, imperfect though it be, of the various aspects of the blackwater fever problem.

The material has been arranged for the most part in alphabetical order, and the various data in chronological sequence.

These data appear to be of very unequal value, but I have not considered it necessary to express my own opinion of the various records, for their contradictory nature is in itself sufficient to show that they should be very cautiously examined before being accepted as fact.

Perhaps some word of explanation is required for the inclusion in the appendices of matter which is only indirectly concerned with b.w.f.

Obscurity still surrounds the history of Peruvian bark and its introduction into Europe, but its discovery and the subsequent isolation of its principal alkaloid quinine, are events of such first-class importance to tropical medicine, that I have thought it not inappropriate to reproduce here the notes I compiled in searching the early literature of the treatment of malaria by Peruvian bark and subsequently by quinine, for possible records of blackwater fever. There exists, so far as I am aware, no account elsewhere of these matters in any concise form.

While the papers written on blackwater fever run into hundreds, yet summary accounts of the disease are extremely few, and these are very incomplete.

It will, I think, be evident from this compendium that a complete and accurate epitome of blackwater fever could not be written until the conflicting mass of statements in the literature are harmonized by more precise observation, by the use of modern methods of investigation, and by a much more rigorous use of the critical faculty than has hitherto obtained.

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Finally, I owe a very special debt of gratitude to the "Leverhulme Research Fellowships" and to the Colonial Office for financial assistance in bringing out this book.

ABBREVIATIONS

Alb. Albumen.
App. Appendix.
B.i.d. *Bis in die.*
B.P. Blood Pressure.
B.w.f. Blackwater fever.
Cell count. Red cell count per mm.^{3}.
D. Death.
d. day.
Eu-Q. Euquinine.
Hgb. Haemoglobin.
Hgc. Haemorrhagic.
Hge. Haemorrhage.
h. hour.
I.M. Intramuscular.
I.V. Intravenous.
m. millions.
Neg. Negative (absent).
P. Pulse.
Par. Parasites.
Pos. Positive (present).
P.m. Post-mortem.
Ppt. Precipitate.
Q. Quinine.
R. Respiration or Recovery.
R.E.S. Reticulo-endothelial system.
S/D. Systolic-Diastolic.
Subcut. Subcutaneous.
T. Temperature.
T.N. Temperature normal.
T.S.N. Temperature sub-normal.

1^a, 2^a, etc. 1 day, 2 days, etc., before Hgburia.

Day 1 = Day of onset of Hgburia.

REFERENCES

Where more than one page reference is given, the Author's name and date follow the last reference.

Where several Authors' names are given, it signifies that the paper is available in more than one journal, or that it was unavailable, but quoted from an abstract.

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STATUE OF PELLETIER AND CAVENTOU . *facing page* 1



STATUE IN PARIS

OF

PELLETIER AND CAVENTOU

Discoverers of the Alkaloid Quinine

(1820)

CHAPTER 1

SYNONYMY

THE following synonyms, selected from a more complete list given in Appendix I., will, we think, suffice to illustrate the features of the disease which have influenced authors in naming it. So far as possible we shall enumerate these in historical sequence. We have collected in groups the synonyms illustrating some particular feature, though a synonym might equally well appear in more than one group, as the name embodies more than one characteristic.

The Urine

1. *Fièvre bilieuse rémittente hématurique* appears in the Gorée hospital (Senegal) statistics for 1855. Whether derived from Guadeloupe (*vide infra*) or no, is not apparent. Barthélemy-Benoit (1865).

Mondot described the urine as 'les urines malaga infusion de café noir, simulant les urines sanglantes.' Mondot (1865).

2. *Fièvre bilieuse hématurique.* This is the first appearance of this synonym in the theses for the Doctorate of Medicine, Paris. Veillard (1867).

Fièvre bilieuse hématurique. 'Telle est la fièvre que les medecins de la Pointe-à-Pitre (Guadeloupe) où elle est plus souvent observée qu'ailleurs, ont nommé *fièvre bilieuse hématurique*, *fièvre jaune des acclimatés et des créoles*. . . . De 1828 à 1838 M. le docteur Lherminier l'a observée frequemment sur les créoles.' Dutroulau (1868), 318.

It seems probable that the name originated in Guadeloupe, but, on the other hand, Duchassaing (1850) does not use this form, but among others '*fièvre rémittente pernicieuse mélanurique.*'

3. *Fièvre bilieuse mélanurique.* 'De la fièvre bilieuse mélanurique' is the title of Bérenger Féraud's celebrated monograph of 1874.

'Le jour où j'ai eu la preuve qu'il n'y avait absolument là tres-frequemment que des principes biliaires et pas un globule sanguin, je n'ai plus pu me contenter, on le comprend, de ce nom de fièvre bilieuse hématurique qui n'est pas exact dans tous les cas . . . j'ai pris le parti de lui appliquer le nom de *mélanurique.*' Bérenger Féraud (1874), 3.

Note.—The term mélanurique was used by Duchassaing (1850) and also by Bérenger Féraud (1872).

4. *Fièvre à urines noires.* Among the people of Guadeloupe, where b.w.f. was known as early as 1847, this term was in use. Pellarin (1876), 85.

5. *Blackwater fever.* The term first used by Easmon (1884), which was derived, as he explains in his paper (1885), from Bérenger Féraud's fièvre bilieuse mélanurique. Easmon (1884, 1885).

This term has remained—almost to the exclusion of any other—in general use in British possessions up to the present day.

Blackwater fever. 25 years ago. . . . In some parts of Texas they call it Black Water Fever because the urine is not red, but really is black. Kiger (1925–26).

6. *Schwarzwasserfieber.* The German equivalent presumably of Easmon's term was first used by F. Plehn (1895) three years prior to the publication of his well-known work *Die Kamerun-Küste* (1898). He makes no comment on the use of the term in his (1895[a]) paper, but in a subsequent article (1895[b]), replying to Below (1895), who maintained that 'Schwarzwasserfieber ist Gelbfieber,' he states that 'Ich haben ihn (der Ausdruck Schwarzwasser-

fieber) mit voller Ueberlegung (full consideration) angewendet.'

Steudel (1895), Doering (1895), Küchel (1895), Kohlstock (1895) and Eschle (1896) also used the term, and Koch (1898, 1899) adopted it in his writings, in which he affirmed the quinine causation of b.w.f.

The Dutch equivalent is Zwartwaterkoorts.

7. *Fièvre hématinurique.* The name proposed by Maurel (1883)?. Corre (1883).

8. *La fièvre hémoglobinurique.* Corre (1883), in his treatise on tropical fevers, entitles the article devoted to b.w.f., *fièvre bilieuse hématurique ou mélanurique (hémoglobinurique)*, but the simpler form la fièvre hémoglobinurique occurs frequently throughout. Corre (1883), 144.

The use of the term was based upon the spectroscopic examination of the urine by Corre himself (1878), Venturini (1880) and Karamitsas (1882).

9. *Haemoglobinuric fever.* The English equivalent was used by Manson (1893) and Field (1899). Burns (1900), writing of 'malarial haemoglobinuria,' says the 'synonyms are blackwater fever (Das Schwarzwasser Fieber), hematuria, hemoglobinuric fever, etc.' Curry (1902) has a paper entitled 'Blackwater (hemoglobinuric fever),' and Hartsock (1902) in a paper entitled 'A case of blackwater fever from the Philippines' also uses the term. Shropshire (1903), Craig (1911) and Deeks and James (1911) simply use the term 'hemoglobinuric fever' in the titles of their papers.

10. *Methemoglobinuria. Quinine has no place in the therapy of malarial methemoglobinuria* or haematuria, as it is called. Goltman (1904).

11. *Bloody chills.* Given as a synonym by Krauss (1904); we may interpret it as a forcible equivalent of hemoglobinuric fever. Krauss (1904).

12. *Methémoglobinurie quinique.* 'De la méthémoglobinurie quinique' is the title of a treatise written by Carreau (1891).

The Biliousness

1. *Accès bilieuse grave.* The term used by Lebeau (1850) in Madagascar. Pellarin (1876).
2. *Résorption biliaire.* The term used by Loupy (1858) in Senegal. Bérenger Féraud (1874), 25.
3. *Fièvre bilieuse grave.* The term used by Barthélemy-Benoit (1865), 11.
4. *Fièvre bilieuse hématurique.* The title used by Barthélemy-Benoit in his series of articles on b.w.f. in Senegal. Barthélemy-Benoit (1865).
5. *Fièvre bilieuse hémoglobinurique.* Used by Bertrand with the qualification ' dite ' (so called). Bertrand (1889).

This synonym has persisted among French authors almost to the exclusion of all others up to the present time.

The Icterus

It is difficult in the early accounts of the disease to know whether b.w.f. or yellow fever is being described, and the difficulty of diagnosis between b.w.f. and other conditions in which icterus occurs is reflected in the terminology.

1. *Fièvre jaune des créoles.* In the West Indies. Barthélemy-Benoit (1865), 11.
2. *Yellow remittent* (Sholl). In North America. Boston (1869).
3. *Swamp yellow fever.* In North America. Bailey (1883).
4. *Gallenfieber.* On the Gold Coast. Fisch (1890).
5. *Pesudo-yellow fever* (Stone). In North America. Jones (1900).

As late as 1895 it was maintained by Below (1895) that ' Schwarzwasserfieber ist Gelbfieber,' a view contradicted by Plehn, F. (1895[b]).

Aetiology, Malaria

From the earliest times the idea has prevailed that b.w.f. is a ' form of malaria.'

1. *Maladie paludéenne icterique.* In reference to cases in Guadeloupe. Duchassaing (1850).
2. *Malignant malarial fever.* In Alabama. Michell (1869).
3. *Fièvre hémosphérinurique palustre.* In Greece. Karamitsas (1882).
4. *Perniciosen Sumpffieber.* (Febris perniciosa haematurica [biliosa]). Le Nobel (1892).
5. *Malarial hemoglobinuria.* In Tennessee. Krauss (1904).
6. *Accident parapaludéen* Firket. Gouzien (1911), 75 (r.).

Aetiology, Quinine

1ª. ' *Sulla intossicazione chinica e l'infezione malarica.*' Tomaselli (1875).
1ᵇ. ' *L'intossicazione chinica e l'infezione malarica.*' Tomaselli (1877).
1ᶜ. ' *La intossicazione chinica e l'infezione malarica.*' Tomaselli (1897).

The above are the titles of Tomaselli's three famous memoirs in which he enunciated the quinine theory of b.w.f.

2. *Malattia del Tomaselli,* is the sub-title to Moscato's paper entitled ' Sulla emoglobinuria parossistica da Chinina.' Moscato (1889).
3. *Haematuric cinchonism,* commonly called malarial haematuria. N. America. Barton (1890).
4. *Febbre ittero-emoglobinurica da Chinina.* Coniglio (1914).

The Blood

1. *Cachaemia Haemorrhagica* (Owens). In North America. Boston (1869).
2. *Purpuraemia* (Riggs). In North America. Boston (1869).
3. *Lipaemia* or *malarial haematuria.* In North America. Martin (1891–2).
4. *Lysaemia* or *malarial haematuria.* In North America. Martin (1896).

The Locality

1. *Fièvre bilieuse de la Guadeloupe et de la Martinique.* Barthélemy-Benoit (1865).
2. *Cane-brake yellow fever.* In North America. Boston (1869).
3. *Swamp yellow fever.* 'The resemblance of this disease to yellow fever is certainly in some cases very striking, so much so that it has been called Swamp Yellow Fever.' In North America. Bailey (1883).
4. *Highland yellow fever.* Some *superficial* observers have named the disease highland yellow fever. Stubbert (1886).
5. *Roanoke yellow fever.* In North Carolina. Field (1899).
6. *Chagres* fever.* *Vide* App. 26.

* The River Chagres was dammed during the construction of the Panama Canal, and now forms Gatun Lake, through which ships pass.

CHAPTER 2

GEOGRAPHICAL DISTRIBUTION

It is impossible, I think, to give any comparative figure indicating the frequency of b.w.f. in the countries and localities named. I have, however, marked with an asterisk those places where blackwater fever is not an unusual condition.

Europe

Austria, Bulgaria*, Czechoslovakia, Germany, Greece*, Holland, Hungary, Italy*, Sardinia*, Sicily*, Poland, Russia*, Yugo-Slavia*.

Seyfarth (1918[b]) says, of South-Eastern Bulgaria, 'blackwater fever is not uncommon,' and records 10 cases. In Greece it would appear to be very common, judging from the numerous cases recorded.

In Italy it is far less so, the records showing only a few cases. In Sicily (Catania), Tomaselli (1897) recorded some 20 cases.

In Russia, Popow and Zeiss (1925) recorded 85 cases collected from the literature in 43 years, i.e., two per annum; but the same authors in 1927 record 10 cases from Suchum and five from Moscow. In Yugo-Slavia, Weselko (1926), in the north of Dalmatia, recorded 49 cases in 5 years.

South-West Asia

Arabia, Cyprus, Palestine*, Persia, Russia—Trans-Caucasia*, Russia—Trans-Caspia*, Turkey.

Arabia: Gill (1916) records 25 cases in 9 years from Matrah and Muscat, and notes that none of these occurred in Arabs or negroes, and adds the statement, which might

be made of many other localities, that there is 'little information available regarding this extensive area' (Arabian Sea littoral or in the Persian Gulf).

In PALESTINE, judging from the numerous records, it is common. Thus Masterman (1896) says that in 1893 there was a 'regular epidemic of malaria, and among the fatal cases a great many presented symptoms we now recognize as being those of Blackwater Fever.' It is after this date—1896—that blackwater fever begins to be recorded, but there is no reason for supposing that it did not exist before this time.

Popow and Zeiss (1927) record 32 cases in 4 years from TRANS-CAUCASIA, and the same authors have observed 98 cases in 1900 in Merw and district (Turkestan).

India

Assam*, Bengal, Bengal Duars*, Bihar*, Orissa, Bombay, Central Provinces, Coorg Province, Hyderabad, Madras*, United Provinces, Ceylon.

In ASSAM, judging from general knowledge, we should say it is not as common as in the Bengal Duars. Powell (1898) records 15 cases, Christophers and Bentley (1908[a]) 13 cases from Tezpur in 30 years, and only five cases from Nowgong in 29 years. From the BENGAL DUARS, on the contrary, the latter authors record 65 cases from the Dam Dim district in 12 years.

Vaughan (1921) has noted the occurrence of a large number of cases in the Ranchi district of BIHAR; and Megaw and Gupta (1927) note that the Singhbhum district 'is notorious' for blackwater fever. *Vide* App. 26.

CEYLON: It has frequently been stated that blackwater fever does not occur in Ceylon, but van Rooyen (1913) records a case, and Castellani and Chalmers (1919) heard of two cases in 12 years, which they say were most probably cases of quinine haemoglobinuria, but give no reasons for their belief. *Vide* App. 26.

Burma and the Far East

Burma, Lower Burma, Upper Burma*, China, Formosa*, Cambodia, Cochin-China*, Laos*, Tongking*, Federated Malay States*, Perak, Selangor, Straits Settlements*, Siam*.

Islands

Borneo, Celebes, Flores*, Java*, Lombok, Papua or New Guinea or Kaiser Wilhelm's Land*, New Hebrides*, New Pommern (or New Britain)*, Philippine Islands*, Solomon Islands*, Sumatra*.

BURMA: While isolated cases are found in many parts of Burma, Fink (1909) states that blackwater fever is endemic in the Myitkyina district, and in 1912 records 20 cases from this locality, and a total of 44 cases from various localities in Upper Burma.

CHINA: A few cases are recorded from the Fukien, Hupeh, Kwang-tung and Yun-nan provinces, while Manson (1907), on the authority of Dr. Wenyon, of Fatshan, states that in 1885 'it [blackwater fever] ravaged like a plague the Chinese army, on the Tonquin border of Kwangsi'; but the original statement of Manson (1893) is different, viz.: 'The fever which ravaged like a plague the Chinese army on the Tonquin border of Kwangsi was frequently accompanied by haemoglobinuric symptoms.' (Manson, P. (1893), 'On African haemoglobinuric fever,' *Trans. Epidem. Soc.*, **12**, 111–41.)

FORMOSA: Here it is common, Kondo (1926) recording 98 cases.

LAOS: While very common in Haut-Laos, in other parts it is described merely as being present or exceptional.

TONGKING: While Pons (1921) describes it as a curiosity in the Delta, yet it is very frequent on the upper reaches of the Black and Claire rivers.

FEDERATED MALAY STATES: Almost annually cases are reported. In 1919 there were 34 deaths. From Perak and Selangor only isolated cases are reported. *Vide* App. 26.

STRAITS SETTLEMENTS: Not particularly common; thus from Singapore only 26 cases are recorded in 26 years.

SIAM: Not uncommon up-country, according to Mendelson (1919). Prommas (1927) treated 26 cases from Chiengmai in 8 years.

BORNEO, CELEBES, FLORES: From the first two localities records are scanty, but Sörensen (1914) reports 16 cases from Flores.

JAVA: From Batavia, De Langen (1918) records 9 cases, and Mense (1924) 11 from Samarang; but on the whole the number of cases reported is few.

LOMBOK: Occurrence noted by Kohlbrugge (1899).

PAPUA: According to Giblin (1922), widespread.

NEW HEBRIDES: Amigues (1907) says it has 'become fairly common,' but there are few records.

NEW POMMERN: One or more cases annually.

PHILIPPINE ISLANDS: Of especial interest, for Craig (1909) (*Malarial Fevers*) speaks of its almost complete absence in the Philippines, yet Garton, according to Reyes (1926), reported 44 cases from Iwahig (Penal Colony), and isolated cases occur elsewhere. *Vide* App. 26.

SOLOMON ISLANDS: A few cases annually, according to Crichlow (1921).

SUMATRA: Only isolated cases in most areas, but Mense (1924) reported many cases from Sibolga in 1923.

Africa

Abyssinia, Algeria*, Angola, Bechuanaland, Cameroons*, Congo*, Dahomey*, Eritrea, French Equatorial Africa*, Gabon* (French Equatorial Africa), Gambia*, Gold Coast*, French Guinea*, Ivory Coast*, Kenya* (formerly East Africa Protectorate), Morocco, Nigeria Northern*, Nigeria Southern*, Portuguese East Africa*, Rhodesia Northern*, Rhodesia Southern* (including Mashonaland and Matabeleland), Senegal*, Sierra Leone*, Somaliland, Sudan (Anglo-Egyptian)*, Sudan (French)*, Tanganyika Territory* (formerly German East Africa), Togo* (since 1920, partly Gold Coast, partly Dahomey), Uganda Protectorate*, Union of South Africa, West Africa*.

Islands

Cape Verde (Saint-Nicolas), Comoro* (Mayotta, etc.), Conakry*, Fernando Po*, Gorée, MacCarthy, Madagascar*, Mauritius*,

Nossi-Bé*, Réunion, St. Louis*, St. Marie, St. Thomé, Zanzibar and Pemba.

There can be little doubt that in most of the places characterized in the above list by an asterisk, blackwater fever is a common or very common condition. We will comment, therefore, on those places where the records are few or even doubtful.

ABYSSINIA: There is only a single record, and this probably represents its rarity, as in the adjoining territories.

SOMALILAND (British and Italian): Cases are rare or doubtful.

ALGERIA: In recent years, at least, fairly commonly reported from the three departments of Oran, Algiers and Constantine. Thus Parrot (1921) estimates about 100 cases between 1899 and 1920, and states that it is taking an important place in the pathology of Europeans in Algeria. Contrasted with this, we have Laveran (1898) (*Traité du Paludisme*) stating that ' Pendant un séjour de cinq années en Algérie je n'ai observé qu'un fait pouvant être classé dans cette catégorie d'accès pernicieux'; and, as late as 1912, Campagne (1913) speaks of it as being extremely rare. *Vide infra* p. 17.

MOROCCO: Two records only.

North America

Alabama*, Arkansas*, California, Colorado, Florida*, Georgia*, Illinois*, Kentucky*, Louisiana*, Mississippi*, Missouri, New York, North Carolina*, Ohio, Pennsylvania, South Carolina*, Tennessee*, Texas*, Virginia*.

What the present-day frequency of blackwater fever in the various States may be, the present survey does not attempt to estimate. The asterisks indicate that in the States so marked the disease has been at one time or another, and in one locality or another within the State, common. *Vide* App. 26.

Central America

Costa Rica*, Guatemala*, Honduras*, Honduras British, Mexico, Nicaragua*, Panama*.

British Honduras: 11 cases in 1930. Probably should be starred.

Mexico: Two cases at Tampico in 1895.

Salvador: I have not found any records in the literature.

South America

Argentine, Brazil*, Colombia*, Ecuador*, Guiana British*, Guiana Dutch, Guiana French*, Paraguay, Venezuela*.

Dutch Guiana: Dr. F. M. Peter, senior physician of the hospital of the Aluminum Company of America, treated 'two or three cases of blackwater fever every year' (correspondence). *Vide* App. 26.

West Indies

Antigua, Cuba*, Guadeloupe*, Haiti*, Jamaica, Martinique, St. Lucia, Trinidad and Tobago.

Jamaica: eight cases, 1913–14; eight cases, 1916–17.

St. Lucia: Two cases recorded in 1926.

Trinidad and Tobago: 20 cases in 1930.

Vide App. 26.

The Literature references of Chapter II are given in Stephens (1934), 37.

CHAPTER 3

HISTORY

AFRICA

1800 (?). *Gold Coast* *

The disease occurs at the beginning of our century (19th) among the occupants of the European forts on the West Coast of Africa, especially on the Gold Coast. It was called yellow fever, and was apparently what we still to-day call yellow fever. Fisch (1896[a]), 271.

1822. *Gold Coast*

Boyle, in his account of the fevers of West Africa, gives an extract from the report of Mr. Tedlie (Tidlie). In this occur the words 'The urine has the appearance of bloody water.' Boyle (1831).

1832. *Gold Coast*

On the Gold Coast the first death attributable to b.w.f. occurred in 1832 among the Basle missionaries who had settled there in 1828. Fisch (1896[b]). Plehn, F. (1898), 104.

1840. *Gold Coast*

It is a form of disease which 50 years ago was very rare, and perhaps because it was overlooked or otherwise diagnosed. Here on the Gold Coast it was first commonly observed in the 'fifties,' and now the greatest number of deaths are caused by it. Fisch (1894), 80.

* Admiral Bouët founded posts there in 1842. Bérenger Féraud (1874), 62. It became English by treaty in 1872.

1846. *Gaboon* *

M. Losédat, a venerable ecclesiastic . . . since 1846, when he arrived in Senegal, told me that he had many times seen malaria followed sometimes by intense bilious symptoms, yellow colour of the skin and the passage of black urine. He also stated that it was currently reported that the 23 Europeans who had formed the first garrison of the post (Gaboon) had all been successively attacked by the disease and had almost all died either at the first attack or from subsequent relapses. . . . He added further that it was the same disease that he found at Gorée (Senegal) on his return there in 1855, as that in Gaboon in 1846. 34.

1848. *Gold Coast*

Extrait du rapport du Dr. Beaujean 1848.

The most common complication (of fever?) arises from the biliary apparatus. This kind of complication, which sometimes reaches an extreme degree (very pronounced icterus, frequency of bilious vomiting, bilious stools, hepatic pain, etc.), is only relieved by an emetic. . . .

A fairly common complication is diarrhoea of which I take no account unless it is very severe; it is to satisfy the patient that I give him a little morphia and laudanum; quinine rapidly clears up everything. Similarly for congestive complications 'des urines sanguinolentes et même sanglantes, des selles dysentériques, des épistaxis.' 39.

1851. *Senegal*

1. Delaruelle . . . avait été souvent malade, entre à l'hôpital de St. Louis le 28 septembre 1851 pour fièvre intermittente et y reste jusqu'au 6 octobre, ayant présenté des phénomènes bilieux intenses. . . . Puis enfin il entre le 12 novembre . . . et l'observation du 13 porte: Fièvre depuis hier au soir avec redoublement, vomissements bilieux;

* Admiral Bouët founded posts there in 1842. Bérenger Féraud (1874), 62.

douleur epigastrique ce matin; *urines sanguinolentes ;* douleur à la région des reins; une selle normale.

Le 14 il y a: *Même état des urines.*

Guérison le 12 décembre. Réchute le 20 décembre. 17.

1851. *Gold Coast*

D . . ., recently arrived from France, had only had some rare attacks of intermittent fever which usually yielded to quinine . . . when suddenly at the beginning of winter he had a fresh attack, considerable pain (brisement) in the limbs, intense lumbar pain, then deep coma. . . . This condition lasted 10 hours when a very copious haematuria supervened. . . . He lost a considerable quantity of blood by the ureter and became anaemic. . . . It is the first time I have seen this complication, and I think it must be rare. Legrain (1858). Bérenger Féraud (1874), 40.

1854–55. *Gold Coast*

Bilious fever generally begins with a violent headache, nausea, a sharp pain in the lumbar regions and limbs. . . . Three of the cases had ' un pissement de sang.' The gunner Visier from Grand Bassam did not shew this symptom, although his biliousness was very severe. The haematuria in the three cases mentioned lasted 3 days. Lajoux (1857). Bérenger Féraud (1874), 46.

1854. *Gaboon*

Day 3. Seen in consultation with M. Ford the American (*vide infra*).

Conjunctiva yellow, the face and the whole body intensely so. Complains of frontal and ocular, hypochondrial and epigastric pain. Eyes brilliant. Treatment: cold drinks, 15° C., sweetened. Leeches, 80, on epigastric and hepatic regions. Bismuth subnitrate every $\frac{1}{4}$ hr. Vomiting, epigastric and hypochondrial pain diminish. Urine red, bloody. Constipation. Supra-orbital headache persists, delirium at times, hallucinations, convulsive movements.

Cannot bear bed-clothes, lies across the bed and falls out. Motions resemble pure blood.

Day 4. The bloody motions persist. Symptoms abate. No motions or urine. Quinine given endermically by application to blisters.

Day 5. Death.

The absence of vomito-negro, and of bloody vomit and other symptoms, sharply separates it from yellow fever. Gabon, le 20 mai 1854. *Signé*: E. Monestier. Bérenger Féraud (1874), 37.

1855. *Gaboon*

Ford, in describing the 'African fever,' Guinea fever, Bulam fever or Coast fever, states: 'The urine is always changed. It becomes scanty in most cases. The colour in ordinary mild cases is brown, in malignant cases *red* or *black*. . . . No man can be considered out of danger while the urine remains red or black.

Malignant Fever. . . . Immediately after the chill (perhaps before it has passed off) the urine, which is usually free, becomes red or black. . . . After a few hours there is an intermission . . . but the yellowness of skin and red urine do not disappear entirely . . . the disease returns with augmented force. The patient is tortured with thirst, but vomits all ingesta; bowels become irritable so as to reject all injections per rectum, the urine assumes a darker hue . . . the alvine evacuations become bloody and the ejections from the stomach become green and finally black. . . . The peculiar symptoms of this fever . . . are yellow skin, red or black urine, together with vomiting of yellow fluids and intense restlessness or stupor, frequent chills following each other at six or eight hours interval, or one violent chill followed by stupor or violent pain in the head.' Ford (1855.)

1855. *Senegal*

2. Coigné, Louis, âgé de 32 ans . . . 2 ans de séjour. Première entrée; accès de fièvre hier, nouvel accès ce

matin. . . . A six heures du soir . . . teinte ictérique répandue sur tout le corps. Depuis quelques heures, urines sanguinolentes.

Autopsie. . . . Le foie est hypertrophié . . . la vésicule biliaire distendue laisse échapper un liquide noirâtre épais. La rate présente un volume remarquable . . . son poids était de 1 kil. 300. Bérenger Féraud (1874), 19.

1855. *Senegal*

According to Barthélemy-Benoit (1865), b.w.f., 'fièvre bilieuse rémittente hématurique,' does not appear in the records of the Senegal hospitals until 1855 (Gorée hospital) and 1857 (Saint Louis hospital), and it was between 1861 and 1864 that its importance among epidemic diseases became greater. It is noteworthy that in 1859 (fourth quarter) 119 cases of yellow fever with 85 deaths occurred, which are not included in the table, but the fact shows that b.w.f. and yellow fever were statistically separated. Barthélemy-Benoit (1865). Stephens (1930).

1861–64. It is of historical interest to record that Barthélemy-Benoit was stationed at Gorée from October 1861 to May 1864, and that he treated 90 cases of b.w.f., and Bérenger Féraud (1874), viii, states when he was head of the Gorée sanitary department he treated 35–40 cases annually. From the statistical tables of these two authors it appears, for example, that in the year 1862 there were about 60 cases in the two Senegal hospitals.

1867. *Algeria*

Obs. viii. G., aet. 36. 7 years in Africa. Ill for 5 days. Works on the railway excavations (terrassements) at Smendou. Admitted to hospital at Constantine Algeria 30 Aug.

30 Aug. Ipéca stibié and injection of quinine 5 decigrammes.

31. 2nd injection, fainting fit of ½ an hour; 3 p.m. vomiting deep green matter, 3rd injection; 8 p.m. 4th injection.

1 Sept. Frequent vomiting, slight icterus; 5th injection, 3 p.m. sulphate of Q., 1·0 g. *per os.* Vomiting shortly after.

2. Vomiting after every drink. Calomel 1·0 g.

3. Vomiting less frequent, urine scanty, the colour of Madeira wine, not giving bile or blood reactions.

4. Vomiting frequent, mental confusion, 3 p.m. vomiting, hiccough almost incessant.

5. Condition the same, death at midnight. Arnould (1867).

1869. *Gaboon, Lagos, Fernando Pò, Sierra Leone, Bight of Benin*

Au Gabon elle sévit particulièrement pendant les mois de janvier, février, mars et avril, qui correspondent à la saison pluvieuse et à la saison qui lui succède. A Lagos et dans tout le golfe de Benin, à Fernando-Pò, elle apparait à toutes les époques de l'année; à Sierra-Leone, elle est surtout fréquente dans les six derniers mois de l'année.

La fièvre bilieuse hématurique est assez rarement observée à bord des batiments. . . . J'en rapporte un cas très-grave qui s'est développé à bord de *l'Ariège* . . . (un an de séjour à la côte). Dudon (1869).

1884–85. *Gold Coast*

Easmon uses the term blackwater fever. Easmon (1884, 1885).

AFRICA. ISLANDS

1850. *Madagascar*

As in simple intermittent fever, a rigor more or less prolonged is the beginning of bilious fever. The rigor is soon followed by vomiting. . . . Diarrhoea of a similar character is often an additional symptom, and I have seen patients pass pure blood per rectum.

Occasionally the vomit is blackish, and so is the urine, the colour of which is such a deep green (verte) that it

resembles ink. . . . In favourable cases icterus spreads all over the body, which becomes a deep yellow orange; the urine loses its black colour, the vomiting stops: generally a good sign. I have rarely seen deep icterus followed by death. In fatal cases the rigor is more prolonged. It often alternates with the body temperature . . . vomiting continues, there is constipation; the urine becomes scanty and thick, icterus is not clearly defined, fever persists, agitation increases, there is a lack of morale. The patient, while conscious of his condition, expresses fear of death, which usually occurs on the 5th–7th day. I have seen 22 cases of varying severity, with three deaths.

When the remission sets in and the bowels are quiet we give an enema of sulphate of quinine 1·0 g. with 15 drops of laudanum. Lebeau, *Rapport du troisième trimestre de* 1850. Dutroulau (1868), 302.

1850–52. *Mayotta*

The first sign that struck our attention was the reddish-yellow colour, the injection of the conjunctiva, the diminution in the quantity of urine, which took on the colour of strong beer. As the fever increased so did the train of the above symptoms, icterus became more distinct—if wanting or slight during life it became very pronounced after death; the urine became of the colour of old Malaga, and we were able to prove the presence of blood. In the worst case we have seen . . . there was acute supra-orbital headache, cramps in the limbs causing the patient constantly to groan, at the same time uncontrollable vomiting . . . without any remission for four days; on the fifth there was some improvement, the vomiting stopped; the urine was almost normal. The temperature of the skin fell, but the pulse remained frequent. Quinine being tolerated, we began to hope, but violent delirium supervened, and at the end of 2 hours of terrible agitation the patient died. Le Roy de Méricourt (1853). Dutroulau (1868), 303.

1851. *Mayotta*

Case of M. Gelineau, who succeeded Lebeau at Mayotta.

Le sieur Solar, aet. 52, resident in Mayotta for 4 years, and consequently has had many attacks of fever, admitted to hospital 5 Dec. 1851. Presents in an extreme degree all the signs of malarial cachexia. The attack of fever lasts until 7 Dec., then apyrexia. . . . Sulphate of quinine 0·6 g. 2 p.m. I was hastily summoned . . . ochreous yellow over the whole body . . . patient collapsed . . . acute supra-orbital headache. Tongue . . . greenish following frequent vomiting . . . acute pain in splenic region . . . constant desire to pass a motion or to vomit . . . much green matter vomited, not blood-stained; stools less green, but abundant. Micturition frequent, the chamber utensil being half full of urine mixed with much blood. I cannot better compare the colour than to that of Malaga wine to which one has added a little water; the patient, seeing this colour, appears to be anxious about his condition. Dutroulau (1868), 304.

1851–54. *Madagascar, Mayotta and Nossi-Bé*

Fièvre pernicieuse ictérique (dite ictéro-hémorrhagique). Il existe à Madagascar une espèce particulière de fièvre bilieuse que nous n'avons rencontrée ni au Sénégal, ni dans aucun point de la côte occidentale d'Afrique, et qui n'est pas décrite dans les auteurs. Cette fièvre a été tour à tour appelée dans le pays, *fièvre hémorrhagique*, *fièvre pernicieuse bilieuse*, *fièvre pernicieuse ictéro-hémorrhagique*, et plus improprement *fièvre jaune*.

Cette fièvre . . . est très commune à Mayotte et à Nossi-Bé. Elle ne frappe jamais d'emblée l'Européen arrivant de France ou de la Réunion. On dirait qu'il faut pour être apte à la contracter avoir passé la filière des accidents primitifs de l'intoxication miasmatique.

Pendant ce premier stade, les urines coulent abondamment; elles ont une couleur rouge foncée qu'on ne saurait

mieux comparer qu'a celle du vin de Malaga. Daullé (1857), 46. Loupy (1862). Dutroulau (1868), 309.

1852. *Madagascar and Mayotta*

The first thing that strikes one on inspecting a patient suffering from ' accès pernicieux jaunes ' is the colour of the whole body and of the conjunctivae; this yellow colour with a reddish tinge could best be compared with that of powdered saffron. There is extreme anxiety and restlessness . . . respiration deep and sighing . . . vomiting of green bile very obstinate, stools loose or normal, haematuria profuse. Sometimes there is obstinate epistaxis.

A severe case. Beaugendre, aet. 30, in Mayotta for the last 5 years. Treated on various occasions for intermittent bilious fever.

17 May. p.m. violent rigor lasting some hours, icterus, haematuria, frequent diarrhoea and vomiting, general prostration, intense lumbar and limb pains, intense supra-orbital headache.

18 (?). Q. sulphate 1·0 g. vomited. Q. sulphate 1·5 g.+ laudanum 12 drops vomited. Numerous stools and vomits up to 4 p.m. Stupor develops. Midnight, progressive coma. Diarrhoea and vomiting reappear.

19. 7 a.m. deep coma, delirium, diarrhoea, vomiting, haematuria.

20. A very offensive blackish motion. Death. Dutroulau (1868), 307.

1865. *Réunion*

B.w.f. occurred only after the introduction of malaria in 1865. Gouzien (1911), 59 (r.).

1881. *Mayotta*

C'est la période qui suit les pluies abondantes qui est la plus insalubre. . . . Cette période correspond au deuxième trimestre de l'année pour l'île Mayotte, trimestre pendant

lequel nous avons observé jusqu'à 22 cas de fièvre bilieuse hématurique. Comte. Bréjon (1881), 79.

1907. *Madagascar*

Ankadinandriana hospital. 'Ce n'est qu'en 1907 que le diagnostic fièvre bilieuse hémoglobinurique apparait sur ces statistiques.' Rigaud (1909), 389.

1907. *Mauritius*

Phoenix district. An epidemic of malaria occurred in 1906, whereas previously there was but little. The first cases of b.w.f. were recorded in Sept. 1907. Gouzien (1911), 59 (r.).

North America [1]

1790.[2] *Alabama*

McDaniel quotes Mabry as having seen cases corresponding to the fever of the present day as early as 1790, near Selma, Alabama. McDaniel (1889). Krauss (1904).

1820.

An article appears in the *Medical News and Hospital Gazette* (? 1832) of New Orleans, by an unknown author, in which he dates a case of haematuria as far back as 1820, and in his remarks on that and other cases, says: 'Whether haematuria, more than epistaxis menorrhagia or any other of the bloody proluvia, be the result of that bugaboo miasmata is questioned.' Stamps (1886).

1837–43. *Illinois, Indiana*

As early as 1837 and up to 1843, I encountered and treated many cases of this disease in the Wabash and White River bottoms in the States of Indiana and Illinois. Day (1885).

1 Much of the early literature of North America has been unavailable.

2 1790 would appear to be erroneous, for Mabry (1870), *vide infra*, says more than 25 years ago, i.e. about 1845.

1843. *Louisiana*

The disease was observed by a number of physicians many years before the close of our civil war. Among others, I may mention Dr. Glidden Young, of Louisiana, 1843. Smith (1900).

1843–46. *Arkansas*

I encountered and treated many cases of this disease . . . from 1843 to 1846 in the White River lowlands in the State of Arkansas. . . . I found the disease more or less prevalent every year. Day (1885).

1845. *Alabama*

It is a mistake to suppose that this is a new form of disease. More than 25 years ago I treated in the vicinity of Selma (Alabama) cases of intermittent fever presenting in a marked degree all the symptoms characteristic of these cases of the present time. Mabry (1870, 1872). Smith (1900). Deaderick and Thompson (1916).

1850. *North America*

The writer confidently asserts that before the year 1850, the cases of haematuria, having the remotest connection with malarial disease, may be counted upon one's fingers; whereas since that date it has appeared almost simultaneously from the western boundaries of our country to the distant islands of East Africa as a sporadic, endemic and epidemic disease. Manson (1886).

1853. *Florida*

Tyson (1886) records that Maxwell observed cases as far back as 1853, and wrote a paper on the subject in 1860. Tyson (1886).

1855. *North Carolina*

In this area, which is adjacent to the Roanoke river in Northampton County, the older physicians tell me that

blackwater fever was unknown prior to 1855, in which year the disease made its appearance. Boyd (1926).

1856. *Louisiana*

According to the latest medical history, a doctor from Monroe, in 1856, was the first physician in the United States to report a case of blackwater fever. Wright (1917).

1859. *Louisiana*

Faget treated the disease as early as 1859, and states that the cases with haematuria and haematemesis had frequently been seen in New Orleans and been mistaken for yellow fever. Inasmuch as Faget considered haematemesis a common sympton of haemoglobinuric fever, it is possible that he himself confounded the two diseases in some instances. Faget (1869, 1870). Deaderick and Thompson (1916).

1859–60. *Louisiana*

In the United States haemoglobinuric fever was first described by Dr. J. C. Cummings of Monroe, Louisiana, in 1859. He reported six cases and refers to numerous cases during the previous season. Cummings (1859–60). Deaderick and Thompson (1916).

1863. *Alabama*

My attention was first called to it in September 1868, when I received specimens of urine and the history of some cases from Dr. R. D. Webb of Livingston, Alabama, who wrote also that it was not known in that part of his state prior to 1863 or 1864. Tyson (1883[b]).

1866. *Texas*

Dr. H. C. Ghent (1868) of Port Sullivan, Texas, in 1866, reported hemoglobinuric fever endemic in parts of Texas. Ghent (1868). Deaderick and Thompson (1916).

1867. *Alabama*

Dr. R. T. Michel . . . of Montgomery, Alabama . . . calls it a malignant malarial fever . . . he dates the history of the disease from the year 1867. Smith (1900).

1867–82. *Alabama*

McDaniel (1883) states: 'All the eighteen cases . . . were of the type referred to in Dr. James Tyson's (1883) paper as *malignant haematuria* called in Alabama haemorrhagic malarial fever and occurred in the writer's practice from 1867–82 inclusive.' McDaniel (1883). Tyson (1883[a], 1883[b]).

1869. *Louisiana*

It has been my misfortune to have had another similar case last fall. To a little girl, seven years old, quinine was administered in different ways, but was invariably followed by haemorrhage of the urinary passages. Cacherê (1869).

1870. *Alabama*

Mr. A. H., aged about 55 years, had suffered from occasional attacks of intermitting fever for the past two years. . . . He had a paroxysm on Monday, August 30th, and then on Tuesday and a third on Wednesday. During the third chill he commenced discharging from the bladder in profuse quantities a bright claret-coloured fluid, without sediment, and at the same time the skin and conjunctivae became intensely yellow. He took quinine freely on each of these days and escaped the paroxysm on Thursday. . . . I visited him at 4 o'clock on Thursday. The conjunctivae were then intensely yellow . . . the stomach was irritable and at irregular intervals ejected a very deep green flakey fluid. The bowels had been acted upon by calomel before I saw the case, and some of this same character of fluid discharged. . . . Friday morning . . the claret-coloured fluid which he had discharged from the bladder (sometimes as much as a quart at a time) every two or three hours since Wednesday,

ceased to flow this morning at 3 o'clock, and there seems to be nothing whatever contained in the bladder, and he is more listless and inclined to be drowsy. . . . Saturday morning . . . Since (last night) he has continued to jerk first one arm and shoulder and then the other, and the same character of movements follow each other in the lower extremities . . . .

Dr. Michel found in the specimen (of urine) bile, albumen, cystine, blood and urine, so this was really a haemorrhage. . . . The patient died at 3 o'clock on Sunday morning. Mabry (1870).

1871. *Arkansas*

He believed the case he recorded to be the first to occur in the State. Du Val (1871). Deaderick and Thompson (1916).

1872. *Georgia*

The affection was first reported in Georgia by Dr. W. A. Greene of Americus. Greene (1872). Deaderick and Thompson (1916).

1880. *Arkansas*

In 1880, Dr. G. B. Malone in Monroe County, Arkansas, reported 155 cases in his practice. Malone (1880, 1881). Deaderick and Thompson (1916).

Central America

1850. *Nicaragua (San Juan del Sur)*

Fluit dagegen hat seit 1850 in San Juan del Sur zahlreiche Fälle bei Fremden, einige bei Eingeborenen gesehen, die meisten während der feuchten Jahrezeit. Mense (1899), 228.

1864. *Costa Rica (Punta-Arenas)*

La fièvre rémittente bilieuse semble y avoir observée assez souvent et y avoir été parfois confondue avec la fièvre jaune. Le Roy de Méricourt (1864), 374.

1864. *Panama*

La fièvre rémittente bilieuse y est frèquente. Le Roy de Méricourt (1864), 286.

South America

1863. *British Guiana*

I made some notes on these disorders more than 10 years ago (i.e. before 1863), when I was one of the medical officers to the General Hospital of British Guiana. Meredith (1873), 309.

1864. *Ecuador (Guayaquil)*

Fièvre rémittente bilieuse.—Elle est assez fréquente et assez grave pour avoir fait croire plusieurs fois a l'invasion de la fièvre jaune. Le Roy de Méricourt (1864), 281.

1874. *British Guiana*

The first case that attracted my attention was that of a medical practitioner in Demerara, who took some quinine to cure himself of an attack of intermittent fever, and found soon afterwards that he passed blood along with his urine.

The second case was that of a young English sailor who arrived in Demerara with his ship and there deserted, and went off to the bush. Some weeks afterwards, he came back ill with fever. . . . I ordered him a good dose of quinine; some little time afterwards he was attacked with serious haematuria, accompanied with abdominal pain.

The third case was a boy aet. 6 who had been suffering from attacks of intermittent fever. . . . I gave him a powder containing one grain of Q. Very soon afterwards I was sent for in great haste because the little patient was passing blood by urethra along with his urine and complained of pain in the umbilical region. The child's father mentioned that he forgot to tell me that his children could not take quinine. He had lost a child aet. 3, who had suffered from attacks of intermittent fever; a little quinine was given to him; profuse haematuria soon followed, then

convulsions and death. I have not met with haematuria from quinine in India. Meredith (1874), 5.

WEST INDIES

1781. *St. Lucia*

Of the History of the Remittent

After the first remission . . . all the preceding symptoms increased, with the addition of a foul tongue, a yellowness of the eyes, and in some cases an universal tinge, delirium, urine in small quantities and very highly coloured, imparting an offensive smell, often a difficulty in voiding it, which sometimes came to a perfect stoppage. . . . 59.

A comatose disposition, remarkable dejection, coldness of the skin, partial cold sweats, hiccup, involuntary stools, *subsultus tendinum*, loss of speech, etc., were certain signs of danger. 60. Rollo (1781).

We think it is doubtful whether this description can be identified as that of b.w.f.

1830. *St. Lucia*

Case LXIX. *Yellow suffusion, bloody urine, etc.* He has suffered two or three times from intermittents. . . . December 12th, 1830 . . . the conjunctivae and the surface of the body of a greenish yellow colour; patches of extravasation on the chest, but not extensive; incessant vomiting of green fluid . . . difficulty and pain in micturition; the urine received in a tumbler is thick, turbid, and deposits a quantity of grumous blood. 167.

State of the Urine

. . . It often contains blood which falls to the bottom of the chamber-pot, in the form of a black grumous sediment; now and then it is clear and of the colour of port-wine. 245. Evans (1837).

1926. *St. Lucia*

Two cases recorded. St. Lucia, *Official Medical Reports* (1926).

1828–1838. *Guadeloupe*

Telle est la fièvre que les médecins de la Pointe-à-Pitre, où elle est plus souvent observée qu'ailleurs ont nommée *fièvre bilieuse hématurique, fièvre jaune des acclimatés et des créoles* . . . de 1828 à 1838, époque de l'immunité pour la fièvre jaune, il (M. le docteur Lherminier) l'a observée fréquemment sur les créoles. Dutroulau (1861), 253; (1868), 318.

1847–48

Duchassaing (1850) also, under the alternative title 'fièvre rémittente pernicieuse mélanurique,' describes cases in 1847 and 1848. There may be some doubt about these, as among the symptoms he records 'vomissement noir' in one case and 'vomissements noirâtres' in the other.

1847. *Guadeloupe*

Obs. XI. L . . . de race blance 14 ans. 17 et 18 decembre 1847. Un faible accès de fièvre intermittente.

19. Troisième accès plus fort. Il prend du sulfate de quinine qu'il vomit.

20. A huit heures du matin, frisson violent, face d'un jaune intense . . . urines noires.

21. Vomissements de matières noirâtres. Duchassaing (1850).

1847. *Guadeloupe*

B.w.f. was known as early as 1847. Pellarin (1876), 85.

1853–54. *Pointe-à-Pitre*

La fièvre bilieuse hématurique des Antilles . . . n'est pas une maladie fréquente; elle est entièrement étrangère à certaines localités. . . . Les années 1853 et 1854 en on offert d'assez nombreux exemples à Pointe-à-Pitre. Dutroulau (1868), 321.

1859. *Jamaica*

R. T., planter, aet. 37, was attacked with intermittent fever on Saturday, the 13th of August, 1859, and until Monday the 15th, when I saw him, the fever had continued with very little intermission. . . . I found the urine to be of a dark porter colour, with a deposit of grumous sediment . . . upper part of the body was of a deep lemon colour. . . . 16th . . . the urine is still of a deep port-wine colour and very scanty; has vomited a good deal of green bilious matter. 18th . . . *no secretion of urine.* 24th–26th . . . almost constant hiccough. Urine . . . totally suppressed for the last two days. 27th. Death. Croskery (1860).

1862. *Guadeloupe*

Toutes les formes des fièvres et notamment la fièvre hématurique y sont endémiques. Pellarin (1862).

1869. *Martinique* (*Saint Pierre*)

On peut dire que l'hématurie telle qu'elle est décrite pour l'ile Maurice ou la Réunion n'existe pas à la Martinique; je n'en ai pas vu un seul cas. Rufz de Lavison (1869), 273.

1872. *Martinique* (*Fort-de-France Hospital*)

(Fièvre bilieuse hématurique) M. l'Abbé C . . . , âgé de 42 ans, d'une constitution ruinée par un très-long séjour dans les colonies, entre à l'ôpital le 4 Octobre et meurt le 19 du même mois. Manceaux (1872).

Europe. General

1764

Huxham[1] in his *Essay on Fevers* does not appear to describe b.w.f. Huxham (1764).

1769

Sénac[2] wrote a book in which he tried to prove that the hidden cause of intermittent and remittent fevers lay in the

1 Huxham, 1694–1768. 2 Sénac, Jean, 1693–1770.

liver. . . . He takes his stand on . . . 2° the yellow or dark colour of the urine in these fevers. Sénac (1769). Pellarin (1876), 86.

1769. *Minorca*

The most part of these fevers make their first appearance in the shape of a true simple or double intermittent tertian. . . . The urine, whether made in the time of the paroxysm or interval, is always clear frothy and of a deep red colour without any separation. . . . Blood drawn from a vein is most commonly florid like scarlet, without any sizey crust: the *Serum* is sometimes tinged with yellow, but oftener red. . . . Cleghorn (1769), 163.

1807

Alibert, in his 'Treatise on Malignant Intermittents,' records the following states of the Malignant Intermittent:

Choleric or dysenteric, hepatic or atrabiliary, cardialgic, diaphoretic, syncopal, algid, soporose, delirious, peripneumonic or pleuritic, nephritic, epileptic, convulsive, cephalalgic, dyspnoeic, hydrophobic, catarrhal, icteric, exanthematic, and varieties not yet properly established.—Alibert (1807).

Alibert (1799), 'Dissertation sur les Fièvres Pernicieuses ou Ataxiques Intermittentes.'

1809

L'état des urines dans les fièvres pernicieuses exige une grande attention. C'est ainsi que la diminution de cette excrétion, et sa couleur noire forment un signe pernicieux. Alibert (1809), 210.

1828

Macculloch in *An Essay on the Remittent and Intermittent Diseases* does not suggest anything of the nature of b.w.f. Macculloch (1828).

1832

He was admitted (London ?) on the 24th November. . . . He was one of those unfortunate persons who were sent by a very wise government to Walcheren. . . . I asked him if he had had ague, to which he replied that he had had the fever at Flushing. The singular circumstance, however, in this man's disease was that when his paroxysms came on he discharged bloody urine. . . . This he said was invariably the case—haematuria every time the cold fit came on . . . the bloody urine was intermittent like the rigors; I never met with an instance of a similar description. . . . Having had aguish fever, however, in the severe form, which he suffered whenever the east wind blows, or he is exposed to cold and wet, or commits any errors in diet, or is guilty of any debauchery, he will be liable to a return of the disease. The diseased heart and bloody urine appeared to have no connexion (one) with the other, but the bloody urine depended on the ague. Elliotson (1831–32), 500.

Deaderick (1910) refers to this as the first record of b.w.f.

1832

Continued Fever. Symptoms.

Occasionally the urine is very dark coloured, and sometimes it is bloody. Elliotson (1832), 35.

1854

Frerichs, in the description which he gives of an epidemic of marsh-fever in Siberia (? Silesia) in 1854, following a flood in the river Oder, records 51 cases of pernicious fever in Breslau and 20 cases of albuminuria—2 with haematuria, 5 with ischuria, but these cannot be considered without control and carelessly as undiagnosed cases of bilious Hgburic fever. Frerichs. Cardamatis (1902[b]), 48 (r.).

1866

Copland in his *Dictionary of Practical Medicine* does not appear to describe b.w.f. Copland (1866).

Danubian Provinces [1]

The Semi-tertian (l'hémitritée) of the Danubian provinces, that other malarial climate with a hot and moist season, is a bilious remittent. The vomiting, the bilious stools, the black urine, icterus commencing from the first paroxysm, the laboured respiration, the restlessness, the delirium, the exacerbation of the symptoms when complicated with gastric and ataxo-adynamic symptoms during the subsequent paroxysms all grafted on a quotidian or double tertian fever: this is the sum total of this fever, which is both bilious and malarial. The enlargement of the liver, the accumulation of green bile in the gall bladder, the absence of gastro-intestinal inflammation, the swelling of the spleen—such are the pathological appearances. Yet Mindererus, who describes this fever, relies on the inefficacy of quinquina to deny its intermittent nature, which J. Frank on the contrary admits, recognising the complete efficacy of specific treatment when care is taken to use evacuants first. Mindererus. Dutroulau (1868), 335.

EUROPE. GREECE

460–370 B.C. (*Hippocrates*)

Du temps d'Hippocrate [2] on l'observa dans l'île de Thasos (Platamon des Évalcides), à Abdère, a Cyzique. 'Après ces temps, il n'existe pas autant que nous savons, des témoignages écrits; seulement après le cours des siècles entiers.' Cardamatis (1901), 7 (r.).

Cette forme palustre, observée, peut-être, déjà par Hippocrate, à Thasos (épidémies, I, 3 const., 1 malade) était, paraît-il, relativement rare ou inconnue, vers les premières années de l'indépendance (1829), dans beaucoup d'endroits de la Grèce, òu aujourd'hui elle est relativement fréquente.

Bien des médecins âgés assurent que ce n'est que dans ces dernières années qu'ils l'ont observée pour la première fois.

Quoi qu'il en soit, le premier cas connu dans la Grèce

1 The definitive union of the Danubian provinces (Wallachia and Moldavia) under the name of Roumania proclaimed and acknowledged by the Porte, Dec. 1861. Haydn's *Dict. of Dates* (1904), 348. 2 460–370 B.C.

moderne a été observé en 1848, à Nauplie, par le docteur Antoniadès, chez le directeur de l'École d'agriculture de Tirynthe. Stéphanos (1884).

Certains auteurs modernes vont même jusq'à reconnaitre des cas d'hémoglobinurie dans les commemoratifs que donne Hippocrate de ses malades dans les premières pages de son livre sur les épidémies. Kouzis (1908).

The purpose of the present paper is to call attention to what appear to be undoubted cases of b.w.f. described in the 'Epidemics' of Hippocrates. (A number of representative cases (6) are given.) *Vide* Appendix II, Philiscus, Silenus, Hermocrates, Pythion, Heropythus, Appolonius. Foy and Kondi (1935), 392.

The 'Epidemics'* contain 42 case-histories. Fifteen of these cases had black urines and 3 red—total 18.

Disregarding 5 cases in women (4 in childbirth and so possibly 'puerperal'), we have left 13 cases.

These cases are given (in brief) in Appendix II. Here we proceed to an analysis of the symptoms which we should expect to find in b.w.f.

HIPPOCRATES. BLACK (OR RED) URINES. CASES 13.

Case.	Fever.	Rigor.	Nausea.	Vomiting.	Hiccough.	Icterus.	Suppression.	D. or R.
3	+	—	—	—	—	—	—	R.
6	+	—	—	+ 24	—	—	—	R.
7	+	—	—	—	—	—	—	R.
9	+	—	—	+	—	—	—	R.
10	+	—	+	+	—	—	—	R.
1	+	—	—	—	—	—	—	D. 6
2	—	—	—	—	—	—	+ 7	D. 11
8	+	—	—	—	—	—	+ 5	D. 5
12	+	—	—	+	—	—	—	D. 11
2	+	—	—	—	—	+ 6	—	D. 27
8	+	—	—	—	—	—	—	D. 8
3	+	+	—	—	—	—	—	D. 10
13	+	—	—	—	—	+	+ 14	D. 34

+ = present. — = no record. The figures after a + = day on which the symptom occurred. Where no figure is given the symptom was initial. The figures after D. = day of death. R. = recovery.

* The term appears to mean the constitution or season of the year favourable to certain diseases.

The Urine

3. Herophon. Black and thin. Day 8, of a better colour.
6. Cleonactides. Day 40, reddish, abundant red deposit. Day 60, abundant white homogeneous deposit.
7. Meton. Day 4, rather blackish with a blackish cloud (eneorema). Day 5, thin and blackish.
9. Heropythos. Thin and black. Day 14, the same. Day 80, of good colour.
10. Nicodemus. Thin and black. Day 2, the same. Day 4, thin with clouds (eneorema). Day 24, white, much deposit.
1. Philiscus. Day 3, black. Day 4, black. Day 5, round particles resembling semen suspended in the urine which varied . . . black.
2. Silenus. Day 1, black with black sediment. Day 2, black. Day 3, blackish. Day 6, suppressed.
8. Erasinus. Day 5, suppressed. Black with round clouds (eneorema) in it.
12. 'Anon.' Thick and red. Day 5, much oily urine. Day 7, similar.
2. Hermocrates. Thick, red, no sediment. Day 5, thin. Day 11, thicker reddish. Thick and red without deposit or thin colourless with clouds (eneorema) floating in it.
8. "Youth." Day 1, thick and blackish.
3. Pythion. Blackish with a cloud (eneorema). Day 4, black with a cloud. Day 7, oily.
13. Apollonius. Thin and scanty. Day 14, black, scanty and thin. (Day 34, death.) Throughout . . . thin and black.

Black Urines

Black urines are mentioned also in the following passages from Hippocrates.

Hippocrates, *Epidemics*, Bk. 1, Third Constitution
(Ardent Fever [1])

XVIII. About the equinox up to the setting of the Pleiades, and during winter, although the ardent fevers continued, yet cases of phrenitis [2] were most frequent at this time, and most of them were fatal. In summer, too, a few cases had occurred. Now the sufferers from ardent fever, when fatal symptoms attended, shewed signs at the beginning . . . acute fever with slight rigors, sleeplessness, thirst, nausea, slight sweats about the forehead and collar-bones, but in no case general, much delirium, fears, depression, very cold extremities, feet and hands, especially the latter . . . the extremities . . . remaining livid and cold; and in these cases the thirst ceased. Their urine was scanty, black, thin, with constipation of the bowels [le ventre se resserrait. Littré]. Nor was there hemorrhage from the nose in any case when these symptoms occurred, but only slight epistaxis.

None of these cases suffered relapse, but they died on the sixth day, with sweating.

The cases of phrenitis had all the above symptoms,[3] but the crises generally occurred on the eleventh day. Jones (1923).

Hippocrates, *Prorrheticos*, Bk. 1

Paragraph 39. In acute diseases, little sweats chiefly in the head, above all with black urine, and in these cases a respiration full of vapour is bad. 521.

Paragraph 95. Trembling, headache, pain in the neck, slight deafness, black urine, turbid (hérissées). Those who have this (set of symptoms), one must expect black motions; this is fatal. 537.

Paragraph 266. In a pain of the back and chest, the

1 The commentators disagree as to the meaning of this term. Fuchs (1866) equates it with typhus.

2 ? = consumption, delirium, meningitis, typhus cerebralis.

3 Dans les phrenitis on n'observa pas tous les symptômes qui viennent d'être décrits (Littré).

emission of bloody urine, if it stops, causes much suffering and is deadly. 643. Littré (1839).

As to the meaning to be attached to the term 'black urine,' *vide* Appendix III.

1832

Gassaud describes pernicious intermittent fevers at Nauplia in 1832, giving a record of 10 cases. He has nothing that can be interpreted as b.w.f. It is of interest to note that quinine sulphate was in use, and in some cases was applied dermatically, *i.e.* to a blistered surface. Gassaud (1836).

1839

Die Malaria hat fürchterlich unter ihnen gewütet; zwei Drittel von ihnen sind dort gestorben. Thomann beschreibt sehr eingehend alle Symptome der perniciösen Malaria, hat auch Chinin in grossen Dosen gegeben; aber nirgends findet sich ein Wort über Hämoglobinurie. Er erwähnt den dunklen Harn wie er bei Fieber beobachtet wird, aber nicht, dass der Urin braun oder schwarzbraun sei. Thomann (1839). Prof. Claus Schilling, Berlin (letter).

1842

'The next in importance after these are the fevers which attack the viscera, the emetic, dysenteric, bloody or black bile fever' (*μελανοχολερικὸς*). Mavroyannis (1842).

1858

A number of Greek doctors have observed that haematuria is a common symptom of the intermittent fever and follows the administration of quinine, and conclude that the haematuria is due to quinine poisoning, or to an idiosyncracy that some individuals possess for this drug, and for these reasons have failed to exhibit quinine in such haematuric cases. Antoniades (1858–59)*.

* Date of publication, 14 June, 1858.

1858

Dem. Konsola, likewise, then a departmental doctor at Vonitsa . . . before 1858 in the case of two soldiers and a young adult, all suffering from intermittent fever had seen Hgburia follow the use of quinine. Cardamatis (1902[a]), 14 (r.).

1859–60

The majority, if not all medical men who have happened to live for some time in extremely marshy parts of Greece, have had experience, not without a certain degree of surprise, of haematurias in intermittent fever following the use of sulphate of quinine, and I am consequently certain that these physicians have, so far as the means at their disposal allowed, made experiments with a view to a firm belief in this action of the drug. My father is one of these observers, for he has carefully observed this action of the drug not only in the case of many others, but also in his own case, and that to his sorrow for he had long been afflicted with intermittent fever during his long period of residence at Vonitsa. Veretas (1859–60)*, 30.

Following the publications of Antoniades and Veretas we have a series of papers discussing the quinine theory of b.w.f.

1861–62

Papavassiliou (1861–62) published a paper with the title 'Five cases of quinine haematuria.' Papavassiliou (1861–62).

1872

Rizopoulos wrote a paper entitled 'Concerning bilious haematuric fever.' Rizopoulos (1872).

1879

'Sur l'hématurie provoquée par la quinine.' Karamitsas (1879).

* Veretas's paper was read before Soc. méd. des. méd. hellènes in Paris 6 Nov., 1858. Published 23 March, 1859.

1882

'La fièvre hémosphérinurique palustre (fièvre bilieuse hématurique).' Karamitsas (1882).

1887

'Haematuria or haemospherinuria from quinine.' Karamitsas (1887).

1888

Five cases of quinine haemoglobinuria recorded by Pampoukis and Chomatianos (1888).

Cardamatis gives the following dates *for the first cases of b.w.f. observed* in Greece by various medical men:—

Mavroyannis (1842). Antoniades (1848) at Nauplia. Rizopoulos (1864) at Lamia. Theophanidis (1868) in Etolia and Acarnania. Chrysopathis (1870) at Messenia. Karamitsas (1873) at Athens. Phrandjis (1874) at Kyparissia. Cardamatis (1901), 9 (r.).

Europe. Italy, etc.

1712

Torti (1658–1741) published in 1709 his *Synopsis*, and in 1712 his famous *Therapeutice specialis*, etc. Torti has a diagrammatic tree (*Lignum Febrium*), enumerating about a hundred different fevers, but '*febris haematurica*' does not occur among them. Torti (1712).

Torti makes no mention of it in his work, although he had a most extensive clinical experience. Marchiafava and Bignami (1900), 484.

Among Torti's otherwise complete descriptions there is no suggestion of b.w.f. Mannaberg (1905), 307.

1779

'Rubini (1779) avait fait connaître l'existence d'une action spécifique sur les voies urinaires de la part du quinquina, mais il en ignorait la cause.' Rubini (1779). Briquet (1853), 208.

Faginoli de Vérone a donné l'histoire d'un enfant qui ressentait de la démangeaison dans l'urètre, en urinant, et rendait quelques gouttes de sang toutes les fois qu'il prenait quelques pilules de sulfate de quinine. Faginoli. Giacomini, 363. Briquet (1853), 209. Littré (1874) (Art. Quinine), 229.

1819, 1820

One is forced to recognize ' La fièvre bilieuse grave et complexe ' in the descriptions which Littré has borrowed from Meli's book on the epidemic of bilious remittent which prevailed at Castelleto * in 1819 and 1820. It is indeed a fever alternately intermittent, double tertian, remittent, continuous, that is to say malarial in type, a bilious disease, an actual invasion of the blood by bile, as shown from the first stage of the attack by the bilious colour of the stools, the vomiting, the motions and urine and by the icterus. Meli (1837). Littré (1868), Art. Bilieuse (Fièvre). Dutroulau (1868), 334.

1851. *Rome*

Allaire, describing bilious fevers in Rome, has no b.w.f. He quotes Meli (1837 ?) on the ' Epidémie de Castelleto, sur le Tesin et dans les environs en 1819 et 1820, pendant l'été et l'automne de ces deux années.' Among the symptoms are nausea, vomiting, icterus, but ' urines safranées.' Allaire (1851).

1877

G. Ravot, Engineer, aet. 30, Cagliari, Sardinia. In passing water he evacuated a liquid which was more blood than urine. Greatly alarmed at this he consulted his doctor who explained the haematuria by telling him *that the excess of haemorrhoidal blood instead of coming out by the rectum had come out by the bladder* and attributed the other symptoms to intermittent fever. Ughetti (1877), 625.

* (1) Castelleto, near southern end of Lake Maggiore; (2) Castelleto, between Lake Maggiore and Biella. About 15 miles N.E. of latter place.

1878. *Toscanella* (*Roman maremma*)

Among the various forms of pernicious fever which I saw during my years of residence in this city I never observed any to which could be applied any other name than *perniciosa ittero-ematurica.*

History 1.

15 Jan. p.m. Q. sulphate 1.5 g.
16. Urine of the night blackish. Troublesome vomiting, unsupportable epigastric distress, pain in the loins. Urine, ' Ematina,' abundant.

I confess frankly that the idea of Prof. Tomaselli that Q. could be accused of the above symptoms never occurred to me. Dott. Nuvoli agreed with my diagnosis of perniciosa ittero-ematurica, a very rare form of malaria, and which he had rarely seen in his long practice.

Two other case-histories. Sulphate of Q. has been unjustly accused, and instead of being the cause of perniciosa ittero-ematurica, is its sole efficacious remedy. Mancini (1878).

Sicily

1812.

Boyle, in his ' Some remarks on the fevers of Sicily,' does not appear to describe b.w.f. Boyle (1812).

1860.

In 1860 Tomaselli observed his first case of quinine intoxication.

Observation 1. *Pernicious intermittent fever—quinine intoxication—death.* Tomaselli (1897), 11.

The dates and titles of his famous monographs are as follows:—

1875. *Sulla intossicazione chinica e l'infezione malarica.*
1877. *L'intossicazione chinica e l'infezione malarica.*
1897. *La intossicazione chinica e l'infezione malarica. Terza editione.*

INDIA

1878. *Bengal*

V.T. Aet. 42. Suffered much from 'fever and bilious attacks' in the Tributary Mahals.

4. March, 1878. 9 p.m. T. 105°. Spleen +. Diaphoretics and demulcents ordered and Q. in a 20-grain dose when the sweating stage had well set in.
5. Jaundiced to the utmost degree, the urine had become almost wholly suppressed, and but a small quantity of almost pure blood was voided from the bladder.
6. T. 99°. Urine about 1 oz. (28·4 c.c.) in the day. . . . Frightfully intense pain in the liver, decubitus dorsal, legs drawn up, patient screaming with agony, constant vomiting.
7. Liver pain absent; jaundice as intense as ever. About 1 oz. of bloody urine, the blood being in greater quantity than the urine.
8. At noon hiccough set in . . . coma was becoming deeper, at midnight he was seized with a general convulsion.
9. 12·30 a.m. death. Birch (1879), 47.

1879. *Bengal*

It has been my lot to see two such cases (of acute malarial poisoning) in their last stage . . . in the Northern suburb of Calcutta. Both were children, a girl aet. 12, a boy aet. 10 or 11. Symptoms were precisely the same in both these cases: high fever, excessive heat of skin, quick and weak pulse, deep yellow discoloration of the conjunctiva, and of the whole skin of the body, within 12 hours of the attack, and bloody urine from the commencement. . . . The girl vomited some blackish tarry-looking substance. The symptoms on the whole very much resemble the yellow fever of equatorial regions. Kastagir (1879), 142.

1885. *India*

1033 cases of *intermittent* fever, 11 with *haematinuria*.
221 cases of true *remittent* fever.
4 well-marked jaundice alone.
2 jaundice with haematinuria.
2 jaundice haematinuria and icteric urine. Both died.

In the two fatal cases there seems to have been a tendency to suppression of urine, together with icteric and haematinous urine.

Case 1. Mian Mir. Fever. Liver +, tender, hypercholia of alvine discharges, vomiting of bilious fluid, icterus ++. Urine dark smoke-coloured, contained casts of bile pigment. Bile reaction of Gmelin and Pettenkofer +. Urine alb. neg., until 2 days before death.

Case 2. Amritsar. Fever, hypercholia; vomiting bright yellow viscous fluid, haematinous but not icteric urine. No alb., but spectroscope and guiac tests = blood. Firth (1885), 367.

1886. *India*

Out of 1033 cases of *intermittent* fever I find 26 to have been accompanied by jaundice simply, that is, 2·5 per cent.; none with icteric urine; and only 11 with haematinuria, or about 1 per cent. Of 221 cases of true *remittent* fever, I find four had well-marked jaundice alone; two had jaundice, together with haematinuria; and two had jaundice, haematinuria, and icteric urine. Both these last two cases died. Jaundice, hepatic tenderness, hypercholia, and vomiting of yellowish-green fluid seem to have been common to all these eight cases. In the two fatal cases, there seems to have been a tendency to suppression of urine together with icteric and haematinous urine. Firth (1886), 193.

1887–1900. *India*

European troops: Intermittent haematuria 9. Haemoglobinuria 10.

Indian troops: Intermittent haematuria 0. Haemoglobinuria 3.

Prisoners: Intermittent haematuria 3. Haemoglobinuria 0.

Stephens and Christophers (1903), 3.

Date.	Locality.	Cases.	Authority.
1879–1907	Nowgong, Assam	5	Christophers and Bentley (1908[a])
1879–1908	Tezpur, Assam	13	Ibid.
1898	Assam	15	Powell (1898)
1887–1908	Bengal Duars Damdim district	65	Christophers and Bentley (1908[a])
1890–1907	Madras, Koraput (Jeypore Agency)	13	De Cruz (1907), 403

Miscellaneous

1826. *Asia Minor, Smyrna*

Clarke in his *Observations on Fever as it has Prevailed at Smyrna during 1825–26* does not appear to describe blackwater. Clarke (1826).

1831. *Tropics (general)*

Hasper in his treatise on tropical diseases does not appear to describe blackwater. Hasper (1831).

1867. *Cochin-China*

La Basse Cochinchine est située entres les 11[e] et 13° degrés de latitude de nord et les 103[e] et 105° degrés de longitude est. Personne jusqu'à ce jour n'a encore fait mention de la fièvre bilieuse hématurique. Records 6 cases. Veillard (1867).

Summary

Africa

In 1855 b.w.f. appears in the statistics of the Senegal hospitals, but isolated records can be traced back possibly to 1822, with greater certainty to 1832, and still more so to 1846. In Algeria, a typical case was recorded in 1867. In Mada-

gascar and Mayotta histories date from 1850, in Réunion from 1865.

America, North

Records go back possibly to 1820, and with certainty to 1837–46, but it is about 1850–60 or even later that it became generally recognized, and its rarity before this time is commented on by several authors.

America, Central

In Nicaragua the history starts in 1850, in Costa Rica in 1864.

America, South

British Guiana furnishes a record in 1863.

West Indies

In Guadeloupe the records go back to 1828–38. In St. Lucia there is a doubtful record in 1781 and a definite one in 1830. In Jamaica a case occurred in 1859.

Europe, general

The record for Minorca in 1769 is suggestive only of b.w.f. Alibert, writing in 1809 in France, speaks of oliguria and black urine, and Elliotson in 1832 in a malarial soldier of the Walcheren expedition records intermittent haematuria which he attributed to ague, but the diagnosis paroxysmal Hgburia cannot be ruled out. The cases of Frerichs in Breslau in 1854 were probably b.w.f., and almost certainly those in the Danubian provinces described by Mindererus.

Europe—Greece

Some authors hold that the cases of 'black urines' recorded by Hippocrates were cases of b.w.f., but they do not appear to have the stamp of that condition. The modern history begins in 1858.

Europe—Italy, etc.

Torti has no description of b.w.f. Rubini is said to have described the specific action of quinquina on the urinary passages. In 1860 quinine intoxication is described in Sicily by Tomaselli, and in 1877 in Sardinia there is a clear case.

India

The history starts as late as 1878.

Cochin China

In 1867.

CHAPTER 4

AETIOLOGY. GENERAL

Age

Fisch saw cases in children of 14 months and 2½ years respectively. Plehn, F. (1898), 105.

Bonnafin records a case in a child 11 months old. Gouzien (1911), 48 (r.).

Child aet: 2. 1st attack. Hgburia, no symptoms, recovery. 2nd attack, aet: 4. Hgburia coffee-coloured, enlarged palpable spleen, jaundice negative; day 2 urine clear, no symptoms, recovery. 'Africa' (1915), 8.

Dr. Mackensie of Gatooma (S. Rhodesia) had a case in a child just over 1 year of age. Thomson (1924[a]), 27.

Dugg. male aet: 6 months, mixed race. Recovered (British Guiana). Giglioli (1932[a]), 14 (r.).

Southern Rhodesia.

(*European- and Rhodesian-born Whites.*)

Age.	Population (1926).	First Attacks. 1924–28.		Rate per 1000.
		Total.	Average.	Average.
Under 1	810	0	0	0
1–4	2922	2	0·4	0·13
5–14	7904	20	4·0	0·50
15–24	6506	40	8·0	1·23

The low incidence in childhood is probably due to the fact that they lead a 'protected' life, in the sense that when quite young they are naturally 'cared for,' and when at school age they attend schools mostly situated in 'non-endemic urban areas.' Ross (1932), 18, 28, 30.

Mackensie Hospital. Demerara River. 1926–31.						
Race.	Total admissions below 16.	B.w.f. Cases.	Rate per 1000.	Total admissions above 16.	B.w.f. Cases.	Rate per 1000.
East Indians	87	5	57·4	226	1	4·4
Mixed . .	722	24	33·2	1232	13	10·5
Portuguese .	31	0	0·0	271	4	14·7
Aborigines .	247	2	8·1	346	3	8·6
Negroes .	607	3	4·9	2957	4	1·3

The incidence of the disease per mille in children, patients below 16 years of age, in the two main racial sections of the population (viz. negroes and mixed), is about three times as high as the corresponding values found for adults. In the East Indian Race the prevalence of child cases is even greater. Giglioli (1932[b]), 18 (r.).

Alcohol

B.w.f. followed a prolonged drinking bout in more than 20 of 45 cases treated at Gorée (251).

Alcohol acts by leading to anaemia, inasmuch as it leads to irregularity in food, inferior as this may be (252).

But it also acts by affecting the liver directly. At any rate it is common in Senegal, after a couple of days' drinking, for the prodromata of b.w.f. to appear on the third day. 253. Bérenger Féraud (1874).

In 3 of my cases excess of drink could certainly be incriminated. Gros (1900), 357.

Alcohol can be excluded with even greater certainty (than venereal disease). A large proportion of the cases occur in total abstainers. . . . Cases do also occur amongst persons known to be intemperate. I have not been able to satisfy myself that these are on the whole more severe or more fatal. Daniels (1901), 49.

Anaphylaxis

Blackwater may be the resultant condition, the evidence

of anaphylaxis to (dead) plasmodium proteid. Cleland (1909), 302.

Q. combining with the albumen of the stomach is absorbed as Q. albuminate. One may assume that it may under unknown conditions act as an antigen. This antigen combined with the malaria toxin produces antibodies which induce Q. sensitiveness in the malarial body. Cardamatis (1912[a]), 521.

The onset and development of b.w.f. is as rapid as that of anaphylaxis. No haemolysin could be detected. The mechanism is of a physical kind as in paroxysmal Hgburia. Hgburia of b.w.f. is not due to hepatic or renal lesions, as the cells of these organs were perfectly normal. Death also is due to anaphylaxis, as the usual lesions invoked to account for death were absent. Anaemia does not produce death so rapidly. Dyspnoea and anuria were of central origin. Porak (1918), 509.

The tissue changes in b.w.f. are absolutely distinct from what is met with in anaphylaxis. A wounded officer received 500 units of anti-tetanic serum hypodermically. 10 minutes later, dyspnoea, and death in 35 minutes. Autopsy : sub-pleural Hges, marked congestion of alveolar walls, and Hges into the lung tissue and bronchi. Acute emphysema. Thymus enlarged, scattered Hges. Spleen the same (no evidence of malaria). Liver, kidney, etc., no changes. Dudgeon (1920), 216.

Q. increased anaphylactic shock in rabbits and guinea-pigs. The minimal lethal dose was reduced 3–10 times. Histamin sensitiveness was not increased. Smith (1920).

Patient aet: 9. Saigon. History of malaria.

1. Nov., 1921. Fever. Quinoform 0·25 g. Some minutes later, violent headache, becomes red, then violet, breathes with the greatest difficulty, gives impression of impending death, better after quarter of an hour. During the day, severe headache, urticarial eruption, fairly intense pruritus, respira-

tory difficulty; by auscultation, numerous scattered 'sibili.' A diagnosis of quinine anaphylaxis was made and 'desensitising' was begun.

17. Very anaemic, daily fever. T. 39·4°, spleen +, blood *P. vivax*+++.
22. Quinoform 0·25 g., 20 minutes later, violent rigors, coughs energetically as if trying to eject a foreign body, complains of not being able to breathe, face swells, whole body becomes violet, eyes injected, lacrimation, breathing more and more difficult, pulse almost uncountable. Treatment: injections of camphorated oil, friction with ether and Eau de Cologne. 1 hour later general urticaria and intense pruritus. Quinoform given in gradually increasing doses, and with only a few slight set-backs.

6 Jan., 1922. Patient takes quinine regularly. Chabaud (1922).

5 cases of malaria after the taking of Q. experienced respectively:—

1. Intense itching in the palms and shortness of breath.
2. Itching eruption over the whole body and violent palpitations.
3. A violent itching eruption in the groin.
4. An urticarial eruption with intense itching and vomiting lasting a month.
5. Griping pains in the stomach, then itching of the palms and soles, then an eruption over the whole body with swelling of the lips and eyelids.

The author discusses the question of the anaphylactic nature of these phenomena. He treated the conditions, apparently successfully, with peptone in ½ gramme doses by the mouth. After the peptone, Q. was given without incident. Mollow (1925), 135.

Anaphylaxis and death

11 June. Hgburia.

12. Icterus citrus yellow, tremors of tongue and fingers, extreme weakness, tongue white and red at margins, urine 1200 c.c. (24 hrs.), cell count, 1·8 m.

13. Intense icterus, frequent grey liquid stools, dyspnoea and polypnoea, R = 30. Panting (*essoufflement*), epigastralgia, urine (night of 12, 13) 100 c.c., death 1 p.m.

The anaemia and the slight post-mortem lesions (kidney normal, *vide* Pathology) insufficient to explain death, attributed to anaphylactic shock on the central nervous system. Porak (1918), 560.

Babesia

It is reasonable to conjecture that the parasite of b.w.f., if not identical with that which causes the Hgburia of cattle, very probably belongs to the same group. Sambon (1898), 868.

Red cell prolongations and inclusions described and figured which probably belong to or are allied to *Babesia* and probably transmitted by one or more species of *Anopheles*. Barreto (1913).

Bacteria

Cocco-bacillus (*B. coli communis*) found by Bréaudat at Tonkin in the blood of 5 cases. Bréaudat (1896). Gouzien (1911), 55 (r.).

In two cases cultures were made from the blood on agar; in both they remained sterile. In one case cultures were made from the spleen and heart's blood; in both pure cultures of *Staphylococcus aureus* resulted. Stephens and Christophers (1900), 23.

Among 80 fatal cases of malaria among British troops in Palestine there was one remarkable generalized infection with *B. perfringens* in which coincidentally and apparently intimately connected with this septicaemia a typical black-

water fever attack supervened eighteen hours before death. Fairley and Dew (1919–20), 122.

In two cases I have found streptococcus-like organisms in the blood. Crichlow (1929–30), 180.

Vide infra Streptococcus.

Chill

A little girl aet: 5 had her usual touch of fever, and felt so well at the end of the slight sweating stage that she escaped the vigilance of her parents, and rushed out of the house into the cool wind to play with her small brother; though immediately captured, and put to bed within an hour, she had a rigor, passed the typical urine, and thereafter went through a mild attack of b.w.f. Nightingale (1909–10), 253.

Considered by some to be a very common immediate disposing cause, this is denied by others. Some even consider that the rigor of a malarial attack is able to produce haemolysis. Chill is supposed to act by a determination of blood to the viscera more especially the haematopoietic organs. Another possibility remains, viz. that the muscular activity and the defensive mechanism of the organ in response to the sensation of cold sets free myo-haemoglobin. Gouzien (1911), 52 (r.).

1. Quartermaster. *Aet:* 23. 6 months at Dakar. No previous colonial residence. Has never had malaria.

17. Feb. On going ashore got wet and felt that he was catching cold.

18. Slight headache, T. 36·6°, 11 p.m. Hgburia, T. 39·9°, blood negative.

2. H. F. *aet:* 24. History of malaria. Rufisque. Previous (exact time?) to his b.w.f. his clothes had often been wet in working in the water, and he had a definite sensation of having caught cold.

3. R. *aet:* 34. 1 year at Dakar. No malaria.

3 Sept. Roused from a siesta by a tornado. In a state

of sweat goes out half nude into the wind and rain. On his return his first words were, 'I have caught cold.' In the evening some malaise.

4. Has to give up his work feeling tired.
5. Urine black. T. 39°. Chartrieux (1925), 69.

'*Chlamydozoa*'

3 blood films contained about 30 endothelial cells showing cell inclusions. The inclusions measured 1–5 μ, majority appearing as rings, staining more deeply peripherally. My suspicion is . . . that they are parasites of the nature of Chlamydozoa. Leishman (1912[a]), 504.

Cell inclusions found in 2 additional cases in endothelial cells in blood films. I still consider that the inclusions are not explicable as phagocyted fragmented red cells. Leishman (1912[b]), 151.

Climate

Besides the malarial factor which produces the suitable internal medium or soil on which b.w.f. develops, indispensable also is a climatic factor, the external medium which profoundly modifies the function of the haematopoietic organs, and chiefly that of the liver, producing a hyperactivity of this organ known as the 'bilious state.' This condition plays a most important part in the development of b.w.f. In a highly malarious country if this climatic factor is absent then b.w.f. is also absent or extremely rare. Gouzien (1911), 44 (r.).

The 'bilious state' of Gouzien, the 'africism' of Glenard, 'cholaemic hepatitis' in other words, is very frequently met with among North Africans and especially among those who live in the littoral zone. Parrot (1915), 5 (r.).

Diet

Differences in food will partly explain different liability to attack in places like St. Louis or Gorée as compared with the river posts. In the former, fresh vegetables are never

completely lacking, while in the outposts salted food and dried vegetables instead of fresh meat and greens are the lot of the European. Bérenger Féraud (1874), 251.

Disease

Dry colic (? Pb poisoning), gastro-enteralgia of the tropics, acute indigestion may be the immediate cause of the haemolysis. Gouzien (1911), 53 (r.).

Disposition

The bilious or sanguineous temperament undoubtedly constitutes a predisposing cause, but this plays a secondary rôle in comparison with marsh cachexia. Barthélemy-Benoit (1865), 307.

Apart from the length of residence on the West Coast, the large number of attacks suffered sooner or later practically always induces the individual disposition. . . . Chronic malaria infections with rare and only slight rises of temperature, in which the Hgb has fallen to a half or even a third of the normal, suffice to produce the b.w.f. disposition. 20.

1.

P. Old Coaster. Many attacks of b.w.f. in West Africa. One lasted 3 weeks, one 14 days, one 10 days. About 2 months after his arrival in Cameroons has 6 attacks.

4.2.95.	duration	2 days.
19.	,,	1 day.
6.3.	,,	2 days (Hgburia). Ill for over 10 days.
24.8.	,,	3 days.
5.9.	,,	1 day (Hgburia). Recovery slow.
17.	,,	1 day.

There is a Q. history in 5 of 6 attacks. In 6th no record. 27.

2.

June, 1895.	B.w.f., duration 24 hours.
Sept.,	B.w.f., ditto.

23. Jan., 1896. 3 a.m. Q. 1·0 g. 5 a.m. rigor, fever, vomiting, uneasiness, slight dyspnoea, cyanosis. 8 a.m. dark red urine, 150 c.c. Much vomiting.
25. 6 p.m. urine clear.
28. Discharged.

Feb. Hgburia, 2 days. 37. Plehn A. (1896).

Just this frequently insufficient dose of Q. 0·5 g. per os (at 5-day intervals) appears in a number of cases to be responsible for the production of a b.w.f. disposition. Ruge (1902), 504.

It is of decisive importance for the development of the b.w.f. disposition that malaria should act uninterruptedly on the body without giving it time to recover from the injury in the interval. 510.

It depends on the activity and mass of those latent forms of the malaria parasite which maintain the infection during the fever-free intervals. 517. Plehn, A. (1903[b]).

Disposition, family

E.C. Aet: 18. Dec. 1875. Hgburia following Q. A brother aet: 11 died of bilious haematuric fever. His youngest brother aet: 9 a short time ago had haematuric fever. Karamitsas (1879), 151.

Certain persons are affected with urticaria whenever they take quinine. I have known such an instance in the case of mother and daughter. Karamitsas (1879), 151.

Case 19. Italy. It is noteworthy that in 2 families 2 sisters fell ill at a short interval, in a third, a brother and sister. Lipari (1889), 568.

It is beyond a doubt that Q. Hgburia is seen quite especially in certain families . . . I know, and the fact is too interesting not to be recorded, several survivors among these families, who on telling me that b.w.f. had made gaps around them, were astonished that they were spared, recognizing as they did that they were paying their tribute to heredity in passing blackwater under the influence of small doses of Q. Carreau (1891). Clarac (1896), 281.

It is important also to mention that a sister of the patient reported the same accidents (Hgburia, etc.) after the use of Q. 23.

They added that various members of the family of the patient's mother, residing in Cartilini, could not tolerate Q. for the same reason. 30.

Á propos of this fatal case I recollect that a sister of Castiglione (the patient) at the age of 6—some 15 years ago—being attacked with malaria took Q. preparations with impunity for a long time. In her last attack after taking Q. the fever assumed the characters of a *pernicious ictero-haematuric* fever, so that I considered it advisable, at a suitable time, to prescribe large doses of Q., following which the fever and the ictero-haematuric symptoms increased in intensity to such an extent that she died on the third day. 37. Tomaselli (1897).

Silchar, Assam

1. American boy, aet: 4. History of 2 attacks of b.w.f.
29 June. 1.30 p.m. Q. sulph. grains 4. 3.30 p.m. hard chill and bilious vomiting. 4 p.m. 3 oz. very dark urine, rich in Hgb, T. 106·3°.
30. 12.40 a.m. T. 97°. Patient was about and lively until 5 July. 1.30 p.m. euquinine grains 4. 2.30 p.m. hard chill. 3 p.m. T. 105·2°. Hgburia.
11. Coma, convulsions. 9 a.m. Death.

2. Sister of above, aet: 9. History of slight Hgburia after Q. in June.

14 Sept. Euquinine grains 2, 3 hours later grains 4, 4 hours later chill and vomiting, 1½ hours later Hgburia. Recovery. Crosier (1900), 491.

Certain families seem more susceptible to the disease than others. Thus, of one family of three brothers, two had it and died with hyper-pyrexia. The third it is stated died with hyperpyrexia without blackwater. Two other pairs of brothers had blackwater fever. In none of these was

there any correspondence in the time of the attacks. Daniels (1901), 49.

In a family, three members, father, mother and daughter, attacked in turn, within a few days with b.w.f., died one after the other 24 hours from the invasion. On returning to Athens from Koutsopodi of Mycénes 4 other members were attacked with b.w.f. but happily recovered. Nine years later one of the daughters was again attacked with b.w.f. but happily escaped death. Kallivokas (1895). Cardamatis (1902[a]), 12 (r.).

Among 22 cases in our own practice, we have had 2 brothers attacked, and other cases where the father or mother and one or more children have had attacks. Kanellis (1906), 831.

Tomaselli believed in a well-marked family tendency. . . . Three such families are known to me. Deaderick (1907–8), 10 (r.).

Family B.	8 members.	Attacks.	Father, 2 daughters.
Family G.	6 members.	Attacks.	Father, mother, son, daughter.
Family T.	8 members.	Attacks.	Mother, daughter. 239.

Patient had lived some years in Rhodesia, where a brother of his died of b.w.f. 240. Borle (1910–11).

The patient's brother was in the hospital at the same time with Hgburia. Brem (1911), 158.

B.w.f. is seldom found to attack father and son or daughter (observed at Taichu and Rigyobi) or brother (observed at Karenko), but it sometimes attacks two persons who live together in the same house. Hatori (1914–15), 650.

P. girl aet: 11. Algeria. Hgburia following quinine, on four occasions, from 6.8.1917 to 4.9.17.

P. boy aet: 7. Algeria, brother of above. Hgburia following Q., on two occasions, 23.10.1918 and 25.10.1918. Parrot (1918), 846.

A. G. female, Cuban, aet: 18. Eight other members of

the family suffered from malaria; one sister developed b.w.f. and was ill from it for 40 days. United Fruit Company (1924), 65.

Mississippi. R. D. (white) Aet: 6, had a malarial chill at 2 p.m. Aug. 23, 1907, turned yellow as gold within two hours, and had copious Hges from his kidneys. T. 106·5°. . . . The writer was debarred from giving Q. . . . because the child's parents claimed that they had lost two children . . . by the family physician then giving the children sulphate of quinine. Kiger (1925–26).

Case 49. In one I established a special hereditary disposition, as the patient's father and grandfather also had malarial Hgburia. Weselko (1926), 658.

A number of cases may occur in the same family or the same house but usually such cases are found to have developed with long intervals between cases, sometimes extending over many years. Exceptionally, more than one case will occur simultaneously in the same house or family. It rarely happens that a large number of cases of b.w.f. come from a small community within a period of a few weeks. Menk (1927), 114.

CUBA.

1. Feria family. Grandfather, father, mother, 9 sons, 5 daughters.

Sex and age.	Places where family lived.			Total attacks.
	Tacajo Viejo.	Mejca.	Julia.	
s.* 9		1 (1925)		1
s. 12	1 (1919)	2 (1926)		3
s. 13		1 (1926)		1
s. 18	2 (1922, 24)	3 (1926)		5
s. 21		2 (1926)	1 (1927)	3
d.* 11	1 (1918)	1 (1926)		2
d. 15		1 (1926)		
d. 16	1 (1924)	1 (1926)		2
d. 17		1 (1925)		
	5	13	1	19

* s. = son, d. = daughter.

The mother has 3 brothers. All had b.w.f. at Tacajo Viejo. She also has 2 sisters who have had much malaria but no b.w.f.

2. Ramirez family, resident in Deleite. Father, mother, 2 sons, 3 daughters. B.w.f. 2 sons (1 death), 1 daughter (3 attacks).
3. Tamayo family, resident in Deleite. 3 brothers, their wives, their children.
   Brother No. 1 and wife. B.w.f. 0. Children, 4 cases.
   Brother No. 2 and wife. B.w.f. 0. Children, 4 cases.
   Brother No. 3 and wife. B.w.f. 0. 10 children, 5 cases.

Dr. Tablada at Central Tacajo has attended a family recording 14 attacks of b.w.f.

4. Lopez family, resident in Deleite. 11 members. No b.w.f.
5. Rojaz family, resident in Deleite. 9 members. No b.w.f.

These families lived next door to or across the street from the 'blackwater families.' The members of the families have fever and as is the custom with families in the fever districts take Q.

In one family with several cases of b.w.f. there was a history of a case of b.w.f. in a Jamaican servant in the same house.

One must bear in mind the possibility that b.w.f. may be more of a house disease than a family disease. Whitmore (1927), 106.

Cases 61 (1923–31), 35 in children age 6 mos. to 16 years.

Cases 61, 22 originated from 9 families.

6 sporadic cases in the same neighbourhood as that of families 1–3. 6 sporadic cases in the same village as that of families 4 and 5. Giglioli (1932[a]).

Family.	Adults and Juveniles.		Cases.	Dates.
1	Ad.	2		
	Juv.	4	3	26.2.27; 25.4.27; 30.6.27.
2	Ad.	?	1	8.9.27.
	Juv.	?		
3	Ad.			
	Juv.		2	14.7.27; 25.10.28.
4	Ad.	2		
	Juv.	8	3	20.3.27; 15.5.27; 1928..
5	Ad.	2	1	15.3.27 (♀ no blood relation of family)
	Juv.	2	1	11.3.27.
6	Ad.	4		
	Juv.	5	3	2.6.27; 12.9.27; 7.5.28.
7	Ad.	1		
	Juv.	3	2 (3?)	27.5.27; 30.5.27; Sep. 1928 (?).
8	Ad.	2		
	Juv.	4	3	28.1.27; 15.2.27; 5.4.27.
9	Ad.	2	1	9.12.27.
	Juv.	2	1	24.10.26. Recurrence 6.10.27.

Ibid. (1932[a]).

Emotion

Has lately been busy cultivating the soil in the missionary garden. He connects the onset of his attack with the violent temper incident to a dispute with another missionary. Plehn, F. (1898), 112.

Lambrinopoulos has informed us that on many occasions he has observed Hgburia following violent moral emotions in a neuropathic male aet: 35. Cardamatis (1910), 105.

Various observers have recorded facts, indicating that an acute sudden emotion may determine the onset. Gouzien (1911), 53 (r.).

Epidemics

Bilious fever has a remittent or continuous course and displays exceptional gravity when complications intervene. . . . It is then that it occurs epidemically, decimating the European strength of our factories and claiming victims in the ranks of our colleagues. Barthélemy-Benoit (1865), 224.

While yellow fever raged in the basin of the high Sénégal, in the valley of the Niger at Ségou a kind of epidemic of bilious haematuric fever occurred, as we have already seen at

Bammako in 1885 (?). In less than 4–5 days, 4 sub-officers at the post were attacked; 3 died in 2 or 3 days, 1 recovered. Primet (1893), 452.

Often it occurs in an epidemic way as happened some years ago at Gorèe, Quittah and Bonny; moreover the number of cases in a place varies strikingly; climatological factors undoubtedly come into consideration for the number and severity of the cases. 1893 was an especially dangerous one; it was the year I came to the Coast. Plehn, F. (1895[a]), 397.

B.w.f. is usually endemic, but in virtue of seasonal influences it may take on the form of a real endemic-epidemic when several persons are attacked at once. In 1895–96 at Kayes 18 cases occurred and 7 of them in August and September.

B.w.f. may be limited to a post or dwelling occupied by several persons. This happened at Kayes in March in the case of 2 officers and a sub-officer occupying the same premises at the ' clothing ' offices. Carmouze (1897), 353.

It was epidemic among the labourers employed in making the canal * through the Isthmus of Corinth. In 1885 there was an outbreak of the disease in Castiades (Sardinia), when twenty were attacked in one prison. Sambon (1898), 867.

It has also been observed in epidemic form at Lamia (Greece) in the years 1858–59, 1865–66, and in 1870. A great number of people were attacked in the towns of Kalamata and Messenia. By reason of this epidemic type one of our colleagues called it *yellow fever*. Cardamatis (1901), 28 (r.).

In 1888 during construction of the canal, although the morbidity from malaria was 70 per cent., Kolovos D.(emetrius) did not observe a single case. Cardamatis (1902[a]), 6 (r.).

In 1885 it broke out in a prison in Castiades, Sardinia,

* Work on the canal was begun in 1882, was broken off in 1889, and begun again in 1890 and ended in 1893. Average number of labourers, 1500.

attacking 24 out of 800 convicts. Deaderick (1907–08), 8 (r.).

China. Kwangsi Province. 'In 1885 according to Dr. Wenyon of Fatshan it (*i.e.* b.w.f.) ravaged like a plague the Chinese army on the Tonquin border of Kwangsi.' Manson (1907), 234.

Note.—The original form of this statement was: 'The fever which ravaged like a plague the Chinese army on the Tonquin border of Kwangsi was frequently accompanied by hemoglobinuric symptoms. (Dr. Wenyon of Fatshan China.) Manson (1893).

Epidemics it is true have been described, but with a want of accurate and detailed observation, which renders it impossible to judge, whether they have been merely the result of large numbers of persons being placed simultaneously under b.w.f. conditions or due to the spread of infection. . . . To quote without particulars epidemics of the disease on railways or in armies has therefore little bearing upon the question. Christophers and Bentley (1908[a]), 47.

Group I Houses.	Cases.	Group II Houses.	Cases.	Group III Houses.	Cases.	Unrelated Houses.	Cases.
1	1	7	6	10	1	12	1
2	2	8	2	11	2	13	2
3	1	9	2			14	3
4	3						
5	1						
6	2						

1915. The first epidemic in Chiengmai was confined to practically one city block and to 3 family connections. 26 cases in 4 months.

1918. 2nd epidemic. A case of b.w.f. among the students of a branch of the Royal Pages College of Bangkok, near Chengmai. 26 cases in the three succeeding years.

The evidence would seem to point to a specific factor, supposedly a malaria parasite, but a variety capable of elaborating a potent haemolysin. Cort (1929), 110.

Pseudo-epidemics

A term applicable to localized outbreaks among limited groups of people subject to the same morbid conditions as occur in canal making earth-works and especially excavation in the vicinity of marshes. Gouzien (1911), 42 (r.).

Exertion

The chief exciting causes of this fever—namely exertion, chill and quinine—have therefore this action in common, that they cause contraction of the spleen. Blacklock and Macdonald (1928).

Globin

Haemolysed auto-blood injected into dogs leads to symptoms of anaphylactic-like shock, dyspnoea, cyanosis, vomiting, defaecation, heart collapse, clonic-tonic contractions, fall of temperature and eventually oedema of the lung, Hgbaemia, and Hgburia.

Medium doses produce rigor and fever, small doses nil. Alkalized or acidified blood similarly produces severe shock. The symptoms are due to the globin of the haemoglobin. In blackwater, the fever and rigor depend on the sudden liberation of stromata probably intravascular, and not locally, e.g. in the kidneys. Haematin plays no part in the symptoms. Borchardt and Tropp (1928), 265.

Gout

Among 37 patients with an acquired gouty diathesis, Hgburic fever occurred 22 times and Q. Hgburia 24 times. Cardamatis (1902[b]), 21 (r.).

Haematoporphyrin

I suggest that the haemolysis which constitutes blackwater fever is due to the presence of an optical sensitizer, probably one of the porphyrins, which is developed under certain conditions causing lowered hepatic activity in the course of the active stages of malarial blood destruction. Hewetson (1925), 109.

Haemolysins (autolysins and isolysins)

In 30 observations at various times on 16 cases a haemolytic action with the blood plasma was obtained in 2 cases. In both bacteria were present. Barratt & Yorke (1909[a]), 65.

B.w.f. predisposition arises at the same time as malarial immunity and consists in the development of haemolytic amboceptors in the blood of the particular person. The predisposition can then in a certain sense be regarded as an immunizing process.

The outbreak of a b.w.f. attack will depend on the complement-content of the blood. If this is low haemolysis may be a quite gradual process without clinical symptoms.

Chill, over-exertion, trauma and especially quinine, act by producing so to speak an explosive development of complement. Experiments to show this were made as follows :—

a. 1 c.c. of a 2·5% suspension of sheep's corpuscles (previously sensitised by haemolysin). 4 tubes, +.

b. 1 c.c. of fresh human serum diluted with saline to 10%, 20%, 30%, and 40% respectively. 4 tubes, giving 4 tubes each of 2 c.c. containing 5%, 10%, 15% and 20% of serum.

c. A control tube containing corpuscles and serum inactivated (heated).

The five tubes incubated for ½ hour at 37°. The haemolytic power of the serum compared before and 4 hours after taking quinine.

Normal persons (5)

6 a.m., blood taken. Then Q. bisulphate 2·0 g. *per os.* 10 a.m., blood taken. In one of 5 the complement had increased by 50%.

Chronic Malaria, Javanese (15)

7 a.m., blood taken. Q. Hydrochloride 1·0 g. *per os.* 11 a.m., blood taken. Result: 6 no change, 1 decrease, 8 increase. In 2 of the 8, the increase was 50%; in 5, 100%; and in 1, 300%.

Intravenous injections of 80 *c.c.* 10% *salt solution*

In 2 no change, in 1 an increase of complement. Intravenous injections of strongly hypertonic salt solutions have been found to decrease the amount of complement in animals, also peptone. de Raadt (1917), 149.

T. aet: 26. 1917. Malaria in Macedonia.
1924. Malaria attacks in France.
25 Sept. Admitted for 'icterus and anaemia.' Spleen +.
1 Oct. Urine 'malaga' colour. T. 37·3°. Icterus intense.
2. Red cells 1·7 m. Resistance, unwashed 3·5, washed 4·5 (‰ saline). Auto- and Iso-agglutinins absent. Autolysins absent. Isolysins present.
13. Isolysins in small quantity.
1 Nov. Ehrlich and Donath–Landsteiner reactions for 'cold haemolysin' negative. Isolysins absent. Bourges (1925), 267.

House

2 officers and a sub-officer at the same time in the same house. Carmouze (1897), 337.

'Blackwater Fever' Houses.—Two houses in particular have this reputation . . . it is doubtful in both houses if a single case was really contracted there. Daniels (1901), 49.

5 of 62 cases of b.w.f. occurred in the same house (Uganda). Wiggins (1922), 57.

13 of 83 cases of b.w.f. occurred in the same house (Uganda). MacMillan (1923), 52.

Over a period of about 20 years, 10 cases of b.w.f. not including relapses occurred in 2 houses, while in the rest of the village (population ?) less than 15 cases occurred. The families in the 2 houses were closely related and were descended from common parents. Millien (1924), 169.

'Blackwater fever houses.' The houses were situated near breeding places of *A. costalis*, and were in every instance unprotected by screening, or, what is probably worse, were imperfectly screened. Generally no attempts were made to

place nets over the beds. Quinine was used intermittently, despised, or regarded as a poison. . . .

A man and his wife both developed blackwater in the same house and died on the same day. In 1923 three members of the same family developed blackwater in the same house. Thomson (1924[a]), 28–32.

Banes, Cuba

A number of cases may occur in the same family or the same house, but usually such cases are found to have developed with long intervals between cases extending over many years. Exceptionally more than one case will occur simultaneously in the same house or family. Menk (1927), 114.

Inoculations

100 c.c. of urine injected into the marginal vein of the ear in a rabbit of 2100 g. The experiment repeated with doses of 110, 130, 150 and 170 c.c. of urine from other cases.

A guinea-pig injected intraperitoneally with 20–30 c.c. of urine. Concluded that (1) the urine does not contain bacteria pathogenic for animals, as animals all recovered after slight symptoms only. (2) That the urine is hypotoxic, attributed to the low urea values of the urine, 9, 8·6, 7, and 2·08 g. per litre in 4 cases. Vincent (1900), 113.

Blood taken during life (from a fatal case with suppression) injected into the peritoneum of guinea-pigs with a negative result. Emulsions of spleen, liver and mesenteric glands injected into the peritoneum of monkeys and guinea-pigs with negative result. Grattan (1907), 241.

Mixed samples of urine obtained from cases of b.w.f. during the acute stages of the disease, previously sterilized at 45° C. with chloroform were used.

Rabbit 1, injected intravenously on 6 occasions. Total 8·75 c.c.

Rabbit 2, injected intraperitoneally on 3 occasions. Total 6·0 c.c.

No ill effects resulted. Dudgeon (1920), 238.

Sierra Leone. B.w.f. death, day 9. Over 2 c.c. of a mixture of blood 3 parts, citrate saline solution 1 part, injected on day 4 of the disease, patient's T. 102°+, into a healthy European. The recipient took Q. for 2 days in order to obviate infection with malaria. The result was negative. Blacklock (1923), 84.

Ten (15?) guinea-pigs were inoculated intraperitoneally with centrifuged deposit from ten (15?) distinct cases of b.w.f.; no spirochaetes were found nor were there any abnormal symptoms. Thomson (1924[a]), 47; (1924[b]).

Banes Hospital, Cuba. About 10 c.c. of blood was removed from the vein of a patient in his first paroxysm of Hgburia and was immediately injected into the vein of the negro. Observation ended at the close of 3 weeks, and the negro failed to develop either malaria or b.w.f. United Fruit Company (1926), 48.

22 Jan. 1 hr. after onset of Hgburia. 10 c.c. of blood injected intramuscularly into *Macacus rhesus*. Up to 18 March, negative.

2 c.c. inoculated into Fletcher's medium for leptospirae. Remained sterile for 22 days. Gupta (1932), 330.

Liver

Haiti. On the basis of my treated cases (15) I hold that in malaria patients—independently of the severity of the infection—blackwater occurs if a liver lesion is present. Special predisposing factors are circulatory stagnation and abuse of alcohol. Naumann (1933), 306.

Locality, change of

Blackwater—from its nature, viz. a severe attack of malaria, often develops under these conditions of travelling from one place to another in Senegambia, and I have seen so many persons attacked a few days after their arrival from stations far unhealthier. . . . It may be that this unfortunate tendency to attack may be the result of a sudden change of temperature; in fact all the stations are as is well

known much hotter than Saint-Louis or Gorée, all the rivers are infinitely hotter than the high sea. Bérenger Féraud (1874), 254.

The natives of a country can contract b.w.f. in passing from one locality to another, e.g. at Tonkin among the troops stationed in the posts in the Delta b.w.f. is unknown, but when transferred to the plateau regions after a sufficiently long stay they suffer from b.w.f. or it shows itself on their return. Gouzien (1911), 49 (r.).

Locality

34 cases. 27 cases were seen in rural residents and seven in townspeople. Deaderick (1914), 873.

Southern Rhodesia.	Total European population (1926).	Cases. 1924–28.	Yearly average.	Rate per 1000.
Rural areas	14,822	106	21·2	1·42
Urban areas and rural townships.				
Pop. under 1000 . . .	5,596	37	7·4	1·32
Urban areas. Pop. over 1000 .	18,756	27*	5·4	0·28

* Only 1 of these cases was a *permanent* inhabitant of a big town, all the others were 'nomadic,' i.e. had been in various country districts, e.g. railway employees, or again transport riders, who may spend 9 of 12 months in country areas. Ross (1932), 21.

Mercurial treatment

A study of clinical records 1845–72, shows that a mercury course, whether for syphilis, or for an endemic condition (hepatitis, dysentery), often predisposes to b.w.f.; it follows in a few months the ingestion of mercury. Bérenger Féraud (1874), 258.

Nomenclature

Jaffa, Palestine, 1883: 'Regular epidemic of malaria and among the fatal cases a great many presented symptoms we now recognize as being those of blackwater fever.' At the time it was called yellow fever. Masterman (1906), 314.

Occupation

In Mayotta the colonists, working daily in the sugar-cane plantations are scarcely more than twice as many as the administration employees of all kinds, yet among them (the colonists) 155 of 191 cases have occurred. Foncervines (1873), 32.

Attacks especially, explorers, soldiers campaigning or on garrison duty in unhealthy districts, custom-house officials in low marshy areas (Dahomey and Ivory Coast lagoons), traders, West Coast of Africa. Gouzien (1911), 50 (r.).

Southern Rhodesia.				
Occupation.	Population (1926).	Cases (1924–28).	Average per year.	Rate per 1000.
Agriculture . .	3672	53	10·6	2·88
Mining . .	1883	26	5·2	2·83
Transport . .	1930	20	4·0	2·07
Commercial . .	2076	14	2·8	1·34
Personal service .	242	1	0·2	0·82
Retired . .	330	1	0·2	0·60
Professional . .	2111	6	1·2	0·56
Industrial . .	2228	5	1·0	0·44

The figures are interpreted as showing that the disease is related to the conditions under which the occupation is carried out and not to the occupation itself. Thus agriculture and mining are rural occupations conducted often in primitive and hitherto undeveloped country. 'Transport' similarly implies close association with rural districts, and in the commercial population no cases occurred in large towns, but exclusively among traders in rural townships or rural areas. Ross (1932), 19.

Parturition

June, 1895. Following an injury, abortion, and consecutive to it, b.w.f. and death in 3 days. Plehn, A. (1896), 25.

20.2.94. B.w.f. directly after a confinement in which there was a considerable loss of blood.

A remittent, resembling a septic fever, with repeated rigors, great anxiety and at times mental confusion. Moderate icterus, spleen+, urine 20–40 c.c., great pain on passing, profuse non-haemorrhagic diarrhoea. Plehn, F. (1898), 147.

In Rhodesia I encountered nine cases in which Q. could be excluded, the time of the last dose varying from about one month to several months previously. In five cases b.w.f. was precipitated by child-birth. Thomson (1924), 112.

'*Protozoa*'

Patient. Bournemouth, England. Death on day 6.

Granular blue bodies with red-stained structures. Not found before the fourth day.

Always exceedingly rare. The diameter of the smallest body was 5μ, the size of the largest was 17 × 10μ. The number of chromatin stained bodies within one cell varied from 40 to 200. The cell or body contains no nucleus. They have some resemblance to Koch's blue bodies (stages in the life history of *Theileria parva*). Coles (1913), 1231.

Pyorrhoea

All my cases (? number) of b.w.f. have had very bad pyorrhoea, or an acute abscess, or middle ear disease or carious teeth. Forbes (1929–30), 153.

Race

Mayotta, 1859–70. (Relative populations not given.)

Caucasian race, 168. Hindu race, 20. Foncervines (1873), 5.

Nyasaland. During the year June 1899 to June 1900 there were 31 cases among 338 Europeans (1898 population), and 2 cases among 200 Indians (Sikhs and others). Daniels (1901), 44.

In the endemic area b.w.f. is extremely rare and mild among the autochthonous native races, but transported from their native country they become as susceptible as Europeans. Syrians, those nomadic traders, with a starved aspect and practising no hygiene, seem especially susceptible. White Créoles and half-bred subjects are remarkably disposed to b.w.f. or more especially quinine Hgburia. This disposition is so well marked in the West Indies, Réunion, Nossi-bé, Mayotta, Comoro Islands, etc., that certain families believe the disposition is an hereditary one. Gouzien (1911), 49, 50 (r.).

Year.	Panama Canal Zone.				Authority.
	Malaria admissions, per 1000.		Blackwater admissions, per 1000.		
	White.	Black.	White.	Black.	
1908	507	190	5·09	0·63	Stephens (1913), 500.
1909	366	163	6·52	0·62	
1910	372	121	3·07	0·34	
1911	334	130	6·61	0·55	
1912	216	74	1·99	0·16	

Candelaria hospital. Madeira–Mamore Railway Company. Porto Velho, Brazil.

Race.	Admissions.	B.w.f.	°/₀₀.	Authority.
West Indians	4,537	5	1·1	Lovelace (1913), 5.
Brazilians	5,751	52	9·0	
European and N. American Whites	14,759	390	26·4	
Spaniards	6,121	245	40·0	

Formosa.				
	Japanese.	Chinese.	Formosans.	Authority.
Population	122,792	7,930	3,213,221	Hatori (1914–15), 649.
Blackwater	161	7	6	

Arabs

B.w.f. occurs sometimes among Arabs who have settled near European stations, and consequently have learnt to take care of themselves with quinine. David (1914), 510.

So far as we know no case of b.w.f. has occurred among Arabs and Berbers (in Algeria), although there is much malaria among them. Parrot (1915), 5 (r.).

Negroes

Banes, Cuba. It is seldom observed in our large negro population during harvest season. These negroes form a large part of the population in the Banes Division. . . . B.w.f. as a rule, occurs in the Cubans of predominantly white extraction, in Spaniards who live in unscreened quarters in malarious districts over long periods of time. Menk (1927), 113.

Africans.				
Locality.	Cases.	Death.	Period.	Authority: Stephens (1929).
Gold Coast . . .	11	4	1893–1927	74
Nigeria Northern . .	21	6	1898–1918	78
Nigeria Southern . .	27	7	1905–1918	79
Nigeria . . .	60	4	1919–1927	79
Nyasaland . . .	13	4	1905–1927	80
Rhodesia Southern .	29	9	1908–1927	81
Sierra Leone. . .	7	2	1909–1927	84
Tanganyika . . .	46	37	1921–1927	87
Togo	2	0	1901–1911	87

Africans

11 cases in 6 months in Kipushi hospital (Belgian Congo) among Banyaruandas and Barudis, recruited in the Ruanda–Urundi territory. The attack in each instance—once the

diagnosis of malaria was made—followed a large dose of Q. 1 to 2 g. Leclef (1931), 293.

Demerara River. British Guiana. 1923–31.

Race.	Pop. ♂.	B.w.f.	Per 1000.	Pop. ♀.	B.w.f.	Per 1000.
European . .	41	3	73·1	24	0	0
East Indians .	150	3	20·0	100	3	30·0
Mixed . .	902	20	22·0	793	17	21·4
Chinese . .	63	1	15·8	35	0	0
Aborigines . .	270	3	11·1	239	3	12·5
Negroes . .	2209	7	3·1	1543	3	1·9

Mackensie Hospital. Demerara River. 1926–31.

Race.	Hospital admissions.	B.w.f.	Per 1000 admissions.
Mixed	1954	37	18·9
East Indians . . .	413	6	14·5
Portuguese . . .	302	4	13·2
Aborigines . . .	593	5	8·4
Negroes . . .	3564	7	1·9

The Negro Race presents a high degree of racial immunity to blackwater; as Deeks and James (1911) pointed out this immunity is distinctly parallel to that which the Negroes, as a race, present towards the clinical manifestations of malaria infection. Giglioli (1932[b]), 14, 15 (r.).

Radiant Energy

Mixtures of Q. salts in various concentration and sheep's red cells exposed to the action of arc-lamp rays. Haemolysis is increased by exposure to light rays.

One of the causes of b.w.f. is possibly the influence of radiant energy whereby Q. present in the red cells and the decomposition products of Hgb act as sensitising bodies. Hintze (1916), 1187.

Rainfall

Southern Rhodesia.				
Month.	Approximate rainfall in inches. Average monthly (1898–1928).	Departures from monthly average 2·2.	B.w.f. (1913–1928). Departures from monthly average 55.	Month.
Oct.	1	— 1·2	— 22	Jan.
Nov.	3	+ ·8	— ·3	Feb.
Dec.	5	+ 2·8	+ 31	Mar.
Jan.	7	+ 4·8	+ 75	Apr.
Feb.	6	+ 3·8	+ 58	May
Mar.	4	+ 1·8	+ 25	June
Apr.	1	— 1·2	+ 7	July
May	0	0	— 19	Aug.
June	0	0	— 40	Sept.
July	0	0	— 32	Oct.
Aug.	0	0	— 40	Nov.
Sept.	0	0	— 40	Dec.
Average		2·2	55	

The difference in the distribution of the values for rainfall and b.w.f. can be made to disappear if a three months' lag is assumed to operate in the case of b.w.f.

The fact that an interval of three months exists between the periods of maximum rainfall and maximum incidence suggests that some other factor must operate. Ross (1932), 37.

Residence

Bilious haematuric fever never attacks any but those individuals who have already spent on an average about 2 years in the colony (Senegal), and all without exception have already experienced the toxic effects of paludism. It may occur in a patient who has not shown any symptom of malaria for a long time. Barthélemy-Benoit (1865), 301.

2 cases after a few weeks in Cameroons. 1 case within the first 6 months on the East Coast (of Africa). Plehn, F. (1898), 106.

First attack of malaria, three weeks after arrival in East Africa. Two months later first attack of b.w.f. Koch (1899), 308.

The earliest date at which I myself saw b.w.f. was 3 months after arrival in Cameroons. Plehn, A. (1903[b]), 515.

In one case I saw b.w.f. after 6 weeks in Cameroons in a merchant who since his arrival had constantly suffered from improperly treated malaria and who lived under miserable conditions. Ziemann (1906), 562.

Case 5. American aet: 40. Residence, Pedro Miguel on the isthmus of Panama, 2 months. No previous attack of malarial fever. Brem (1906), 1897.

11 men and 1 officer of U.S.S. 'Des Moines' on the West Coast of Africa a little over a month. June, 1910. Went ashore for 36 hours: had not been ashore at night previously (? ashore previously in day-time). None had a malarial history. 10 days after their return, 7 developed b.w.f., 3 malaria, 2 remained normal. None of the b.w.f. cases received Q. previous to the time of exposure (? after the exposure). Sutton (1911), 352.

In my cases the shortest period of residence was 5 months in Rhodesia in a patient who had come direct from England. Thomson (1924[b]), (7).

A case that had only resided in tropical Africa 14 days and so only after homeopathic doses of quinine. Nocht (1929), 25.

In one of my cases (on the Gold Coast) $13\frac{3}{4}$ years before the first attack. Fisch (1896[a]), 272.

An old captain who for over 20 years had acted as overseer of a factory in Cameroons and who almost always had enjoyed good health was attacked with a very severe form just before leaving the colony. Plehn, F. (1898), 106.

'A case of b.w.f. occurring after twenty-three years residence in Central Africa' (title). Howard (1907).

Another patient, 40 years of age, born in Rhodesia, had b.w.f. for the first time with two attacks in thirteen months. Thomson (1924[a]), 27.

Residence, post-tropical

1 previous attack of b.w.f. The patient during his 10 months' sojourn in Europe was completely well, his second

attack occurred at sea before he had reached Africa. Küchel (1895), 448.

4 years in Cameroons. 7 attacks of b.w.f. Had lived a year in Germany and from time to time fever. Blood *P. vivax*. 4 attacks of b.w.f. following Q. in 25 days. Koch (1899), 315.

P. aet: 30. Strensall, England. Invalided from West Africa, Aug. 1906, after b.w.f. 5 years and 4 months later treated for influenza with a mixture. 4 months later, Hgburia, T. 100·5°, vomiting neg., icterus neg., parasites neg. Later (when convalescent), Hgburia again passed, T. 101°. Slight icterus, next day urine clear. No quinine previous to either of these attacks. Altogether 5 years and 8 months elapsed since leaving the coast before the first attack. (The Diagnosis of paroxysmal Hgburia was not excluded.) Skelton (1912), 457.

Manson met with a case in England in which a severe attack followed by a still more severe and prolonged relapse was the first manifestation of a b.w.f. infection that must have been acquired at least nine and a half months previously, the time that elapsed since the patient left Africa. Manson-Bahr (1921), 104.

B.w.f. in France six months after leaving Dakar, Senegal. Hamet (1923), 505.

Length of Residence

Years of Residence.	Cases.	Deaths.	Years of Residence.	Cases.	Deaths.	Authority.
1	12	4	7	0	0	Fisch (1914), 31.
2	16	8	8	3	0	
3	15	2	9	0	0	
4	10	1	10	1	0	
5	2	1	11	0	0	
6	1	0	12	2	1	

Gold Coast. No population data for the respective periods given. The 6 cases in years 8–12 had already had 1 or 2 attacks.

Years of Residence.	Cases.	Cases.	Cases.	Cases.	Total.
Under 1	10		9		19
1		21		16	37
2	42	40		26	108
3	79	27		23	129
4	37	12	(1–5)	10	59
5	9	5	87	13	114
6	(5+) 8			5	13
7				6	6
8				5	5
9		(6–10)	(5–10)	2	2
10		9	49	8	66
10–15			24		24
15–20			26		26
20+			24	35	59
Total .	185	114	219	149	667
Authority	A	B	C	D	

A. Under 1 year, cases 10. 3 months 1, 6 months 3, 9 months 5, 10 months 1. Bérenger Féraud (1874), 107.

B. A correction is required, as the number of persons in any residential period steadily diminishes. The affect of this correction does not effect the character of the curve. Daniels (1901), 45.

C. Uganda (1922–28).

D. Colonial Office Schedules. Africa (Unpublished).

Southern Rhodesia. 1924–28. (Europeans not born in Rhodesia.)							
European population (1926).	Length of residence in years.	Number of first attacks.	Number of second or multiple attacks.	Total.	Of 100 attacks there are		Authority.
					first attacks.	second or more attacks.	
3761	0–4	32	8	40	80	20	
2867	5–9	17	11	28	60	40	Ross
2420	10–14	15	9	24	62	38	(1932),
2932	15–19	9	14	23	39	61	26.
1329	20–24	4	13	17	23	77	
1200	25–29	0	4	4		100	
1182	30+	3	3	6	50	50	

The number of first attacks is so small in comparison to the total population that it cannot appreciably affect the total population remaining, after the first attacks have passed into the second attack class.

With *increasing* residence the tendency to a first attack *decreases*, but the tendency to a second attack *increases*.

Sarcolactic Acid

On the evidence brought forward by us we conclude that sarcolactic acid is the causal agent in the production of the haemolysis in b.w.f. and these haemoglobinurias. Blacklock and Macdonald (1928), 149.

The further fact that hyperlactacidaemia could not be demonstrated in cases of malignant tertian and b.w.f., only serves to confirm the conclusion reached on other grounds that the haemolysis of b.w.f. is not brought about by any increase of lactic acid formation in the blood or internal organs. Ross (1932), 163.

Season

The most severe cases of bilious haematuric fever occur during the (rainy) winter, June to Oct. 15, 302, or rather in the after-season, Oct., Nov., and Dec. 307. They are associated with the drying of the flooded lands. It is also the season at which malaria acquires its maximum intensity. 387. Barthélemy-Benoit (1865).

Mayotta. 1859–1 Aug., 1870.						
Month.	Cases.	Departure from average 16.	Month.	Cases.	Departure from average 16.	Authority.
Jan.	8	− 8	July	15	− 1	Foncervines (1873), 5.
Feb.	17	+ 1	Aug.	14	− 2	
Mar.	22	+ 6	Sept.	9	− 7	
Apr.	18	+ 2	Oct.	20	+ 4	
May	20	+ 4	Nov.	16	0	
June	21	+ 5	Dec.	10	− 6	

Relative number of cases on the supposition that 100 cases occur each month.*

Month.	Senegambia.		R. Casamanca. R. Rio-Nunez.		Gold Coast.		Gaboon.	
	Cases.	Departure from 100.	Cases.	Departure from 100.	Cases.	Departure from 100.	Cases.	Departure from 100.
Jan.	107	+ 7	120	+ 20	130	+ 30	170	+ 70
Feb.	86	− 14	130	+ 30	100	0	150	+ 50
Mar.	83	− 17	50	− 50	125	+ 25	80	− 20
Apr.	52	− 48	20	− 80	145	+ 45	70	− 30
May	72	− 28	0	0	110	+ 10	150	+ 50
June	38	− 62	70	− 30	75	− 25	220	+ 120
July	50	− 50	210	+ 110	90	− 10	0	0
Aug.	141	+ 41	70	− 30	60	− 40	150	+ 50
Sept.	140	+ 40	170	+ 70	75	− 25	80	− 20
Oct.	180	+ 80	270	+ 170	40	− 60	150	+ 50
Nov.	126	+ 26	70	− 30	110	+ 10	80	− 20
Dec.	86	− 14	20	− 80	130	+ 30	0	0
	1200		1200		1200		1200	

The figures for Senegambia cover a period of 10–20 years, those for the Gold Coast and Gaboon 3–5 years. A seasonal prevalence appears to be shown most clearly

Sanitary Posts, 1897–99, and Dahomey Hospitals, 1894–99.

Month.	Cases.	Deviations from average 7·4.	Authority.
Jan.	16	+ 8·6	Gouzien (1900[a]), 87 (r.).
Feb.	9	+ 1·6	
Mar.	8	+ 0·6	
Apr.	4	− 3·4	
May	7	− 0·4	
June	5	− 2·4	
July	3	− 4·4	
Aug.	5	− 2·4	
Sept.	4	− 3·4	
Oct.	7	− 0·4	
Nov.	9	+ 1·6	
Dec.	12	+ 4·6	
	89		

* *Vide* App. 26.

by the Senegambia and Gold Coast figures. The actuals are not given. Bérenger Féraud (1874), 242.

Seasonal pseudo-epidemics (q.v.) during especially severe winters have been noted by Corre and Bonnafin since 1874 in Mauritius, 43.

B.w.f. occurring during the cold season is usually due to a re-infection, less commonly to a malarial relapse. In the dry season it is usually due to a relapse due to a chill induced by the Harmattan, the dry tornadoes before the rains. In Senegal there is a difference of 15° C. between the day and night temperature. 47.

The view is held by certain authors that the disposition to blackwater is caused by *P. falciparum*, while the actual attack is due to re-infection with this or other species of parasite.

B.w.f. with a remittent type of temperature occurs almost exclusively in the winter season (Dahomey), and is due to a re-infection, whereas b.w.f. with an intermittent type of temperature is due to a relapse and occurs in the dry season.

Month.	Northern Nigeria, 1899–1911.		Southern Nigeria, 1899–1911.	
	B.w.f. cases corrected for a month of 30·4 days.	Departure + or — from average 18·8	B.w.f. cases corrected for a month of 30·4 days.	Departure + or — from average 20·1.
Jan.	29·5	+ 10·7	19·6	— 0·5
Feb.	15·2	— 3·6	21·7	+ 1·6
Mar.	13·7	— 5·1	19·6	— 0·5
Apr.	9·1	— 9·7	19·3	— 0·8
May	7·9	— 10·9	13·7	— 6·4
June	9·1	— 9·7	14·2	— 5·9
July	17·7	— 1·1	27·4	+ 7·3
Aug.	26·5	+ 7·7	29·5	+ 9·4
Sept.	26·4	+ 7·6	13·2	— 6·9
Oct.	22·6	+ 3·8	21·6	+ 1·5
Nov.	20·3	+ 1·5	25·4	+ 5·3
Dec.	27·5	+ 8·7	15·7	— 4·4
	225·5		240·9	

While this view holds good for most cases, yet there are exceptions. Yet it cannot be denied that relapses usually due to chill (*a frigore*) characterize the dry and fresh season. 21. Gouzien (1911) (r.).

Mr. Stott has calculated for me that it is 131 to 1 against the Northern Nigeria distribution being simply a random one. Further, if we take into account the *amount* of departure, it is 1000 to 1 in favour of the effect being due to season. In the case of the Southern Nigeria figures some other factor seems to be at work and the probability is reduced to 7 to 1. Stephens (1913), 492.

All cases. Isthmian Canal Commission Hospitals, 1907–12.			European cases. Ancon Hospital, 1908–12.		
Month.	Actuals.	Departures from average 33·7.	Actuals.	Corrected for pop. and month of 30·4 days.	Departures from average 20·1.
Jan.	34	+ 0·3	28	27·8	+ 7·7
Feb.	53	+ 19·3	23	25·1	+ 5·0
Mar.	35	+ 1·3	23	22·8	+ 2·7
Apr.	34	+ 0·3	19	18·4	− 1·7
May	32	− 1·7	15	14·3	− 5·8
June	24	− 9·7	15	15·2	− 4·9
July	28	− 5·7	13	12·8	− 7·3
Aug.	33	− 0·7	20	20·1	− 0·0
Sept.	31	− 2·7	19	19·8	− 0·3
Oct.	24	− 9·7	23	22·2	+ 2·1
Nov.	36	+ 2·3	29	29·7	+ 9·6
Dec.	40	+ 6·3	14	13·4	− 6·7
	404	Av. 33·7	241		Av. 20·1

We have six cases in the Ancon figures below the average coming together, making a probability of 131 to 1 in favour of a seasonal incidence, although in this case our confidence is reduced by one-third owing to the average being only over 5 years instead of 13 as in the Nigerian figures. A similar conclusion can also be drawn from the Isthmian Canal figures. Stephens (1913), 497, 498.

Southern Rhodesia, 1913–28.			
Month.	Actual admissions per month, 30·4 days.	Deviations from average 55·1.	Authority.
Jan.	33·3	— 21·8	Ross (1932), 33.
Feb.	54·8	— 0·3	
Mar.	86·2	+ 31·1	
Apr.	129·7	+ 74·6	
May	112·7	+ 57·6	
June	80·0	+ 24·9	
July	61·9	— 6·8	
Aug.	36·2	— 18·9	
Sept.	14·2	— 40·9	
Oct.	22·6	— 32·5	
Nov.	15·2	— 39·9	
Dec.	14·7	— 40·4	

The distribution of cases and the extent of departure from the average over these fifteen years must lead to the assumption that the seasonal incidence of the disease is not an accidental happening, but that the probabilities are that it is a real feature of the epidemiology of the disease in Southern Rhodesia. (*Vide* also Ch. V, Aetiology—Malaria.)

Sex

Demerara River. British Guiana. 1923–31.						
Race.	Pop. ♂.	Pop. ♀.	B.w.f. ♂.	B.w.f. ♀.	Per 1000 ♂.	Per 1000 ♀.
Negroes . .	2209	1543	7	3	3·1	1·9
Mixed . .	902	793	20	17	22·2	21·4
East Indians .	150	100	3	3	20·0	30·0
Aborigines .	270	239	3	3	11·1	12·5

Authority : Giglioli (1932[b]), 14 (r.).

Southern Rhodesia. Europeans. 1924–28.					
Pop. (1926).		B.w. cases.		Rate per 1000.	
♂.	♀.	♂.	♀.	♂.	♀.
21,808	17,366	140	30	6·40	1·70

Authority : Ross (1932), 16.

Spirochaetes

East Indian. One of 4 cases of Hgburia.

Blood: Spirochaetes 7–16 μ, 1 to 5 fields; Plasma spheres (Koch's blue bodies); *P. vivax*, scanty.

Blood inoculations into guinea pigs, negative. Urine: spirochaetes negative. Post mortem: Icterus in all organs, oedema of lungs, no Hges. Ashburn, Vedder and Gentry (1912), 198.

Case with clinical symptoms of blackwatèr. Spirochaetes in blood and organs post-mortem. 3 cases of Weil's disease reported from district. Schüffner (1918).

P. falciparum, also present. Thomson (1924[a]), 44.

The spirochaete is figured in *Trans. Roy. Soc. Trop. Med. and Hyg.*, **28**, 37.

Dr. Esquier told us of the discovery he had made of the finding of numerous spirochaetes 22–24 μ long in a liver smear from a European case of b.w.f. Blood during life, *P. praecox*, spirochaetes absent. Noc (1920), 678.

2 cases. Brazzaville Congo.

Spirochaetes found in the deposit resulting from a triple centrifugation of the blood, absent in the urine.

The spirochaetes from one case inoculated into guinea-pigs.

After a 3rd passage in series the guinea-pig developed haematuria and Hgic lesions, icterus absent.

Post-mortem: fatty liver, congested kidneys, intra-peritoneal Hges, Hgic spots in lungs, bloody urine in the bladder.

Spirochaetes in liver, lungs and blood, morphology 6–9 μ by 0–0.2 μ, 3–4 undulations. Blanchard and Lefrou (1922), 699.

A spirochaete occurs in ' infectious icterus ' of the Congo.

The cases are limited to the parts of the river Congo known as Le Couloir, and especially along the Rivière-Noire and the Léfini. Spirochaetes are not found in cases of Hgburia arising at Brazzaville. Blanchard (1924), 271.

Leopoldville. In 2 of 8 cases, using triple centrifugation,

spirochaetes, actively motile, 6–9 μ, 4–5 regular spirals. In one case seen in blood on day 4. Not found in urine. Van Hoof (1924), 291.

4 other cases described. Blanchard and Lefrou (1926), 345.

F. Luigi, aet: 40. 3 years in Katanga, Belgian Congo.

13 May, 1924. Admitted at Bologna. Blood neg., urine Hgb. positive, serum albumen and serum globulin negative.

15. Blood repeatedly centrifuged, rare spirochaetes present.

16. Centrifuged blood, rare spirochaetes, 6–9 μ by 0.2–0.3 μ. 2 guinea-pigs inoculated intraperitoneally with blood.

12 July. G.-pig 1. Killed. Rare spirochaetes in blood and liver.

3 Aug. G.-pig 2. Alive. All examinations negative.

All examinations of control g.-pigs negative. A spirochaete in spleen of patient figured. Franchini and Maggesi (1925), 96.

Laos. 12 Nov., Hgburia; 14, neg.; 18, Hgburia; 19, neg.; 21, Hgburia; 22, neg.; 25, Hgburia; 26, neg.

25 Nov. *P. vivax.*

9 Dec. Triple centrifugation, spirochaetes abundant.

25–28. Febrile attack, T. 40°, spirochaetes abundant. Spirochaetes 6–8 μ, often 20 μ, rigid with rapidly vibrating extremities resembling those of icterohgic fever. Similar spirochaetes found also in a case of fever resistant to Q. and arsenic.

Pathogenic action: guinea-pigs inoculated with blood of these 2 cases died, some in a few days, some in 20–30 days. Some survived, but their blood subinoculated into g.-pigs produced a fatal infection.

Spirochaetes were not found in any of the inoculated animals, but the organs showed a yellow pigment giving after ' unmasking ' the Prussian blue reaction.

At Laos there exist two forms of Hgburia, the first and most common and least fatal that associated with malaria, the second in which malaria does not provide a satisfactory explanation. Ott (1932[b]), 532.

Streptococcus

Boinet has in Indo-China described a streptococcus which he found in the blood of a patient for a long time suffering from malaria and attacked with b.w.f. Cardamatis (1902[b]), 13 (r.). (*Vide supra Bacteria.*)

Sunstroke

Many men practising in the tropics are agreed that exposure to the sun very frequently induces an attack of malaria . . . it is intelligible therefore that b.w.f., in its character of a malarial affection, may be the result of exposure to sun. Bérenger Féraud (1874), 256.

This patient attributes his b.w.f. to the fact that while suffering from a remittent fever, he exposed himself to the sun on a very hot day. Crosse (1892), 66.

18.5. T+, no rigor, restlessness, sunken features, intense icterus, urine dark red, 300 c.c. during the day.
6.6. Soon restored to health again.
25. Relapse after most intense exposure to sun. Plehn, A. (1896), 34.

Isolation in some cases is clearly a determining factor. Gouzien (1911), 53 (r.).

Syphilis

'Is Syphilis a Factor in Blackwater Fever?' (title). Napier (1913).

Vide also *infra*, Ch. 6, *No Quinine*. Rudolf (1925), 964.

Trauma

A fulminating case very clearly consecutive to a traumatic haemarthrosis in an alcoholic and atheromatous subject. Gouzien (1911), 53 (r.).

SUMMARY

1. Among accessory aetiological factors are enumerated such causes as alcohol, chill, diet, disease, emotion, exertion, gout, parturition, sunstroke, syphilis, trauma, but it rarely seems possible to attribute to any of them, e.g. chill, the aetiological importance this latter has in the development of paroxysmal Hgburia.

2. 'Disposition,' whether personal—and even hereditary—or familial, may involve some at present unknown factor, but the known factor malarial infection appears always to be present. Similarly in the case of 'b.w.f. houses' and so-called 'epidemics' presumably implying some unknown infective agent, malaria cannot be excluded.

3. Aetiological importance has been assigned to bacteria and protozoa (other than malaria) and inoculations have been made in the search for these agents, but with negative result. The presence of spirochaetes in certain cases in certain areas appears to have no more than local significance.

4. The mechanism of the Hgbic process has been attributed to such diverse agents as haemolysins, radiant energy, sarcolactic acid, or has been considered in a general way as an anaphylactic phenomenon, but these opinions are largely speculative.

5. We are on more certain ground where statistical evidence can be applied, as in the case of such factors as age, sex, race, period of residence, occupation, locality, rainfall and season, and the evidence on these points is given in a series of tables.

CHAPTER 5

AETIOLOGY. MALARIA

Malaria among Europeans and Bengalis

Among sixty persons resident in the Dam Dim district to our knowledge over fifty have suffered from attacks of fever (malaria) during the year. . . . Some forty-five out of the sixty persons have made more or less systematic use of quinine. 28.

Constant infestation. A factor which we must emphasize, since it is to our minds one of the conditions always associated with b.w.f. countries, is the almost daily inoculation with sporozoits. 28. . . . A process of continuous infestation calling strongly to mind what occurs in cattle living in a piroplasma country. 29.

Association with malaria also applies to questions of change of residence, of season, and of locality, to the existence of b.w.f. houses and the special susceptibility of relations and of persons living in the same place to incur b.w.f.; such cases seem always most simply explained by the amount of malarial infection that has been experienced. . . . The more minutely we enquire into conditions we find therefore not discrepancies, but an even closer relation between the incidence of b.w.f. and the intensity of malaria. 45.

Blackwater fever and malaria in India

Opening up of the soil. Of far more importance than mere extra facilities for breeding of anopheles are . . . admixture of susceptibles with the infected; the depressing effects of hardship, especially affecting the weaker, who in turn by becoming malarial disseminators take their part in

the vicious cycle . . . in these huge labour camps we find malaria in its intensest and most pernicious form. . . . Europeans and others . . . dwell not apart from but in the midst of the natives. 22.

Blackwater fever in the Duars (India). It is in the Duars that b.w.f. is most prevalent. 24.

The most obvious feature(s) in the Duars is the prevalence and intensity of malaria infection.

Splenic and Parasite Indices %. (36 tea-gardens.)

S.	P.	S.	P.	S.	P.	S.	P.
100	96	92	62	85	94	72	52
99	82	92	96	84	96	67	72
96	75	92	85	83	73	61	36
96	88	91	91	82	93	55	35
95	75	90	58	80	87	50	20
95	83	90	94	78	60	90	83
95	89	89	82	78	65		
93	78	89	86	75	60	Christophers and Bentley (1908a), 25.	
93	85	89	98	75	60		
93	90	87	87	72	52		

Generally occurs among those who have had malaria attacks of moderate severity or who have suffered from febrile malaise not necessitating recourse to bed. As a liver abscess may follow a slight attack of dysentery, so b.w.f. may follow sub-acute malaria. Gouzien (1911), 46 (r.).

Malaria admissions.	B.w.f. developed in	Non-malaria admissions.	B.w.f. developed in.	Authority.
40,928	102	42,000*	4†	Deeks and James (1911), 30.
3,063	32	16,347	1‡	Ross (1932), 73.

* Cases diagnosed as Typhoid, Pneumonia, Amoebic Dysentery, Tuberculosis, etc. (medical and surgical).

† In the surgical wards: 3 after well-defined malarial paroxysms, 1 after quinine in a patient with a history of much malaria.

‡ Dysenteric symptoms regarded by the doctor as of malarial origin.

Correlation between Malaria and B.w.f.

European Admissions for Malaria and B.w.f. Ancon Hospital, Panama. 1908–12.					
Month.	Malaria.	Departure + or — from average 1092.	B.w.f.	B.w.f. moved 4 months back.	Departure + or — from average 20.
Jan.	1,041	— 51	28	15	— 5
Feb.	940	— 152	23	15	— 5
Mar.	761	— 331	23	13	— 7
Apr.	624	— 468	19	20	0
May	717	— 375	15	19	— 1
June	1,297	+ 205	15	23	+ 3
July	1,850	+ 758	13	29	+ 9
Aug.	1,455	+ 363	20	14	— 6
Sept.	1,107	+ 15	19	28	+ 8
Oct.	1,202	+ 110	23	23	+ 3
Nov.	1,071	— 21	29	23	+ 3
Dec.	1,044	— 48	14	19	— 1
	13,109		241		

If we move the b.w.f. figures back for 4 months there is a strong *positive* correlation expressed by $r = + \cdot 50 \pm \cdot 04$ ($r = 1$ implies perfect correlation), tending to show that the two diseases are connected, for not only is there a correlation between the seasonal and secular variations (not shown here)

Southern Rhodesia Hospitals, 1913–22.				
Month.	Malaria admissions.	Departures from average.	B.w.f. admissions.	Departures from average.
Jan.	642	+ 92	20	— 11
Feb.	778	+ 228	42	+ 1
Mar.	1153	+ 603	61	+ 20
Apr.	1265	+ 715	90	+ 49
May	920	+ 370	90	+ 49
June	478	— 72	74	+ 34
July	279	— 271	41	0
Aug.	196	— 354	27	— 14
Sept.	139	— 411	11	— 31
Oct.	198	— 352	12	— 29
Nov.	243	— 317	11	— 30
Dec.	317	— 233	13	— 28
	Av. 550		Av. 41	

which might occur, and yet not necessarily imply any connection between the two diseases at all, but there is also a coincidence between the magnitude of the oscillations of the two diseases, which, so far as the figures go, suggests that there is a real connection between the two. Stephens (1913), 502.

The seasonal incidences of the two diseases absolutely coincide, and from this we conclude that malaria and blackwater are one and the same disease or that the factors governing their transmission are identical. Thomson (1924[a]), 19.

Southern Rhodesia.				
Month.	Malaria (1913–28). *Average* number of admissions per month (30·4 days).	Blackwater (1913–28). *Actual* number of admissions per month (30·4 days).	Malaria deviation from average (54).	Blackwater. deviation from average (55·1).
Jan.	60	33·3	+ 6	− 21·8
Feb.	79	54·8	+ 25	− 0·3
Mar.	105	86·2	+ 51	+ 31·1
Apr.	125	129·7	+ 71	+ 74·6
May	94	112·7	+ 40	+ 57·6
June	46	80·0	− 8	+ 24·9
July	29	61·9	− 25	+ 6·8
Aug.	19	36·2	− 35	− 18·9
Sept.	14	14·2	− 40	− 40·9
Oct.	20	22·6	− 34	− 32·5
Nov.	25	15·2	− 29	− 39·9
Dec.	30	14·7	− 24	− 40·4

The *actual* monthly malaria admissions are approximately the figures in column 2 × 15 (the period of years). The plus or minus departures from the average in the case of malaria and b.w.f. occur together, and the range of deviation is of considerable extent on both sides. Ross (1932), 33, 35.

The malaria curve reaches lowest value in September (− 40) and begins to rise in October (− 34), reaching its maximum in April (+ 71). The blackwater curve reaches its lowest value in December (− 40·4) and begins to rise in

January (— 21·8), thus shewing a 3-months lag. B.w.f. rises more rapidly than malaria, so that it has reached its maximum (+ 74·6) in the same month as malaria, viz. April, but the fall of the curve is slower, so that malaria reaches its lowest point (— 40) in September, while it is only 3 months later, viz. December, that b.w.f. reaches its lowest point (— 40·4). Ross (1932), 33, 35, 66.

If the length of the epidemic phase of each is measured by the period during which the cases recorded are greater than the monthly mean over the whole fifteen years, it is seen that in both diseases this period lasts for 5 months. 66.

There is a lag period of 2 months between the two diseases, judged by the period when admissions are above the mean. This lag . . . would suggest that the conception that b.w.f., if connected with malaria, occurs subsequent to infection with the latter, is correct.

If this assumption be true, the course of the b.w.f. curve in its more rapid rise and its less rapid fall would suggest that malaria rapidly (with a lag of 2 months) makes its effect felt in the form of b.w.f., but also that when malaria ceases *relatively* to act, it still has an after-effect as shewn by the delayed fall of the b.w.f. curve.

There seems no escape from the conclusion that the frequency of previous malarial infection in cases of b.w.f. must be looked upon as unique and a factor of undoubted significance. Ross (1932), 70, 71.

Interval between First Malaria Infection and Blackwater.

Case.	Interval in months.	Case.	Interval in months.	Case.	Interval in months.
1	1·6	6	5·5	12	8
2	5	7	4	13	5·5
3	5	8	4	15	8·5
4	5	10	5·5	16	5
5	4	11	4·5		

The data refer to soldiers who had not previously been in a malarious country. The intervals are those between the

occurrence of the first recognized attack of malaria and b.w.f. The average period is 5 months. Arkwright and Lepper (1918[a]), 128.

In one case in Rhodesia four months only elapsed between the first possible infection with malaria and the first onset of b.w.f. Ross (1932), 75.

Parasites

I first found them (parasites) in 1892, shortly before the attack in great numbers. There are mainly 2 forms. The first stain readily; they are disc-like soft structures which apparently often cling to the red cells or are found free in the plasma. Here and there they show a radial structure. Besides these there are forms which stain with difficulty apparently with a very thick almost horn-like membrane. Flat circular structures $3 \times 1\ \mu$, often in numerous groups. Both are $\frac{1}{3}$–$\frac{1}{4}$ of a red cell in size. Here and there one finds a burst sheath. After the attack numerous spores occur, small longish forms, free or sticking to the red cells. Fisch (1896[a]), 271.

	Cases.	Parasites positive %.	Authority.
1. Hgburia prior to but not subsequent to admission to hospital . .	15	0	Deeks and James (1911), 44.
2. Hgburia prior and subsequent to admission	113	23	
3. Hgburia not prior to but subsequent to admission	102	59	

In most cases the blood was examined only at the time of admission.

Day 1[a].		Day 1.		Day 2.	
Cases.	Parasites +.	Cases.	Parasites +.	Cases.	Parasites +.
90	61 70%	310	145 46%	278	67 24%

1[a] = 1 day before Hgburia. The protocols are given in Appendix IV.

Absence of Parasites

From the above table it is seen that parasites in the peripheral circulation are absent in about one-third of the cases on the day before onset (90 cases, 61 positive).

The following are examples :—

(1) 28.7.1928. Par. neg.
29. Par. neg.
30. Par. neg. Q. grains 15.
31. Par. neg. Q. grains 15, 10 a.m. and 2 p.m., 6 p.m. Hgburia.
Par. neg. up to 17.8.1928.

(2) 29.7.1928. Par. neg.
30. Par. neg.
31. Par. neg.
1.8. Par. neg. Q. grains 15 10 a.m. and 2 p.m., 6 p.m. Hgburia.
Par. neg. up to 16.8.1928.

(4) 25.11.1928. Par. pos.
26. Par. pos. Q. grains 10 × 3.
27. Par. neg. Q. grains 10 × 3.
28. Par. neg. Q. grains 10 × 3.
29. Par. neg. 10.30 a.m. Hgburia.
Par. neg. up to 8.12.1928.
Yorke, Murgatroyd and Owen (1929–30), 335.

Disappearance of Parasites

Time of blood examination.	Cases.	Parasites	%.	Authority.
Day before onset . . .	9	8	88·8	Panse (1902).
Day of onset (*a*) before onset .	11	8	72·7	
(*b*) after onset .	11	6	54·5	
Within 12 hours after onset .	12	6	50·0	
More than 12 hours after onset.	31	9	29·0	

Day.	Time.	Q. grains.	Hgburia.	% of red cells infected.	Authority.
15	6 p.m.	10			Brem (1911), 154, 178.
	8 p.m.			15·6	
16	9 a.m.			9·4	
	10 a.m.	10			
	7 p.m.			3·6	
	9 p.m.	10			
17	4 a.m.			·46	
	5.30 a.m.		+		
	8.30 a.m.		+	·13	
18			+	0	

25–27. *P. falciparum.*

28. Q. grs. 15. 8 a.m. and 11 a.m., Hgburia, parasites positive.

29–30. Par. pos., 5.35 p.m. death.

1 Dec. 8.35 a.m. Smears from brain, spleen, bone-marrow, and liver negative. Brem (1911), 162.

Day 1[a]. Hgburia neg. 9% of red cells infected with *P. falciparum.*

Day 1. Hgburia pos. (9.30 p.m.).

Day 2. Parasites neg. Brem (1912), 130.

Days 1 and 2. *P. vivax* ++.

Day 3. Blood negative.

Day 5. Death. P.m. Numerous spleen and marrow smears negative. In liver a single parasite found. Ameuille, Sourdel and Marcorelle (1918), 559.

Parasitic Relapses

I encountered five cases in which no parasites were found during the Hgburia, but true parasitic relapses with asexual rings of *P. falciparum* occurred from 5 to 14 days after cessation of acute symptoms. Thomson (1924[a]), 39 (1924[b]).

On admission, parasites negative. *P. falciparum* positive on the 8th day after the urine had become negative for

about 6 days, *i.e.* a relapse during convalescence. Manson-Bahr and Sayes (1927), 273.

9. March. Parasites +, Q. grains 15.
10. Parasites —, Q. grains 15 × 3.
11. Parasites —, Q. grains 15 × 3.
12. Hgburia. Q. grains 15, parasites neg. (*vide infra*, Spleen puncture).

A month later, parasitic relapse. Yorke, Murgatroyd and Owen (1929–30), 339.

17–22 Feb. Parasites negative.
24. Plasmochin Co., soon after, b.w.f.
25. Parasites neg.
2 March. Tooth extraction. Malaria attack. *P. falciparum*, positive. Mühlens and Knabe (1931).

Three cases (of 41 ?) were seen in which from 7 to 10 days after the cessation of Hgburia parasites made their reappearance in the blood, accompanied by the clinical manifestations of malaria. Ross (1932), 74.

Pigmented Leucocytes

Case.	Day.	Parasites.	Pig. leucocytes.	Case.	Day.	Parasites.	Pig. leucocytes.
1	3	—	+	12	3	—	—
6	2	—	+	15	4	—	—
8	2	—	+	16		—	—
10	2	—	+	18	3	—	—
11	2	—	+	19	1	—	—
14	3	—	+	23	4	—	—
17	6	—	+				
		7 —	7 +			6 —	6 —

Authority : Christophers and Bentley (1908[a]).

Cases 10.	Day 1.	Day 2.	Days 4–6.
Parasites pos. . . .	6	0	1
Pigment pos. . . .	8	6	4

Authority : Christophers and Bentley (1908[a]). Stephens (1913), 485.

Spleen Puncture

Case.	Day.	Hgburia.	Parasites.	Pigment.	Authority.
19	1	+	Doubtful	—	
20	1	+	—	+	
22	2	+	+	+	
24	4	+	+	+	
26	2	+	—	+	Christophers and Bentley (1908[a]).
7[a]	9*	—	—	—	
11	6	—	—	—	
12	2	+	—	—	
12	3	—	—	—	
14	4	+	—	—	
15	1	+	—	—	
16	3	+	—	—	Barratt and Yorke (1909[a]), 155.

* 2 hours after death.

9 March 1929. *P. falciparum.* 11 parasites in 500 microscope fields, Q. grains 15.

10. Q. grains 15, three times.

11. Q. grains 15, 10 a.m., 2 p.m., 6 p.m.

12. 8 a.m. Hgburia, 11 a.m. spleen puncture, rings and schizonts negative, disintegrating parasites negative, an occasional crescent, an occasional pigmented cell, free pigment little if any.

'A month later.' Relapse of malaria, blood positive. Yorke, Murgatroyd and Owen (1929–30), 366.

Inoculated Malaria

13.3. *P. vivax* inoculated intravenously.

18.3–2.4. 16 febrile attacks, 12 with rigors.

2–9. Neopanchinal * (extract of cinchona bark) given.

10. Q. hydrochloride 0·5 × 2. Afternoon Hgburia.

11. Red cell count 920,000. Schilling and Jossmann (1924), 1498.

Vide also pp. 99 and 133. "No Quinine." Rudolf (1925).

* A teaspoonful = ·125 g. Q. base.

Parasite Species

As regards the species of parasite present in the attack of malaria which heralds the onset of b.w.f., it would seem that too much significance is placed upon the species then present as indicating the variety of malaria which has led to the development of susceptibility. Ross (1932), 74.

P. vivax

M. A. ♀ aet: 30. Roman campagna.

1883. Contracted malaria again. Q. prescribed, but the patient could not take a large enough quantity, for every ingestion caused grave symptoms and Hgburia and great weakness.

1889. Irregular intermittent fever. The patient absolutely refused to take Q., because she knew she said that Q. poisoned her.

May 1890 (?). Fever, vomiting, sweating. Q. prescribed, but when the patient had taken but one dose, in little more than an hour, giddiness, nausea, rigor vomiting, Hgburia. Blood *P. vivax*. Pecori (1900). Carducci (1907), 237.

Among 41 cases collected by me, there were 5 in which the b.w.f. attack was associated with the usual (simple) tertian. As in East Africa among 63 cases of tropical malaria, some 7 were due to (simple) tertian, the frequency of association of b.w.f., with tropical fever (*P. falciparum*) is not greater than what arises from the ratio of the two forms of malaria. The preference of b.w.f. for tropical fever (*P. falciparum*) is thus only apparent. Koch (1899), 308.

Cases 9. *P. falciparum* 6. *P. vivax* 3 (Herrick).
Cases 16. *P. falciparum* 10. *P. vivax* 3 (Curi).
Cases 2. *P. falciparum* 1, *P. vivax* 1 (?) (Brem).
Brem (1906), 1994.

1 Dec. Rome. *P. vivax*. 12 noon. Q. 1·5 g. in three doses, one every hour. 6 p.m. rigor. T. 40°,

epigastric oppression, 11 p.m. 'dark' urine. (Death.) Carducci (1907), 227.

	Cases parasites present.	% *P. falciparum.*	% *P. vivax.*	Authority.
Malaria . .	23,410	74	26	Deeks and James (1911), 14, 46.
Blackwater . .	89	76	24	
Malaria . .	9,155	65	30	Lovelace (1913).
Blackwater . .	178	49	42	
In a few cases *P. falciparum* and *P. vivax* were combined and in a few cases of malaria *P. malariae* was present.				

In the great majority of cases we saw b.w.f. follow *P. falciparum*, in 4 cases after *P. vivax*. Seyfarth (1918[a]), 270.

P. malariae

M. M., aet: 23. Italy. A history of Hgburia following Q. A cousin subject to similar attacks after taking Q. In hospital *P. malariae*. Q. 0·40 g. Hgburia. Grocco (1896). Carducci (1907), 230.

Girl, aet: 18. Italy. Aet: 6. Had malaria. Was given a small dose of Q. in coffee. A few minutes later she became pale, then cyanotic with a rigor, vomiting and high T. for 24 hr., urine like blood, then blackish, normal in 2 days, transient icterus. Aet: 11. Being tormented with a bad toothache, the dentist prescribed Q. in a pill, with a resulting ictero-haematuric fever so grave that it was feared she would die. Recovery in a few days. Remained well then until aet: 18. Renewed attacks of fever. *P. malariae*. Q. given. Hgburia. Vincenzi (1897). Carducci (1907), 231.

Germany. Patient aet: 42. Never been south of Klusenberg. Lat. 47°.

13 Sept., 7.30 a.m. Q. 0·5 g., 9 a.m. violent pains, vomiting. 2 p.m. urine cherry red. Clear next day.

8 Oct. Blood. *P. malariae.*

27. 11.30 a.m. Q. 1·0 g., 1.30 p.m. pains in the back, 3 p.m. rigor, 5.30 p.m. dark ruby-red urine. Otto (1902), 58.

22.5.1901. German East Africa. Hgburia. Blood negative.

30.7. Blood. *Quartana duplex.*

7.9. Blood. *P. falciparum.* Panse (1902), 10.

Nagrakata. Duars India. Blood examined on the first day showed quartan parasites and pigmented leucocytes. Christophers and Bentley (1908[a]), 190.

12.8.1913. W. Africa. Blood. *P. malariae.*

15. Hgburia. Blood, negative. Stephens (1915), 429.

12 Aug. 1913. 5 p.m. T. 103·4°. Blood. *P. malariae*, Q. grains 6.

13. Routine treatment of Q. continued.

15. 4 p.m. frequent shivering, 10.30 p.m. T. 104·8°, 10.45 p.m. very black urine 28·4 c.c. Parasites and pigment negative. Death. 'Africa' (1915), 18.

Child aet: 7, from Sassari.

October. The fever returned. Q. 0·4 g. A few hours later Hgburia. On two other occasions Hgburia following Q. 0·2 g.

24 November. T. 39·2°, spleen and liver much enlarged. Blood. *P. falciparum*, and *P. malariae.*

25. 9 a.m. Q. 0·15 g., 12 noon, Hgburia. Moreschi (1920), 217.

G. H. aet: 46, general paralysis. England. Therapeutic malaria (quartan).

23.2.34. Rigor 10. Q. sulphate grains 10, t.d.s.

24. Rigor 11, T. 105°, Q. continued.

26. T. 99·6°, no rigor, icterus, urine dark, Q. continued.

27. Icterus increased, urine deep red. Oxy-Hgb, subjective symptoms slight, Q. stopped.

3.3. Urine normal. Bamford (1934), 765.

Case 12. Patient 2 years in Dar-es-Salaam. Much fever in Germany. 6, 8, and 10 April, 1901, fever. 11 April, 1901. 10 a.m. Q. 0·75 g., 3.30 p.m. 0·75 g. Next morning Hgburia, blood *P. malariae*, although from the patient's statements regarding fever, viz. on 6th, 8th and 10th April, one would have suspected simple tertian. Kleine (1901[b]), 480.

The parasite was probably *P. ovale* as this has a quartan-like morphology, but a tertian periodicity.

Summary

Malaria as an aetiological factor is considered in the following aspects :—

1. The conditions of life in regard to malaria under which a community providing b.w.f. cases lives. Conditions summarized as those of 'constant infestation' embracing the conditions found in labour aggregations, and among those engaged in 'opening up the soil' and in like operations.

2. The correlation existing between the seasonal occurrence of b.w.f. and malaria over a number of years.

3. The occurrence of b.w.f. amongst hospital admissions for malaria, and its non-occurrence amongst non-malaria admissions.

4. The parasitic infection of b.w.f. cases (quinine-takers) before, during and after the onset of Hgburia.

5. *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, all have been found in b.w.f. cases. The relative frequency of these species in any particular area is reflected in the frequency of these species found in b.w.f. cases in some of the examples presented.

CHAPTER 6

AETIOLOGY. QUININE

Popular Beliefs

West Indies

Continué plus longtemps le traitement quinique peut constituer un danger et l'on n'est pas éloigné à la Pointe-à-Pitre, à attribuer à l'abus qu'on en faisait autrefois les accidents hémorrhagiques, qui étaient bien plus fréquents alors qu'aujourd'hui. Dutroulau (1868), 341.

Africa. Mayotta

En effet, dans les premiers temps de la substitution du sel quinique aux préparations de quinquina, il s'est repandu dans l'Inde cette opinion que l'emploi de la quinine prédisposait aux accès bilieux et, il y a quelques années encore, les individus qui étaient dans ce pays depuis quelque temps avaient une répulsion invincible contre le sel fébrifuge, universellement employé cependant. Bérenger Féraud (1874), 105.

West Indies. Guadeloupe

L'opinion qui attribue au sulfate de quinine la propriété de provoquer l'apparition des urines noires, n'est justificé, que je sache, par aucun observation clinique positive; . . . L'opinion publique est si bien faite sur ce point que vous entendez dire, tous les jours, d'un malade qui a des urines noires, ce n'est pas étonnant, il y a pris beaucoup de quinine. Une raison qui aurait de la valeur, si le fait était prouvé, c'est qu'on ne voit la fièvre hématurique dans le pays que depuis qu'on se sert de la quinine. Pellarin (1876).

Diego-Saurez

These fevers being amenable to cinchona, it is on this drug and its preparations that I have insisted during the disease. There are many among the civil population who through ignorance or certain prejudices absolutely refuse to submit to it; according to some this Hgic symptom arises not from malaria, but from Q. and the giving of it before the actual attack. According to some Creole women, sulphate of Q. produces uterine troubles, metrorrhagias, even abortion, and they absolutely refuse to take this drug, attributing to it menstrual troubles which come rather in the category of Hges due to malaria. Cartier (1888), 171.

Africa. Cameroons

The view is widespread that extensive use of Q. produces a disposition to b.w.f., and frequently the author had to struggle against a certain quinine shyness in treating ordinary malaria. Plehn, A. (1896), 20.

N. America

The editor of the *Journal* can find any number of such cases in the Mississippi Valley, providing he has money to induce a subject to take a dose of quinine; they generally take arsenic. Anon (1899).

Drs. Louis and Lynch of Carroll's Prairie, Texas, assert that quinine sometimes produces the hemorrhage. While admitting that they are old physicians and have treated a great many cases, the author does not agree with them. Stirling (1899).

The Delta physicians (Tennessee), as well as the laity have learned by experience that the administration of quinine with these conditions present, is fraught with danger frequently precipitating an attack. Jones (1900).

In this view of the action of sulphate of quinine, I am sustained by most if not all the physicians of my section of the country—viz. the Colorado and Brazos Bottoms (Texas).

It would be difficult to induce one of them to administer quinine in malarial haematuria even after the haemorrhage has been checked, for fear of reproducing it. Smith (1900).

West Indies and Africa

The white creoles and half-breeds show a remarkable idiosyncracy. In certain countries (Antilles, Nossi-Bé, Mayotte, etc.) quinine is an object of dread, which one cannot attribute to superstition, for unhappily it is based on fatal cases of Hgburia, some of them all the more regrettable, as quinine was given in spite of the repeated warning of the patient or his friends. Children show the same susceptibility as adults, and creoles and half-breeds retain their susceptibility away from their native country. They are permanent 'haemolysophils' as contrasted with the temporary haemolysophils who have acquired the susceptibility by a sojourn more or less long in an endemic zone, and who lose it rapidly and completely on returning to temperate climes. Gouzien (1911), 63 (r.).

N. America

There seems to be a growing belief in some sections that there is a certain causal relation between quinine and haemoglobinuria. . . . On the Ouachita river (Louisiana) there was a deeply-rooted belief among the laity that quinine would produce the disease; with some it amounted to a morbid fear, and the knowledge that they were taking the drug during an attack added greatly to the gravity of the prognosis. Thornhill (1921–22).

S. Rhodesia

She gave a history of Q. idiosyncracy and irregular taking. The whole family had a distinct fear of the drug. After a long talk with the parents, in which the value of Q. was advocated, a dose was administered, and this was quickly followed by b.w.f. of short duration. Thomson (1924[a]), 113.

New Guinea

The Japanese in this territory (Rabaul, New Guinea) have a particular aversion for taking Q. while the fever is high, as they have the impression that at such times Q. is very apt to precipitate an attack of b.w.f. Calov (1925), 396.

Greece

During my visit to different villages, I found in most cases that the quinine distributed by the care of the commissions was kept intact in the family cupboards, although more than one member of a family was at the height of a malaria attack, without taking quinine, for the idea is prevalent among the people that quinine ought not to be taken during the fever, for it is then harmful. . . . I may mention in this connection an observation I have several times made, and which bears on this superstition, which prevails among certain individuals in regard to this injurious action of quinine taken during the fever. It happens sometimes in the case of those who are weak and anaemic due to malaria and prolonged starvation, and who have not taken quinine prophylactically, that the injection of Q. produces malaise, an aggravation of the disease, a petechial eruption, or haemoglobinuria. Moutoussis (1925).

N. America

The writer was debarred from giving quinine to prevent a recurrence of the malarial chill at 10 a.m. of August 24th because the child's parents claimed that they had lost two children, while living at Alexandra, La., by the family physician then giving the children sulphate of quinine. Kiger (1925–26).

PATIENTS' BELIEFS

New Guinea

8.3. Patient found unconscious on the floor, moist icteric skin, T. 38·6°. (Urine?)

9. Fairly well. Declines his doctor's treatment, as he believes that quinine has brought on his illness. Schellong (1890), 65.

Cameroons

24.4. 9 a.m. Q. 1·5 g., 3 p.m. rigor. T. 39·5°. 5 p.m. excited, anxious, short of breath, icterus, Hgburia.

8.5. Discharged. Later a slight attack of b.w.f. following Q. and some simple fever which got well without Q. Patient did not venture to take it from fear of again getting b.w.f. 32.

25.2. 1st attack of b.w.f. Q. 3·0 g. taken. Later, again some b.w.f. attacks which in his opinion were treated with too much Q.

4–7.5. Phenocol 4·0 g. daily (from fear of haemolysis by Q.).

7. As the fever continued and the patient was visibly worse, 11.30 a.m. Q. 1·5 g., 1 p.m. rigor, T., 6 p.m. sweating, vomiting, icterus; since the morning, urine 50 c.c. inky black. 32. Plehn, A. (1896).

Cameroons

1. H. has had much fever and 3 attacks of b.w.f. Red cell count 3·21 m., white 6900, rings and crescents. He is straightaway given Q. 1·0 g., which he takes very unwillingly, as he says that Q. always in his case causes fever. One hour later, there followed a moderate rigor and Hgburia. Feeling of nausea, no vomiting, moderate icterus, T. 40·1°, urine dark red, 6 hrs. T.N., 9 hrs. Hgb. neg., 13 hrs. Alb. neg. Case 29, 145.

2. Has had much fever and b.w.f. several times, always he states after a dose of Q. Skin pale and livid. Spleen tender and palpable. Red cell count 3·8 m., white 7200, Hgb. 64%, rings and parasites of various sizes. Patient consequently in spite of his determined opposition is given

Q. 1·0 g.; 3 hours later a violent rigor, T. 39·4°, vomiting, slight icterus, spleen tenderness increases. Urine red, no casts, 'pigment' masses, no red cells. Duration of fever 9 hrs. Duration of albuminuria about 70 hrs. Case 34, 150.

3. 6.6.94. 7 a.m., Q. 1·0 g., 9 a.m. rigor, 11 a.m. T. 40·3,° acute precordial oppression, dyspnoea, at times loss of consciousness and delirium, urine blackish-red, scanty. 155.

23.7. 10 a.m. Q. 1·0 g., 6 p.m. rigor, uncontrollable vomiting, T. 40°–41°, parasites positive, urine burgundy red. 157.

28–29.8. Slight attacks of fever. These he treated himself with hot baths and hot drinks, as he is afraid to take Q.

30.8. 7 a.m. Q. 1·5 g., 10 a.m. rigor, T. 40·2°, urine burgundy red, icterus moderate. Duration of Hgburia 23 hrs. Case 43, 158. Plehn, F. (1898).

West Africa

1. 29.6. 4 p.m. injection of Q. hydrobromate. The urine remains clear. The patient having attributed his initial haematuria to quinine, and as we had ourselves noticed a certain amount of darkening of the urine following our hypodermic injection on 22·6, we had some hesitation in using it again at once. 33.

2. Sister P., a nun of the Porto-Novo mission. Long resident on the coast of Africa. Has had several intermittent haematurias during the last 3 days, which she thought must be due to Q. 39. Gouzien (1900[a]) (r.).

India

He was a German missionary who had been brought down from the Rumpa Hills to Rajahmundri. He was put on quinine as a matter of course, though much against his own wish, as he informed me that the drug had on a previous

occasion produced bloody urine. I rather scouted the idea, but the urine shown me at my next visit was undoubtedly Hgburic. Each time the drug was repeated this symptom was observed; when the drug was omitted the urine was non-Hgburic. The patient died from hyperpyrexia, T. 109°. Marsden (1900), 532.

Africa. Congo

Patient does not willingly take quinine. Has never taken a regular quinine treatment after his attacks of fever.

10.6.1903. 4 p.m. about, rigor followed by T. Q. 0·5 g.
11. 4 p.m. about, rigor and T. Q. 0·5 g.
12. 10 a.m. Q. 1·0 g. 4 p.m. violent rigor and bilious vomiting, urine Met. Hgb.
13. Convalescence complete and rapid. Patient refuses to follow a methodic Q. treatment. Obs. 12. Broden (1906), 37.

Panama

The patient told Dr. Herrick that blackwater always followed when he took Q., and for that reason he, the patient, had suffered much from malaria, as he was afraid of the results of taking Q. Dr. Herrick obtained his consent to administer a very small dose.

21 Feb. 11 a.m. Q. 1 grain, 1 p.m. 99 c.c. of very dark urine.
22. 4 a.m. urine clear. Deeks and James (1911), 63.

Africa

Patient said he could never take quinine, and did not, therefore, take it. During residence in hospital, even 2 grains of euquinine (after rising by a daily increase of grain $\frac{1}{3}$ from grain $\frac{1}{2}$) gave a relapse of haematuria. 'Africa' (1915), 45.

Experimental Cases

Experimental Hgburia

P.P. aet: 22. History of Hgburia whenever he took Q.

Date.	Q.	Hgburia.	
16 Apr.	+	+	Q. grains 3 given when patient feeling quite well. 1½ hours later rigor. T. of 4 hours' duration. Lumbar pain, reddish-black urine, clear at night.
3 Nov.	+	+	3 a.m. Q. grains 3, Hgburia neg.; 4.30 a.m. Q. grains 3; 11.30 a.m. Hgburia, T.N. fatigue, and lumbar heaviness.

E.S. aet: 33. History of much fever and Hgburia when he took Q.

Date.	Q.	Hgburia.	
	+	+	Apyrexia. 7.30 p.m. 5-grain pill; 8.30 p.m. 5-grain pill; 9 p.m. rigor, T., lumbar heaviness, Hgburia.

E.C. aet: 18. Fever in August and November 1875. Two younger brothers have had b.w.f., one of whom died of it.

Date.	Q.	Hgburia.	
Dec.	+	+	At the end of an attack of fever, took a large dose of Q. An hour later a very violent rigor. Hgburia.
Dec.	(quinquina)	—	
	+	—	Q. taken on several occasions without Hgburia.
16 Oct.	+	+	15 Oct. 3 p.m. T. 39·5°; 16 Oct. 3 a.m. Q. grains 5; 4 a.m. feels weak, lumbar pain, desire to micturate. Hgburia.
2 Nov.	+	—	Feeling well, but anaemic. Q. sulphate grains 15 in 3 hours. No effect. Karamitsas (1879).

Date.	T.	Q.	Hgburia.	Hours after last dose of Q.	Authority.
Case 1.					
11	37·2	+	+	1½	Pampoukis and Chomatianos (1888).
19	38·3				
20		+	+	1	
25	39·9		−		
26		+	−		
31		+	−		
1		+	−		
7		Cinchonine	−		
10		Q. +	+	?	
Case 2.					
28	38·3	+	+	shortly	
29	36·7	+	+	2	
4		+	+	2	
6		+	−		
later		+	−		
16		+	+	?	
20		+	−		
Case 3.					
30	+	+	+	1	
4		Cinchinine	−		
5		Cinchonine	−		
9		Quinoidine	−		
10		Cinchonine	−		
12		Quinine	+	3	

12 Sept. 4 a.m. Q. 0·5 g.

8 a.m. Experienced for the first time all the symptoms of the special action of quinine.

1 Oct. 3 p.m. Forgetting the previous result patient took Q. 0·5 g.

6 p.m. The usual phenomena, rigor, high T., haematuria, vomiting, prostration.

7. 5 a.m. Q. 0·25 g., 6 a.m. Q. 0·25 g.

9 a.m. Continuous salivation with attempts at vomiting. Urine deep red.

13. 5–6 a.m. The experiment was repeated. Q. 0·5 g.
7 a.m. Reddish-brown bloody urine, rigor, vomiting, icterus, high T., prostration, lumbar pain, despondency, and aversion from quinine preparations. Tomaselli (1897), 95.

Girl aet: 19 with a history of fever and intoxication following the use of quinine.

Date.	Q.	Hgburia.	
15 June	—	+	Evening. Rigor, T. 39·9°, icterus, vomiting, headache, pain in right hypochondrium, parasites neg., Hgburia.
17	—	+	Similar attacks on 17 and 20 June. Icterus more developed. Spleen +, liver +, Hgburia.
20	—	+	
3 Aug.	+	+	9·15 a.m. Q. hydrochloride 0·5 g.; 10·15 a.m. epigastralgia; 12.15 p.m. T. 39·7°, P. 133, R. 60; 5 p.m. icterus. Hgburia.

The patient remained in hospital until Ap. 1895. Her health was good, as it had been before malaria affected her, and the menses returned, but it was always in our power to change this condition into the abnormal one described. It was only necessary to give the girl Q. ·10 g. to induce the whole series of phenomena. We made the experiment with Q. on 21 Aug., 15 Sept., 19 Oct., 15 Nov., 13 Jan., 22 Feb. and 6 April, and on each occasion, the toxic phenomena ensued with marvellous precision. Murri (1896), 115.

Young girl. History of slight fever attacks.

Q. 0·5 g. daily for 14 days. After the last dose Hgburia, high T., slight icterus. 3 days later Q. 0·75 g., 10 hours later Hgburia, T., icterus. 4 days later (by way of experiment) Q. 1·0 g., Hgburia, no fever. Clavac (1896). Plehn, A. (1897), 149.

A girl infected with malaria, but who had not had an attack for a long time. Given Q. for toothache. Hgburia resulted.

Returning to a malarial district had an attack of quartan.

Q. again given. Hgburia followed and death. Vincenzi (1897). Carducci (1907). *Vide supra P. malariae.*

Case 9. His first attack of b.w.f. followed the taking of Q. a few hours previously. Every time he took Q. b.w.f. followed. History of 10 such attacks. Patient now very anaemic and having daily febrile attacks.

Day 1. Q. 1·0 g. Some hours later, rigor, Hgburia.
Day 6. Hgburia negative.
Day 8–11. Daily fever to 40° or over between 12 noon and 1 p.m. Blood *P. vivax*. Arsenic tried without avail.
Day 43. 8 a.m. Q. bihydrochloride subcutaneously; 10 a.m. very severe rigor, lasting half an hour, pain in the limbs, vomiting, restlessness, great weakness, and premonition of death, Hgburia, 250 c.c., icterus; 2 p.m. urine dark red 250 c.c., somnolence. 10 p.m. death. 309.

Case 13. Some weeks ago b.w.f. after Q. according to patient's statement.

Day 1. In hospital. T. 38·5°.
Days 9–11. Fever, parasites positive.
Day 12. Q. 1·0 g., a few hours later Hgburia.
Day 13. T.N. Hgburia neg., parasites neg.
Day 14. Parasites neg. As a relapse of malaria was feared Q. 1·0 g., Hgburia.
Day 17. Parasites neg. Q. given on this day instead of on day 16 to avoid any coincidence with a febrile attack occurring every 2 days. Q. 1·0 g., a few hours later, rigor and Hgburia. 313.

Case 14. 4 years in Cameroons. 7 attacks of b.w.f., always after Q. In Germany for 1 year. For the last 4 months febrile attacks from time to time. A febrile attack and on 3rd day another attack. *P. vivax* present. Advised to take methylene blue and no Q. on account of his b.w.f.

disposition. Another physician ordered him Q. Scarcely had he taken it when a severe attack of b.w.f. followed.

Day 2 (in hospital). Q. 0·1 × 4. Hgburia. T. 40·5°.
Day 6. Q. 0·1 × 4. Hgburia. T. 41°.
Day 14. Q. 0·1 × 4. Hgburia. T. 39·4°.
Day 24. Q. 1·0 g. Hgburia. T. 42° (about).

From day 2 (in hospital) to day 24 almost daily rises of T. 315.

Case 17. 11 months in Cameroons.

Day 1. 6 a.m., Q. 1·0 g.; 8·30 a.m., rigor, T., Hgburia.
Day 14. Fever. No Q. taken until
Day 24. Q. 0·5 g., 2 hours later Hgburia.

A month later. Fever. Q. 0·25 g., a few hours later Hgburia.

Day 1. In hospital in Berlin. Parasites positive, Q. 0·1 g., $2\frac{3}{4}$ hours later rigor, T. 39·2°, Hgburia. 325. Koch (1899).

Cameroons. 22 Sept., 1900. Q. 0·5 g. *per os.* Three hours later marked Hgburia lasting 4 days, Hgb 38%. Q. treatment stopped. During the return journey to Europe there was another rise of T. and Q. 0·25 g. was taken as an experiment; temporary Hgburia resulted.

3 previous attacks of b.w.f. following Q.
6.9.1900. Blood, *P. falciparum.* Q. 0·1 g. hypodermically and after some days Q. 0·2 g. and so on.
27. From this time onwards Q. 0·5 g. every 7th and 8th day.
31.10. Patient wishing to be discharged, he was given experimentally Q. 1·0 g. *per os.* 8 hours later Hgburia. T. 100·2° (maximum).
1.11. Urine clear.

S. suffered on three occasions from b.w.f. always consequent upon the use of quinine. Last attack March 1900. Admitted into hospital and treated with methylene blue.

Increasing failure of strength. Blood, *P. falciparum.* On this account a further experiment with Q. was made.

22 April, 1900. Q. 0·3 g. *per os.* Hgburia at once set in and was followed by anuria. Death.

7.10.1900. In Cameroons. Q. 0·5 g. 4 hours later Hgburia.

10.11. Q. 0·5 g. Next morning Hgburia.

4.1.1901. Q. 0·1 g. 6 hours later Hgburia, icterus.

12.3. In Hamburg. *P. falciparum.* As methylene blue did not abolish the parasites, with the patient's consent on

2.4. 8 a.m. Q. hydrochloride 0·1 g. in cachet. 10 a.m. a violent rigor. Patient clung tight to the bed so as not to fall out. T. 40·4°, collapsed appearance, rapidly increasing intense icterus, profuse vomiting, fluttering pulse.

4. Hgburia cleared. Kleine (1901[b]), (1901[c]), 667.

Mr. S. He had been in the habit of taking methyl-blue as a substitute for quinine, of which he had so great a horror that he could not be persuaded to try it. He was ordered nutrient enemata and was put on full doses of methyl-blue for two days and then Warburg's tincture was tried.

15 Nov. As there was no improvement, after consultation with his German colleague half a gramme of quinine sulphate was mixed with his morning enema without his knowledge. About mid-day he passed half a pint of port-coloured urine with a trace of albumen, but there was no alteration in his general symptoms, and the next urine, passed after five and a half hours, was normal. Hodges (1902).

October. 11 a.m. Q. 1·0 g. Between 8 and 9 p.m. Hgburia.

December. In Germany. At first fever every 2–3 days, later every 8th day. For fear of b.w.f. no Q. given.

4 Feb. T.N. *P. falciparum.*

5. T.N. Par. neg. Scanty polychromasia. Q. 0·3 g. subcutaneously.
6. T.N. A distinct increase of polychromasia, 2–4 polychromatic corpuscles in each field, numerous makrocytes, mikrocytes and shadows. Urine normal. On account of the blood findings no Q.
7. T.N. *P. falciparum.* Polychromasia still considerable, therefore no Q.
8. T.N. *P. falciparum.* Polychromasia still distinct, but less than on 6 Feb., shadows, makrocytes, distinct anisocytosis. 4 p.m. Q. 0·3 g. subcutaneously as parasites were still present. A bigger dose was not given on account of the still striking blood picture. 8.30 p.m. (about), b.w.f. attack, T. 39·6°. Ruge (1902), 504.

Patient . . . declared that quinine always gave him blackwater.

Oct. 1902 in England. 5 p.m. Q. grains 10. About midnight, vomiting, diarrhoea and frequent micturition. He noticed that his urine was black.

11 March, 1903. 7 p.m. Q. grains 10. Midnight diarrhoea, vomiting . . . blackwater.

12. Admitted. T. 99·6°.

13. T.N., felt quite well until

23. when Dr. Manson decided to test his statement that quinine gave him haemoglobinuria. 9 p.m. Q. grains 10. He slept until 1 a.m., and then with a moderate rigor, nausea, and diarrhoea, passed a large quantity of blackwater. 2 a.m. T. 99°. Ross and Low (1903[a]), 1139. (1903[b]), 138.

'En 1897 à Dakar nous eûmes l'occasion d'assister à l'expérience saissisante de Dumas dans laquelle un sous-officier rétabli d'une première atteinte grave de fièvre bilieuse hémoglobinurique, consentit à prendre 1 gr. 50 de sulfate de quinine et vit 5 heures après réparaitre la fièvre et l'hémoglobinurie.' Marchoux (1904), 5.

F. has been in the Congo for 2 years. Some days ago b.w.f. following quinine.

Days 1–3. Hgburia, Q. daily.

Day 6 (3rd day after Hgburia). 4 p.m. Q. 1·0 g., 6 p.m. Hgburia. T. 104°.

7. Slight icterus, slight lumbar pain, spleen palpable, liver not tender, general condition good. 4 p.m. urine clear.

8. Convalescent. Suspecting quinine susceptibility, Q. 0·5 g. + Laudanum 15 drops given.

9. Q. as before.

10. 6 a.m. Q. as before; 6 p.m. Q. as before.

11. 6 a.m. Q. 0·5 g.; 6 p.m. Q. 0·5 g.

12. 6 a.m. Q. 0·5 g.; noon Hgburia, T. 102·2°, no icterus, no vomiting, no headache; 10 p.m. Hgburia, neg.

13. No fever. Urine, no albumen. Broden (1906), 27.

S.H. Aet: 28. Capetown. History of 4 attacks of Hgburia, following the taking of Q. in half an hour.

20 April. *P. falciparum.*

23. 8 a.m. Received by accident a dose of Ferri et quin. citras grains 10 (Q. grains 1½), intended for the patient in the next bed. He did not know that the medicine contained Q.

10 a.m. He noticed that his urine was black, and immediately came to the conclusion that he had had some Q.

6 p.m. T. 102°; 10 p.m. T. 99·4°. Urine clear.

11 p.m. Q. taken, a dose ordered by the house physician —consequent upon his T. of 102° at 6 p.m.—who was unaware of the Q. taken in error.

24. 2 a.m. Severe rigor, T. 104·2°, vomiting, icterus, Hgburia.

25. 6 p.m. Q. grains 6; 10 p.m. Hgburia. T. 102°.

8 May. 8 a.m. the original dose (given by mistake) given

again, as doubt had arisen whether this small amount of Q. could induce an attack.

10 a.m. patient again passing red water; 6 p.m. T. 104·2°. Ketchen (1906), 1258.

14 Feb., 1907. Patient, Frenchman who had been on the Isthmus (of Panama) six years, was admitted to Ancon hospital. He had suffered from several attacks of malaria, and during each attack had taken quinine, with the result that he invariably manifested a paroxysm of hemoglobinuria. His temperature was irregular after his admission (for fracture of humerus).

21. 11 a.m. Q. 1 grain (with the patient's consent); 1 p.m. 99 c.c. of very dark red urine; 4.30 p.m. T. 101°.

22. 4 a.m. 454 c.c. clear in colour, no albumen. Deeks and James (1911), 63. Brem (1911), 156.

Patient, a Christian Scientist on Madeira Mamore Railway Co., Porto Velho, Brazil. Two previous definite and separate attacks of chill and fever. On the third attack—at the entreaty of his friends—he took 5 grains of Q. In a few hours Hgburia supervened and the next day he died. This was the only quinine the man had ever taken in his whole life. Lovelace (1913), 684.

Child. Aet: 7. Of Sassari.

October 1918. Q. bisulphate 0·4 g. A few hours later the patient noticed blood in the urine. This happened on two other occasions after a tablet of 0·2 g. only, so that Q. was abandoned.

24 Nov., 1918. T. 39·2°. *P. malariae.*

25. 9 a.m. Q. hydrochloride 0·15 g. *per os.*

12 noon. Urine of the colour of laked blood. Rigor. T. 39·6°. Urine clear in the evening. Q. stopped and Nov-arsenobenzol given.

3 Dec. Q. 0·05 g. *per os.* 6 hours later, rigor, Hgburia.

8. Q. 0·02 g. *per os.* 3 hours later, rigor, Hgburia.

13. Q. 0·025 g. *sub. cutem.* 3 hours later, Hgburia, rigor, T. 40°–41°, icterus. Moreschi (1920). Schiazzi (1923), 293.

A Greek boy who had had malaria, and in whom a dose of Q. was followed by Hgburia with the development of an intense grade of anaemia. It was thought the matter might be a coincidence, and accordingly, as there were special reasons for Q. treatment, a further small dose of 10 grains was given after an interval of a week or two, but with the same dramatic effect of an intense haemolysis with severe anaemia. Phear (1920), 4.

1. Girl aet: 8. Admitted with a history that every time she took Q. she had b.w.f.

28. *P. falciparum.* 6 p.m. Q. bihydrochloride grains 2; 9 p.m. nausea, Hgburia. T. 102·2° (29th).

30. T.N. Hgburia, negative. Q. stopped.

7. 12.30 p.m. Q. grain $\frac{1}{3\cdot2}$, with sod. bicarb. grains 2; 4.30 p.m. restless, nausea; 4.45 p.m. Hgburia. T. 100°. 107.

2ª. Boy aet: 10. A distinct history of Q. producing Hgburia.

15. *P. falciparum.*

17. a.m. T. 98°. Q. grains 2½ hypodermically; p.m. T. 99·4°.

18. a.m. T. 98°. Q. grains 2½; p.m. T. 100°. Hgburia.

19. a.m. Hgburia.

20. Hgburia neg.

21. a.m. Q. grains 3; p.m. T. 99·4°.

22. Night of 21–22. Hgburia. 109.

Note.—The data in the chart have been followed. They differ slightly from the text.

2ᵇ. 3 weeks later readmitted. T.N. *P. falciparum* present.

25–31. Q. injections increasing from grains 2 to grains 8 daily.

6. Q grains 2, sod. bicarb. grains 7 at 2 p.m., 6 p.m. and 10 p.m.

7. 1 a.m. rigor. T. 99·8°. Q. 4-hourly as before.

8. Night of 7–8. Hgburia. Epigastric and lumbar pain. 109.

3. ♀. History of quinine idiosyncracy and irregular taking. The whole family had a distinct fear of the drug.

Severely anaemic, icterus, spleen half filling abdomen, *P. falciparum* positive.

Q. administered, quickly followed by b.w.f. of short duration. Recovery. 113.

4. ♂. Repeated attacks of malaria. One attack of b.w.f. Admitted to hospital. Blood, negative. Q. treatment, beginning with grain $\frac{1}{2} \times 3$, and finally

4th. Q. grains 5×3.

5th. Q (?).

6th. Severe black water. T. 103·8°.

7th. T. 102·8° (minimum).

8th. T. 103·8° (maximum).

9th. T. 102°. Death. 113. Thomson (1924[a]).

1. ♀. aet: 7. B.w.f. 2 years previously. At the present time was regarded as well.

Day 1. Child swallowed portion of a tablet of Warburg's tincture (Q. 8 grains to the ounce), mistaking it for a sweet. 1 hour later, rigor and Hgburia, which rapidly cleared.

Day 5. Sod. bicarb. followed by Q. hydrochloride grain 1. There immediately followed a severe rigor and intense Hgburia. 79.

2[a]. History of 3 previous attacks of b.w.f. and that these were invariably occasioned by the taking of Q.

Day 1. *P. falciparum.*

Day 3. Q. bihydrochloride grain 5, intramuscular. Hgburia.

2[b]. A month later, readmitted.

Day 1. *P. falciparum.* Arsenical treatment.

Day 6. It became necessary to employ Q. Alkalies in large quantity given.

Day 7. 9 a.m. Q. grains 5; 10.30 a.m. rigor, Hgburia. 79. Ross (1932).

Quinine Tolerance

Minimal Doses

My case of *P. falciparum* infection must be unique, in which Q. ·01 g. produced Hgburia, ·005 g. Hgbaemia and ·004 g. albuminuria. Ziemann (1900), 643; (1906), 569.

Dr. Herrick obtained his consent to administer a very small dose.

21 Feb. 11 a.m. Q. 1 grain; 1 p.m. 99 c.c. of very dark red urine. Deeks and James (1911), 63.

On the 9th day after her first attack it was again decided to attempt Q. treatment in small doses gradually increasing.

12.30 p.m. $\frac{1}{32}$ of a grain was administered in cachet with 2 grains of sodium bicarbonate.

4.30 p.m. She became restless and complained of feeling sick.

4.45 p.m. She passed thick dark-coloured urine like stout, T. 100°.

Each attack was typically Hgburic fever of short duration. Thomson (1924[a]), 107.

Increased Dose

Patient indisposed, took Q. 1·0 g. and noticed that 2 hours later his urine was bloody. Within 5 weeks this occurred twice again.

6.9.1900. (In Koch's wards.) *P. falciparum.* T.S.N. Patient given subcutaneously, Q. 0·1 g. and then for some days 0·2 g. and

27.9. Q. 0·5 g. every 7th and 8th day.

31.10. Q. 1·0 g. *per os*, 8 hours later Hgburia.
8.11. Q. bihydrochloride 0·5 g. subcutaneously. No Hgburia.

If Q. hydrochloride 1·0 g. is given on a non-fasting stomach, about 29% appears in the urine in 24 hours. Of a subcutaneous dose of 0·5 g. only 10%. The absorbed quantity of Q. which induced Hgburia was thus about 6 times greater than the quantity previously tolerated. Kleine (1901[b]), 480; (1901[c]), 606.

1.8.1901. 3 p.m. T. 37·2°. *P. falciparum.*
4 p.m. Q. 1·0 g.
8 p.m. T. 38·7°.
2. 7 a.m. T. 36·8°, parasites negative, Q. 1·0 g. Afternoon, Hgburia, no symptoms.
4. Early. Q. 0·25 g., urine neg., blood neg.
5. Q. 0·5 g. well tolerated.
6. Q. 0·5 g. well tolerated.
7. 8 a.m. Q. 1·0 g. Afternoon, Hgburia. No symptoms except loss of appetite. Panse (1902), 22.

I recollect two b.w.f. convalescents whom I wished to habituate to Q. 0·1 g. was tolerated without any reaction; after 0·2 g. a typical attack resulted. In the case of one of these patients the experiment was repeated many times with the same result.

I know an official abroad whose b.w.f. disposition is so great that Q. 0·5 g. with certainty produces b.w.f. even when taken when quite well. This case, through the regular use of Q. 0·25 g., has remained fever-free for years. Plehn, A. (1903[c]), 551.

Mrs. C. was suffering quotidian malarial paroxysm. Quinia sul. was prescribed morning and night in gram doses after Koch's method. The paroxysm occurred next day at the usual hour. Quinia was increased to three grams daily; the next morning the paroxysm was on time and hemoglobinuric. Shropshire (1903), 603.

Vide 'Quinine Fever,' Nocht (1905).

30.4.1903. Q. in powder, dose unknown.
1.5. 10 a.m. Q. in powder, several rigors during the day, 5 p.m. Hgburia.
2. 5 p.m. urine neg., 8 p.m. Hgb +.
3. Urine, Hgb —. Afternoon, Hgb +
4. Urine, Alb. —. Evening Q. 0·25 g.
5. Evening Q. 0·25 g.
6. Evening Q. 1·0 g.
7. 10 a.m. feeling cold, fever; 11 a.m. Hgburia; 2 p.m. urine neg.; 4 p.m. Hgb +; 7.30 p.m. Hgb —.
8. Urine, alb. neg. Obs. 10, 33.
10.6.1903. Q. 0·5 g. 4 p.m. rigor, fever.
11. Q. 0·5 g. 4 p.m. rigor, fever.
12. 10 a.m. Q. 1·0 g., 4 p.m. violent rigor and in a few minutes Hgburia (met.-Hgb). Obs. 12, 37. Broden (1906).

J.K. aet: 14. Schoolboy. Sofia.
11 April, 1908. Q. 0·4 g. ½ hour later, rigor, Hgburia.
13–16. T.N. Blood, *P. vivax*.
17. T. 38·6°. Feeling of cold, then heat and sweating, spleen 2 fingers. 8 p.m. Q. ·02 g. in capsule; 10 p.m. rigor, Hgburia.
24 Ap.–11 May. Methylene blue treatment, beginning with ·05 g. twice.
2–16 June. Q. treatment, beginning with ·005 g. once, and ending with 0·2 g. × 5.
17 Sept. Fever. *P. vivax*. Q. 0·02 g., Hgburia. A systematic Q. course again begun.
March 1909. No more fever. Mollow (1910), 1338.

Bouffard at Kayes (Senegal) witnessed the following case. Patient had been getting for some days Q. 0·5 g. for an obstinate malarial attack. A new medical man, considering the dose inadequate, suddenly raised it to 1·5 g. The same evening Hgburia ensued and the patient died some days later. Gouzien (1911), 61 (r.).

P. aet: 27. During 3 years in Cameroons has had much

malaria and in the last year repeated attacks of blackwater, as the smallest dose of quinine induced an attack.

27.12.1910. At Hamburg. Spleen to umbilicus. Blood neg., Hgb. 65%.
29. An abscess (? filarial) on right upper arm opened. A quinine cure begun with 0·01 g.
31. Q. hydrochloride 0·05 g., urine normal.
2.1.1911. Q. 0·1 g., blackwater, rigor, icterus; T. then fell to normal.
7. Q. 0·05 g.
8. Q. 0·06 g. with gelatine pap.
9. Q. 0·08 g. (4 × ·02) with gelatine, Hgburia.
11. Q. 0·08 g. (4 × ·02), Hgburia.
14. Q. 1·0 g. (5 × ·02) with cholesterin 3·0 g. in olive oil, Hgburia.
20. Q. 0·8 g. (4 × ·02) with cholesterin 3·0 g., Hgburia.

Cholesterin does not raise the 'threshold' dose of Q. which produces Hgburia, which was between 0·06 and 0·08 grammes. Werner (1913), 8.

Day.	Total Q. in grammes.	Separate doses.	Grammes of Calcium Chloride.
1	·01	1	4
2	·02	2	4
3	·04	4	4
4	·08	8	4
5	·10	1	4
6	·20	2	4
7	·30	3	4
8	·40	4	4
9	·50	5	4
10	·60	6	4
11	·70	7	4
12	·80	8	4
13	·90	9	4
14	1·00	10	4
15	1·00	4	4

Scheme for obtaining tolerance to Q. in those cases where Hgburia has followed Q. The cure is not begun until apyrexia is established. The urine is examined several

times daily. If albuminuria appears Q. is stopped. Also if T. (4-hourly) rises, Q. is stopped. The occurrence of pallor or icterus is also a sign for cessation.

(The prophylactic treatment followed is 1·0 g. (in 4 doses of 0·25) on 2 consecutive days weekly.) Job (1917), 93.

In 7 of 11 cases there was an increase in the Quinine dose before the onset of b.w.f.

Case.	Q. grains. Increase from —	to —	Days before b.w.f.	Authority.
1	10	30	1	Arkwright and Lepper (1918[a]), 132.
2	0	30	2	
	30	60	1	
3	0	5	2	
4	0	30	7	
5	0	20	2	
6	15	30	7	
7	0	30	1	

The variation in the amount of Q. necessary to produce b.w.f. gave rise to the idea that each patient susceptible to b.w.f. had a critical dose which produced the disease and that smaller doses could be tolerated without ill effect. Case 4 was unable to tolerate 30 grains, Case 5 was able to tolerate 20 grains, Case 6 was unable to tolerate 60 grains. Gaskell (1920), 9.

15 Nov. Q. 5 grains b.i.d. was administered.

18. Dose was increased to 10 grains t.i.d., when there was a return of bloody urine and the Q. was stopped.

This is a condition which I have repeatedly noted . . . it is wise to begin with a very small dose—from 2–5 grains. United Fruit Company (1924), 65.

Rhodesia. ♀. Born Ap. 1927. 6 wks. later, Euquinine grain ½, daily.

1928. Fever of 3 or 4 days.

1927–June 1929. Euquinine daily except in cold months Ap. to July.

June 1929. Fever. Q. grain ½ daily.

Day 1. Sept. 10 a.m. Q. grain 1. Afternoon b.w.f.

Day 2. „ Urine clear, Q. grain 1, Hgburia. No more Q.

3 wks. later. Q. grain 1, Hgburia.

Dec. 1929. Q. grain ½, 3 hours later Hgburia. All the symptoms subsided in a day or two.

Jan. 1930. Q. grain ½, a mild attack of b.w.f.

1–3 Aug. 1930. England. Q. grain ½ daily.

4–5. Q. grain 1, patient in the evening became feverish and cross.

6. Early, Hgburia, icterus.

It was not until after the second definite attack of malaria that she (the patient) became hyper-sensitive to the drug. Yorke (1930), 477.

Boy aet: 6 . . . the patient used to get attacks of Hgburia, jaundice and high temperature each time Q. was administered to him. Blood *P. falciparum*. Spleen +.

1. Q. bihydrochloride, or Q. base, or euquinine grain $\frac{1}{12} \times 2$. Yawning, weakness, Hgburia (slight).
2. Q. bihydrochloride, or Q. base, or euquinine grain 1. Pain in abdomen and limbs, jaundice, Hgburia. T. +.
3. Q. bihydrochloride grains 2½. Pulse quick and feeble, intense pain in limbs and abdomen, great prostration, jaundice, Hgburia. T. up to 105°. Symptoms somewhat alarming, but subsided in 48 hours.
4. Q. bihydrochloride grains 5. Hgburia, severe prostration, drowsiness and the condition was almost fatal. Brahmachari, Brahmachari and Banerjea (1932), 118.

Time Relationships. Short Intervals

Q. 1·0 g., rigor 5 minutes later. Case 31[2]. Plehn, A. (1896), 48.

The priest, Alfio Bellecci, had frequently had attacks of malaria and probably for the same reason had attacks of acute

facial neuralgia. The neuralgia recurred daily and was definitely intermittent. Convinced of the (malarial) nature of the neuralgia, he had recourse to quinine 1·0 g. in 3 doses. Hardly had he taken the last dose, i.e. 3 hours after the first, when almost instantaneously, as the patient expressed it, he was taken with an unusual state of excitement, nausea, general shivering, fairly high T., much oozing of blood from the gums and icterus (Hgburia negative). The symptoms subsided gradually in about 10 hours. The neuralgia recurring in a simple form—without fever and Hgb—I waited for a second attack to convince myself of its simple nature, and then prescribed Q. bihydrochloride 0·5 g., but after about 2 hours the symptoms described above reappeared. Tomaselli (1897), 33.

Advised to take methylene blue and no Q. on account of his b.w.f. disposition. Another physician ordered him Q. Scarcely had he taken it when a severe attack of b.w.f. followed. Case 14. Koch (1899), 315.

1. Patient ill for 2 days. Better after a cold bath on the night of 24 May. 25 May, 9 a.m. headache, Q. 0·75 g. Immediately afterwards, blackwater. Feels very weak, 'as if the blood had left his limbs.' No quinine taken for 2 months previously. 15.

2. 19–20 June, night of, patient feeling feverish, took Q. 1·0 g. *Shortly* afterwards passed dark urine. 29. Gouzien (1900[a]) (r.).

Cameroons. Patient received Q. 0·5 g. on account of a slight attack of fever. Directly after a rigor came on, and he lost consciousness, T. 41·7°. Camphor and ether injections. Protracted convalescence. Kleine (1901[c]), 666.

1. Day 1. Blood, 'Tertiana duplex.'
   Day 2. The same. Early in the day with a low temperature Q. 0·75 g. Immediately, a rigor, blackwater. 18.

2. 'Tertiana' repeatedly found microscopically, was treated for some days with methylene blue. Then by someone else with Q. Directly afterwards blackwater.

Later, 3 attacks of Hgburia after Q. 4 × 0·1 g. on each occasion, finally a severe attack after Q. 1·0 g. During the whole period parasites absent. 18. Panse (1902).

A girl aet: 8 subject to Q. Hgburia 2 weeks after her last attack has a fresh relapse of intermittent fever; her doctor gave her again Q., but immediately after taking the drug she had a fresh attack of grave Hgburia and died in 24 hours.

J. Théophanidis, having cured with hypodermic injections of Q. a patient with b.w.f., attempted to use the same treatment for obstinate intermittent fever from which the patient suffered in the following 3 years. He injected Q. 2HCl grains 10, and a quarter of an hour later there followed rigors, frequent bilious vomiting, intense icterus, black urine, T. 40°, severe prostration, anuria, dyspnoea and death in 24 hours. Cardamatis (1902[a]), 42 (r.).

Hgburia followed *immediately* after taking a large dose of Q., and disappeared spontaneously in 2 hours, with no rise of T. or any constitutional disturbance. Blanchard (1924), 269.

Day 1. T. normal for 7 days, then a rise. Q. grains 8 given. Almost immediately red followed by black urine passed.

Day 2. Icterus. Urine cleared. T. fell to normal in about 10 days. Schilling and Jossman (1924).

After a preliminary dose of sodium carbonate the child was given 1 grain of Q. hydrochloride, with the result that a severe rigor immediately followed. Ross (1932), 79.

Time Relationships. General

Last dose of Q. before b.w.f.	No. of cases, 26.	Authority.
Up to 12 hrs.	18	Daniels (1901).
13–24 ,,	4	
1–2 days	2	
3–4 ,,	2	

Q. or Eu-Q. taken on day.	No. of Cases, 29.	Authority.
3^a	7†	Hatori (1914–15), 653.
2^a	1†	
1^a	21	
1	26*	

1^a, etc. = days before onset.

* In many cases Q. or Eu-Q. must have been taken before the onset, but in other cases it is not evident when exactly the Q. or Eu-Q. was taken.

† But also on Day 1, but whether before or after b.w.f. is not evident.

Last dose of Q. before b.w.f.	No. of cases, 111.	Authority.
None	6	Nigeria (1915–16, 1919, 1920, 1921, 1922).
A few hours	17	
Up to 12 hrs.	73	
13 hrs. to 36 hrs.	14	
5 days	1	

Hour of the day.	No. of Cases that took Q. at each hour.	No. of cases of b.w.f. that occurred at each hour.	No. of cases that took Q. every 3 hours.	No. of cases of b.w.f. that occurred every 3 hours.
1^a	0	3		
2	2	5		
3	3	3	5	11
4	2	4		
5	4	5		
6	19	3	25	12
7	23	3		
8	27	15		
9	24	10	74	28
10	16	19		
11	18	23		
12 n	16	27	50	69
1	2	10		
2	10	17		
3	8	10	20	37
4	7	17		
5	9	19		
6	14	9	30	45
7	13	3		
8	8	9		
9	9	3	30	15
10	6	10		
11	0	4		
12 m.	0	9	6	23
	240	240	240	240

Hour of the day.	No. of cases that took Q. at each hour.	Intervals in hours at which Hgburia followed Q.							
		0.	1.	2.	3.	4.	5.	6.	6+.
1[a]	0								
2	2		1	1					
3	3		1				2		
4	2			1					7
5	4			1	1	1		1	
6	19		2	5	2	2	1	6	24
7	23		2	1	5	3	6	1	7, 7, 7, 8, 9
8	27		1	6	8	2	1	2	7, 8, 8, 9, 9, 9, 9
9	24	2	2	2	6	2	3	3	7, 8, 9, 14
10	16		1	3	1	5		2	7, 7, 7, 7
11	18		6	4	3	1		1	7, 9, 9
12 n	16	1	1	1	2	6	2		8, 8, 8
1	2			1	1				
2	10			4	2	3		1	
3	8	1		2	2				12, 17, 20
4	7		2	2	1	1		1	
5	9			2	1	1	1		7, 8, 15, 16
6	14			2	1	4	1	3	12, 14, 16
7	13			1	2	1	3		7, 7, 8, 10, 10, 14
8	8			3	1			2	8, 16
9	9			1	1	2	1		7, 8, 8, 15
10	6		1	1					7, 10, 10, 12
11	0								
12 m.	0								

Intervals between Q. and Hgburia (240 Cases).

Hour of the day at which Q. was taken.	No. of cases of Q.	No. of cases of Hgburia that followed within 6 hrs.	%.	No. of cases of Hgburia that followed later than 6 hrs.	%.
12–3 a.m.	2	2	100	0	(0)
3–6	9	8	90	1	(10)
6–9	69	56	81	13	(19)
9–12 n.	58	47	81	11	(19)
12–3	28	25	89	3	(11)
3–6	24	17	70	7	(30)
6–9	35	24	66	11	(34)
9–12 m.	15	7	46	8	(54)
	240	186	77·5	54	22·5

Note.—12–3 = all times from 12.0 to 2.59, and so on.

After Q. Hgburia follows within 6 hours in 77·5% of cases and later than 6 hours in 22·5% of cases.

After Q. Hgburia follows within 6 hours in a greater percentage of cases in the hours 12 midnight to 3 p.m. than in the hours 3 p.m. to 12 midnight.

The protocols are given in Appendix V.

Absence of Quinine History

No quinine *

Jan. 1894. ♀ aet: 19. Two of usual Q. doses taken. Shortly afterwards rigor, vomiting, dark brown urine, and icterus on following day. For 15 days free from fever. Then 5 fresh attacks. Q., which had been abandoned for some time, again taken, followed in ½ an hour by similar symptoms. Then fever-free for another 15 days.

April 1894. In hospital at Ravenna. On 2 or 3 occasions 'Q. intoxication' followed the giving of Q. 0·5 g.

June 1894. In hospital at Bologna. In bed, no treatment. No Q.

15. p.m. rigor lasting ½ hour; 2 hours later drank water, then vomiting, urine reddish brown (? Hgb). T. 39·9°. Blood negative.

17. No Q. Very similar attack.

20. No Q. Very similar attack. Icterus. Spleen +. Liver +. For further history *vide supra*, 'Experimental cases,' Murri (1896).

Mid-June. B.w.f. without having taken any Q. for the last 10 days. Lasted 1 day. No Q. Three weeks later slight fever. Patient did not venture to take Q.

24 July. *P. falciparum.*

29–31. Phenocol 3–4 g. without any result.

6 Aug. Q. 0·75 g. I.M.

7. 5.30 p.m. Q. 1·0 g. *per os*, 10 p.m. general condition good.

* The term as generally used would appear to mean that Q. had not been taken a few days or so before the onset of b.w.f.

8. 1 a.m. shivering, fever, vomiting, strangury, tenesmus. Up to 6 a.m. 525 c.c. dark red urine. 35.

Fever every 14 days, lasting 2 days. On each occasion took Q. 1·5 g.

1.1.96. Fever and Q.

8. No Q. since 1st, and without any assignable cause, at night rigor, fever, vomiting, headache and backache. Hgburia. 51. Plehn, A. (1896).

In 16 of 168 cases which I saw myself the last recourse to Q. was a long time ago; a negro had certainly practically never seen Q., and in a further 7 cases where only 2–4 days had elapsed since the last dose Q. can hardly be held responsible for the b.w.f. Altogether 24 of my 168 cases without a Q. aetiology. Plehn, A. (1903[b]), 514.

W. aet: 25. Has had one mild attack of b.w.f.

7.2.24. Simple malaria attack. No quinine given.

8. 10 a.m. slight shiver, 3 p.m. T. 40·1°, icterus slight, urine Burgundy red, neutral, sp. gr. 1024, albumen 2·9 g. per litre (Esbach), no casts, bile neg., blood: rings, 10 p.m. T.N., Hgburia negative.

Duration of fever 12 hours; of Hgburia 12 hours; of Albuminuria 15 hours. Case 30. 146.

D. 2 months in Cameroons. Hitherto no fever and has taken no quinine.

30.5.99. T. 40·6°. Vomiting. Icterus. Liver tender, spleen palpable. Blood; rings scanty. Urine, deep dark red, 420 c.c. in 24 hrs.

31. T.N. Urine clear, icterus almost gone.

1.6. T. 39·9°. Icterus distinct, urine clear.

2. T.N. Urine normal.

3. T. 39·6°. Icterus negative, patient but slightly affected.

Duration of Hgburia 18–19 hrs. Case 35. Plehn, F. (1898), 150.

M.A. Portuguese, has lived long in the Congo and

has had much fever. Patient states that he has not taken Q. for several days and his associates confirm his statements.

7.2.1900. Sense of cold, then a shiver, evening T. 104°, urine black, no deposit, Oxy-Hgb.

8. Very ill, incessant vomiting, headache, icterus ++, urine no deposit, no red cells.

9. 10 a.m., urine clear. Alb. neg. 76.

8.2.1900. Sister G. of the Croix-Rouge, much fatigued from nursing the sick. In the evening . . . fell asleep. . . . In a few minutes she awoke, feeling ill, and went to bed. No shivering, and had taken no drug. Passed a bad night and on

9. her urine was black (Oxy-Hgb), T. 104° about, no vomiting, slight icterus, blood neg.

10. Urine of the night clear, no albumen. 77. Von Campenhout and Dryepondt (1901).

Cases 39.

2. Precise data lacking.

2. Patients formally assured me that they had not taken Q. before the attack.

35. The commencement of the attack was preceded—by a few hours—by the taking of a certain dose of Q. Broden (1906), 63.

1. P.B. Labourer aet: 18. No previous attack of malaria. Has never taken Q. 10 April, a violent and prolonged rigor, T. 40°, several lots of Hgburic urine passed, vomiting, icterus.

2. C.B. aet: 22. 25 Oct., 1904. Rigor. T. 40·2°. Three hours later, and without having taken any Q., the patient passed black urine. Kanellis (1906), 824.

26.4.1906. 1 p.m. Patient felt cold and afterwards warm. Profuse sweat followed, slight headache, severe backache and vomited freely. No definite chill. He noticed his urine was dark at the onset of the paroxysm. The patient had taken no Q. before dark urine was noticed,

and he took none until the night of 26th, at which time he had one dose of 20 grains. Brem (1906), 1903.

Jamaican woman, on the Isthmus of Panama 2 years. A prolonged attack of fever three months after coming to the Isthmus. She then took medicine, but did not think it was Q. A little fever now and then during past eight months, but took no Q. The patient was eight months pregnant. . . . Semi-comatose, passed very little urine. She had taken no Q. There was no uterine hemorrhage. Urine per catheter shewed Hgburia, albumen 0·8 per cent. (Esbach). Recovery was good. Patient did not abort. Brem (1911), 174.

19 of 133 cases of b.w.f. admitted to hospital as such, had no record of previous Q. Deeks and James (1911).

3 of 18 cases no Q. for at least a week before the onset of the attack. Fletcher (1914), 32.

Formosa. Many authors have observed the occurrence of b.w.f. in individuals who, being afraid of contracting b.w.f. or out of sheer neglect (as in the case of the Chinese), did not take any Q. at all for malaria. In some cases the patients declared that the taking of a quack medicine brought on the attack of b.w.f. Hatori (1914–15), 653.

Landsturmmann. Aet: 43. Southern Albania.
17 Dec. T. 39°. *P. vivax.*
11 March. Without previous Q. and any assignable cause, T. 39·1°, *P. vivax*, urine black, no pain, appetite good, icterus, spleen 2 fingers.
12. T.N. Urine rapidly clearing. Wiener (1917), 913.

One patient (Case 11, a fatal case) stated that he had taken no Q. for a week before the onset of b.w.f., although he was disobeying orders by evading it. Arkwright and Lepper (1918[a]), 133.

Nigeria. In 3 of 22 cases no quinine had been taken. Connal (1922[b]), 8.

In Rhodesia I encountered 9 cases (? of 83) in which

quinine could be excluded, the time of the last dose varying from about one month to several months previously. Thompson (1924[a]), 112.

Patient inoculated with *P. vivax* for quaternary syphilis. Allowed to undergo nine rigors. Then quinine treatment and neokharsivan. 88 days after the last paroxysm and 71 days after last Q. on

18 Feb. a.m. T. 98·8°, 3 p.m. T. 103·6°, black urine passed, no vomiting, hiccough or jaundice. Abdominal pain marked.

22. Red cells in urine. Bacilluria.

18–26. No malaria parasites found. Rudolf (1925).

Euquinine

Patient aet: 20, 8 months on a Cacao plantation, Cameroons, 1 attack of b.w.f.

3 Ap. On board ship. Attack of malaria. Unwilling to take Q.

6. Decided to take Q. Q. hydrochloride 0·2 g.; evening, fever.

7. Morning. Euchinin 1·0 g.; evening, fever.

8. a.m. Euchinin, 11 a.m. urine dark red, 1 p.m. rigor lasting ½ hour, anuria.

9. 3.20 p.m. death. Richter (1900), 377.

We have seen 2 cases in 1897 in patients who had had Hgburia following Q.

Vellopoulos prescribing for a patient who had intermittent fever after an attack of b.w.f observed Hgburia follow 4 times in 3 weeks, after taking euquinine ·35 g. every 2 hours.

Théophanidis having prescribed Eu-Q. for 3 consecutive days to six patients with malaria and who had had haematuria following Q. saw 4 of them recover while the 2 others had attacks of b.w.f. Cardamatis (1902[a]), 16 (r.).

Vide Appendix 26, and *supra*, Aetiology. Disposition, family.

SUMMARY

Popular beliefs. The belief that Q. provokes an attack of b.w.f. has prevailed in many countries since the introduction of the drug in 1820.

Personal beliefs. Many patients the subjects of b.w.f. have attributed the onset of the attack to a dose of Q. taken shortly before.

Experimental cases. In many cases these beliefs have been put to the test, frequently but not always with a positive result. In some of these cases the result has been fatal.

Diagnosis. No certain criteria appear in the literature for distinguishing between what has been termed Q. Hgburia and b.w.f.

Minimal doses. Appear in certain cases to be sufficient to induce Hgburia.

Increase of dose. Patients appear to be tolerant of a certain dose of Q., but intolerant of an increase beyond a certain limit.

Time relationship of Q. and b.w.f. In some cases the onset appears to be ' immediately ' after taking Q., but more commonly after ' a few hours.' An analysis of these time relationships has been made from which it would appear that b.w.f. follows the giving of Q. within 6 hours in about $\frac{3}{4}$ of the cases. It is not possible to say whether this sequence is causal or accidental, for although the data show that Q. is taken in the majority of cases at 6–9 a.m., and that the majority of cases of b.w.f. occur at 9–12 n., the latter periodicity may be due to the fact that this is the natural time of occurrence of b.w.f, or it may be associated with the fact that malarial rigors have a maximum periodicity about this time.

The data are insufficient to show at what interval b.w.f. follows Q. at any particular hour or 3-hour period of the day.

No Quinine history. A number of cases are on record in which no Q. appears to have been taken at a ' short period ' antecedent to the onset of b.w.f.

That, however, Q. is a dominant factor in the aetiology of b.w.f. is the almost inescapable conclusion from a survey of the clinical records.

CHAPTER 7

AETIOLOGY. CINCHONA, CINCHONINE, PLASMOQUIN

Cinchona

The fever having mitigated, I wished to try decoction of Calisaya * bark which was tolerated without any inconvenience, but after a long intermission of about 12 hours the fever reappeared in intensity and type as originally. It was then a case for repeating the decoction, but this time the result was very different. In about 5 hours after having taken the decoction a fresh attack of fever occurred, no longer simple as before, but accompanied with new symptoms, rigors, vomiting of bile, haematuria, icterus, etc. Tomaselli (1897), 12.

Goanese aet: 25. Many years in East Africa. Much fever, which he treated with an Indian mixture.

13.9. 6 a.m. a dose of the mixture taken. Midday (about) rigor and b.w.f. Admission. Icterus, T. 39·7°, spleen +, Hgburia, parasites neg.
16. Urine normal.

(The mixture was analysed and consisted of an extract of bark, the amount taken by the patient containing 0·3 g. quinquina bases.) Panse (1902), 13.

Certain authors (Tomaselli, Mouillac) have seen Hgburia follow the administration of powder of quinquina. Mouillac. Gouzien (1901), 58 (r.).

About a month and a half after the first Hgburia attack following cinchonine, a 5% decoction of cinchona cortex

* The yellow or *Cinchona calisaya*, or Bolivia bark, introduced 1775–1800.

was tried, but this also produced Hgburia, although it had been well tolerated after the attacks of quinine Hgburia. Moreschi (1920), 220.

So far as my knowledge goes, so long as one uses for malaria not quinine, but decoctions of the bark, blackwater is unknown, or at least very rare. Nocht (1929), 22.

Cinchonine

Child aet: 6. Sassari. Italy.

1. Absence of any family history of Q. intolerance. The Q. intolerance developed between 30 and 60 days from the first attack of malaria (*P. falciparum* and *P. malariae*) after giving Q. HCl. 4·0 g. hypodermically, and Q. bisulphate 8·0 g. *per os*, over a period of 30 days. Hgburia developed with as small a dose as ·015 g.

2. Cinchonine hydrochloride intolerance, subsequent to the Q. intolerance, developed in 27 days from the beginning of cinchonine treatment, after a dose of ·5 g.; a maximum dose of 1·1 g. and a total of 8·95 g. having been given during a period of 26 days. The intolerance rapidly increased, extremely grave attacks following a dose of ·04 g.

3. Intolerance also was shewn to quinidine, cinchonidine and optochin. Moreschi (1920).

Cinchonine unlike quinine does not increase the haemolysis of haemolytic amboceptors *in vivo*. Nocht (1929), 22.

Plasmoquin

Cases 11. Baluchistan (1932) 1, (1933) 5. North-Western Frontier Province (1932) 2, (1933) 2, (1934) 1. All with one exception (a Hindu) natives of the Punjab or the frontier.

Quinine and plasmoquine prior to the attack in 7 (6 ?). Quinine alone in 1 (?). Plasmoquine alone in 3.

P. falciparum (*P.f.*) 4. *P. vivax* (P.v.) 5.

In table Q. = quinine, P.Q. = plasmoquin, A. = atebrin,

	Day.	Parasites.	Q.	P.Q.	A.	Vomiting.	Icterus.	Cyanosis.	Hgburia.	D., R.
1.	25	*P. f.*	+	+						
	29		+−	+−						
	30					++	++		+	D.
2.	20	−	+	+						
	22		+	−			+			
	23		+			++	++		+ O.	
	24		−			++ h.				R.
3.	15	*P. v.*	+							
	16				+					
	20		+	?	+	+	+			
	21	−					+			
	22						++		+ O.	
	23								An.	
	26								An.	D.[5]
4.	31	*P. v.*		+						
	2			−		h. +		+	+	
	3								+ An.	D.[2]
5.	1	*P. f.*			+					
	5				−					
	6			+						
	8			−			+	+	+ M.	
	10									D.[3]
6.	2	*P. v.*	+	+						
	7		+	+						
	8		−	−			+	+	+ M.	
	9					+				R.
7.	9	*P. f.*	+	+						
	10		+	+						
	11		−	−			+			
	12						++		+	R.
8.	2	*P. v.*			+					
	10			+	−					
	11			+−			+			
	12								+ ?	R.
9.	31	*P. v.*	+	+						
	4		−	−						
	5					++	++	+	+	
	6									D.[2]
10.	8	*P. f.*	+							
	10		+	+						
	13		+	−		+	+		−	
	14		−			++	++		+	D.
11.	30			+						
	31			+						
	1			+		++			+	
	2						+			
	10								An.	D.

D.^{2}, etc. = day of death, R. = recovery, h. = hiccough, An. = Anuria, O. = OxyHgb., M. = MetHgb.

Amy (1934, 1935).

Vide Treatment, Electrargol, and App. 22.

SUMMARY

Cases are recorded where the apparent aetiological factors were cinchona, cinchonine and plasmoquin.

CHAPTER 8

SYMPTOMS

Abdomen

Ascites

Day 2. Urine 308 c.c. Bicarbonate of soda, 150 grains, water 1 pint, I.V.
Day 3. Suppression, saline 3 pints.
Day 4. Urine 392 c.c. Saline 2 pints.
Day 5. Urine 870 c.c. Saline 1 pint.

During the next 3 days he had recurrent attacks of haemoptysis and moist râles were heard at both bases. Ascites developed and subsequently some generalised oedema. Owen and Murgatroyd (1928), 504.

Colic

Day 18. Improvement maintained. Saline enemata, three of 200 c.c.
Day 19. Saline enema, 200 c.c.
Day 20. Some vomiting in the morning; about 9 p.m. very acute colic, the patient writhing on his bed and crying out. P. 84, apyrexia. Injection of morphia.
Day 22. Saline enema 200 c.c., Q. hydrobromate hypodermically, renewed colic in the evening, quickly relieved by morphia and a laudanum ether draught. 20 (r.).

Day 4. Great weakness, embarrassed respiration, sighing. 9 a.m. caffeine hypodermically, saline injection, 90 c.c. hypodermically. Enema followed by bilious stool; vomiting ceased; fairly acute colic in the afternoon. 64 (r.).

Day 2. Abundant bilious stools in the night with gas and colic. 39 (r.). Gouzien (1900[a]).

Peri-umbilical colic

Vide infra, Distension.

Distension

Day 2. Abdomen slightly distended, supple, doughy, widened in the sub-umbilical region. *No motions for 4 days.* 190.

Day 2. T. falls, no reaction after cold sponging (25°). A cold sweat over the body, pulse thread-like, epigastric tympanitis develops, restlessness, coma vigil.

Day 3. 7 a.m. death. 212. Pellarin (1876).

Day 6. Bowels have not acted, and he complains of some fullness in the abdomen, which is slightly tympanitic. Frequent eructations. Easmon (1885).

Cases 43. Tympany 3. Frequently there is intense tympany. 108.

Day 1. Abdomen somewhat tender, slight tympany.

Day 2. The tympany has increased, making difficult the examination of the liver and spleen. 120.

Day 2. The whole abdomen tender. Meteorism. 135.

Post-mortem. Gut meteorically distended, overlying the lower part of the liver. 127. Plehn, F. (1898).

Day 4. Admission. Patient very corpulent. Intense pallor, icterus, dyspnoea, slight stupor. Abdomen distended. Enlargement of liver and spleen not detected. Panse (1902), 7.

The stomach is often distended, and the patient complains of a feeling of fulness and discomfort. This distension may extend to the intestine, and be accompanied by a feeling of painful weight or even acute colic, especially peri-umbilical. Gouzien (1911), 27 (r.).

Day 1. Jaundiced and vomiting. Slight abdominal distension.

Day 7. Abdomen rather distended. Fairley and Bromfield (1934–35), 153.

Rigidity

Day 1. Liver cannot be exactly palpated owing to the rigidity of the abdomen. Seyfarth (1918[b]), 137.

Day 3. The abdominal muscles were somewhat rigid, making it difficult to palpate the spleen or liver. Fairley and Bromfield (1934–35), 154.

Tenderness

In 8 of 43 cases abdominal tenderness recorded. Plehn, F. (1898).

Vide also Pain, Epigastralgia.

Symptoms. General

Acidosis

The extreme thirst, the great nausea and vomiting (even although the disease may be running an almost afebrile course), the complaint of want of air or 'air hunger,' and the pain and tenderness of the abdomen are each and all characteristic of acidosis, acidaemia or acid intoxication. MacGilchrist (1913–14), 159.

Adenitis

Glandular enlargement was noted in three of the collected cases, in each case in the neck. In one of these cases there was extensive suppuration, terminating fatally. In some cases of malaria there is glandular enlargement (Nyasaland). Daniels (1901), 56.

Algidity

1. 20 Sept. Day 3. 7 a.m. A very restless night, no sleep, urine still black, P. 92, skin almost cold, symptoms of algidity, recovery. 363.
2. 7 Oct. Day 30. The patient appears to be still weaker this morning.

8. Condition the same, delirium continues, but with fairly frequent lucid intervals, complains of a constant feeling of cold, recovery. 367.

3. Day 36. 10 a.m. Some shivers, the skin is almost cold, P. very rapid, almost imperceptible, intense thirst, anxious respiration, delirium, dry tongue, involuntary motions, death. 375. Bérenger Féraud (1874).

Day 5. In a very prostrate condition, the skin cold and clammy. Crosse (1892), 72.

I record (case 23[2], day 16) in 48 cases. Plehn, A. (1896).

Day 8. In the evening dyspnoea increased, especially after slight movement in bed, patient became restless and his extremities cold. Barratt and Yorke (1909[a]), 198.

Anuria

Duration

The patient then passed urine for the first time for 63 hours in quantity about a pint, in colour as black as tar. Recovery. Stewart (1896).

After 5 days complete anuria, 500 c.c. of bloody urine passed . . . complete anuria for a further 8 days until death. Taute (1919), 542.

Frequency

Cases.	Anuria.	Deaths.	Deaths from all causes.	Authority.
32	3	3		Bérenger Féraud (1874).
53	4	4	5	Plehn, A. (1896).
46	4	4	8	Plehn, F. (1898).
35	4	3	9	Panse (1902).
20	2	2	2	Da Costa (1906).
34	2	2		Christophers and Bentley (1908[a]).
20	3	3	4	Barratt and Yorke (1909[a]).
240	22	21		

Onset

Day 1. 10 a.m. Q. 0·5 g., 1 p.m. rigor, repeated vomiting, high T.; 2 p.m. urine dark red scanty; 5–10 p.m. only a few drops, then no more until

Day 2. 7 a.m. 160 c.c. black brown. Plehn, A. (1896), 25.

Already on the day after the attack there was complete anuria. Plehn, F. (1898), 116.

Suppression usually occurs when the urine is beginning to clear, and this drop (below normal, as the urine clears) may be taken to indicate a tendency towards it.

A temporary suppression could be accounted for, when it occurs early, by the irritation set up by the haemoglobinuric urine; and the late cases by the combination of the fall of the blood pressure, the anaemia and the cessation of the excretion of diuretic constituents of the urine (haemoglobin), but neither of these sufficiently explain the persistence of the suppression. They might explain the commencement, but not the continuance. Daniels (1901), 57.

Hgburia ceased on the third day and the urine became clear. Suppression of urine then supervened. Death followed (? day). Christophers and Bentley (1908[a]), 187.

Symptoms

The symptoms of uraemia were absent even in almost complete anuria of many days' duration. The symptoms were :—

1. a slight headache; 2. inconstant vomiting; 3. no oedema of ankles; 4. no convulsions; 5. no impairment of consciousness.

The prognosis in such cases is very bad, but not hopeless. Plehn, A. (1896), 14.

Day.	Urine c.c.	
1		8 a.m. T. 36·4°, Q. 1·0 g.; 11.30 a.m. rigor, T. 41·0°. Hgburia, violent vomiting, pain in spleen and chest.
2	Small amount	9 a.m. T. 36·4°. Evening, small amount of urine.
3	A few drops	At stool. Icterus, no headache, no oedema.
4	45	Lumbago, frequent vomiting. Urine greenish-yellow.
	25	p.m.
5	141	Similar in character to that on day 4.
6	97	Sp. gr. 1008, greenish-yellow, no casts, on boiling ppt. = $\frac{1}{8}$. No casts, urinary epithelium. Hgb. 25%, nausea and lumbago better.
7	120	Sp. gr. 1009.
8	181	Sp. gr. 1010. On boiling $\frac{1}{15}$ Alb. Face puffy. No ankle oedema.
9	90	(Some lost at stool.) Vomiting. Nutrient enemata.
10	245	Sp. gr. 1008, 1009, $\frac{1}{15}$ Alb., vomiting increasing, uncontrolled by morphia. Enemata rejected. Weakness.
11	71	Prolonged vomiting of abundant fluid, green bile-stained matter.
12	320	Vomiting persists, hiccough. No food taken.
13	54	$\frac{1}{20}$ alb. Diarrhoea.
14	54	Trace Alb. Diarrhoea.
15	(?)	Said to be more abundant. Diarrhoea profuse, vomiting, P. 80.
16	0	T. 35·6°. Breathing with sighs and groans indicating pain. Afternoon, rapid loss of strength, limbs cold, facies hippocratica, involuntary motions, Cheyne-Stokes R., ether injections, death in the evening. R. first ceases, then P. Case 23[2]. Plehn, A. (1896), 40.

The symptoms associated with this suppression are not those of uraemia. Consciousness is maintained till near the end; convulsions are very rare, and even muscular twitchings are unusual. Vomiting is usually marked. The temperature is often subnormal. 57.

In occasional cases, as in some of the suppression cases in yellow fever, the patient is perfectly rational and conscious just before death. The cerebral symptoms that occur are drowsiness, irritability and sometimes mental weakness or confusion. Delirium during sleep is common. Convulsions are very rare. Coma only occurs, and not always even then, shortly before death. Life is usually prolonged for 3 or 4 days after the onset of suppression, but may be as long as nine days. Loss of vision has been complained of. The pupils are in some cases dilated. There is a steady loss of muscular strength in most cases, but not in all. Muscular

twitchings are usually absent, even to the last. As a rule there is much vomiting, and often hiccough. Occasionally an 'uraemic smell' has been noted, but this is not usual. Anasarca does not occur. The urine may be free from albumen towards the end. 62. Daniels (1901).

Anuria is certainly of cerebral origin induced by the toxic properties of metabolic and retention products. Plehn, A. (1903), 529.

Day.	Urine c.c.	
1		Midnight, Hgburia, vomiting, epigastralgia, lumbago, some colic. Great weakness in legs, restlessness, 'wandering,' T. 40·1°, P. 96. Profuse sweating
	500	following antipyrin, cessation of vomiting. Fair night.
2		Admitted. General condition satisfactory, icterus ++, bilious motion following enema, urine still black, fairly abundant; 7 p.m. clearing; afternoon, 2 bilious
	190	motions, vomiting; 9 p.m. T. 38·9°.
3		Quiet night, 1 bilious vomit, 1 bilious stool after enema, icterus deep greenish-yellow, itching about the eyes, slight headache, lumbago negative, general weakness. Afternoon, urine gradually diminishing, motion the colour of palm oil, green vomit fairly profuse, bitter salty taste in mouth, headache, somnolence, profuse
	(50+140)	sweating; 9 p.m. restless, general fatigue, constant
	190	epigastric weight.
4		1–5 a.m. asleep.
		6 a.m. urine 60 c.c. clear; 7 a.m. small quantity. Green vomit, 2 very bilious stools, icterus ++. Afternoon,
	170	frequent green vomit, brown bilious motion, urine clear, 170 c.c.
5		Relatively quiet up till midnight, then restless, vomiting. No urine since 8 p.m. of d. 4, fairly acute headache. Vomits 5–6 times almost pure bile, tongue coated, no motion in spite of enema, icterus fading, pulse firm and full. Evening, T. 37·4°, urine 280 c.c.,
	280	deep yellow.
6		Rests at intervals, no vomiting since last night. 11 a.m. vomiting begins again, icterus disappearing, no motion except bilious matter. Evening T. 37°, P. 84, urine
	300	normal.
7	320	Nausea, no vomiting.
8		Bilious vomiting in the night, 2 formed motions, yellow.
	380	Continuous nausea, T. 36·5°; noon, vomiting.
11		Profuse diarrhoea and obstinate vomiting, diarrhoea for 6 days. Recovery.

Treatment consisted of subcutaneous injections of saline, saline enemata, simple enemata, dry cupping, etc. Gouzien (1900[a]), 74 (r.).

Day 5. T. a.m. 36°, p.m. 38°, P. 84, R. 31. Oliguria, great prostration, unable to articulate, absence of vomiting.

Day 6. T. a.m. 36°, p.m. 36·2°, P. 74, R. 28.

Day 7. T. a.m. 36·2°, p.m. 36·6°, P. 78, R. 28. Anuria, semi-comatose.

Day 8. Symptoms of uraemic intoxication.

Day 9. Death. Case 2.

Day 2. General condition very bad. Great agitation, occasional bilious vomit, icterus, pain chiefly epigastric, digital hyperaesthesia. 4 p.m. worse, micturition less frequent, T. 40·2°, P. 100, R. 58.

Day 3. 6 a.m. Anuria. General state grave, difficulty in taking drugs and food, T. 38·2°, P. 98, R. 43; 11 a.m. uraemic excitation; 6 p.m. death. Case 7. Da Costa (1906).

Day 1. h. 5.30–12. Collapse.
h. 12–21. Extreme agitation, no delirium.
h. 21–. Semi-comatose, cries out at intervals.

Day 2. h. 8. Anuria.
h. 9. Sub-comatose, inert.
h. 11. Coma complete.
h. 15. Death. Parrot (1921).

Day.	Urine c.c.	
1	28·4	10 a.m. urine passed. 1 motion. Profuse sweating following treatment.
2	0	Very little sleep, restless, 10 motions, saline injections.
3	0	Vomiting and retching, 11 motions, 400 c.c., 30% glucose intravenously, Digitalis, Pituitrin.
4	0	Severe kidney pain, especially over right kidney. Nephrotomy performed (p. 336). 800 c.c. saline intravenously.
5	28·4	Vomiting. 1000 c.c. saline. Shortly afterwards urine passed. T. 97°–99°.
6	6·2	Vomiting. Pituitrin 1 c.c., shortly afterwards urine passed. Saline 1000 c.c., 1 motion, T. 98°, P. 88.
7	0	T. 98°, P. 84, volume decidedly weak.
8	0	T. 97°, P. 84, volume poor, R. shallow and sighing. Death suddenly at 10.15 a.m. No mental aberration, no symptoms of uraemia, no convulsions or muscular twitchings. Gage (1925), 125.

The Attack. Classification

Blackwater can be divided into 4 categories corresponding to the types of ordinary malaria.

1. *Slight or intermittent.* Slight symptoms of icterus and of melanuria. The attack is separated from the following ones by intervals of 18 or 24 hours.
2. *Moderate or remittent.* The symptoms and reaction are more intense.
3. *Severe or pseudo-continuous.* The intoxication is greater.
4. *Fulminating or continuous.* Like pernicious (malarial) attacks or even acute yellow fever.

Slight attacks may, however, have a remittent course, and grave attacks an intermittent one. Bérenger Féraud (1874), 117.

Haemoglobinuric fever . . . is an acute specific fever. . . . Three varieties exist: the sthenic, the insidious and the pernicious.

The *sthenic.* The attack is sudden, the fever is high at the beginning, the urine is copious, recovery is common.

The *insidious.* The attack is insidious as in a case of remittent fever, but Hgburia and jaundice intervene and early suppression of urine occurs. Recovery is not to be expected.

The *pernicious.* The onset is sudden, the temperature quickly rises high and quickly falls, jaundice appears at once, and suppression of urine occurs within 24 hours. Recovery is not to be expected. Connolly (1898), 882.

Hgburias associated with malarial infection are divided into 2 groups: (1) spontaneous, (2) quinine. The spontaneous group is divided into:—

(a) *accessual.* The attacks (of Hgburia) accompany the febrile attack (pernicious-ictero-Hgburia).

(b) *post-accessual.* Developing after the end of the attack when parasites have disappeared from the blood.

(c) *post-malarial.* Developing a long time after the attack when the patient is apparently cured of his infection.

The above forms develop without any drug, while the Q. group develops after Q. The Q. group is also divided into :—

Accessual and *post-malarial*, according as the malaria is active or is spent. The *accessual* are finally divided into *constant-accessuals* and *occasional-accessuals*, according as the attack develops always or only occasionally or once after Q. Carducci (1907), 225.

Clinically, we may divide hemoglobinuric fever into 3 types :—

1. *The paroxysmal.* When after a severe chill with attendant fever, there is an onset of blackwater, the duration of the whole attack being from a few to twenty-four hours.
2. *The sub-continued.* When the febrile attack or the blackwater, or both, persist from one to three days.
3. *The continued.* When the passage of blackwater persists for four or more days, with high fever; or the fever may be moderate or absent.

Suppression of urine occurs in all types. Deeks and James (1911), 69.

1. *Intermittent.* Apparently corresponding to malaria relapses. It is seen most often in the dry season. The commonest febrile type is quotidian, sometimes becoming tertian. 11. The Hgburia disappears more or less completely during the intermittence. 16.

2. *Remittent or subcontinuous.* Corresponding to a rapid succession of parasitic generations. Occurs at the time of re-infections, *i.e.* in the winter. 12. The Hgburia is

usually continuous but sometimes increases with the rises of T. 16.

3. *Complex and abnormal forms.*

(a) *Anuric.* In 2 or 3 days or in a few hours, anuria. Hyperpyrexia, or more rarely apyrexia, vomiting ++, hiccough, icterus ++, foetid diarrhoea, caramel-coloured or even bloody, extreme prostration or extreme agitation, mortal terror. 32.

(b) *Cardiac.* Initial gravity. Dyspnoea, drawn features, cyanosis, algidity, a syncopal condition almost from the onset. 35.

(c) *Uraemic.* Anuria sets in not suddenly, but progressively, usually after cessation of the fever and Hgburia. Albuminuria persists and facial oedema develops. Vomiting ++, eructations, hiccough, fibrillary twitchings or muscular spasms. Convulsions of delirium are exceptional, usually stupor and coma. Punctiform pupils and fixed eyeballs give a characteristic expression. Intelligence often clear. Itching may be extreme. Temperature usually sub-normal. Cheyne-Stokes respiration is rare, and only when the uraemic development is relatively slow. Death in 6–12 days. 35.

(d) *Haemorrhagic.* Very rare. Purpura, epistaxis, haematemesis, melaena. 37.

(e) *Typhoidal.* Hgburia has ceased, but T. remains about 40°. A secondary infection is added. Dry foul tongue, intense thirst, gurgling in right iliac fossa, meteorism, foetid diarrhoea, incontinence, mild delirium, carphology, *subsultus tendinum*, a foetid smell, râles in lungs, at times a dry cough. Pulse dicrotic, irregular, uncountable. Death from syncope. 37.

(f) *Septicaemic.* Very rare. Symptoms much as in typhoidal form. Acute tenderness in loins, pyuria.

P.M. kidney, multiple abscesses. 42. Gouzien (1911) (r.).

1. *Abortive.* Sometimes ambulant, frequently only noticed accidentally, usually produced by a small prophylactic dose of Q.

2. *Ordinary.* Usually starts with a rigor, then high fever, vomiting, a feeling of anxiety, Hgburia and in a few hours icterus, which reaches its greatest intensity on the 3rd day. At the end of the 2nd or on the 3rd day T. falls and the urine soon after clears, albumen a day or two later. At the same time icterus fades, but the blood Hgb% reaches its lowest value some days later. Suppression is common, exceptionally from the onset, usually on the third day, suddenly or after oliguria on the 2nd day.

3. *Prolonged febrile.* T. remittent or more or less completely intermittent, each rise being perhaps accompanied by a rigor and vomiting. Anuria is exceptional, rather there is polyuria. The destruction of red cells proceeds unchecked, continuing after the subsidence of symptoms. Hgb. cannot be estimated owing to the dirty brown-green colour of the blood. Recovery exceptional. Death 4–5 days.

4. *Fulminating or toxic.* Begins with coma and anuria. Icterus scarcely perceptible. Death in 24 hours.

5. *Haemorrhagic.* Copious Hges from stomach and gut. Death 2–3 days. Plehn, A. (1914), 1414.

1. *Ambulant.* In old 'malarias' who have lived for years in a b.w.f. district. They have acquired a relative immunity against malaria and have had a number of attacks of b.w.f. Rigor may be absent and even a slight shivering hardly noticed.

2. *Mild and medium severity.*

3. *Severe progressive form.*

4. *The fulminating form.* High irregular fever with a tendency to hyperpyrexia before death.

5. *The autolytic (fermentative).* Corresponding to the

cyclical form of other authors. Hgburia lasts a few days and then ceases, giving way to polyuria. There also occurs a peculiar intermitting fever with rigors (often 2 a day) with great (fall in Hgb value) anaemia.

6. *The anuric.* Ziemann (1924), 536.

Guatemala. Classification of 20 Cases into Types.

Symptoms.	Acute (12).	Sub-acute (5).	Paroxysmal (3).
Rigors	Severe	No repeated rigors.	Rigor 1–2 hours initiating each Hgburia.
T.	103°–105°	101°–103°	T. often 105°. Then T.N. Then 2nd attack.
Icterus	Slight at first but progressive	++	
Retching and vomiting	Persistent	Not frequent or troublesome	Some bilious vomiting.
Urine		Black and abundant	Hgburia in successive attacks
Constipation	Always		
Spleen, liver	+, painful on pressure	+, especially spleen	
Pain	Headache ++ Backache ++ Epigastralgia		
Restlessness and delirium	Extreme. No sleep. Delirium in some	No extreme restlessness with delirium	Frequently mild delirium
Weakness	Extreme	Some	
Anaemia		Marked pallor of mucosae and palms of hands	(Many symptoms similar to those of other types)
Thirst	Intense	Suffer less from thirst	
Gums		Gingivitis, bleed easily	

Aguilar (1926), 63.

Symptoms.	I. Mild to Moderate.	II. Fulminating and Toxic.	III. Anuric.	IV. Continued and Intermittent.
Frequency	Majority			
Rigor	+ or —	Severe		
Temperature	Falls with the Hgburia	Tends to fall after rigor	Pyrexia, then subnormal	Falls with the Hgburia
Post. Hgbic. Temp.	Sometimes			Most common
Vomiting	+ or —	Severe	Usually distressing	Infrequent
Hiccough		Distressing	Persistent	Infrequent
Icterus	+ or —	Intense if patient lives 24 hours	Highest development	Well-developed
Van den Bergh units	3·3–21·6	6·5–28	18·4–59·0	6·2–11·4
Headache			+	+
Backache			May be constant	+
Pulse		Rapid, irregular	Rapid, then may fall to 50–60	About 100
Respiration			Shallow, Cheyne-Stokes	
Mental state		Restless, anxious, delirium	Slight drowsiness or giddiness or mentally active	
Blood : anaemia	Variable	Extreme		Intense
N-retention	—	+	+	
Urine : colour	Red to dark brown	Dark brown at start	Bright red to greenish-brown	Usually intermittent of long duration
quantity	Normal	Polyuria	Anuria, early or late	
ketonuria		Early and increases	Early or late	
Convalescence	Rapid			
Death	Partly due to previous debility	In 1 day or as late as 3 days	7–10 days	

It cannot be pretended that all cases of b.w.f. fall into one or other of the above types. Ross (1932), 210–221.

Multiple attacks

Initial Attacks.	Second Attacks.	%.	Authority.
30	5*	16	Bérenger Féraud (1874).
35	15*	43	Plehn, A. (1896).
46	14*	47	Plehn, F. (1898).
160	30*	20	Christophers and Bentley (1908[a]).
233	14*	6	Deeks and James (1911).
181	29	16	Graham (1912).
148	33	22	'Nigeria' (1915–22).
136	33*	24	Daniels (1901), 58.

* 2 or more attacks.

Vide also App. 26.

Initial Attack

4 Jan. 'Old Coaster.' Numerous attacks of b.w.f. a.m. Q. 1·5 g.; 1 p.m. rigor of 3 hours, fever, vomiting; 5 p.m. urine dark brownish red.
5. Urine clear.

Recurrence 1

19 Feb. a.m. Q. 1·0 g.; p.m. rigor, T. 40°, urine, 'quite dark'; was not present.
21. Urine clear.

Recurrence 2

6 March. a.m. Q. 1·5 g.; 12 noon rigor, T. 40° +, urine deep black, scanty, severe icterus, great restlessness.
7. Urine clear, vomiting persists, diarrhoea.
9. Convalescence halts, urine 200–300 c.c. daily.
15. Urine in excess of normal.

Recurrence 3

24 Aug. a.m. T.N., Q. 1·0 g.; 2 hours later rigor, Hgburia.
26. Urine clear.

Recurrence 4

5 Sept. a.m. T.N., Q. 1·0 g.; 1½ hours later, rigor, fever, vomiting. In 2 hours T. 38°, then 2nd rigor, T. 40°+, urine dark red; 9 a.m. 3rd rigor, urine yellowish-brown.

6. Vomiting, gastritis, enteritis, insomnia, slow convalesence.

Recurrence 5

17. 12 midnight awakes with a rigor, vomiting, sweating, urine dark red; 9 a.m. slight icterus, great weakness, urine clear.

11.30 a.m. rigor, 'oppression,' severe cyanosis, T. 40·5°, P. 80 strong, urine again dark red; 7 p.m. weak, urine normal. Plehn, A. (1896), 27–29.

Patient had been 15 months in East Africa. Apparently 10 attacks (each following quinine) in this period, the first attack 2 months and 3 weeks after his arrival. Koch (1899), 308.

136 patients. 33, 2 or more attacks.

The longest interval between the first and second attack is nine years. Daniels (1901), 58.

Attacks (*réchutes*) subsequent to the first which occur without a malarial reinfection. All attacks which occur outside the endemic zone, and for the most part all attacks which occur even in this zone, not in the endemic–epidemic season.

Attacks (*récidives*) due to a malarial re-infection. Their occurrence coincides almost exactly with the seasonal endemic–epidemicity of malaria. Gouzien (1911), 43 (r.).

14 of 34 cases had previous attacks. 1 previous attack, 7 cases; two, 3; four, 1; five, 1; six, 1; seven, 1. Deaderick (1914), 873.

Some old residents in Africa have passed through 10 or more attacks with impunity. Manson-Bahr (1921), 106.

Cases 28.

One Attack 20.

Two Attacks 5. Intervals in years between 1st and 2nd attacks, $\frac{5}{24}$, $1\frac{1}{6}$, $2\frac{3}{4}$, 6, 7.

Three Attacks 3. Intervals between 1st and 2nd attacks, 3, $3\frac{3}{4}$, ?. Intervals between 2nd and 3rd attacks, 1, $1\frac{1}{4}$, ?. Connal (1922[a]), 5.

Oct. 1919. Invalided from Senegal to France.

24 Oct.–23 Dec. Hgburic attacks (1–4).

17 Feb.–7 May. Hgburic attacks (5–7).

8 May. Hgburia (8), T. 39°, vomiting, subicterus. *Vinum quinquinae.*

19. Hgburia (9), T. 37·4°.

28. Hgburia (10), T. 38·1°.

13–14 June. Q. hydrochloride, then *Pulv. quinquinae* daily.

28. Hgburia (11), T. 39°, subicterus. Discharged. No quinine.

19 Nov. Hgburia (12), T. 39·7°, icterus, vomiting. Spleen +, liver +.

22. Q. ·10 g., Hgburia (13); one hour later, shivering, vomiting, no T. Hamet (1923), 505.

Types of Attack

1. *Abortive*

Vienna. Repatriated soldier.

1.1.1920. *P. falciparum*, T. 38·5°, spleen +, liver +, tender.

23. Fever. Q. 2·0 g. in 4 hrs., icterus, anuria lasting 24 hrs., comatose condition. Chief symptoms, pain in the gall-bladder and splenic regions. Liver +, spleen +. Blood serum: bilirubin ++, haematin traces.

24. Urine 400 c.c., Hgb neg., bilirubin neg., albumen pos., urobilinogen ++, urobilin ++. Sediment: red cell débris ++, haematin masses, leucocytes, epithelium. Q. treatment omitted.

The attack on the 23rd might have been regarded as a liver affection without knowledge of the malaria. The anuria could be explained as a reflex spastic condition. Barrenscheen and Glaessner (1923), 410.

2. '*Afebrile*'

Nyasaland.

Day 1. Max. T. 99·8°.
Day 2. Max T. 99·8°.
Day 3. Max T. 100·4°. Daniels (1901), 69.

1.8.1901. 3 p.m. *P. falciparum*; 4 p.m. Q. 1·0 g. *per os*; 8 p.m. T. 38·7°.
2. 7 a.m. T. 36·8°, blood negative, Q. 1·0 g. *per os*; afternoon, Hgburia slight, T. 37·2°.
3. p.m. Urine clear.
4. Q. 0·25 g.
5. Q. 0·5 g.
6. Q. 0·5 g.
7. Q. 1·0 g. (8 a.m.); afternoon, Hgburia.
8. Urine clears.

T. not above 37° since 2.8.1901. Panse (1902), 22.

Mauritius.

1. Creole aet: 28 complains of bilious gastric and intestinal trouble. Anaemia, sub-icterus, tongue coated, diarrhoea, spleen +, liver +, T.N.

After 2 days in hospital, Hgburia at night, no symptoms, urine clear in the afternoon.

2. ♀ aet: 22, married, complains of nervous trouble, malarial cachexia, T.N. Hgburia at night, no symptoms. Vinson (1909).

3. *Ambulant*

Among old malaria cases in West Africa some of whom had a record of 10–12, 30 or even 34 attacks of b.w.f. rigor is absent, even a slight shiver hardly noticed. Red urine passed, usually quite clear. After 2 hours all is normal again and T. has fallen. Ziemann (1918).

Even in England, one has seen a case who was walking about and was unaware of the fact that he was passing haemoglobin in the urine in quite noticeable quantity. Blacklock (1923), 83.

4. *Anuric*

Vide infra, Micturition.

5. *Haemorrhagic*

Almost complete suppression for 8 days, with constant bilious vomiting and hiccough, and in which haemorrhage from the gums and later from the skin occurred before death. 'Africa' (1914), 19.

25 Oct. 11.30 a.m. Rigors, fever, vomiting, bloody urine a few drops, *P. falciparum*. Great distress, frequent vomiting, conjunctivae injected, pain in loins, gums swollen and bleeding, epigastralgia. T. 102·4°. P. 120. Urine in small quantities, containing red cells and casts. Haematemesis, melaena, haematuria. T. fell to subnormal, pulse slow.

30. Icterus, later delirium and intermittent pulse.

4 Nov. Death. 'Africa' (1915), 70.

6. *Hyperpyrexia*

Day 4. 7 a.m. T.N.; 3 p.m. T. 41°; 4.30 p.m. T. 42° collapse; 5 p.m. death. Plehn, F. (1898), 115.

Each time the drug (Q.) was repeated this symptom was observed, when the drug was omitted the urine was non-Hgburic. The patient died from hyperpyrexia, T. 109°. Marsden (1900), 532.

Hyperpyrexia is not common, though pyrexia is often severe. It occurred after the Hgburic period. It does not seem to be controlled by quinine or antipyretics.

Chart 10. Day 3. Morning. Urine clear. Evening about 10 p.m., T. 106·8°, death (?).

Chart 11. Day 3. Urine clear. Day 5. Lowest T. 104°, highest 107·5° (106·2° on the chart), death. Daniels (1901), 58.

Kindia. French Guiana. Syrian aet: 32 about. Aug. 1905. B.w.f.

22 Sept. 1905. a.m. Q. 0·5 g. in tabloids; 1·30 p.m. Hgburia; 3 p.m. admitted to hospital. Sub-icterus of skin and conjunctiva; 4 p.m. T. 40·1°; 8 p.m. 40·3°. Nausea (without vomiting). Ipecacuanha 1·5 g., abundant vomiting and relief. Abundant drink, caffeine, saline injection, and three saline enemata. 9 p.m. semi-conscious.

23. 6 a.m. T. 40·2°; 2 p.m. 40·8°; 7 p.m. 40·9°. Saline injection and enemata, caffeine 0·89 twice, drinks. 6 a.m.–2 p.m. urine 1000 c.c., malaga colour, involuntary bilious stools (*Taenia* segments), icterus yellowish-black. The shirt, the sheets, the cotton wool used for cleaning the skin are stained yellow. Literally, *he sweats bile*.

24. 6 a.m. T. 40·2°; 9 a.m. 40·4°; 10 a.m. 40·2°; 2 p.m. 40·6°. Urine, night of 23–24 over 1000 c.c., not counting that passed under him. Involuntary stools (a metre of *Taenia*), no urine since the morning, coma; 3.10 p.m. death. Vomiting throughout was rare, icterus intense. Continuous hyperpyrexia. Guillon (1907[a]), 132.

Day 1. a.m. Q. grains 4; 1 p.m. T. 40°, vomited black material like coffee grounds. Much distressed, epigastric pain. Passed red urine, looking like blood. Violent delirium. Face and hands of a markedly brownish-yellow colour. T. rose to 43°, death. Barratt and Yorke (1909[a]), 225.

In ordinary attacks an enormous rise of T. sometimes precedes death. O'Zoux (1911), 121.

Usually an indication of the imminence of death. Never observed by me in Southern Rhodesia. Ross (1932), 228.

Vide infra, Temperature.

7. *Polyuric*

Vide infra, Micturition.

8. *Septic*

Day 1. ♀ 'lying in.' 11 p.m. rigor; 12 p.m. urine, looked like blood.

Day 2. 12 noon. Up to this time, urine 1500 c.c., then 80 c.c., looking like fresh arterial blood, T. 38·7°, P. 110, icterus moderate, gastritis, constipation; 2 p.m. T. 40°+, abundant urine, dark red.

Day 3. Great unrest at night, urine 1000 c.c., dark red, T. 40°, P. 150, short systolic murmur over heart, vomiting. Eruption of purple spots with a vesicular centre on chest, belly and forehead.

Day 4. T. 38·4°, P. 150, urine 500 c.c., yellow-brownish-red, vomiting increasing, patient sinking, *facies hippocratica*, skin dirty grey, urine hardly coloured.

Day 5. T. 38·5°, T. 40·2°, P. 150–160. Petechiae fading, great weakness; 9 p.m. P. 132, extremities ice-cold, covered with sweat, hiccoughing, increasing weakness, death.

P.M. General intense anaemia, an area of red softening in right optic thalamus, spleen +, nephritis, haemorrhagic gastritis, heart degeneration. 39.

The case is one of downright bleeding through the urethra with all the symptoms of a severe septic fever. 55 Plehn, A. (1896).

Vide infra, Icterus, Temperature.

Breath

Day 6 (?). Vomiting and hiccough as soon as anything is given to the patient, foetid breath, the whole body exhaling a repulsive smell. Bérenger Féraud (1874), 167.

During the first week in hospital he was continually nauseated, usually vomiting . . . he became more drowsy, his speech became thick, his breath uriniferous, and his face

more and more oedematous. *Vide* Blood-acidosis, Wakeman and Morrell. Wakeman and Morrell (1929), 169.

Day 4 (?). Anuria. His breath smelt of urine. Wallington (1926–27), 358.

Collapse

1 in 48 cases. Plehn A. (1896). 5 in 43 cases. Plehn, F. (1898).

Complications

Abdominal

Abdominal complications are unduly common, and in my series of cases (70) there were: Appendicitis, 1 (fatal); intussuception, 1 (fatal); gastritis, 4 (1 fatal); cholecystitis, 1 (recovered). In addition several cases of severe colic and obstinate constipation. Carmody (1929), 389.

Anuria

Anuria with consecutive uraemia is the commonest complication. Typhoid and septic complications are those which threaten the heart. Gouzien (1911), 6 (r.).

Bacilluria

Youth aet: 6. German. West Africa.

The urine was extremely scanty, the pulse thread-like, so that I gave the boy up. Improvement set in after a blood-letting of 150 c.c. with subsequent subcutaneous injection of saline 250 c.c.

Next day the urine was much better. Noteworthy was the development of a *B. coli* infection at the same time. Ronnefeldt (1929), 225.

Bed-Sores

Day 13. More or less somnolent, 4 involuntary stools, incontinence of urine, pale, no deposit, bed-sores.

Day 17. Bed-sores almost healed. Bérenger Féraud (1874), 217.

Biliary Obstruction

Stools colourless. The urine is very scanty and of the colour of ink or tar water, and contains much bile, Hgb and albumen. All 3 cases were early fatal. In post-mortems of 2 cases no mechanical obstruction could with certainty be established. Plehn, A. (1914), 1416.

Bronchopneumonia

Cases 36. 2 developed bronchopneumonia. Carmody (1925), 106.

Colitis

Death on day 3. Complications, colitis and ascaridosis of the gut. Rapoport (1928), 70.

Erysipelas

Vide infra, Cutaneous System.

General

Hyperpyrexia (1). Suppression of urine (2). Vomiting attended with extreme weakness (1). All these complications terminated in death. Barratt and Yorke (1909[a]), 175.

Hepatitis and Liver Abscess

Hepatitis is fairly common among those who have previously had an attack of b.w.f. 4 cases of hepatitis among 31 cases of b.w.f. 1871. (Two cases recorded; one some months after b.w.f., the other during the attack.) Bérenger Féraud (1874), 209.

Nephritis

I am inclined to think that the disintegration products of the blood can be excreted without inflammation of the kidney, but in other cases, especially by unsuitable control of the patient, severe nephritis can arise. Such can rapidly take place, and the urine is from the start of normal or raised sp. gr. and contains casts. Or it can occur later when the Hgburia has quite or almost quite ceased. The amount of

urine, which before was perhaps abundant, diminishes, the sp. gr. rises to normal or above, and casts previously absent appear in the sediment. We may in this case speak of a 'Secondary nephritis.' Plehn, A. (1896), 13.

Uncommon. Oliguria, casts and much albumen (in urine) persist after the Hgburia ceases. These usually quickly disappear, but the inflammatory condition of the kidney may only be discovered post-mortem. Plehn, A. (1914), 1416.

Otitis media

Cases 34. Only two with complications. Acute tonsilitis and otitis media not proceeding to suppuration. In the same patient in different attacks. Deaderick (1910), 197.

Pleurisy

Day 2. Icterus, spleen +, liquid stool, urine dark brown. On the following days, embarrassed breathing and pain in the chest due to a dry pleuritic rub. 16.

Dry pleurisy is not uncommon. I have only seen 1 case (of 15). Others in German East Africa record it as not rare, and it no wise worsens the prognosis. 40. Steudel (1894).

Day 6. He maintained the improvement during the day, but had slight incontinence of faeces and urine with pain on micturition.

Day 7. In the afternoon he became distressed and appeared to have considerable pain over the front of the right chest, where pleuritic friction was audible. The application of antiphlogistine gave relief and the condition appeared to resolve. Low, Cooke and Martin (1928).

Tonsilitis

Vide supra, Otitis media.

Wuchereria bancrofti

Day 4. A thick blood film showed *W. bancrofti*. p.m. the parent forms were not found. 'Africa' (1915), 22.

Convalescence

Amblyopia

Rapid and progressive convalescence, but has complained of impairment of vision for some days. Plehn, A. (1896), 43.

Amnesia

Vide infra, Pyuria.

Boils

Perhaps the furunculosis which is seen in various cases during convalescence is due to trophic disturbances; at least it must be recognized that the skin is especially involved during the prolonged and usually profuse secretion of evil-smelling sweat. Steudel (1894), 41.

Bronchopneumonia

Day 11. The patient continued in a weak intensely anaemic condition until day 11, when crepitant râles appeared in both bases of the lungs and spread all over them.

Day 12. During the night an accumulation of mucus in the larynx almost caused asphyxia. Gray (1898), 26.

Constipation

1. Colic, rigidity of abdominal muscles on the right side, acute tenderness. Treatment with antispasmodics, warm enemata, castor oil. Bérenger Féraud (1874), 203.

2. Convalescence may be delayed (more rarely than by diarrhoea), by an actual gastero-enteralgic crisis with obstinate constipation and tender abdominal walls. Gouzien (1911), 6 (r.).

Cystitis

Day 3. Hgburia neg. Convalescence is delayed by the persistence of cystitis, which is evident 3 days later through the appearance of the urine, the ammoniacal smell and the distinct alkaline reaction. Plehn, F. (1898), 141.

Death

7.5. Hgburia.

26. Appetite returned and complete convalescence had set in, when at night, after a huge meal, the patient suddenly cries aloud, with an attack of suffocation—cyanosis—and in a few minutes death, apparently from a lung embolus. Plehn, A. (1896), 33.

Diarrhoea

16 Sept. Hgburia.

8 Oct. Hgburia (recurrence). Some diarrhoea.

15. Convalescence not definitely established.

27. Diarrhoea.

14 Nov. Patient weak, bloody mucus in stools for last 2 days, then the diarrhoea became serious.

1 Dec. Stools purulent, the condition gravely acute.

20. Stools became diarrhoeic again and chronic diarrhoea continues until

1 Jan. when discharged. Bérenger Féraud (1874), 207.

Convalescence may be delayed by an obstinate and foetid diarrhoea, with flatulence and meteorism. Gouzien (1911), 6. (r.).

Dysentery

Urine cleared after two days, but fever continued longer. Convalescence complicated with dysentery. Christophers and Bentley (1908[a]), 211.

Epistaxis

Convalescence was delayed by repeated severe epistaxis. Plehn, A. (1896), 26.

Twice during convalescence we have seen very obstinate epistaxis. Clarac (1898), 74.

Herpes Praeputialis

Herpes praeputialis during convalescence. For some weeks after the attack was free from 'fever.' Daniels (1901), 65.

General

Convalescence is attained in an astonishingly short time provided that absurdly large doses of quinine do not destroy it. The number of corpuscles and the Hgb percentage increase by 20% within 7–8 days, and an increase of 10% in the same time is the rule. Plehn, A. (1896), 58.

23.2.96. Hgburia, painful micturition, constant vomiting, sleeplessness, exhaustion, shivers or has a rigor with every breath of air.

25. Lies passively on his back, with eyes closed and dependent lower jaw. T. 37·2°.

1.10.3. Very slow convalescence. Dempwolff (1898), 160.

In cases of medium intensity one may put at 12 or 15 days the interval between the onset of Hgburia and the date of the first getting up, but convalescence is sometimes very long. Gouzien (1911), 7 (r.).

Indigestion

Convalescence was fairly rapid, but was marked by a great tendency to suffer from indigestion. Christophers and Bentley (1908[a]), 211.

Muscle infiltrates

To trophic disturbance is possibly attributable the peculiar muscle infiltration (extensive infiltration in the upper thigh) in Case 9, unless it were due to thrombosis or embolus associated with the transfusion; Martin (1889)* has described such infiltrates in remittent fever as the site of the malaria. Steudel (1894), 41.

Nephritis

Day 20. T. 38° for some period daily, at short intervals. Icterus has decreased. Albumen and casts have never completely disappeared. To-day T. 40°,

* *Aertzliche Erfahrungen über Malaria der Tropenländer*, Berlin.

parasites positive, great increase of albuminuria. Invalided home in December on account of the kidney lesion. Plehn, A. (1896), 25.

Neuralgia

One patient had a for a long time intolerable neuralgia. Clarac (1898), 74.

1 of 28 cases had three attacks of trigeminal neuralgia in the early stages of convalescence. Connal (1922[a]), 7.

Parotitis

One case had a fatal suppurative parotitis. Clarac (1898), 74.

Pneumonia

Patient aet: 38. Bronchitis for several days, together with some pain in the chest. There were no other signs of pneumonia, and hot applications to the chest relieved the pains. Quinine grains 5 every hour.

8. Hgburia.
9. a.m. urine clear; p.m. T.N.
10. Patient up for breakfast, went to bed at noon with pain in chest.
15. Death from pneumonia. Burns (1900), 1260.

Pyuria, Amnesia, Impaired Cerebration

Pyuria continued for some weeks and there were considerable fluctuations in the blood pressure suggestive of instability of the vaso-motor centre, resulting from the prolonged bulbar anaemia to which he had been subjected. There was almost complete amnesia regarding his illness, and for some time his cerebration and reaction times were slowed. Fairley and Bromfield (1934–35), 315.

Sweating

Convalescence may occasionally be preceded by a short, ill-defined period of critical sweats, azoturia and phosphaturia, and at any rate does not begin definitely with the

cessation of Hgburia, and is not clearly separated from the acute period of the attack. Gouzien (1911), 6 (r.).

Syncope

Syncopal attacks may occur during the course of convalescence. Gouzien (1911), 6 (r.).

Testicular pain

In one case unbearable testicular pain. Clarac (1898), 60.

Tetanus

8 Dec. Hgburia.
16. Convalescent.
20. Following a Q. injection (? date) a scab and sore "as big as sixpence."
21. Acute pain in neck and in the temporo-maxillary joints during the night. In the morning, *risus sardonicus*, swallowing almost impossible.
22. Death.

A case of tetanus had occurred in the same ward a year previously. Clarac (1898), 60.

Cutaneous Eruptions, etc.

Boils

A fortnight before his present illness he broke out in boils one of which assumed a carbuncular character, and gave him much pain. Easmon (1885).

Day 13. Numerous superficial boils on the back.
Day 18. On the left shoulder blade a large boil necessitating a broad and deep incision. The small boils are healing.
Day 28. The large boil is quite clean but others have appeared. Steudel (1894), 22.

15.1.96. Hgburia.
2–21.2. Slow convalescence.
27.2–11.3. Several large boils on the right cheek.

11.3. Incised, pus discharged, patient much distressed and fears an attack of fever. Dempwolff (1898), 158.

Day 12. A restless night. The patient has taken cold during his sleep; he suffers from his stomach and appears to be a little weaker. Swelling of the right cheek with a boil. Gouzien (1900[a]), 69 (r.).

Urine dark for 4 days, and jaundice marked. Severe kidney pain felt, and attack followed by 20–30 boils on the face. Recovery. Christophers and Bentley (1908[a]), 225.

Boils and Carbuncles

10 Aug. B.w.f. Patient suffering from acne and prickly heat. *P. falciparum* pos.

13. Urine clear, anuria, 3–6 c.c. at an urination.

20. Improvement, urine increasing, parasites negative.

1 Sept. An eruption of boils, on back, buttock, flanks, forehead, around the mouth and elsewhere. Gums swollen and bleeding. (Patient had been treated with quinine, and with a mixture of iodine perchloride of mercury and bicarbonate of soda in frequent small doses to combat vomiting.) Later several large carbuncles formed.

12. Carbuncles improved and sloughs separating. Patient less apathetic.

16. Parasites positive. (Q. grains 5 on 8th, 9th and 10th.)

18. Semi-delirium, death. 'Africa' (1915), 16.

Dermographia

F.E. aet: 20. Jérémie, Haiti.

Day 1. Very emotional, tears roll down both cheeks as I talk to him, pallor and flush follow one another, tremor, increased reflexes, distinct dermographia, icterus, vomiting, urine deep red. Naumann (1933), 303.

Dryness

14 June, 1893. Hgburia, somnolent, semi-conscious, frequent vomiting.

15. At night T. rises again. Patient quite unconscious, icterus has increased. Skin flaccid and pale, as dry as leather.

17. Death. Plehn, F. (1898), 113.

Day 9. Sweating moderately, extremely ill, with face a dirty yellow, skin like thin leather, wax-like fingers, motionless body, pulse getting weaker. The patient appeared to be moribund. (Recovery.) Skrodzki (1910), 710.

Ecchymosis

Female, aet: 37. Paris.

Day 2. Isotonic glucose saline 250 c.c. injected into the thigh, a little above a fairly large extensive cutaneous ecchymosis which appears to have arisen spontaneously. In spite of this the anuria is absolute. Achard and Saint-Girons (1912), 751.

Erysipelas

Day 51 (3rd day of relapse). Urine clear, slight icterus, slight vomiting. An erysipelatous swelling of the nose, involving in 2 days the eyelids, then later the head, and especially the nape of the neck. The condition gradually subsided. Bérenger Féraud (1874), 221.

General

Vesicular, bulbous and petechial eruptions have been seen in grave cases. Gouzien (1911), 32 (r.).

Haemorrhagic

Day 5. A haemorrhagic eruption on the forehead, eyelids and around the axillae. Gouzien (1900[a]), 34 (r.).

Herpes

0 of 34 cases. Deaderick (1910), 196.

Day 2. Severely ill, mutters a good deal and has fear of death. Lips dry, some herpes vesicles on the upper lip. Seyfarth (1918[b]), 130.

Day 3. Death. P.M. On the upper lip signs of herpes labialis. Rapoport (1928), 70.

Itching

Day 5. Hiccough has stopped, icterus decreasing, urine none.

Day 7. T. 37·4°, P. 92. Has not slept owing to troublesome itching of the skin, urine normal. Taken into hospital in Australia and still suffered from paroxysmal attacks of itching. Case 14. Schellong (1890), 69.

Day 3. Midnight and 6 a.m., total urine 100 c.c., icterus intense, greenish-yellow. Itching of the face and especially around the eyes. Gouzien (1900[a]), 75 (r.).

Day 7. Urine 120 c.c. by catheter, turbid, yellow, Hgb negative, sediment $\frac{1}{3}$ consisting of leucocytes. Intense itching of skin, death. Van Campenhout and Dryepondt (1901), 78.

Itching is only exceptionally associated with icterus. Plehn, A. (1903), 521.

Scratches or more or less extensive erosions caused thereby are due to the intense itching which occurs in certain cases complicated by uraemia, but icterus itself is not accompanied by itching. Gouzien (1911), 32 (r.).

Cases 49. 9 complained of continual itching. Weselko (1926), 658.

Papular

Day 13. An eruption of small papules on the face, which were still troublesome on day 15. Bérenger Féraud (1874), 217.

Polymorphic

Day 12. On the back a polymorphic, punctiform, papular and pustular eruption. Georgopoulos (1933), 69.

Purpuric

Day 1. 11 p.m. rigor; 12 p.m. urine passed that looks like blood.

Day 3. On the chest, abdomen and forehead, an eruption of violet spots the size of a millet seed to that of a lentil, with central vesicular miliaria-like vesicle. Plehn, A. (1896), 40.

One patient had purpura. Deaderick (1910), 197.

Day 3. Over his abdomen, shoulders and elbows there were dark purpuric blotches. (Death.) Fletcher (1914), 41.

Pustular

Day 14. The skin is covered with a red pustular eruption and little petechiae 1 mm. in diameter. Complains of intolerable itching. Death. van Campenhout and Dryepondt (1901), 71.

Urea

Day 12. The condition is worse. Distressing vomiting of bilious matter mixed with some clotted blood. Icterus has quite gone, the skin has a dirty livid colour and there are urea crystals on it. No urine. Plehn, F. (1898), 118.

Urticaria

Day 5. During the night there has appeared a generalized urticarial rash of large irregular patches of a livid leaden colour with a raised edge. Blistered areas were covered with a greyish leaden exudation with some vesicles filled with a brownish serum at the edges. In the evening the rash had almost com-

pletely disappeared. Day 6. 1 a.m. death. Pellarin (1876), 191.

Day 3. Urticarial rash over face, body and limbs. Brem (1906), 1904.

El Centro, Colombia, S.A.

Admitted with severe *P. falciparum* and *P. vivax* infection, urticaria following Q. administration. B.w.f. began on 3rd day after adrenalin. Paterson (1922–23), 542.

Cyanosis

Cases.	Present.	No record.	Authority.
32	1	31	Bérenger Féraud (1874), 173.
48	4	44	Plehn, A. (1896), 29, 30, 33, 37.
43	3 (Lividity)	40	Plehn, F. (1898).
9	3	6	Fairley and Bromfield (1934–35).
11	4	7	Amy (1934, 1935).

Day 5. Patient much exhausted. Cyanotic hue of the face; respiration, 'anxious,' jerky.

Day 6. The cyanotic colour has given place to an earthy one. Bérenger Féraud (1874), 174.

Recorded in 3 of 9 cases.

1. Day 2. The nails were cyanosed and the skin yellow. 150.
2. Day 5. Dyspnoea, cyanosis, restlessness. One of the peculiar features of the illness was the leaden grey colour of the skin and mauve tinting of the lips and ears. 152. *Vide* Methaemoglobin.
3. Day 4. The patient was collapsed and very jaundiced, the lobes of the ear were mauve and the nails a leaden grey. 154. Fairley and Bromfield (1934–35).

Death

Causes

1. Asphyxia of cardiac origin.
2. Intravascular clotting in the main arteries.
3. Exhaustion and coma. Barthélemy-Benoit (1865), 219.

Day 3. The pulse stopped before the breathing. Crosse (1892), 77.

1. *Heart failure* in febrile stage (2). 116.
2. *Anuria* through auto-intoxication—acute inflammation and Hgb infarcts of kidney (2). 119.
3. *Anuria* and *thrombus formation* in heart (1). 121.
4. Thrombus formation in heart, during transient anuria (1). 123.
5. Kidney lesions (2). 125, 127. Plehn, F. (1898).

There are three main causes of death: suppression of urine, cardiac failure and hyperpyrexia. 56.

Cardiac failure is common. It has in several cases been the cause of death as a result of slight exertion. 58.

Severe case followed by acute lobar pneumonia and death on day 7 (?). 75. Daniels (1901).

Cases 9. Anuria 2. Anuria (dyspnoea) 2. High fever 2. Obstinate vomiting, fear of death 1. Hypostatic pneumonia 1. Heart failure 1. Panse (1902).

Cases.	Deaths.	Uraemia within 48 hours.	Uraemia after 48 hours.	Toxaemia within 48 hours.	Toxaemia after 48 hours.	Asthenia after 48 hours.
50	11		8	1		2
8	3		1	1		1
35	3		1			2
8	0					
5	1			1		
6	0					
61	16	4	4	4		4
19	10		4	2		4
4	1		1			
196	45	4	19	9	0	13

The cases were treated in various ways.

Q. treatment *per os*: Cases 93. Deaths 17. 18%.

Q. treatment hypodermic: Cases 19. Deaths 1. 5%.

Q. little or none: Cases 61. Deaths 16. 26%. Shropshire (1903), 604.

Day 9. 7 a.m. Urine 8 c.c., subsequently none; 4 p.m. very severe dyspnoea; 7 p.m. patient died during an attack of dyspnoea. Barratt and Yorke (1909[a]), 218.

Cases 10 Suppression 2. Exhaustion 8. Deaderick (1910), 198.

Heart failure is a common cause of death among alcoholics with affected myocardium. 28 (r.).

Cases 32. Uraemia 25. Hyperpyrexia 1. Collapse 1. Myocarditis 2. Secondary infection 1. Suppurative nephritis 2. 77 (r.). Gouzien (1911).

Cases 35

Suppression of urine 13.

Severe vomiting 10. (Excluding group 1.)

Continued fever 8. (Excluding groups 1 and 2.)

Parasitic infection 4. (Not implying non-infection in groups 1, 2, 3.) Deeks and James (1911).

Malarial infection. Among 20 deaths that I have seen associated with b.w.f. 5 of them or 25% were due to pernicious malaria infections. Brem (1911), 155.

Cases 54. Patients 45. Deaths 15. Réunion.

1. Syncope the 4th day after cessation of Hgburia. Patient had Hgic stools.

2. Haematemesis 6th and 21st hour.

3. Uraemia.

2. Progressive weakness 5th and 6th day after cessation of Hgburia.

3. Intense icterus.

2. Combination of fever, Hgburia and icterus.

2. Unknown, in 7th and 12th hours.

7 cases during Hgburia, 8 cases after Hgburia. In ordinary attacks an enormous rise of T. sometimes precedes death. O'Zoux (1911), 121.

Day 3. Blood urea 0·5 g. per 1000 c.c.

4. Blood urea 2·04 g. per 1000 c.c. Urine 17 c.c. Urea 1·5 g.

5. Urine 5 c.c. Urea 6·2 g.
6. Death. Urine 5 c.c. Urea 6·2 g.

Anuria is insufficient to account for death, as when anuria has lasted 8–10 days, it has not had time to induce uraemic symptoms which characterize fatal anurias. But it may have played a part in causing the retention of toxins, inducing prostration, the cardiac failure, to which the patient succumbed. Achard and Saint-Girons (1912), 756.

Distension of the abdomen, hiccough and suppression of urine characterized 5 fatal cases. Connal (1916), 13.

Relapse on day 6. Death before Hgb appeared in the bladder, but p.m. the tubules of the kidney were distended with freshly excreted haemoglobin-stained material. Gaskell (1920), 11, 13

Anuria: In 30 of 36 fatal cases.

Complete anuria 18. A few ounces daily 10. A fair excretion 2. Phear (1920), 5.

Thrombosis or embolism of the pulmonary artery produced a fatal termination in two cases Dudgeon (1920), 221.

Cases 26. Deaths 8. Nigeria.

Suppression of urine 4. Cardiac failure 3. Hge. from a duodenal ulcer 1. Connal (1922[b]), 10.

Cases 83. Deaths 14. Uganda.

Suppression 7. Uraemia 2. Heart failure 5. MacMillan (1923), 51.

Deaths 7. Uremia, 4. Myocarditis and nephritis 1. A complicating malaria 1. Polyuria with an output of large quantities of urine 994 to 2272 c.c. 1. United Fruit Company (1924), 69.

Cases 70. Deaths 23. Uganda.

Cardiac failure 18. Suppression and cardiac failure 2. Suppression 2. Uraemia following suppression 1. MacMillan (1925), 59.

Cases 81. Deaths 22. Uganda.

Cardiac failure 17. Suppression and cardiac failure 2. Suppression and uraemia 2. Exhaustion 1. MacMillan (1926), 69.

The main causes of death in b.w.f. are (1) syncope, (2) acute haemolysis, (3) suppression of urine, (4) hyperpyrexia, and (5) asthenia. Low, Cooke and Martin (1928), 645.

Causes of death.	Cases.	Deaths.	Authority.
	67	28%	
Suppression of urine . . .	14%	80%	Shelley
Coma	10% +	84%	(1931–32),
Cardiac failure . . .	2	2	135.
Severe anaemia . . .	1	1	

Acidotic coma. 61½ hours from the onset, death in acidotic coma, with severe dyspnoea, R = 50. Fairley and Bromfield (1934–35), 154.

Day of Death

Day.	Deaths.	Day.	Deaths.	Day.	Deaths.	Day.	Deaths.
1	1	8	13	15	2	21 +	3
2	9	9	4	16	1		
3	19	10	5	17			
4	25	11	4	18	1		
5	21	12	4	19	1		
6	5	13	3	20			
7	7	14	5	21			
Week 1	87	Week 2	38	Week 3	5	Week 3+	3
	65%		28%				

The protocols are given in Appendix 6.

G. Oeconomou records the case of a priest the subject of haemorrhoids who whenever he took Q. (especially during the last weeks of his life) experienced a vague sense of malaise; one day taking Q. grains 15 at a single dose, passed blackwater and 3 hours after taking the dose yielded up the ghost. Cardamatis (1902[a]), 42 (r.).

Day 43. Double tertian parasites.

Day 44. 8 a.m. Q. 0·5 g. subcutaneously; 10 a.m. rigor, shortly after Hgburia, death 12 hours later. Panse (1902), 18.

Death may occur in 12 hours, or in about 24 or 36, but also later, 4th or even 7th day. Seyfarth (1918[a]).

Death occurred during Hgburia in 6 of 8 cases. Connal (1922[a]), 9.

In anuria death may occur as late as 8th, 10th or 11th day (2 cases) after the development of the condition; . . . is usually described as occurring between the 7th and 10th day. Ross (1932), 216.

Of 21 deaths from anuria, 8 occurred in the first week, 9 in the second week (5 on the 10th day) and 3 in the third week and 1 unspecified. *Vide supra*, Anuria.

Premonition

Day 2. 7 a.m. Q. 2·0 g. Immediately T. which had fallen goes up to 39·2°. 11 a.m. P. very weak and intermittent. R. laboured. Noon. Extreme anxiety, restlessness and feeling of death. Tinnitus, stupor. (Recovery.) Plehn, F. (1898), 128.

8 a.m. Q. 0·5 g. 10 a.m., extraordinarily violent rigor of half an hour duration, pains in the limbs, vomiting, restlessness, great weakness and premonition of death; 10 p.m. death. Koch (1899), 310.

Day 7. At times he squinted and had cramps in the legs and shoulders, and he felt that he was dying; complained a good deal of heaviness of his limbs, death day 9. Crosse (1892), 73.

Day 6. 1 a.m. marked feeling of death; 3.15 a.m. after short loss of consciousness, death. Panse (1902), 20.

The fear of impending death was present in one case which recovered. Connal (1916), 11.

Day 1. Condition on admission was very grave, and patient had feeling of impending death. Recovery. United Fruit Company (1924), 65.

Death rate

Cases.	Deaths.	%.	Authority.
61	15	24	Barthélemy-Benoit (1885).
86	21	24	Ibid., 387.
268[1]	66	24	Béranger Féraud (1874), 235.
642	158	24	Cochrane (1885), 598.
14	2	14	Crosse (1892).
53	5	9	Plehn, A. (1896), 54.
35	15	43	Ibid.
46	8	17	Plehn, F. (1898).
17	5	29	Koch (1899).
40 (1894–6)	9	22	Gouzien (1900[a]), 90, 60.
53 (1897–1900)	0	0[2]	Ibid.
16	4	25[3]	Van Campenhout and Dryepondt (1901).
35	9	26	Panse (1902).
21	1	5[4]	Broden (1906).
12	7	60[5]	Ibid.
20	2	10	Da Costa (1906).
185	46	25	Christophers and Bentley (1908[a]).
20	4	25	Barratt and Yorke (1909[a]).
1347*	329	24[6]	Cardamatis (1910).
1134*	83	7[7]	Ibid.
133	27	20[8]	Deeks and James (1911).
100	9	9[9]	Ibid.
92	18	10[10]	Gouzien (1911), 80.
80	2	2·5[11]	Ibid., 99.
181	37	20	Graham (1912).
136	36	26	Phear (1920).
146	34	23	Nigeria (1915–22).
1014	201	19	Uganda (1928).
489*	105	21	Stephens (1929).

1. 286 elsewhere. 2. Saline treatment. 3. Q. if parasites found. 4. Q. if parasites found. 5. Q. 1·5–1·8 g. injected daily. 6. Q. treatment. 7. No Q. treatment. 8. B.w.f. prior to admission. 9. B.w.f. subsequent to admission (Q. in both categories). 10. Various parts of W. Africa; in some cases no drugs available. 11. No quinine. Saline treatment, etc.

* Compiled from the literature.

Death rate in first and multiple attacks

One Attack.	Deaths.	%.	Multiple Attacks.	Deaths.	%.	Authority.
190	65	34	56	11	20	Col. Office (unpublished).
20	8	40	14	2	14	Deaderick (1910).
85	14	16	17	6	25	Hatori (1914–15), 654.
119	41	34	56	12	23	Ross (1932), 88.
414	128	31	143	31	21	

Death Symptoms

Babinski

21 May. Patient in agonal condition. Tendon reflexes almost unobtainable. Babinski reaction on the left side. Death. Franchini and Maggesi (1925), 98.

Coma vigil

Day 2. Pulse filiform, epigastric tympanitis, restlessness, coma vigil, death (7 a.m. day 3). Pellarin (1876), 212.

Kernig's sign

Comatose on admission. Retraction of neck and positive Kernig's sign. Deeks and James (1911), 83.

Opisthotonus

Kaiser-Wilhelmsland.

In 2 (of 3 fatal) cases the patients were from the beginning unconscious and reactionless, breathing quick difficult snoring, with foam from the mouth, coma ending directly in death which occurred in opisthotonus with passage of faeces and urine. Schellong (1889), 721.

1 Sept. 9–14 h. prolonged rigor, Hgburia; 15 h. T. 39°; 16 h. 41·5°. Covered with sweat. Cries out incoherently. His limbs at one moment in convulsive movements, at another flexed. It was necessary to press heavily on the fore-arm to expose the fold of the elbow for puncturing the vein. 17 h. head hyper-extended, eyes rolling, jaws clenched, body in opisthotonus. Reflexes extremely active, the patient has spasms when touched or stroked. Later a nervous dyspnoea sets in with no definite rhythm, face cyanotic, and conjunctivae sub-icteric. Involuntary urine and faeces, in fact a pernicious cerebro-meningeal attack. 18·30 h. death. Ott (1932), 537.

Stertor

Day 15. 2 p.m. The patient is unconscious, breathing stertorous, pulse small and intermitting. No urine. Plehn, F. (1898), 119.

Defecation

Constipation

Cases 12. Condition of bowels at onset: Constipation 5, regular 2, open 3, loose 2. Brem (1906).

Constipation is the rule at the onset, but more or less frequency results from the early use of purgatives. Gouzien (1911), 27 (r.).

Diarrhoea

Day 1. a.m. Rigor lasting until noon. In the evening Hgburia. During the day a dozen perfectly liquid stools. 126.

21 Nov. Hgburia. Calomel 1·0 g. in 5 doses.
22. Two motions.
23. Hgic stomatitis.
24. Frequent diarrhoeic stools. Slight tenesmus.
8–11 Dec. Numerous bloody stools. Death. 157.

Patient has taken Q. 4·0 g., calomel 2·0 g.

5 Oct. Stomatitis, foetid breath, vomiting, hiccough.
6–7. Frequent foetid stools.
9. Death. 166.

During the night rigor and fever, in the morning Hgburia.
1 March. Bilious vomiting, very frequent bilious stools.
2. Frequent bilious stools making it difficult to give enemata.
14. Diarrhoea still continues. Recovery. 172.
Bérenger Féraud (1874).

Case 13. Day 1ª. Profuse sweating, incomplete fall of T., nausea, profuse diarrhoea, Q. 1·0 g.

Case 14. Day 1. Q. 1·25 g., in spite of the pronounced Q. effect, the attack returns again at midday with great intensity, violent vomiting, profuse diarrhoea, and 'bloody' urine. Schellong (1890), 68.

20 Feb., 94. B.w.f. directly after considerable loss of blood from a confinement. Urine 20–40 c.c. passed at a time. Profuse non-hgic diarrhoea. 148.

7 June. Hgburia. T. 39·5°, intense icterus, headache, slight stupor, diarrhoea, tenderness of the abdomen. 154.

30 Aug. B.w.f. Rigor, headache, backache, dyspnoea, slight delirium, icterus moderate, profuse diarrhoea. 158. Plehn, F. (1898).

4 Jan. About midnight b.w.f. Epigastralgia, lumbago, colic.

10. Enema castor oil, 50 g.

11. Bilious vomiting, urine 100 c.c., continual nausea, 3 motions.

14–20. Profuse diarrhoea (about 8 motions a day) (dysentery last year), obstinate vomiting, constant insomnia. Gouzien (1900[a]), 79 (r.).

Cases 33. Onset with diarrhoea 2. (Cases 2 and 29.) Christophers and Bentley (1908[a]).

Day 1. T. +. Patient suffers from vomiting and diarrhoea, has painful cramps in muscles of legs, Q. grains 5.

Day 2. Restless. 10 a.m. Q.HCl. grains 6; 11.15 a.m. restless, T. 103·5°; 12 noon, urine 150 c.c., very dark chocolate-coloured. Spectroscope, Hgb —. Barratt and Yorke (1909), 178.

Day 1. Hgburia, rigor, vomiting, icterus and diarrhoea.

2. Vomiting and diarrhoea troublesome. Bladder empty.

6. Nephrotomy.

7. Abdominal distension and hiccough troublesome, diarrhoea recommenced.

9. Death. 'Africa' (1914), 38.

Cases 39. Diarrhoea 3. No record 36. Connal (1916), 11.

Day 6. Patient worse, great weakness, restlessness, anxiety. Heart sounds clear, soft. Icterus deeper, 2 fluid motions. Vomiting somewhat less. Has

passed a few drops of urine. Day 7. Death. Seyfarth (1918[b]), 134.

Day 1. Developed tenderness in the vicity of the spleen and diarrhoea. Fairley and Bromfield (1933–34), 147.

Diarrhoea, haemorrhagic

4.10. 8 a.m. Q. 1·0 g.; 11 a.m. violent rigor lasting 4 hours, T. 41·3°, air hunger, oppression, and simultaneously profuse bloody vomit, and much blood in the numerous diarrhoeic stools. 10 hours later T.N. The bloody urine, vomit and motions last for 3 days. Great weakness. Plehn, A. (1896), 46.

26 Nov., 93. Hgburia.

27. Anuria, bloody vomit and bloody diarrhoea. Plehn, F. (1898), 116.

4 patients had frequent motions; in 3 the colour of the faeces was normal, in the fourth bilious.

4 patients had bloody stools, lasting 3–6 days. Hge. from the gut is often combined with haematemesis. Kohlbrugge (1899), 103.

Day 5. Severely ill, groans and mutters, slight icterus, vomiting less; 3 diarrhoeic blood-stained stools, mixed with some blood, strongly faeculent. Seyfarth (1918[b]), 134.

Dysentery

Gastro-enteritis with dysenteric symptoms appear to have occurred in several cases. This I have not seen. Daniels (1901), 56.

Flatus

Day 2 (?). Noon, the bowels were well opened; evening, complained of colicky pains and flatus; towards night, diarrhoea and vomiting less severe.

Day 3. Soda and peppermint have relieved the troublesome feeling of colic. Crosse (1892), 69.

Incontinence

23.9. Hgburia.

8.10. T. 35·6°, cold extremities. Afternoon, rapid loss of strength, cold limbs, facies hippocratica, involuntary motions. Death. 42.

Day 2. T. 40·3°. Continuous vomiting, some drops of bloody black urine passed with the involuntary motions. 49. Plehn, A. (1896).

Day 10. A very restless night. Incontinence of the gut. Can only retain a nutrient enema for a few minutes. He complains and mutters continuously of acute pain in the body. Bloody discharge from the mouth. Day 12. Death. Plehn, F. (1898), 119.

Involuntary defecation occurred before death (Case 3).

4 Jan. Hgburia.

7. Hgburia neg. For 3 days the patient was critically ill. He was restless, irrational, vomiting almost incessantly, and had involuntary passage of feces and urine (Case 5). Brem (1906).

26. Hgburia.

30. Very weak, P. 120, R. 36; 6 a.m. bed saturated with urine, and faeces had also been passed in the bed; 7.30 p.m. death. 'Africa' (1914), 21.

30.10.17. Completely delirious on admission. Incontinence of urine and faeces.

31. T. 37·5°. P. 110. R. 30; deep, stertorous. 4 p.m. death. Seyfarth (1918[b]), 131.

Melaena

Day 3. Bowels moved by the oil (castor). Discharges black and tarry. Cochrane (1885), 594.

Day 1. Bowels moved by an enema; motions were quite black and mixed with a darkened fluid, evidently blood. Crosse (1892), 67.

Day 4. *Facies hippocratica.* Skin dirty grey-yellow, lips bloodless, 2 motions said to be deep black.

Day 5. Death. Plehn, A. (1896), 40.

Not uncommonly there is diarrhoea at the beginning of the attack, and in rare cases, owing to the passage of Hgbous serum into the gut, it has a deep black tar-like appearance. Plehn, F. (1898), 108.

Day 1. B.w.f. this morning, vomiting incessantly, icterus, T. 101·6°. He had considerable diarrhoea; during the day six black tarry stools; stated that he had been passing similar stools for the past 3 or 4 days. Barratt and Yorke (1909[a]), 235.

10.11. 10 a.m. T. 103·6°. Vomiting during the day, thirst, nausea, pains in the back. Three dark liquid motions. Urine quite clear, albumen a trace.

11. 2 p.m. T. 104°, Hgburia. A large quantity of urine was passed but with considerable straining. Frequent motions containing both bile and haemoglobin.

12. Vomiting and diarrhoea persistent.

13. Death. 11.

20. Fever and diarrhoea.

21. 3 a.m. Hgburia, vomiting, rapid pulse, laboured respirations. Profuse diarrhoea throughout; dark foul stools containing latterly blood and mucous shreds.

25. Death. 63. 'Africa' (1914).

Case 16. Epistaxis and melaena are noted as 'complications.' Arkwright and Lepper (1918[b]).

Day 1. A black diarrhoeic stool. Death in 41 hours. Parrot (1921).

Day 3. 3.30 p.m. Dyspnoea with grunting expiration and melaena. Fairley and Bromfield (1934–35), 151.

Definition

Une pyrexie qui, sans considération du type et pouvant les revêtir tous, présente pour caractère essentiel et souvent unique les symptômes prononcés et persistants de l'état bilieux : ictère, vomissements, selles, urines caractéristiques de cet état, et pour caractères graves les phénomènes adynamiques, hémorrhagiques et autres, pouvant être attribués à une alteration profonde du sang et des solides. Dutroulau (1868), 301.

La fièvre bilieuse mélanurique est une pyrexie paludéenne à type variable (intermittente, rémittente ou semi-continue) caracterisée : 1° par des vomissements bilieux verdâtres abondants et persistants; 2° par une coloration ictérique de la peau et de tous les tissus; 3° par une teinte brune ou noirâtre très—remarquable des urines qui frappe et malade et médecin tant elle est insolite et accentuée.

La réunion du second et du troisième caractère est pathognomique; elle a pour diagnostic une valeur infiniment plus grande que le premier qui se rencontre dans une grande quantité d'accès paludéens simples, gastriques ou bilieux très-différents de la maladie qui nous occupe. Bérenger Féraud (1874), 1.

Cette fièvre a pour caractères :—

1°. Le type intermittent ou rémittent habituel;

2°. L'association de symptômes bilieux vrais à certains phénomènes qui relèvent de l'hémaphéisme : un ictère ordinairement intense, très précoce, apparaissant dès le début de l'atteinte, en même temps que des urines fortement albumineuses, rouges ou noires, n'offrant pas la réaction des pigments biliaires mais celle de l'hémoglobine;

3°. Une médiocre tendance à l'état typhique, une évolution rapide, dans les cas graves, qui se terminent le plus souvent par collapsus ou par intoxication urémique;

4°. L'éclat en certaines régions paludéennes et seulement

chez certains sujets, déjà soumes à l'influence malarienne créoles, acclimatés, ayant éprouvé antérieurement des accès de fièvre intermittente. Corre (1883), 146.

B.w.f. is an *accident* that can arise under the *influence* or through the *shock* of numerous causes singly or in combination, when the action takes place in a *terrain* slowly prepared by a *malarial infection*, the latter being contracted in an *endemic-hemoglobinuric terrain*. Gouzien (1911), 54 (r.).

Diagnosis

Although I have observed many points of analogy between these two diseases, I will follow M. Lebeau, and until my colleagues in Madagascar furnish us with new data, especially from autopsies, we will not venture to assert that there was an epidemic of yellow fever at Mayotta, but we can say that there was an epidemic of *bilious fever, haemorrhagic*. Le Roy de Mericourt (1853).

Some physicians were led to consider it identical with yellow fever, others a simple variety of it. These are the opinions that appeared to prevail formerly, of which Pugnet was one of the chief supporters. Pugnet. Pellarin (1876), 86.

Irregular heart action and loud murmurs over the orifices generally permit with great certainty of a diagnosis of thrombus formation. 215.

Blackwater fever.	Yellow fever.	Authority.
1. Icterus develops in a few hours after the onset of fever and quickly deepens	Icterus first appreciable in 2–3 days	Plehn, F. (1898), 182.
2. Haemorrhages a rare symptom	A very common symptom	
3. Very rare	Blood shot conjunctiva common	
4. Very rare	Bloody vomit common	
5. Hgburia	Bloody urine very rare	

Malarial Hgburia.	Quinine Hgburia.	Blackwater.
1. Hgburia	Symptoms resemble those of an attack of b.w.f., but are not so acute	1. Hgburia
2. Fever		2. Fever
3. Rigor		3. Rigor
4. Vomiting	Jaundice slight or absent	4. Vomiting
5. Prostration		5. Intense weakness
6. Anaemia		6. Anaemia
Negative. Rarity of severe jaundice		*Additional.*
		(*a*) Anorexia
		(*b*) Headache
		(*c*) Pains, back and legs
		(*d*) Nausea
		(*e*) Diarrhoea
		(*f*) Thirst
		(*g*) Constipation
		(*h*) Jaundice
		(*i*) Hyperpyrexia
		(*j*) Coma

From a study of this table of differential aids, one must conclude that although it may in the future be possible to distinguish accurately between a malaria, a quinine and a blackwater Hgburia, this cannot by such aids be done to-day. If b.w.f. is a disease which presents itself in an acute form, and in an acute form only, then it is, indeed, a disease *sui generis* and incomparable with any other known disease. Blacklock (1923), 81.

Quinine Hgburia

1. Black urine in all cases follows the first taking of Q.

2. The attack never occurs later than 1 h. to 1½ h. after Q.

3. Recurrences occur solely after complete elimination of Q., and can certainly be averted by giving Q. while it still exists in the body.

4. There is leucopenia and monocytosis, or even a normal blood in non-malarials, while in b.w.f. there is a leucocytosis.

5. Hgbaemia is absent in Q. Hgburia, always present in b.w.f.

6. The red-cell resistance is always feeble in Q. Hgburia, but in b.w.f. (10 cases) there is no lowered resistance. Manoussakis (1931).

Dysphagia

Day 7. 1 a.m. effortless bilious vomiting, great prostration, skin hot and burning, unconscious for 1 hour and a quarter, P. 140, *subsultus tendinum*, trismus, dysphagia; 1.45 a.m. death. Bérenger Féraud (1874), 196.

1. 4th day of attack, prostration greater, continual somnolence, high T., tongue coated and dry, tremors of lips and hands, speech embarrassed, involuntary micturition, dysphagia. 25.

2. 6th day of attack, delirium increases in the evening and the temperature is higher. A little dysphagia. 8th day. Deglutition is easier. 31. Gouzien (1900[a]) (r.).

Epigastralgia

Vide infra, Pain.

Epistaxis

7 March. Appears to be beginning convalescence.
8. Epistaxis this morning rather difficult to control.
9. A fresh rather profuse epistaxis . . . considerable anaemia and weakness.
20. 10 a.m. slight epistaxis. Syncope in the evening.
21. At night slight epistaxis.
22. Two not very profuse epistaxes. . . . A good night; the patient was able to rest. 175.

11 Sept. Fever and rigors, Hgburia.
14. Persistence of icterus and vomiting.
15. Epistaxis in the morning, vomiting ceased about mid-day, urine clear.
16. No repetition of the epistaxis. 215.

15 Feb. Rigor lasting 2 hours, icterus developing rapidly all over the body, urine blackish like coffee, bilious vomiting.
24. Patient daily improving, urine normal.
20 March. 'Tamarin, fer, rhubarbe deux paquets. Potion: extrait de quinquina: sulfate quinine, 2 gr., 4 p.m. Fever, prolonged rigor, urine black scanty.

23. Two slight attacks of epistaxis during the day.
25. 3 a.m. slight epistaxis. 221. Berénger Féraud (1874).

Day 4. Patient's nose bled this afternoon.
Day 11. Some epistaxis to-day. Crosse (1892), 86, 87.

28.12.94. Day 10. Red cells 2.57 m., Hgb 33%.
At the beginning of January 1895, convalescence was on several occasions delayed by severe epistaxis, causing a transient fall in the Hgb value. Plehn, A. (1896), 26.

Day 5. Patient still better in the afternoon, except for the headache, which persists. In the evening profuse epistaxis, which immediately relieved the headache and brought down the temperature, which showed a tendency to rise.
Day 6. Complete apyrexia; giddiness has gone, a fresh but slight epistaxis. 16 (r.).

A very common symptom, estimated by Bérenger Féraud (1874), 140, to occur in a $\frac{1}{5}$th or $\frac{1}{6}$th of the cases. It rarely appears before the 5th or 6th day, and may be considered a favourable sign. Gouzien (1911), 29 (r.).

Day 9–13. Troublesome attacks of epistaxis accompanied by severe headache, and possibly associated with the jaundice, which by this time was well marked. Owen and Murgatroyd (1928), 503.

Gall-stones

Gall-stones are of frequent occurrence in patients who have suffered from blackwater fever, or severely from malaria . . . without exception composed entirely of calcium bilirubinate, whereas cholesterin-stones were the variety recovered from the majority of cases free from such history. Ross (1932), 229.

Vide supra, Biliary obstruction, and *infra*, Sequelae. Chotelithiasis.

Gastritis

Among the regular accessory symptoms gastritis merits consideration. It favours the acute vomiting, especially during anuria. Enteritis is not so common. Plehn, A. (1903), 529.

Gingivitis

Day 3. Great weakness, P. 102–106, R. 24–26, skin less hot, a powdery condition of the gums, some dry white crusts on the lips. Case 2. Pellarin (1876), 190.

With the Hgburia, he had also bleeding from the gums. Dutt (1916), 460.

Sub-acute type of haemoglobinuric fever. The tongue was pale and coated, gums showed gingivitis and bled easily, and there was a fetid odor to the breath. Aguilar (1926), 63.

Vide also Aetiology. Quinine. Short intervals. Tomaselli.

Haematemesis

Pernicious type. (Western Equatorial Africa.)

Haematemesis is frequently copious, but the characteristic black vomit of yellow fever is absent. . . . The tongue and lips are black, vomiting continues, and Hge from the gums, mouth and back of the throat breaks forth in addition to the haematemesis. Connolly (1898), 883.

Hges are not a usual feature of the disease, but occur in some cases. The commonest form is epistaxis, but in two there was haematemesis, and in one Hge from the bowel. Daniels (1901), 56.

Dutch East Indies. Hges from the gut lasted 3–6 days. They are often combined with haematemesis. Kohlbrugge (1899), 103.

Haemoptysis

2. 8. 28. Urine 308 c.c., suppression threatening. Bicarbonate of soda 150 grains, water 1 pint, I.V.

3. Suppression complete (confirmed by catheter), 3 pints of solution given I.V.
4. Urine 392 c.c. 2 pints of solution, I.V.
5. Urine 870 c.c. 1 pint of solution, I.V.
6–8. Recurrent attacks of haemoptysis, moist râles at both bases, ascites and some generalised oedema.

For the next fortnight drowsy, condition resembling a severe uraemic toxaemia; jaundice slight, convalescence slow. Owen and Murgatroyd (1928), 504. Yorke, Murgatroyd and Owen (1930), 339.

Haemorrhages

Day 2. High fever, icterus, black urine scanty, vomiting infrequent. A red patch on the left upper eyelid as big as a 50-centime piece. Red spots as big as a lentil on the left cheek and chin not disappearing on pressure. 51.

Day 4. Incontinence of faeces and urine, vomiting of reddish mucous matter, 5 p.m. death. Foncervines (1873), 51.

Cases 48.

Hges occur especially in the pleurae, stomach and intestine. In the pericardium (1), subcutaneous tissue (1), optic thalamus (1), retina (1). Plehn, A. (1896), 16.

Day 14. Complains of severe pain in the body. Bloody flow from the mouth.
Day 16. Death. P.M., bloody sordes on lips. Plehn, F. (1898), 119.

Cutaneous and mucosal Hges, and Hges into the stomach and other organs occur. Seyfarth (1918[a]), 272.

El Centro, Colombia, S.A. B.w.f. began on 2nd day after Q. grains 30. Profuse Hge from stomach and bowels. *P. falciparum* ++. Death. Paterson (1932–33), 542.

Heart

Blood pressure (S/D)

Day.	Case 1.	Case 2.	Case 3.	Case 4.	Case 5.	Case 6.	Case 8.
1	80/50	100/66	126/72	108/52	138/90		108/55
2					110/75	90/40	
3						80/46	
						108/52	
	R.	R.	D.	R.	R.	D.	R.

Case 7. Day 9. The veins were distended, the larger arteries such as the carotids and brachials visibly pulsated with each heart-beat and a peculiar thrill was evident to the palpating finger. The B.P. S./D. = 132/56. Fairley and Bromfield (1934–35), 313.

Cardialgia

1. Onset of attack with cardialgia, precordial distress, agitation, vomiting, diarrhoea. 42.

2. Severe cardialgia at the time of the rigor. 42.

3. 12 noon rigor, scanty urine, the colour of venous blood, cardialgia, precordial distress (angst). 44.

4. Precordial distress and cardialgia accompany the rigor, initiating the b.w.f. attack. 47. Plehn, A. (1896).

Murmurs

Day 7. Diarrhoea continued, pulse dicrotic, a loud systolic bruit over the pulmonary area; the patient complained of occasional palpitation. Crosse (1892), 94.

Day 10. 6 a.m. P. 90, stronger, heart dulness not increased, 1st sound very soft, 2nd sound accentuated at the apex, double at the base. 49.

Day 8. Patient of a yellowish livid cyanotic colour, distressed by most acute dyspnoea, giving the impression of cardiac asthma and compelling the patient to sit bolt upright. No increase of heart dulness. Over the orifices, indistinct systolic bruits, apparently anaemic bruits. 30.

Day 3. Skin a dirty olive grey, lips scarcely coloured, great weakness, T.N., P. 120, anaemic murmurs, heart itself normal. 36. Plehn, A. (1896).

Day 6. Distinct apical systolic bruit, P. weak intermitting.

Day 8. Death. Plehn, F. (1898), 122.

Vide Prognosis.

Case 11. Day 3. First sound not sharp. Distinct murmurs over each orifice, most distinct at the apex.

Day 5. Death.

Post-mortem: 2 hours after death. Both ventricles contain larger and smaller pencil-size red clots and white laminated marginal thrombi fairly rich in cells. Valves competent.

Case 12. Day 6. Distinct systolic apical murmur, P. weak intermitting.

Day 8. Death.

Post-mortem: In both ventricles fresh dark-red and greyish-white laminated clots between the trabeculae.

Case 13. Day 5. Systolic murmurs over all orifices, clearest at the apex.

Day 7. Death.

Post-mortem: 2 hours after death. Right ventricle and both auricles contain dark red and greyish-white marginal clots from that of a knitting-needle to that of a pencil in size. Valves intact.

Case 14. Day 13. Murmurs over the orifices, clearest at the apex.

Day 15. Death.

Post-mortem: In the right ventricle, both appendages and in the auricles, greyish-white and red firm clots between the trabeculae and partly firmly adherent to the insertion of the valves. Plehn, F. (1898).

Day 3. Dulness increased a finger's breadth to the right and left. A weak systolic murmur at the base.

Day 7. The systolic murmur was sharp, very loud and gave a thrill. The pulse was less full, with weak force and gradually less regular. Skrodzki (1910), 711.

In severe cases the heart sounds are distant and muffled and a soft (adventitious) bruit is heard at the apex. Coupled with this is a pulse of 150–160, sighing respiration, profuse sweat, continuous agitation—syncope. Gouzien (1911), 29 (r.).

Day 4. Soft systolic bruit over mitral area and rough systolic bruit over pulmonary valve. 'Africa' (1915), 65.

Day 3. Systolic murmur.

Day 5. Murmur transmitted to the axilla, best heard over the nipple. Lahille (1915).

Pericarditis

Day 2. Incessant vomiting, dry cough, acute epigastric and retro-sternal pain, intense phrenic neuralgia, dry pericardial friction, over an area as big as a 5-franc piece, medio-sternal.

Day 4. Phrenic neuralgia and pericardial friction gone. Amblard and Eschbach (1917), 814.

Pulse dicrotic

Day 4. Weakness greater, continuous somnolence, hyperpyrexia, delirium. Pulse dicrotic, good tension. 140–144. 25 (r.).

Day 5. Bad night, insomnia, sub-delirium, icterus intense. P. rapid, dicrotic, compressible. 30 (r.). Gouzien (1900[a]).

As the anaemia advances the pulse usually becomes dicrotic. Daniels (1901), 55.

Day 2. T. 39·9°. Spleen palpable by deep inspiration, P. 112, dicrotic, R. 36. Panse (1902), 6.

Day 7. Oedema has increased, P. 92, slightly dicrotic. Lahille (1915).

Pulse, intermittent

In 2 of 48 cases. Plehn, A. (1896). In 8 of 43 cases. Plehn, F. (1898).

Rate

Day 1. 1 a.m. Hgburia; 12.30 a.m. rigor, oppression, severe cyanosis, T. 40·3°, P. 80, strong. 29.

Day 1. 11 a.m. Q. 1·0 g.; 2 p.m. rigor, T. 41·2°, P. 90. 37.

I have often come across strikingly low pulse-rates in comparison with the temperature. Seldom does the pulse exceed 120 even with temperatures of over 40° C. 55.

Day 1. T. 101·3°, P. 132.
Day 2. T. 104·0°, P. 150.
Day 3. T. 102·7°, P. 150–160.
Day 4. T. 104·3°, P. 150–160. 55. Plehn, A. (1896).

Day 14. Every slight movement makes the pulse irregular and increases the rate to 130. Plehn, F. (1898), 126.

Day 5. The pulse has kept firm and full during the whole illness, contrary to what one usually finds. Gouzien (1900[a]), 77 (r.).

Day 2. On admission T. 39·5°, P. 152. Panse (1902), 7.

Usually at the onset the pulse is forcible and of good tension 112–120, but to this congestive stage there rapidly succeeds a state of vascular hypotension, characterised by weakness, rapidity and compressibility. In grave cases P. may be 152–160. Only rarely does one find a want of relationship between P. and T., the latter falling rapidly, while P. maintains great frequency and feebleness. Gouzien (1911), 29 (r.).

Pulse rate in anuria

Case 14. Day 4. T. 37·2°, P. 92. Anuria.
Day 5. T. 36·9°, P. 92. Anuria.
Day 6. T. 37·1°, P. 88. Evening, hip-bath, micturition.
Day 7. T. 37·4°, P. 92. (Recovery.) 69.

Case 15. Day 2. a.m. T. 37·4°, P. 100.
p.m. T. 37·0°, P. 96. Anuria, hip-bath. No result.
Day 3. Mid-day T. 37·0°, P. 100.
p.m. T. 37·3°, P. 100. Urine 100 c.c. by catheter.
Day 4. T. 36·9°, P. 92. Urine 10 c.c. by catheter. (Death.) 70. Schellong (1890).

Day 4. Urine 0 c.c. P. 98, regular, good tension. Visible pulsation of carotids, temporal and abdominal arteries.
Day 8. Urine 26 c.c. Epigastric and carotid pulsation more intense. Profuse sweats. Lahille (1915).

As the temperature falls to subnormal, and the icterus increases, its rate becomes less and less, and cases have been seen in which it falls as low as 50 or 60. Ross (1932), 216.
Vide also Icterus, Bradycardia.

Syncope

23 June. Admitted, urine colour of malaga. Q. 1·0 g.
24. Some bilious vomiting, patient very weak. Q. 1·0 g.
25. Icterus fading; 3 p.m. a transient syncope; 8 p.m. extreme epigastric distress; about midnight slight syncopal attacks, pulse falls.
26. 2 a.m. pronounced delirium, alternating with syncopal attacks. These increase in spite of sinapisms; 3 a.m. death during a prolonged syncope. Bérenger Féraud (1874), 198.
Day 2. 8 p.m. T. sub-normal. Patient completely powerless. On putting to bed, in spite of all care,

collapse. Recovery after 5 ether injections, thereafter slow convalescence. Plehn, F. (1898), 141.

Day 6. Restless night. P. running, 152–160, R. 44–48. Syncope on trying to go to the lavatory. Gouzien (1900[a]), 66 (r.).

Collapse and a semi-syncopal condition result from the grave anaemia. Gouzien (1911), 6 (r.).

Day 1. a.m. Q. grains 5. 6 p.m. Hgburia.

Day 2. 1 a.m. T. fell from 101° to 95°. Very severe rigor with vomiting and collapse, almost pulseless. R. very rapid. Rallied after strychnine and brandy. 'Africa' (1914), 30.

Day 4. Inclined to be delirious. 10 a.m. symptoms of syncope threatened, after an attempt at defaecation; 1.20 p.m. death. 'Africa' (1915), 19.

Icterus

and Anuria

17 Dec. Hgburia.

22. Anuria, slight icterus.

28. Icterus quite gone; the skin has a pale livid appearance.

1 Jan. Death. Plehn, F. (1898), 118.

Suppression of urine for about 30 hours. Jaundice in this case was slight. Yorke, Murgatroyd and Owen (1930), 339.

Icterus reaches its highest development in cases of anuria. Ross (1932), 216.

and Bradycardia

But rarely observed. Gouzien (1911), 28 (r.).

Colour

Day 4. T. 37·1°, 36·8°. Deep brownish-yellow colour of the skin and sclerae. Mucosae of lips and mouth hardly visibly tinged with red.

Day 5. Skin, greenish-brown yellow, the arms and legs bright golden-yellow. Plehn, A. (1896), 52.

Day 3. The skin, extremely dry, is of a greenish-yellow colour. Gouzien (1900[a]), 16.

Conjunctival

Day 1. Aspect livid, leaden, slightly icteric. Sclerotics yellow, but only on their inner side. Pellarin (1876), 209.

In the very severest cases only visible on the sclerae, the skin is a dirty grey, as in the case of a septic bleeding gravid woman. Plehn, A. (1896), 12.

Begins in the conjunctiva, *frenum linguae*, soft palate cheeks—later on in the chest and limbs. Gouzien (1911), 28 (r.).

The clinical picture presented by the appearance of the eye . . . is very characteristic and persists for a considerable period after the b.w.f. has ceased. The conjunctiva is of a uniform lemon-yellow tint, varying in depth of shade, but always lighter near the cornea, according to the severity of the case, and the depth of the jaundice. The sub-conjunctival vessels seem depleted and are exceedingly pale. In the malarial eye, the blood-vessels are always more or less injected and the icterus is less marked and less uniform. Deeks and James (1911), 71.

Development

In a grave case it is present from the beginning. During the cold stage the skin is dull and earthy, but as the temperature rises the icterus is more pronounced and may rapidly attain a maximum. In the morning the patient may show only a very slight sub-icteric tinge, but icterus may be pronounced in the evening with a rise of temperature. The colour is rarely ochrous, but is that of saffron. Sweat, saliva, or other excretions are not icteric, but the serum

from a blister is. Occasionally the icterus develops later and more slowly, and is less uniform and less distinct, signs of gravity in the case. Icterus persists for several days, slowly giving place to an earthy tint characteristic of anaemic cachexia. 216.

In slight and severe cases icterus develops promptly, but in still more severe cases it is only clearly shown a few hours before death and more intensely afterwards. 220. Barthélemy-Benoit (1865).

It is not uncommon to see icterus slightly pronounced in the gravest cases. Pellarin (1876), 213.

Case 11. Day 2. Quite slight icterus visible. 67.
Case 13. Day 2. T. 37·5°. Icterus universal. 68.
Case 15. Day 1. A fresh paroxysm beginning with an extraordinarily violent rigor. Patient is agitated by the suddenly occurring universal icterus and dark 'bloody' urine. 70. Schellong (1890).
3 Aug. 1894. 9.15 a.m. Q. 0·5 g.; 12.15 p.m. T. 39·7°, P. 133, R. 60; 5 p.m. first signs of icterus. (Time of Hgburia?)
10. Icterus negative. Murri (1896), 116.

Is most developed in non-fulminating cases, and reaches the intensity seen in yellow atrophy of the liver or phosphorus poisoning. It reaches its greatest intensity with the fall of T. Plehn, A. (1896), 12.

In pernicious cases intense pigmentation may rapidly pass into a clearer dirty-white earthy colour. Gouzien (1911), 28 (r.).

21.21.8. Colour of face normal, *herpes labialis inferior*, blood *P. falciparum* and *P. vivax*.
25. 8 a.m. condition good; 10 a.m. Q. 1·0 g. intramuscular; 12 noon slight rigor, T. 39·6°, later a very severe rigor; 3 p.m. completely yellow; 4 p.m. Hgburia 250 c.c., cell count 1·2 m., Hgb 30%;

9 p.m. cell count 880,000, Hgb 30%; 11 p.m. deep citron yellow colour of skin.

26. 1.45 a.m. death. Seyfarth (1918[a]), 277.

Duration

It tends to disappear on the 3rd or 4th or even the 2nd day in slight cases. Corre (1883), 188.

After a few days the colour fades and resumes the yellowish 'hellgraubraun' characteristic of the European in Cameroons. The sclerae retain the colour somewhat longer. Plehn, A. (1896), 12.

After 48 hours the urine commenced to clear, the spleen rapidly reduced in size, and the jaundice largely disappeared, but a marked bronzing of the skin remained, and was still present some months later. Christophers and Bentley (1908[a]), 211.

Usually lasts 3–5 days, but in grave cases it persists beyond convalescence, the colour changing from pale yellow to ochre, saffron. Gouzien (1911), 28 (r.).

Icterus was apparent on the 2nd day of the disease and lasted for about 5 days after T. had become normal—13 days in all. 'Africa' (195), 10.

The Hgburia lasted for 36 hours and there was no relapse. Jaundice was pronounced and lasted for 2 or 3 weeks. Yorke, Murgatroyd and Owen (1930), 338.

Eruptions

In severe cases is sometimes accompanied by vesicular or bullous eruptions or petechiae. Corre (1883), 188.

Excretions

Sweat, saliva, or other excretions are not icteric, but the serum from a blister is so. Barthélemy-Benoit (1865), 216.

Day 1 (?). Skin deeply jaundiced. Pillow-cases and bedclothes stained yellow. Patient had had atebrin 1·0 g. No atebrin detected in the serum. Amy (1934), 276.

Frequency

Cases.	Present.	Absent.	No record.	Authority.
32	29		3	Béranger Féraud (1874).
15	15			Crosse (1892).
48	38		10	Plehn, A. (1896).
43	38	2	3	Plehn, F. (1898).
14	11		3	Gouzien (1900[a]).
38	21	1	16	Panse (1902).
20	20			Da Costa (1906).
14	14			Brem (1906).
24	17	5		Broden (1906).
19	9		10	Barratt and Yorke (1909[a]).
23	20			'Africa' (1914), 56.
20	19			'Africa' (1915), 53.
39	31		8	Connal (1916).
17	15	1	1	Arkwright and Lepper (1918).
10	10			Seyfarth (1918[b]).
7	7			Gaskell (1920).
49	20*			Dudgeon (1921).
5	5			Yorke, Murgatroyd and Owen (1930).
156	143			Ross (1932), 136.
9	8		1	Fairley and Bromfield (1934).

* Only those cases included in which bile pigment in the plasma was established ('True jaundice').

Itching

Dutroulau first pointed out that it is never accompanied by itching. Corre (1883), 188.

Vide supra, Cutaneous System.

Pre-haemoglobinuric

In the opinion of not a few medical men it may precede the Hgburia, but that is not our opinion. . . . In those cases where it appears to precede the Hgburia, the icterus is the residue of preceding bilious remittent attacks. Corre (1883), 188.

30.8.01. 7 a.m. T. 36·4°, parasites fairly numerous; 8 a.m. Q. 1·0 g.; 3 p.m. a few parasites.

31. T. 37·2°, parasites negative; 8 a.m. Q. 1·0 g. *per os*; 1 p.m. urine clear, slight icterus; 5 p.m. Hgburia. Panse (1902), 14.

The observation was made in this case of the occurrence of transient jaundice on two occasions before the severe attack of b.w.f., malaria parasites being present on the second occasion; these preliminary attacks of jaundice may have represented the occurrence in the blood of—in a less degree—the same changes produced by the same cause as was active during the attack. 83.

The importance of pre- and post-Hgburia states which are inherent parts of the disease is apt to be lost sight of owing to the exclusive use of the term ' Blackwater ' Fever. Some such term as ' Occult ' or ' Subliminal ' b.w.f. might be used to express these conditions. 86. Blacklock (1923).

Subacute jaundice was regularly present in the individuals (4) prior to the attack of Hgburia. Kligler (1923), 203–212.

28.7.28. History of malaria, spleen palpable during deep inspiration, parasites negative.

30. 6 p.m. Q. 15 grains.

31. 10 a.m. Q. 15 grains; 2 p.m. Q. 15 grains; 2.30 p.m. becoming slightly jaundiced; 4 p.m. rigor T. 100°; 6 p.m. Hgburia T. 104°. Owen and Murgatroyd (1928), 503.

Post-haemoglobinuric

Cases 38. Icterus appeared on Day 1 in 17, Day 2 in 12, Day 3 in 1. Query in 8. No record in 12. Plehn, A. (1896).

Is generally visible directly after the rigor, and increases in intensity very quickly. It can be as intense as it is usually seen on the second day. Plehn, A. (1903), 520.

Cases 21. In 5 of 21 cases where the fact was noted icterus was absent on day 1. Broden (1906).

Cases 20. 5 at the same time or immediately after Hgburia. 1, 15 hours after. 14, on day 2. ' Africa ' (1914), 56.

Cases 19. 10, 1 day after Hgburia. 5, 2 days. 2, 3 days. 1, 4 days. 1, 6 days. ' Africa ' (1915), 53.

Cases 31. 25 on day 1, 2 on day 2, 4 no record. Connal (1916), 11.

Post-mortem

Sometimes more pronounced after death, at any rate the colour at death is retained *post-mortem*. Again, if at death the tint is only sub-icteric, *post-mortem* it is more intense in the fatty and cellular tissue. Barthélemy-Benoit (1865), 105.

In 3 of 16 fatal cases (with bile pigment in blood plasma), these having died on the 5th and 7th day of the disease, jaundice developed at the onset of b.w.f., but icterus was absent at autopsy. Dudgeon (1920), 209.

and Prognosis

Vide infra, Treatment.

and Quinine

In hospitals in temperate regions I have frequently seen icterus arise during prolonged and intense Q. treatment and its disappearance after omitting the Q. Seyfarth (1918[a]), 273.

Sine Hgburia

15 March. 12 noon rigor; 2 p.m. antipyrin grains 10; rapid and free perspiration. Q. grains 30 and a purgative. At night, laudanum 30 drops.

16. 3 a.m. rigor T. 99·4°, pain over kidneys and spleen, slight jaundice; 5 p.m. T. 101·5°, P. 120, perspiration; 8 p.m. T.N., P.N.

17. Urine dark brown, bile positive, albumen negative. Crosse (1892), 83.

Case 2.

29 June, '94. After 2 days indisposition, a.m. rigor. Soon after, urine of a distinct icteric colour; p.m. T. 39·7°, Q. 1·0 g. given, but patient brings it up again, profuse vomiting of green matter.

30. a.m. T. 38°; 5 p.m. T. 37·5°, headache, sleepy, vomiting ceased. Spleen, 1 finger, urine icteric colour, a little albumen.

Case 3.

30 June. 3 days indisposition; a.m. shivering, urine icteric, alb. positive, bilious vomiting; 5 p.m. T. 38·8°.

1 July. Conjunctiva slightly icteric, urine clear, no longer icteric, alb. negative. 761.

Case 6.

14 June, 1895. Patient awakes with a stiff neck and sharp pain in the region of the right occipital nerve on trying to turn the head, Q. 0·5 g. twice, massage.

15. Q. 1·0 g., condition unaltered, massage.

16. 9 a.m. after great mental excitement, rigor with very painful cramps, especially in the right arm, and less in the right leg, and bilateral facial cramps, especially on the right side. Rigor lasts for ½ hour. T. 39·9°, profuse bilious vomiting; p.m. T. 38·9°, urine, doubtful yellow froth, albumen negative. Patient lies relaxed and apathetic, conjunctiva white, head held stiffly, pain over the occipital nerve, vomiting of bilious stuff, spleen palpable, 1½ fingers, urine reddish brown, no yellow froth, no albumen.

17. No more vomiting, urine distinctly icteric, albumen slight, conjunctiva slightly icteric; 12 noon restless; 4 p.m. rigor, with cramps in face on both sides, and in right arm. Vomiting returns, urine somewhat darker.

18. Fair night, head more moveable, pain slighter, urine of the same colour, albumen moderate, icterus (of the body ?) distinct.

19. Occipital pain less, head movable in all directions but still with pain; 10 a.m. rigor of short duration, urine a little darker.

20. Urine almost clear, very little albumen. 762. Doering (1895).

A.H. white ♂, aet: 39. Never had hemoglobinuric fever. Slight fever, ' dumb-chills ' and light jaundice for 3 weeks. No quinine for 2 months. Badly salivated from calomel.

29 Nov. 1906. Passage of ' bloody water.' 4½ hours later T. 99·8°, P. 92, marked jaundice of skin and sclerae, vomiting, liver region tender, spleen to ant. sup. spine and within 1½ inches of umbilicus, blood parasites positive, Hgb 65%, highest T. 101·5°.

Urine ' port-wine ' colour, acid 1014. Alb. neg. Hgb neg. Biliary colouring matter abundant. Cleared in 36 hours. Deaderick (1907–8).

Another case (= the above case), one of estivo-autumnal malaria, was seen in which the urine was so loaded with bile pigment that until it was examined chemically the case appeared to be b.w.f. Deaderick (1910), 198.

Those cases in which the destruction of the red cells is not sufficient to cause the appearance of Hgb in the urine, we can regard as transitional cases. In these Hgb is converted into bilirubin and appears in the urine as such. Seyfarth (1918[a]), 273.

4 March, 1926. Conjunctivae lemon yellow, red cell count 1·3 m., Hgb 39%, leucocytes 5700, parasites negative.

6–9. Parasites negative, spleen 2 fingers.

9–19. Q. increased from grain $\frac{1}{32}$ to grain $\frac{1}{2} \times 3$.

20. Severe headache, nausea, splenic pain, spleen 4 fingers, slight vomiting, T. 100·2°.

21. Intense jaundice, red cell count 1·25 m, Hgb 35%, leucocytes 6000, parasites negative, bilirubinaemia 2·5 units, Hgburia negative.

23. Icterus gone.

During the icteric period the urine was examined daily for Hgb, but always with negative result. Urobilin was not present in greater dilution than 1 in 10.

Intravascular haemolysis sufficient to produce marked clinical jaundice but no Hgburia. Ross and Peall (1927), 53.

Gorthynia, Greece.
13 May, '29. O.A. aet: 14. ♀.
15. Hgburia +, red cell count 1·9 m, *P. falciparum.*
17. Hgburia —. Bile —.
24. Red cell count 1·02 m.
27. Acute pain in right hypochondrium, liver enlarged to within 3 c.m. of umbilicus, T. 40°.
28. T. 37°. Liver decreases as rapidly as it had enlarged. Intense icterus, urine deep blackish red, Hgb —, bile pigment ++, bile salts ++, faeces intensely bile stained. Chaniotis (1932), 215.

Liver

It appears to be established that malaria and b.w.f. are connected with one another. From our experience we consider that the liver plays a considerable if not the chief part in the pathogenesis of b.w.f.

Enlargement of the liver, if not demonstrable by percussion and palpation, can always be established by X-rays. In addition there is urobilinuria, and finally icterus, which must be considered as a dys-function of the endothelium system of the liver and spleen. Subjectively also in slight cases of malaria there is pain in the liver, which may increase at the end of a severe attack to actual colic. . . . If we summarize the three cases (of b.w.f.) we find the same picture in varying extent. Common to all is the prominence of liver symptoms, in the shape of increased haemolysis, in the last two cases accompanied by Hgburia. This increase of symptoms from an icterus with anuria, bilirubinaemia and haematinaemia to fully developed b.w.f. leads us to believe that we are dealing simply with a greatly exaggerated physiological and pathological aspect—in other words that every case of malaria is potentially one of b.w.f. Barrenscheen and Glaessner (1923), 409.

Colic

7.2.1920. Increasing icterus, count 1·32 m, T. 37·3°.
8. Rigor, T. 38·4°, sharp epistaxis, evening, very acute colic-like pains in liver region. Liver ++, tender.
9. Anuria since the night, coma, count 620,000, Hgb 17%. Blood serum: dark brown, Hgb neg., haematin ++, bilirubin ++.
10. Death. Barrenscheen and Glaessner (1923), 409.

Enlargement

Cases.	Present.	Absent.	No record.	Authority.
48	1	10	37	Plehn, A. (1896).
43	1	1	41	Plehn, F. (1898).
14	4	3	7	Gouzien (1900[a]).
38	14	5	19	Panse (1902).
14	2		12	Brem (1906).
20	10*		10	Da Costa (1906).
19	1	4	14	Barratt and Yorke (1909[a]).
17	8	4	5	Arkwright and Lepper (1918[b]).
10	3	2	5	Seyfarth (1918[b]).
5	1		4	Yorke, Murgatroyd and Owen (1929–30).
9	4		5	Fairley and Bromfield (1934–35).

* Congested.

28.2. Hgburia.
1.3. Liver 2 fingers below the costa.
23. Liver gone back. Panse (1902), 8.

During his attack enormous acute enlargement of both liver and spleen occurred, which subsided 3 days after the Hgburia ceased. Recovery. Christophers and Bentley (1908[a]), 229.

Day 1. 10 a.m. liver negative.
Day 2. Liver negative.
Day 3. Liver enlarged, right lobe 2 fingers, left lobe 4 fingers, tender point over the gall-bladder. Motions golden yellow. Amblard and Eschbach (1917), 814.

Liver pain or tenderness

Cases.	Present.		Absent.		No record.	Authority.
	p.	*t.*	*p.*	*t.*		
32	8	3			21	Bérenger Féraud (1874).
15	6	3		1	7	Crosse (1892).
48	1	3		1	44	Plehn, A. (1896).
43		11			32	Plehn, F. (1898).
14		1			13	Gouzien (1900[a]).
38		4			34	Panse (1902).
14		1			13	Brem (1906).
20		(10)*			20	Da Costa (1906).
19					19	Barratt and Yorke (1909[a]).
17		2		1	14	Arkwright and Lepper (1918[b]).
10		1			9	Seyfarth (1918[b]).
5	1				4	Yorke, Murgatroyd and Owen (1929–30).
9		2			7	Fairley and Bromfield (1934–35).

p = pain. *t* = tenderness. * congested.

Day 1. Liver normal.

Day 2. Very tender on pressure and palpation. Not enlarged. Case 11. 33.

Day 2. Left lobe painful and tender on pressure. Not enlarged. Case 17[3]. 37. Plehn, A. (1896).

Lungs

Bronchitis

Day 26. For the last two days fairly frequent cough with easy expectoration; a little pain over the sternum.

Day 27. Cough not so frequent, expectoration very feeble, sternal pain gone. Bérenger Féraud (1874), 374.

17.11.1891 (day 4). Slight bronchial catarrh.

21–25. T.N. Patient only troubled by the frequent expectoration of muco-purulent matter.

1.12. Signs of catarrh quite gone. Kohlstock (1892), 428.

In 7 of 43 cases râles at base of lungs recorded. Plehn, F. (1898).

Day 1. Over the base of the lungs, slight signs of bronchitis. 113.

Day 3. Catarrh at the base of the lungs. 122.

Day 1. Over the lungs behind at the base, dry râles. 131.

Day 1. Dyspnoea, over both lungs behind at the base, dry râles and creaking. 154. Plehn, F. (1898).

Day 4. Weaker, somnolence, hyperpyrexia . . . frequent cough, auscultation negative.

7. Very much better.

8. Cough fairly frequent, breath sounds somewhat harsh, no râles.

9. Cough persists, general condition good, in spite of weakness and great pallor. 26 (r.).

14 Aug. 2 p.m. b.w.f.

18. Urine almost normal.

19. Icterus less, extreme exhaustion, but pulse better, 96, dry cough, nervous. 50 (r.). Gouzien (1900[a]).

The only unfavourable symptom was an irritable cough, which made the patient inclined to vomit and disturbed his rest. 'Africa' (1914), 50.

Day 4. He was desperately ill. T. 96·6°. The pulse was fair. The lungs showed considerable bronchitis with râles and rhonchi over both bases. Low, Cooke and Martin (1928).

Tracheitis

Day 5. Partial suppression.

10. Tracheitis developed.

12. Death. 'Africa' (1914), 56.

Pleurisy

Vide supra, Complications.

Micturition

Frequency

In many cases there is a frequent desire to pass water, but a passage of a catheter shows that there is no accumulation of urine due ' to an arrest of excretion.' Corre (1883), 168.

The haemoglobinuric urine appears to act as a diuretic. There is evidence, however, that it acts as an irritant on the genito-urinary tract.

Micturition is frequent; sometimes urine is passed every hour or even more frequently. This is particularly so during the second day. At this time much bladder epithelium is found in the urinary deposit. Daniels (1901), 57.

Much variation . . . was exhibited in respect of the passage of urine, in some attacks urine being passed frequently, in others retained long in the bladder. 75.

Day 1. During the night, passing water about 25 times in very small quantities. 186. Barratt and Yorke (1909[a]).

The first micturition is preceded by an urgent desire to pass water, which is renewed some dozen times in the 24 hours. Gouzien (1911), 30 (r.).

Incontinence

Day 12. Prostration, somnolence, 2 involuntary motions, urine very pale, incontinence.

Day 13. Somnolence, 4 involuntary motions, incontinence of urine, which continues to be pale, no deposit. (Recovery.) Bérenger Féraud (1874), 217.

Incontinence on days 8, 9 and 11. (Recovery.) Owen and Murgatroyd (1928), 524. Yorke, Murgatroyd and Owen (1929–30), 341.

Case 6. Day 3. 11.15 a.m., 99·4 c.c. of very dark urine by catheter, but there had been incontinence just previously, 5.15 p.m. death.

Case 9. Day 1. Vomiting green bilious matter every few minutes and passing black urine in the bed.

Day 3. Sphincters incompetent, death 61½ hours from onset. Fairley and Bromfield (1924–5).

Retention

Case 4. He had had retention of urine since admission. . . . Urination was induced by a hot enema, and about 1000 c.c. of greenish-red urine was voided.

Case 8. Catheterisation was necessary during the first three days. The minimum output of urine for 24 hours was 30 c.c., the maximum 450 c.c.

Case 13. Admitted 27 Ap., 1906, 5 p.m. There was retention of urine until 28 Ap., 1 p.m., when 150 c.c. was voided. Brem (1906).

Day 3. After to-day patient was unable to pass his urine. On passing a catheter it was found that he had a urethral stricture. Barratt and Yorke (1909[a]), 236.

Lady, aet: 24. Northern Transvaal.

Day 2. Urine running drop by drop from the urethra. I could feel a large tumour extending from the symphysis to three fingers breadth above the umbilicus. This was undoubtedly the bladder. I catheterised her and removed about four pints of black, stinking urine. Day 4 death. Borle (1910–11), 239.

Girl, aet: 6. Prague. Daily febrile attacks of 8–9 hrs. at night. Q. 0·15 g. × 4. Next day bladder full to navel and child could not pass water. By catheter blood-red urine, Oxy-Hgb. The child had occasionally received Q. from her father, a war-malaria patient. Langer (1924), 636.

Case 7. Day 5. In the evening . . . retention of urine developed necessitating catheterisation.

Day 9. Polyuria with retention persisted, 3030 c.c. being removed by catheter.

Day 10. Passed a few ounces of urine naturally. Polyuria persisted, some 1950 c.c. of urine neutral to litmus, being removed by catheter. Fairley and Bromfield (1934–35), 312.

Strangury

Vide infra, Pain.

Haemoglobinuria

Absence of Hgb in first urine

11.11. 8 p.m. Q. 1·0 g., 12 midnight violent rigor, high fever, urine clear.

12. T.N., no further Q. apparently; 12 noon, renewed rigor, high fever, Hgburia, icterus. Plehn, A. (1896), 45.

19.8. 9 p.m. Q. 1·5 g.

20. 8.30 a.m. violent rigor, T. 40°, pains in the back and nausea, headache, stupor, light delirium, icterus negative. Urine: Alb. abundant, hyaline casts, Hgb negative.

10 a.m., urine, turbid dark brown, filtered yellow.

12 noon, urine blackish red, filtered ruby red. 129.

20.8. 6 a.m. Q. 1·5 g.

9 a.m. Rigor, T. +, icterus, vomiting, headache, backache, stupor.

10.45 a.m. Urine: Alb. pos., Hgb. neg.

12 noon. Urine: blackish red, filtered ruby red. 137. Plehn, F. (1898).

In some cases the first specimen of dark urine examined was not so dark in colour as that passed a few hours later. Arkwright and Lepper (1918[a]), 384.

Hgburia duration

Case.	Duration in days.		Case.	Duration in days.		Authority.
	Hgburia.	Albuminuria.		Hgburia.	Albuminuria.	
1	3	'permanent'	18	1	3	Plehn, A. (1896).
2	3	5 ?	19	2	2	
3	4	10 ?	20	1		
4	2	2	21	1	1	
5	2	2	22	4	4 D.	
6[1]	1	1	23[1]	2	2	
6[2]	1	1	23[2]	2	14 D.	
6[3]	2	4 ?	24[1]	1	1	
6[5]	1	1	24[2]	3	6	
6[6]	1	1	25	3	3 ?	
7	4	4	26	1	1	
8[1]	2	2	27[1]	6 ?	6 ?	
8[2]	3	9 D.	27[2]	3	3	
9	2	2	28	4		
10[1]	1	1	29[2]	1	1	
10[2]	2	2	30	3	3	
11	2 ?	12 D.	31[1]	1	1	
13	5		31[2]	1	1	
15[1]	1	1	31[3]	10 ?	10 ? D.	
15[2]	1	1	32	2	3	
16	1	1	33	3		
17[3]	3	3	35	3 ?	9	
17[4]	2	2				

D. = Death.

Case.	Hours.			Authority.
	Fever.	Hgburia.	Albuminuria.	
20	35	41	48	Plehn, F. (1898).
21	25	31	38	
22	25	30	50	
24	11	19	30	
26	8	8½	8½	
27	40	55	120	
29	6	9	13	
30	12	12	15	
32	6	6	8½	
33	48	54	60	
34	9	19	70	
35	40 (16 + 15 + 9)	18½	18½	
36	8	8	36	
37	14	16	36	
38	8	9	144	
43	20	23	23	
44	21		23	

Case.	Days.		Case.	Days.	
	Hgburia.	Albumin-uria.		Hgburia.	Albumin-uria.
142	2	2	174	3	3
144	4	6	176	1	2
146	2	3	178	2	2
152	1	1	189	4	4
153	2	4	202	3	3
155	1	1	203	3	3
157	3	3	204	4	8
162	5	5	206	3	3
168	3	3	208	1	1
170	2	2	209	1	1

Hgburia lasted 1 day in 5 cases, 2 in 5, 3 in 6, 4 in 3, 5 in 1. Albuminuria lasted 1 day in 4 cases, 2 in 4, 3 in 7, 4 in 2, 5 in 1, 6 in 1, 8 in 1. Deeks and James (1911).

Albuminuria in 16 of 19 cases cleared in 24 hours after the Hgb had ceased. Connal (1912).

Case.	Hgburia.		Albuminuria.		Case.	Hgburia.		Albuminuria.	
	Hrs.	Days.	Hrs.	Days.		Hrs.	Days.	Hrs.	Days.
61	4				54		2		6
50	4		18		52		3		3
50		3½		9	55		3		3
47	12			4	57		3		4
59	12		24		66		3		5
56	few				67		4		5
56	few			13	49		4		5 D.
53	few		18		46		5		5
64		1	26		65		5		5
62	12	1	60		68		5		5 D.
63	14	1		4	60		5		8
58		1			48		16*		21

* Hgburia on days 1, 2, 7, 8, 9, 16.

Albuminuria lasted in 14 of 24 cases for variable periods after the cessation of Hgburia. 'Africa' (1914), 60–65.

Case.	Hgburia.		Albuminuria.		Case.	Hgburia.		Albuminuria.	
	Hrs.	Days.	Hrs.	Days.		Hrs.	Days.	Hrs.	Days.
11	3			1	21		4		4 D.
13	12			3	18		4		4 D.
9		1		2	19		4 + 1		4 + 1
7	4	1	12	2	20		6		6
2		2		4	5		6		6
6		2		D.	3		4 + 3		9
10		2		8	12		7		12 D.
14		2		3	1		9		11
15		2		12	4		9		13
17		3		3	16		11		11 D.
8		4		11					

Albuminuria lasted in 13 of 21 cases for variable periods after the cessation of Hgburia. 'Africa' (1915), 65–71.

Albumen oxy- or met-Hgb, and débris which so suddenly appear at the onset of the disease and are followed by an abundance of renal cells and casts, as rapidly disappear, and the urine returns to normal. In 3 cases the normal was reached on days 2, 5, 9, respectively. Dudgeon (1920), 239.

Case.	Hgburia.	Albumin-uria.	Case.	Hgburia.	Albumin-uria.
	Days.	Days.		Days.	Days.
4^1	1 +	4	6^1	2 +	12
4^2	1 +	4	6^2	1 −	7
5*	3 +	60			

* A case of suppression.

Gaskell (1920), 12.

Duration of Hgburia in days.												
Cases.	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	Authority.
41	11	6	12	10	2							Fisch (1896[a]), 275.
38	14	11	11	0	2							Plehn, A. (1896).
22	13	7	2									Plehn, F. (1898).
10	4	3	3									v. Campenhout and Dryepondt (1901).
21	5	4	8	2	1	1						Panse (1902).
21	8	6	4	2	1							Broden (1906).
15	1	6	5	1	2							Da Costa (1906).
14	4	3	6	1								Chazal (1908).
143	23	35	46	28	7	3	1					Deeks and James (1911).
11	2	2	2	2	2	1						Fletcher (1914).
104	11	22	25	25	7	7	4	2	1			'Nigeria' (1916–22).
48	12	18	7	6	3	1	1					'Uganda' (1922).
68	13	20	20	7	4	1		1	1	1		'Uganda' (1923).
54	14	17	14	3	4	2						'Uganda' (1925).
68	23	17	16	6	4	1				1		'Uganda' (1926).
142	52	35	18	21	9	4	1	1		1		'Uganda' (1927).
17	7	7	1	1	1							'Nigeria' (1928).
114	29	28	27	16	7	4	3					Ross (1932), 222.
951	246	247	227	131	56	25	10	4	2	3	0	

Relapses and fatal cases excluded.

Duration of Hgburia. Cases 26.					
Days.	Including relapses.	Excluding relapses.	Days.	Including relapses.	Excluding relapses.
6 h.	1	1	8	1	1
2	4	5	9		
3	4	5	10	1	1
4	6	6	11		
5	2	2	12		
6	5	3	13	1	1
7	1	1			

Connal (1922[a]), 8.

Cases 49. 2–6 h. in 28, 14–24 h. in 9, 48 h. in 5, 72 h. in 4, 120 h. in 2, 168 h. in 1. Weselko (1926), 658.

El Centro, Colombia, S.A.

Cases 21. −1 day 4, 1–2 days 6, 2–3 days 4, 3–4 days 5, 4–5 days 2. (Fatal cases included.) Paterson (1932–33), 542.

and Red cell count

Blood.			Urine.	
Day.	Red cell count (m.).	Hgb (%)	c.c.	Hgburia as red cells (c.c.).
2[a]		75		neg.
1[a]		65		neg.
1		55	95	trace
			90	4·5
			200	0·5
2	2·6	45	250	0·625
			110	0·055
			200	0·33
			625	0·00
			360	1·98
3	1·15	35	570	neg.
4	0·80			
				7·99

In all, the Hgb of 17 c.c. of *normal blood* or about 2.5 g. Hgb was passed unaltered in the urine. Ross, Thomson and Simpson (1910), 309.

Case 3.				
Day.	Red cell count (m.).	Haematocrit volume.	Hgb (%).	Hgburia as blood (c.c.).
1	3·6		72	36·2
	3·45	32·5	70	
2	2·77		64	38·6
3	1·58		36	90·5
4	1·60	13	15	19·4
5	1·52		21	
6	1·42		27	
7	1·84		40	
				184·7
Case 4.				
Day.	Red cell count (m.).	Haematocrit volume.	Hgb (%).	Hgburia as blood (c.c.).
1	4·20	31·5	82	4·3
2	4·25	29	81	0
3				0
4				0
5				0
6	4·26	30·8	81	0
7				0·2
8	4·40	26·4	77	
	4·41	28·6	77	3
9		27		0·3
				7·8

Yorke, Murgatroyd and Owen (1929–30).

and Malaria

1. Pernicious malaria, cases 8. In 2 the urine was typical blackwater. In 3 to the naked eye probably haemoglobinous. In 1 reddish-brown urine with a suggestive greyish-brown sediment. In 2 Hgb demonstrated only in the sediment (guiac and turpentine test). Controls in the case of mild or moderate malaria were negative. Brem (1911), 154.

2. Pernicious malaria, 27 cases (including previous 8). In 8, the urine was blackwater. In 6 suggestive of Hgburia. In 8, a trace of Hgb. In 5 negative (guiac and turpentine test).

No spectroscopic data are given. The records do not indicate whether these cases were receiving quinine or not. Brem (1912), 130.

Malignant tertian. Cases 3. All gave a high bilirubin value (indirect reaction) of 6 or 6 + units. On examination of the urine all gave a + reaction for Hgb (benzidine test, but a — reaction spectroscopically). 139.

Mild and unsuspected Hgburia can occur during a typical attack of malignant tertian malaria. 146. Ross (1932).

and Parasites

Date.	*P. falciparum.*	Q.	T.	Hgburia.
12 Aug.	+		12 noon 40·2°	
		2 p.m. +	4 p.m. 40·2°	8 p.m. +
13	+	12 noon +	2 p.m. 40°	8 p.m. +
14	—		11 p.m. 40·2°	—
15, 16	—		T.N.	—
17	—	7 a.m. +	2 p.m. 39·5°	+

12 and 13 Aug. Parasites present. Hgburia followed Q. injections.

17. Parasites absent. Hgburia followed Q. *per os.*

The duration of Hgburia on 12 Aug. is not stated. Mann (1902), 530.

Of my 168 cases 8 were purely intermittent; 19 had a remittent character. I have not included those cases where after the first typical attack induced by parasites + Q., a second generally slighter attack followed (Post-accessual Hgburia of Bastianelli). Plehn, A. (1903[b]), 529.

Bignami and Bastianelli found once the coincidence of the Hgburia with the sporulation of the parasites.

When the Hgburia persists . . . and even the spleen contains no amoeboid parasites it is possible that the destruction of the blood corpuscles caused by the small parasites previously present continues for reasons that we do not understand. . . . Bastianelli proposed to designate the first cases as ' accessual,' the second as ' post-accessual ' Hgburia. Mannaberg (1905), 319.

Vide supra, Attack. Classification.

% of red cells infected.			
Hgburia of blackwater intensity.	Gross appearance of urine suggestive of b.w.f.	Hgburia trace.	Hgburia negative.
15·6 15·4 15·2 12·6 9·0 5–10 3·2 1–2·5	43 23·5 17·6 11·4 5–10 5–10	29 6·2 5–10 5–10 5–10 2–3 1–2·5 1·25	8–10 2·3 2·0 1·25 1·25
8	6	8	5

Brem (1912), 130.

The test for Hgburia used was guiac and turpentine. No spectroscopic examination of the urine.

and Quinine

Day.	Q.	Hgb-uria.	Q.	Hgb-uria.	Q.	Hgb-uria.
1	+	+	+	+	+	+
2	—	—	—	—	—	+ —
3	—	—	—	—	—	—
4	—	—	—	—	—	—
5	—	—	—	—	—	—
6	—	—	—	—	+	+
7	—	—	—	—	—	+
8			+	+ —		+ —
9						
10					Panse (1902), 27.	
11						
12						
13						
14						
15						
16						
17	+	—				
18	—	— + —				
19	—	+				
20	—	—				
	128		131		133	

Day.	Hour.	Q.	T.	Hgb-uria.
1		?		+
2		—		—
	11 a.m.	—	38·2°	Dark
	1.30 p.m.	—	39·8°*	brown
	4 p.m.	—	T.N.	—
	5 p.m.	+†		
	8 p.m.		Rigor	+
	9 p.m.			—

Plehn, F. (1898).

* Without Q. T. rises to 39·8° and urine becomes dark brown (Hgb ?).
† After Q. rigor occurs and Hgburia.

Day.	Q.	Hgb-uria.	Q.	Hgb-uria.	Q.	Hgb-uria.	Q.	Hgb-uria.	Q.	Hgb-uria.
1[a]									+	
1	+	+		+	+	+	+	+	+	+
2	−	+	+	−+		+	−	+		+
3	−	+		+−		−	+	−		+
4	−	+				−	+	−+		+
5	−	+				−	+	−		+
6	+	−			+	−	+	−		−+−+
7	+	−			+	−	+	−		+*
8	+	−			+	−	+	−	+	+−
9	+	−			+	−	+	−	+	+−
10	−	−			+	−	+	−	+	−+
11	−	−			+	−			+	−
12	−	−			+	−			+	+−
13	−	−			+	−			+	−+
14	−	−			+	+			−	?
15	−	−				−			−	−
16	−	−							−	−
17	−	−								
18	−	+								
19	−									
20	−	−								
21	Case 1.		Case 9.		Case 4.		Case 8.		Case 9.	
	Da Costa (1906).				Barratt and Yorke (1919[a]).					

* The text and the chart differ.

Day.	T.	Q.	Hgburia.	Remarks.
9 Jan.	+	+	−	This is an unusual case.
10	+	−	−	Hgb on 11th, when
11	+	−	+	last dose of Q. had
12–17	T.N.	−	−	been taken on 9th, and
18	,,	+	−	following the admin-
19	104°	−	+	istration of Q. on the
20–26	T.N.	−	−	18th and 27th. Deeks
27	,,	+ (t.d.s.)	−	and James (1911), 110.
28	104°	−	+	

Day.	Q.	Hgb-uria.	Q.	Hgb-uria.	Q.	Hgb-uria.	Q.	Hgb-uria.	Q.	Hgb-uria.	Q.	Hgb-uria.
1	+	+	+	+		+	+	+	+	+		
2	+	+	−	+		+	−	+−	−	+−		
3	+	−	−	−	−	+	−	−	−	−		
4	+	−	−	−	−	+	−	−	+	−		
5	+	−					−	−	−	+−		
6	+	−					−	−	+	−	−	+
7	+	−					−	−	+	−	+	−
8	+	+					−	−	+	−	+	−
9							−	−	+	−	+	+12h
10							+	+	+	−	−+	−
11								+−	+	−	+	+8h
12									+	−		
13									+	−	8h, 12h = duration of Hgburia in hours.	
14												
15					+							
16					+							
17					+	+						
18			(21) +	−	−	+−						
19			(22) +	+								
20			(23) −	+−								
	Case 2.		Case 4.		Case 6.		Chart X.		Chart XI.		Penington (1931–32).	
	Gaskell (1920).						Thomson (1924a).					

and Temperature

Date.	T.	Hgb.	Date.	T.	Hgb.
20 Sept. 1 p.	39·1°	+	7 June 6 a.		(Q.)
20 7 p.		−	8 a.	39·5°	+
8 p.	38·4°		8 7 a.	T.N.	−
			10 a.	+	
21 2 a.	Rigor	+	12 n.	39·1°	+
6·45 a.	40·2°				
6 p.	T.N.	−			
Plehn, F. (1898), 129, 154.					
28·4	38·7°	+*			
29	40·3°	+*			
30	40·3°	−			
1·5	39·9°	−	* Met. Hgb.		
2	37·6°	−			
3	37·6°	−			
4	39·5	+			
5	39·7°	+			
6	38·4°	−			
Broden (1906), 10.					

18.10.1910. p.m. Rigor, T. 39·5°, Hgburia.

T. of a remitting character followed for 15 days, while the Hgburia lasted 9 days. It was extraordinarily characteristic that Hgb appeared in the urine only during the few hours when the T. was at its height. Werner (1913), 10.

Date.	Time.	T.	Hgb.	Authority.
24	8 a.	99°	—	'Africa' (1914), 22.
	12 n.	103°	+	
25	8 a.	100·4°	—	
	12 n.	101°	+	
27	8 a.	99°	—	
	8 p.	103°	+	
28	8 a.	99·2°	—	
	12 n.	103·2°	+	
31	8 a.	99°	—	
	12 n.	104·8°	+	

Vide App. 26.

Relapses (Intermissions)

Duration

Month.	Initial Hgburia.	1st R.	2nd R.	3rd R.	4th R.	Page.
Nov.	19–22	30–31				98
Nov.	27–1	17				99
Feb.	10–14	18–19	20			100
Apr.	6–9	23–25				101
Jan.	?–1	7	27			102
July	26–28	11–12				103
Oct.	27–28	29–30				108
May	13–15	30				108
May	18–21	26				109
Sept.	1–6	9–11				110
Jan.	11	19	28			110
Jan.	22–23	30				112
July	17	19–20	25			114
Apr.	16	26	29			114
May	26	27	28	30	31	118
Jan.	8–10	13				119
May	30	3				120
Sept.	29–1	1				126
Nov.	30–1	11				132
July	29–3	7–10				135

Note.—One figure signifies that the Hgburia lasted for 1 day or part of a day on the particular date. Deeks and James (1911).

No. of relapse.	Duration in hours (approximately).			
	Hgburia +.	Hgburia —.	Hgburia +.	Hgburia —.
1	77½	56	6	8
2	44	7	16	2
3	2½	42	2	20
4	8½	43½	4	1
5	15	54	1	6
6	2	12	12	2
7	34½	72	2	14
8	1	20½	7	17
9	6½	17	3	43
10	7½	66	4	
11	6	17		
	3½			
	Graham (1912).		Yorke, Murgatroyd and Owen (1929–30), 352.	

Day.	C.c.	Hgb.	Met. Hgb.	Authority.
1		+	+	Barratt and Yorke (1909[a]), 211, 247.
2		+	+	
3		+	+	
4		+	+	
5		+−+	+−	
6		−+−+		*Vide* App. 26.
7	1136	−+−	−+−	
8	1079	+−	+−	
9	1374	−+−	−−−	
10	1220	−+−+	−−+−	
11	860	−	−	
12	1640	+−+−	−−−−	
13	1170	−+−	−−−	
14	1290	−	−	

The period of time between the initial attack and the subsequent relapses varied from 20 hours to 17 days.

The duration of Hgburia in the relapses bore no relation to that of the initial bout. Ross (1932), 223.

Frequency

Cases.	Intermittent cases.	Authority.
46	16	Plehn, F. (1898).
5	1	Stephens and Christophers (1900).
15	5	Daniels (1901).
35	7	Panse (1902).
20	3	Barratt and Yorke (1909[a]).
34	2	Deaderick (1910).
233	20	Deeks and James (1911).
73	11	Brem (1911), 161.
18	2	Arkwright and Lepper (1918[a]), 133.
7	1	Gaskell (1920).
78	6	Phear (1920).
305	41	Macmillan (1923–26). Ross (1932), 223.

It remains briefly to consider the intermitting form of b.w.f. I do not mean a series of malarial attacks which are complicated with slight Hgburia, and which repeat themselves so long as the destruction of the parasites is incomplete, but more or less typical b.w.f. attacks occurring daily or several times daily in the absence of parasites. Such cases are not too frequent. Among my 168 cases, 8 were purely intermittent, 19 remittent. Plehn, A. (1903[b]), 528.

Number

Intermittent cases.	Number of relapses.											Authority.
	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	
3	2									1		Barratt and Yorke (1909[a]).
											1	Graham (1912).
20	14	5		1								Deeks and James (1911).
2	1								1			Yorke, Murgatroyd and Owen (1930).
17	8	5	1	2	0	1						Ross (1932), 223.

One of Macmillan's cases experienced no fewer than sixteen relapses in a period of twenty days, with eventual recovery. Ross (1932), 223.

Quantity of Urine

Whilst there is much haemoglobin, the amount passed is usually much above normal. As the urine clears it falls below normal and may remain below for days or only for a brief period. Daniels (1901), 57.

Anuria

Day.	Urine.					
	C.c.	C.c.	C.c.	C.c.	C.c.	C.c.
1		50				
2	0	100	0		60, 5–8	0
3	0	0	0	0	0	200
4	0	4	0	0	0	0
5	0 D.[5]	5	0	0	D.[5]	0
6		7	0	0		0
7		7	0	0		1000
8		7	0	0		D.[8]
9		70	0	120		
10		300	0	0		
11		800	D.[11]	0		
12				0		
13				0		
14		D.[20]		0 D.[15]		
	182.	Case 33.	116.	117.	119.	121.
	Bérenger Féraud (1874).	Plehn, A. (1896).	Plehn, F. (1898).			

D.[5], etc. = Day of death.

Day.	Urine.				
	C.c.	C.c.	C.c.	C.c.	C.c.
1	200			170	
2	110	0		0	56
3	0	0	0	85[c]	0
4	7	0 D.[5]	50 R.	170	0 D.[4]
5	0			85	
6	9–15			85	
7	6–10			71	
8	20			71	
9	10			199	
10	D.[10]			284	
11				D.[11]	
Page	161	7	9	238	11
	Dempwolff (1898).	Panse (1902).		Grattan (1907).	'Africa' (1912).

Day.	Urine.			Day.	Urine.		
	C.c.	C.c.	C.c.		C.c.	C.c.	C.c.
1	437	365	560	6	33	73	500[c]
2	18	10	840	7	48	92	1400[c]
3	21	22	336	8	41	84	840[c]
4	11	48	336[c]	9	23·5[c]	8 D.	420[c]
5	17	92	544[c]	10	43[c] D.		D.
Case	7[a]	11	16	Case	7[a]	11	16

The transverse lines = cessation of Hgburia. D. = Death. c = by catheter.

Barratt and Yorke (1909[a]), 119, 120.

Day.	Urine.			Day.	Urine.		
	C.c.	C.c.	C.c.		C.c.	C.c.	C.c.
1	117	114		6	15	50	15
2	170	0	170	7	28	0	30
3	0	15		8	17		17
4	37	20	180	9	39		40
5	0	17					D.[11]
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'Anuric type of blackwater.'

In those cases in which suppression was almost complete and in which the oliguria was accompanied by great increase in the nitrogenous constituents of the blood, complete anuria for more than two days was rare. Ross (1932), 165.

Day.	Urine (c.c.).								Remarks.
	Case 1.	Case 2.	Case 3.	Case 4.	Case 5.	Case 6.	Case 7.	Case 8.	
1	2170	810	1920	390	1750	1420	1500	3140	Mild to moderate uncomplicated cases. Ross (1932), 166.
2	2140	3095	1123	520	960	1130	2460	2850	
3	2020	2140	1090	660	840	780	2030	2110	
4		1425	944	750	1150	1300		2075	
5		2360	1188		1480	1725			
6		1480	3120		1700	1690			
7			2330		2080		-		

Day.	Urine (c.c.).		Day.	Urine (c.c.).		Remarks.
	Case 1.	Case 2.		Case 1.	Case 2.	
1	1890	841	5	2040	737	Continued and intermitting type. Ross (1932), 166.
2	1740	383	6	1800	539	
3	2430	974	7	2350	826	
4	1470	826				

Polyuria

Day.	Urine.					Authority.
	C.c.	Colour.	Day.	C.c.	Colour.	
1	Plentiful	Deeply coloured	4	2500	Less deep	Bérenger Féraud (1874), 330.
2	4500		5	1800	Bile —	
3		Black, bloody	6	1000	Bile +	

Date.	Hgb-uria.	Urine, c.c.	T.	Blood Hgb. %.	Date.	Hgb-uria.	Urine, c.c.	T.	Blood Hgb. %.	Author-ity.
8.10	+	200	102·7°		12	—	Abundant			Plehn, A. (1896), 42.
9	+	2055			13	—	Very abundant		14	
10	+	3140		21	14					
11	—	3000		14	15				18·5	

Date.	Urine, c.c.	Hgb-uria.	Blood, Hgb. %.	Icterus.	Max. T.	Authority.
11		+	(Patient then takes Q. 10 g.!)			Plehn, F. (1898), 123.
12	1273	+	72	Slight	38·5°	
13	2021	+	68	Conjunctival	38·3°	
14	2260	+	42	Not increased	37·9°	
15	3428	—	49	Less	38·6°	
16	2120	—	47	Hardly visible	37·9°	
17	Death			Gone	37·5°	

Date.	Urine, c.c.	Hgb.	Date.	Urine, c.c.	Hgb.	Authority.
28	724	+	8	1136	—	Gray (1898), 23.
29	355	+	11	2953	—	
30	369	—	12	3095	—	
1	412	—	13	3891	—	
2	383	—	15	2897	—	
3	497	—	16	2812	—	
4	440	—	17	Normal	R.	

Second attack lasting 8 hours, occurred during recovery from typhoid. T. rose to 106° and polyuria followed. Recovery. Christophers and Bentley (1908[a]), 218.

Day.	Urine, c.c.	Day.	Urine, c.c.	Day.	Urine. c.c.	Day.	Urine, c.c.	Day.	Urine, c.c.	Author-ity.
1		10	4560*	17	2220†	1		8		Brem (1911).
2	660	11	4140	18	5010	2	1080	9		
3	796	12	2190	19	3960	3	1800	10	2400‡	
4	1792	13	3630	20	2370	4	2340	11	2100	
5	3264	14	2310	21	2550	5	2400	12	2400	
6		15	3720	22	2130	6	2700	13	3120	
7		16	1680			7		14		
Page	170					173				

* Relapse of Hgburia 5 days after the initial day of Attack 1.
† Relapse of Hgburia 15 days after the initial day of Attack 1.
‡ Relapse of Hgburia 9 days after the initial day of Attack 1. Urine of 12 hours only.

Urine 3749 c.c. was passed in the 24 hours preceding death. Deeks and James (1911), 95.

Day.	Urine, c.c.	Day.	Urine, c.c.	Authority.
1–8	Large quantities, 3409–4745 c.c. daily until death, day 8.	1		'Africa' (1914).
		2		
		3	2045	
		4	3067	
			Death, day 4.	
	31		49	

Toxic and fulminating type

Day.	1.	2.	3.	4.	5.	Case.	Authority.
Urine, c.c.	3388*				Death	1	Ross (1932),
Urine, c.c.	825	2160	2030	710†	Recovery	2	166.

* In 17 hours. † In 11 hours.

Day.	Urine, c.c.	Urine urea, %.	Blood urea, mgm. per 100 c.c.	Plasma bicarbonate, CO_2 per 100 c.c.	Pus.
4	Polyuria	2·1	120	52·4, 33·1	
5	2940	2·1	219	54·8	
6	2790c	2·4	340	62·5	Pus
7	3780c	2·4	214	73·5	
8	3150c	2·2	191	79·2	
9	3030c	2·2	165	67·8	
10	1950c	2·2	197	70·6	
11	2965		160	71·2	
12	2550		168	64·9	
13	3000	2·0	142	66·8	Pus
14			106	63·6	
15	4140	1·6	92	60·5	
16			88	59·7	
17			87	55·0	Pus
19			62	60·2	
21			57	50·3	
23			45	57·2	
26			39	55·2	
28			28		

c = by catheter.

A rapid development in a polyuric type of case of renal acidosis associated with a decreased alkali reserve equalling 33·1 c.c. CO_2 per 100 c.c. plasma. 316.

Marked nitrogen retention with a maximal blood urea of 340 mg. per 100 c.c. Urea is a powerful diuretic, and its retention and increase in the blood and tissue fluids are probably responsible for the natural tendency to polyuria in so many cases of b.w.f. which recover. 324. Fairley and Bromfield (1934–35).

Rate of secretion

Hour.	Day 1.		Day 2.		Day 3.		Day 4.		Case.
	C.c.	Hgb.	C.c.	Hgb.	C.c.	Hgb.	C.c.	Hgb.	
2			119, 94	+	96	+	17	—	
6		+	159, 114	+	77	+	17	—	
10	114, 213	+	162	+		+		—	1
2	199	+	139	+	25, 8	+		—	
6	105, 113	+	153	+		—	17	—	
10	218, 139	+	91	+		—		—	
	1101		1031		206		51		
2		+		+		—			
6		+	38, 34	+		—			
10		+		—		—			2
2	116	+		—		—			
6		+	45	—	34	—			
10	45, 40	+		—		—			
	201		117		34				
2				+		—			
6			28	—	34	—			
10	99	+		—		—			3
2	94	+	40	—	62	—			
6		+		—		—			
10	54	+		—	54	—			
	247		68		150				

The figures show an increase in the amount secreted during the Hgburic period followed by a drop below normal as the urine clears, and a slow return to normal (not shown). Daniels (1901), 78.

Nervous System

Amnesia

Day 26. There was almost complete amnesia regarding his illness, and for some time his cerebration and reaction times were slowed. Fairley and Bromfield (1934–35), 315.

Vide infra, Uraemia.

Anaesthesia

The day before the onset of b.w.f. he complained of right hemi-anaesthesia with burning sensations in hands and feet lasting some hours. 'Africa' (1914), 36.

Anxiety (*anguish, oppression*)

7 in 48 cases. Plehn, A. (1896).
8 in 43 cases. Plehn, F. (1898).
1 in 10 cases. Seyfarth (1918[b]).

Day 1 (?). Anxiety so great that the patient cries out. Case 31[3]. Plehn, A. (1896), 49.

Day 2. Great anxiety and restlessness. Very great irritability, distressing vomiting, anuria. 122.

Day 1. High T. marked icterus, violent vomiting, great air-hunger, agitation and feeling of anxiety. 148. Plehn, F. (1898).

Aphasia

El Centro, Colombia, S.A. Blackwater (?) commenced 9 days after admission with *P. vivax*. Q. and plasmoquin for 4 days before onset. Cyanosis, aphasia and spastic paralysis present. The Hgburia was possibly the result of plasmoquin poisoning. Death. Paterson (1932–33), 542.

Aphonia

Day 3. 7 a.m. P. 120, R. 36. Inclined to be drowsy; 8 a.m. digitalis and strychnine for heart failure; 11.30 a.m. somnolent, P. 120, R. 48, digitalis and strychnine; 4 p.m. quite conscious, could move his arms, but could not talk. (Death.) 48.

Day 3. I was in a very weak condition; the muscles of my vocal cords becoming paralysed, I could not speak. (Recovery.) 53. 'Africa' (1914).

Confusion

Day 2. General condition grave, dulness of expression, intelligence blunt, no delirium. Barthélemy-Benoit (1865), 23.

Day 3. No sleep, vomiting (green) throughout the night. The features are tired, the face anxious, the patient 'is like an idiot.' Béranger Féraud (1874), 219.

Day 1. Severe vomiting, headache and backache, mental confusion. 137.

Day 1. Urine scanty, 20–40 c.c. at a time. Pronounced feeling of anxiety and some mental confusion. 147. Plehn, F. (1898).

Convulsions

18.10.1900. Hgburia.
19. Hgb negative. Fever of no definite type until
3.11. *P. falciparum*. General condition not improved. Apathy alternates with excitability. Repeated clonic contractions of the legs. In the evening a definite hysterical convulsive attack.
9. Death, preceded by high fever and convulsions. Panse (1902), 6.

Cramp

Day 3. Fairly severe headache all day, cramp in the calves. 9 p.m. severe headache, cramp in the legs, epigastric pain. 126.

Day 1. 7 p.m. slight icterus, lumbar pain, feeling of constriction at the base of the chest, painful micturition. Cramp in the calves during the whole of the attack. 363.

Day 17. Rise of temperature beginning with cramps in the fingers and toes. Urine reddish. 372. Bérenger Féraud (1874).

Day 2. T. 38·2°, very restless night. Patient complains that on falling asleep he always gets cramp in the calves. Case 14. Schellong (1890), 68.

Day 1[a]. T. became raised; patient suffers from vomiting and diarrhoea, and is very restless. Has painful cramps in muscles of legs. Barratt and Yorke (1909[a]), 178.

Female, aet: 37. Paris.

20 Ap. 1912 (day 2). Much agitated, replies to questions with volubility and without precision, complains incessantly of very painful cramps in both arms, especially the fore-arms. Treated with opiate frictions, the painful contractions cease. Achard and Saint-Girons (1912), 749.

Cases 49. 3 had clonic tonic cramps. Weselko (1926), 658.

Delirium

2 in 48 cases. Plehn, A. (1896).

10 in 43 cases. Plehn, F. (1898).

3 in 10 cases. Seyfarth (1918[b]).

In severe cases delirium occurs. Patients talk irrationally, try forcibly to get out of bed and are only with difficulty stopped. 108.

Day 1. Acute pain in the spleen, and periods of delirium. 130. Plehn, F. (1898).

Delirium (identical)

1903. Blackwater. During the attack delirium. Counting plates (used in his engineering work) into a heap moving them from left to right; having made the stack, he then got the idea that all this was all wrong, and restacked them from right to left.

1926. Blackwater. He experienced delirium absolutely identical with that of his previous attack. Senior-White (1928), 271.

Dreams (nightmare)

1 in 48 cases. Plehn, A. (1896). 1 in 43 cases. Plehn, F. (1898).

Day 6. Sleep frequently disturbed by very exhausting nightmare.

Day 17. Vomited all night, general malaise and pains in the limbs, distressing nightmare. Bérenger Féraud (1874), 364.

Day 6. No sleep. Broken dreams. No motions since onset of attack except for dry grey scybala removed by enema. Pellarin (1876), 191.

Day 1. Oliguria. Afternoon slight delirium, patient complaining of bad dreams, and acute pain in the back. Plehn, F. (1898), 130.

Day 3. After some slight sleep, at midnight the patient becomes excited (nightmare) and vomits. Exhaustion, answering questions but slowly in a broken voice. Gouzien (1900[a]), 48 (r.).

Drowsiness (*somnolence, stupor*)

2 in 48 cases. Plehn, A. (1896).

9 in 43 cases. Plehn, F. (1898).

Day 6. Restlessness, sub-delirium, broken dreams, and sometimes prolonged drowsiness.

Day 8. Patient very exhausted, almost continuous somnolence.

Day 9. Recovery. Barthélemy-Benoit (1865), 22.

Day 4 (?). Had a restless night, urine normal in colour, rather drowsy all day. 84.

Day 13. Extremely weak condition; in the night was light headed.

Day 14. Slightly better, but very drowsy. T. 101·9°, P. 123, R. 34. 87.

Day 2 (?). The patient had been drowsy, the skin was moist, and the jaundice deeper. 89.

Day 1. 8 p.m. His hands and feet were cold and he was perspiring heavily, vomited a great deal, and was drowsy all day. 95.

Day 7. At night he was *very* drowsy. Recovery. 105. Crosse (1892).

In severe cases deep somnolence occurs. Patients lie in an apathetic condition and faeces and urine are passed under them. Plehn, F. (1898), 108.

In the severe cases, mental confusion and drowsiness

became marked on the second day, often accompanied by an increase of the vomiting which had usually begun on the first day. Gaskell (1920), 11.

Formication

Some patients suffer from formication all over the body, while in others numbness of the extremities may be accompanied by cryaesthesia. Gouzien (1911), 31 (r.).

Day 2. 2 a.m. T. rises again with violent vomiting and a rigor of ¾ h. duration. Great prostration, tingling in fingers and toes. Plehn, F. (1898), 130.

Hyperaesthesia

Digital hyperaesthesia in 8 of 20 cases. Da Costa (1906).

Insomnia

4 in 48 cases. Plehn, A. (1896). 3 in 43 cases. Plehn, F. (1898).

The majority, especially at the onset, suffer from persistent and terrible insomnia. Gouzien (1911), 31 (r.).

Day 4. Vomiting very severe and bilious. Hiccough troublesome throughout. Insomnia constant. Urine 230 c.c. Death. 'Africa' (1914), 29.

Jactitation

Hiccough is another very distressing condition. There is also a nervous jactitation peculiar to the disease. Sparkman (1901), 290.

Kernig's sign

Comatose on admission; retraction of neck and positive Kernig sign (Case 20). Deeks and James (1911), 83.

Mentality

Day 7. At times the patient was quite comatose; at others more or less sensible and irritable. (Death, day 9.) Crosse (1892), 73.

All the cerebral symptoms of b.w.f. can be explained by the anaemia of the brain . . . the extreme lassitude and

lack of tone, the common condition of drowsiness, while the patient if roused has his mind clear. Further, the striking condition of neurasthenia, with frequent alarm for trifling reasons, or in the case of many, excitability and irritability. Again, paraesthesiae and hyperaesthesiae are not uncommon. Most patients were very sensitive to a needle-prick. . . . The seldom absent photophobia must be attributed to hyperaesthesia of the optic nerves. The obstinate vomiting, often paroxysmal, is also in the main of cerebral origin. Steudel (1894), 41.

22 July. 5 p.m. Hgburia. Later, rigor, vomiting, stupor, great restlessness. Will take neither drugs nor nutriment.

23. Lies in bed apathetic. Headache, vomiting, mentally not quite clear, restless sleep, slight tremor of the hands. Somewhat delirious, and on account of his deafness, thinks that if anyone has said anything he is being maligned. Consequently, a very irritable disposition and extreme obstinacy and resistance. Only with great trouble can the patient be induced to drink (fear of vomiting). Lips dry, tongue coated, appetite bad, thirst moderate. Doering (1895), 762.

Day 7. Patient extremely irritable and complained of intense thirst. There was some vomiting. Hot water enemata revived him greatly. Urine 436 c.c. Gray (1898), 26.

Mentality in anuria

6 Nov. 100 c.c. of urine during night, black by reflected, red by refracted light.

7. Contracted features, much sunken, great restlessness. All symptoms worse except T., which has almost completely fallen. Skin cold and covered with a viscid sweat. Profound weakness, intelligence completely preserved. Patient fully realizes his con-

dition and is extremely anxious about his young children.

8. 7 a.m., death. Pellarin (1876), 301.

There may be slight drowsiness or giddiness, but pain is not usually complained of, and the patient remains conscious and mentally active.' Ross (1932), 216.

Numbness

Day 1 (?). Patient suffered from chilliness, nausea, headache and numbness of the feet. 88.

Day 1. In the evening complained of numbness of extremities and hepatic and splenic uneasiness. 92. Crosse (1892).

Numbness of extremities in 3 of 43 cases. Plehn, F. (1898).

Patients often complain of numbness of extremities. Crosse (1899), 120.

Day 3. Frequent vomiting of greenish fluid and complaint of numbness in legs. 'Africa' (1912), 33.

Nystagmus

Vide infra, Uraemia.

Paralysis

12 Sept. Hgburia.

23. For the last 2 or 3 days patient has had paralysis of the left arm and leg; sensation is preserved; he complains of acute pain in the upper third of the arm.

3 Oct. Commences to move the left leg.

8. Slight movement in the shoulder.

9. The movements of the leg are complete. Bérenger Féraud (1874), 217.

Day 9. Definite improvement, intelligence returning. Slight ptosis of left eye(-lid) and labial commissure of the same side.

Day 18. Face normal. Strength returning. Gouzien (1900[a]), 32, (r),

Restlessness

Cases.	Present.	Absent.	No record.	Authority.
48	9		39	Plehn, A. (1896).
43	9		34	Plehn, F. (1898).
14	1		13	Brem (1906).
10	3		7	Seyfarth (1918[b]).

Day 3. Broken sleep, the patient constantly turning in his bed. Headache still acute. Bérenger Féraud (1874), 147.

Day 2 and 3. Vomiting and restlessness, very severe. Case 107. Deeks and James (1911), 91.

Sciatica

Day 2. 9 a.m. severe attack of shivering, which lasted for half an hour, hands and feet icy cold, and at the same time, severe sciatica. Crosse (1892), 81.

Spasms

Day 2. The vomiting is preceded by restlessness, anxiety, rambling, transient delirium and spasmodic movements of the arms hands and lips, pallor of the face, lividity.

Day 3. Death. Pellarin (1876), 212.

Tremors

Day 3. Extreme weakness, in spite of active agitation and sub-delirium. He talks incessantly, the hands continually trembling (history of constant dyspepsia, probably of alcoholic origin).

Day 4. Greater prostration, somnolent, hyperpyrexia, tongue coated and dry, trembling of the lips and hands, embarassed speech, delirium. 25 (r.).

Day 4. A bad night, insomnia, sub-delirium, vomiting, icterus, prostration, muscular tremors. 30 (r.). Gouzien (1900[a]).

Unconsciousness

Patient had on account of indisposition taken half a grain of Q.; half an hour later he lost consciousness and remained insensible for six hours. Dark urine, then anuria for two days. (Recovery.) Kleine (1901[c]), 666.

Vertigo

Day 2. Vertigo and a sense of emptiness in the head. Urine less deep, less scanty (100 c.c. about). Painful epigastric constriction. T. 36·8°. Gouzien (1900[a]), 45 (r.).

OCULAR

Amaurosis (*quinine*)

♀, aet: 20.

27 July. Hgburia.

28. Intense icterus, bloody urine 200 c.c., Q. 1·0 g. × 5.

29. Improvement. In the morning Q. 1·5 g., midday complains of tinnitus; 1 p.m. suddenly repeated bilious vomiting, rigor, high T., delirium with loud shrieks until 3 p.m.; 2.30 p.m. Q. 0·5 subcutaneously; 5 p.m. Q. 1·0 g. in tablets; 8 p.m. patient complains that she cannot see. Q. stopped, evening antipyrin 1·0 g., the previously scanty sweating becomes profuse. Total Q. 3·0 g. At night absolutely insensitive to electric light.

30. Profuse sweating, evening urine almost clear. Noon, can count fingers 1 m. distant with difficulty.

1 Aug. Vision almost normal.

16. Convulsive epileptic attack. Küchel (1895), 447.

Amblyopia

An occasional complication, 4 cases in 1871, and 4 or 5 in 1872. The patients are very anaemic. Pupils more dilated and less contractile than usual. In two cases the outline of the pupil not quite circular. Patients are unable to bear a full light. Twilight suits them best. They complain of foggy vision. Ophthalmoscope: at first a

hyperaemia of the retina and choroid, later there is anaemia of the retina and the blood passes in spurts through the empty vessels. Similar conditions occur in anaemia following other causes. Bérenger Féraud (1874), 212.

Day 1. Profuse bloody vomit, and much blood in the numerous diarrhoeic stools.

Day 18. Has made little progress towards recovery, and suffers much from defective vision, especially in the right eye.

Day 26. Convalescence sets in. Defective vision persists. Ophthalmoscope reveals no change. Plehn, A. (1896), 46.

During convalescence reads print with difficulty and recognizes people only at a short distance away. Previously sight was normal. Vision improved later. Gouzien (1900[a]), 35 (r.).

At one time T. rose to 108°, but fever ceased on day 5. A remarkable feature of this case was the occurrence of double amblyopia, from which patient subsequently recovered. Christophers and Bentley (1908[a]), 222.

Among unusual symptoms, impairment of near vision. Connal (1916), 11.

Cases 49. 1 case of blindness on day 2 produced by retinal Hges, and lasting about 2 months. Weselko (1926), 658.

Asynergism

Day 7 (?). Extreme weakness, . . . face drawn and the two upper eyelids do not move synergically. Bérenger Féraud (1874), 167.

Haemorrhages

14.11.1891. Hgburia.

18. In both eyes around the papilla and macula lutea numerous fresh Hgic patches on the retina. Central vision, not much affected; considerable restriction of the visual field.

1.12. Patient convalescent, headache from time to time, vision considerably diminished.

Right E. S. 6/25. Left E. S. 1/25. 0·8 'buch-stabirend.'

Vision restricted in both eyes, centrally, and to the left 30°, to the right 20°. Slight pallor of the optic discs, narrowing of the vessels, small Hges around the macula lutea, and numerous choroidal patches. Kohlstock (1892), 428.

Day 14. Convalescence proceeding rapidly, Hgb 34%. Patient has complained for some days of defective vision.

Day 17. Retinal haemorrhages in both eyes, Hgb 42·5%.

Day 23. The purplish-red discolorations have turned white. Vision again restored. Hgb 45%. Plehn, A. (1896), 63.

Day 24. Convalescence fully established. Exit from hospital delayed by reason of slight trouble of vision.

Right eye: a triangular patch with the upper angle blunted, peripherally deep red, centrally brown. The transverse diameter $1\frac{1}{2}$ that of the papilla, the vertical = that of the papilla, situated almost exactly in the centre of the macula.

Left eye: a dark red crescentic shape patch, darker at the periphery than centrally. Greatest diameter twice that of the pupil, vertically $\frac{3}{4}$ of the pupil, situation as in the right eye. Below the papilla there is also a small red patch in contact with a vessel. The patches are actually retinal haemorrhages forming a film (' en nappe '). Boisson (1896[a]), 379.

R. act: 27. Feb. 1916. B.w.f. in Senegal. Invalided to France.

3 June, 1916. Hgburia.

25. Complains of dimness in left eye. Left eye, V = 3/10, with a feeling of mist and scotoma. A very small macular Hge, bounded above by a horizontal

line passing through the centre of the macula, semicircular below. In addition, there is a small punctiform Hge in the course of the inferior temporal artery (à deux diamètres papillaires environ en dehors).

Right eye, V. = 7/10. Does not complain of anything, but after dilatation with atropin a small punctiform Hge. of the macular region is found. Genet (1917), 375.

20 June. Complained that there was a dark spot in the centre of the right eye.

26. Complained of flashes of light, mist and spots in the left eye, which was normally weak, short-sighted and astigmatic. Photophobia in both eyes.

12 July. Below the papilla of the right eye was a haemorrhagic incomplete triangular area, 2 × 1·5 mm. The left eye showed no lesion.

20 Aug. Haemorrhage no longer detectable. Connal (1922), 379.

17 Nov. Urine 'becoming red in colour.' Hgb passed apparently until

27. Admitted, Hgburia, profound anaemia.

29. Transfusion, 360 c.c. of blood.

30. Defective vision. Ophthalmoscope: retinal haemorrhages. Yorke, Murgatroyd and Owen (1930), 350.

Keratitis punctata

Patient had *keratitis punctata* and two small haemorrhages on the temporal side of the disc, near the centre of the *macula lutea*. The *keratitis punctata* pointed to a past history of spirillum fever. 'Africa' (1915), 45.

Photophobia

Day 9. The anaemia (Hgb about 8%) rapidly increases and serious symptoms develop such as complete numbness in the cold hands, but with pronounced

hyperaesthesia over the whole body, as also photophobia, so that by day the patient wears grey spectacles. Steudel (1894), 13.

Day 5. Patient gravely ill. Dyspnoea, cyanosis and restlessness were marked, and there was photophobia, mental irritability, hiccough and vomiting. Fairley and Bromfield (1934–35), 152.

Pupils

Day 7. Passed little or no urine. Pupils very small but reacted to light. The breathing heavy and blowing, the skin cold, death day 9. Crosse (1892), 73.

Day 2. Quite unconscious, answers not a word, pupils small, react to light, involuntary urine and faeces. In the evening consciousness regained, at night unconscious.

Day 3. 7 a.m. conscious; 9 a.m. T. rises, unconscious. (Death.) Plehn, F. (1898), 115.

Day 4. Intense icterus, green vomit, very frequent grey liquid stools, epigastric pain, dyspnoea, R. 30, P. uncountable, T. 36°. Urine 100 c.c. in night of 3rd and 4th days. Pupils normal. Death 1 p.m. Porak (1918), 560.

Strabismus

Day 4. At night delirium, slight convergent strabismus to left, inequality of pupils, no choroidal tubercles, no rigidity of the neck, reflexes increased, speech difficult, death (? when). Naumann (1933), 303.

Yellow vision

I have never seen this icterus produce itching or visual troubles, *e.g.* xanthophia. Foncervines (1873), 13.

Day 2 (?). He had general jaundice, the conjunctivae were markedly yellow, and objects appeared to have a yellow tinge. 68.

Day 1. He was all over of a dark greenish-yellow colour, said that objects looked yellow. 71.

Day 1. Drowsy and restless, he had a cold perspiration and said things looked yellowish. 75.

Day 1. Markedly jaundiced but did not see objects yellow. 95. Crosse (1892).

Oedema

Day 13. Complains that his feet swell when he tries to get up.

Day 18. Owing to the oedema of the legs arising when the patient walks, the urine—which is abundant—was examined, but contained no trace of albumen. Béranger Féraud (1874), 340.

Day 13. After a short walk it was noticed that there was some oedema of both ankles. Urine, albumen negative. Crosse (1892), 82.

30.5. B.w.f.

6.6. Heart dullness not increased, over the orifices indistinct systolic (anaemic) murmurs, face somewhat puffy, but no oedema. 30.

7.5 (day 1). 50 c.c. of ink-black urine.

13. 7 c.c. of urine.

14. Face oedematous, 7 c.c. of urine, fatty epethelium, no casts. 33. Plehn, A. (1896).

1 Sept., '93. Hgburia lasting 3 days. Since then has suffered from profound weakness, shortness of breath, palpitation of the heart and persistent nausea.

13. Unable to stand. Wax-like, somewhat puffy appearance, slight oedema about the ankles. T.N.

15. The oedema on account of the horizontal position (in bed) has almost disappeared. Plehn, F. (1898), 126.

Day 8. Injection of saline 250 c.c.

Day 9. Slight oedema of the face which is waxy and very pale. Gouzien (1900[a]), 32 (r.).

Day 6. General condition good, slight vomiting once, urine 35 c.c.

Day 8. Lethargic and feeble; in the evening dyspnoea increased, slight anasarca of hands and face. Barratt and Yorke (1909[a]), 198.

Day 2. Saline injection 200 c.c. 3 enemata of 500 c.c. each. Urine 150 c.c.

Day 3. Saline enema and lactose (50 g. per litre) enema. Urine 50 c.c.

Day 4. 2 lactose enemata. Urine 0 c.c.

Day 5. Slight pretibial oedema. Urine 50 c.c. (catheter). Saline enema 250 c.c. Lactose enema 250 c.c.

Day 6. Oedema of face, lids and tibia. Urine 10 c.c. (catheter).

Day 7. Oedema has increased. Urine 0 c.c.

Day 8. Saline injection 300 c.c. Urine 26 c.c. Profuse sweats.

Day 9. Death. Lahille (1915).

In 1 of 39 cases, ascites and oedema of the scrotum. Connal (1916), 11.

In 1 of 28 cases oedema of face neck and chest as the urine was clearing but getting less in amount. Connal (1922[a]), 7.

4 Jan. B.w.f.

6. Antivenomous serum 20 c.c., repeated in the evening. Glucose serum 45‰ 250 c.c. subcutaneously. Cups to the liver and kidneys.

7. The same treatment + an enema with $CaCl_2$ 1/100[e].

8. Antitetanic serum used as the antivenomous stock was exhausted.

20. Oedema (pitting on pressure) of legs extending gradually to abdomen. No cardiac lesion, urine, albumen, a trace.

23. Oedema of flanks. Cardiac tonics and diuretics.

28. Oedema gone. Feyte (1932), 832.

Otitis and mastoiditis

28 Feb. Hgburia.
8 March. Epistaxis.
20. Epistaxis.
1 April. Acute ear-ache.
4. At times very painful exacerbations, discharge fairly abundant.
6. Sensation of weight in mastoid region.
11. Pain in right, temporal, orbicular and frontal regions.
16. Continuous pain, especially in mastoid region. The discharge from the ear has almost stopped.
25. Pain in mastoid region more acute, spreading to the temporal region and posterior parts of the neck, no discharge.
28. Pain much decreased, the head moved more easily, hearing unimpaired.
29. Discharged. Bérenger Féraud (1874), 172.

Pain

Abdomen

Cases.	Present.	Absent.	No record.	Authority.
15	1		14	Crosse (1892).
49			49	Plehn, A. (1896).
43	10t		33	Plehn, F. (1898).
14			14	Gouzien (1900a).
14	2		12	Brem (1906).
20			20	Da Costa (1906).
19			19	Barratt and Yorke (1909a).
39	3		36	Connal (1916), 11.
10			10	Seyfarth (1918b).
17	3		14	Arkwright and Lepper (1918b).

t = tender.

Day 1. The spleen is painful and somewhat enlarged. The whole abdomen is somewhat sensitive to pressure. Plehn F. (1898), 131.
Day 2. There has been headache, vomiting, constipation and abdominal pain. Brem (1906), 6.
Day 1. He complained of great abdominal pain and of

having been very constipated; mustard plasters were applied to abdomen; sod. bicarb. and liq. hydrarg. perchlor. every two hours.

2. Mag. sulph. Bowels opened. Calomel grains 3.
3. Bowels not satisfactorily opened, enema given, little result. Complains much of colicky pain in abdomen.
4. Complained of much pain in right iliac region.
5. Mouth and tongue sore, bleeding easily (Hg poisoning).
6. Some diarrhoea with blood and mucus.
20. Severe cramp-like pains in abdomen.
28. Large pale motions, no fermentation, once daily. 'Africa' (1912), 33.
29. Midnight, rigor, vomiting, severe abdominal pain, headache. Water darker than usual (Hgburia ?).
30. 2.30 a.m. considerably pain of a colicky nature and a tendency to vomit. 'Africa' (1914), 49.

Day 2. Bowels have acted several times loosely, and containing much mucus.

Day 4. 9 a.m. Very weak, T. 99°, P. 112, small and soft. Complains of severe pain over the whole abdomen, which pain he has had since the day before onset. 'Africa' (1915), 21.

Bladder

Day 1. 11.30 p.m. rigor lasting 25 minutes associated with vomiting and tenderness over the bladder and spleen. Fairley and Bromfield (1934–5), 150.

Body

Cases.	Present.	Absent.	No record.	Authority.
49	2		47	Plehn, A. (1896).
43	2		41	Plehn, F. (1898).
14	1		13	Brem (1906).
19		1	18	Barratt and Yorke (1909[a]).
17			17	Arkwright and Lepper (1918[b]).
10	1		9	Seyfarth (1918).

Day 12. Patient very weak. Complains of pain in the body, which is tender all over.

Day 15. Acute headache and pain in the body. The abdomen is tender, especially the liver region.

Day 16. Death. Plehn, F. (1896), 118.

Pain all over the body followed in 24 hours by Hgburia. 'Africa' (1915), 65.

Epigastric

Cases.	Present.	Absent.	No record.	Authority.
32	15	2	15	Bérenger Féraud (1874).
15	3		12	Crosse (1892).
49	1		48	Plehn, A. (1896).
43			43	Plehn, F. (1898).
14	3		11	Gouzien (1900[a]).
14			14	Brem (1906).
20	11		9	Da Costa (1906).
19			19	Barratt and Yorke (1909[a]).
39	2		37	Connal (1916), 11.
17	2		15	Arkwright and Lepper (1918[a]).
10			10	Seyfarth (1918[b]).

Day 4. Vomiting less.

Day 5. Fairly good night, vomited once. Bowels well opened, acute epigastric pain, spleen and liver tender on pressure.

Day 6. Bilious diarrhoea throughout the day. Case 17. Crosse (1892).

Day 2. Giddiness and a feeling of emptiness in the head. Painful constriction in the epigastrium. Gouzien (1900[a]), 45 (r.).

Day 4. He complained of epigastric, hypogastric and lumbar pains. Epigastric tenderness was noticeable. 'Africa' (1915), 39.

Girdle

In one case there was a sensation of tightness round the waist, which is possibly similar to the feeling expressed by another of the patients as a pressing desire to pass urine. 'Africa' (1915), 52.

10.8.96. Q. 1·0 g., urine clear.

11. Q. 1·0 g. × 2, urine clear. At night, sudden alarming acute back and girdle pains. Dempwolff (1898), 162.

Day 2. A new paroxysm. Urine very frothy; port-wine colour, T. 40·9°, P. 112, nausea and bilious vomiting, girdle pains. O'Neill (1882). Mannaberg (1905), 325.

Glans penis

Day 4. Pain in glans penis on urination, strangury is more acute, urine 2260 c.c. 124.

Day 1. Onset with shivering and distressing nausea, acute strangury, urination with pain in glans penis. 160. Plehn, F. (1898).

Headache

Cases.	Present.	Absent.	No record.	Authority.
32	17	2	13	Bérenger Féraud (1874).
14	4		10	Crosse (1892).
49	8	1	40	Plehn, A. (1896).
43	18		25	Plehn, F. (1898).
14	5		9	Gouzien (1900[a]).
14	13	1	0	Brem (1906).
20			20	Da Costa (1906).
19	1		18	Barratt and Yorke (1909[a]).
17	1		16	Arkwright and Lepper (1918[b]).
10			10	Seyfarth (1918[b]).

Day 1. He had also slight headache, severe backache and vomited freely. Brem (1906), 20.

Day 1[a]. He had a very severe headache.

Day 3. Headache still troublesome. Barratt and Yorke (1909[a]), 186.

From day 9 to day 13 epistaxis and severe headache were troublesome symptoms. Yorke, Murgatroyd and Owen (1930), 338.

Hepatic

Cases.	Present.		Absent.		No record.	Authority.
	p.	t.	p.	t.		
32	8	3			21	Bérenger Féraud (1874).
15	6	3		1	7	Crosse (1892).
48	1	3		1	44	Plehn, A. (1896).
43		10			33	Plehn, F. (1898).
14		1			13	Gouzien (1900[a]).
38		4			34	Panse (1902).
14		1			13	Brem (1906).
20		(10)*			20	Da Costa (1906).
19					19	Barratt and Yorke (1909[a]).
39	1				38	Connal (1916), 11.
17		2		1	14	Arkwright and Lepper (1918[b]).
10		1			9	Seyfarth (1918[b]).
5	1				4	Yorke, Murgatroyd and Owen (1929–30).
9		2			7	Fairley and Bromfield (1934–35).

* Congestion.

p = pain, t = tenderness.

Hepatic pain a marked feature, both of the early attacks and also in the rises of temperature in the post-Hgburic period. Daniels (1901), 64.

Pain in the hepatic region may be more or less generalized over the whole liver area, or localized in the region of the gall bladder—tenderness rather than pain. Ross (1932), 230.

Hypochondria

1. Palpation of the epigastric and hepatic regions causes acute pain, chiefly in the left hypochondrium. Barthélemy-Benoit (1865), 18.

Day 1. Hypochondria painful on pressure, but no increase of dulness. Corre (1883), 148.

Case 15. Day 1. Patient complains of pain in the pit of the stomach. This as well as the right hypochondrium is sensitive to the softest pressure. By

percussion the lower border of the liver not enlarged. Schellong (1890), 70.

Hypochondrium.				
Cases.	Present.	Absent.	No record.	Authority.
32	6		26	Bérenger Féraud (1874).
14	1		13	Crosse (1892).
10	2		8	Seyfarth (1918[b]).
Hypogastrium.				
32	5		27	Bérenger Féraud (1874).
14	1 p + t		13	Brem (1906).
19	2		17	Barratt and Yorke (1909[a]).
17	2		15	Arkwright and Lepper (1918[b]).

Hypogastrium

Day 1. Acute pain in the lumbar and hypogastric region.
Day 2. The lumbar pain has much diminished, but the hypogastric persists.
Day 3. The hypogastrium is still very painful and also the perinaeum. Bérenger Féraud (1874), 369.

He was much distressed and complained of pain in the abdomen, putting his hands to the hypogastric region. Barratt and Yorke (1909[a]), 225.

Legs

Cases.	Present.	Absent.	No record.	Authority.
14	2*		12	Crosse (1892).
43	3		40	Plehn, F. (1898).
14	1		13	Gouzien (1900[a]).
14	2†		12	Brem (1906).
19	2		17	Barratt and Yorke (1909[a]).

* Pain and heaviness. † Limbs 1, legs 1.

The patient, like the last, complained of pain and heaviness in the legs. Crosse (1892), 77.

Day 1. Violent pains in lumbar region, general weakness and shooting pains in the legs. Gouzien (1900[a]), 39 (r.).

Day 1. Agonising pains in loins, epigastrium and legs, midnight Hgburia. 'Africa' (1914), 61.

Lumbar

Cases.	Present.	Absent.	No record.	Authority.
32	11	3	18	Bérenger Féraud (1874).
49	4		45	Plehn, A. (1896).
43	10		33	Plehn, F. (1898).
14	6		8	Gouzien (1900[a]).
14	5	3	6	Brem (1906).
20	2		18	Da Costa (1906).
19	4		15	Barratt and Yorke (1909[a]).
39	8		31	Connal (1916), 11.

Its maximum intensity corresponds to the maximum of the fever; it diminishes with the latter, but does not cease entirely so long as the urine remains bloody. Barthélemy-Benoit (1865), 214.

It makes its appearance early, and its duration corresponds to the period of Hgburia. In cases characterized by oliguria or anuria, it is as a rule a persistent symptom during the whole of the anuric period. Ross (1932), 230.

Micturition

Cases.	Present.	Absent.	No record.	Authority.
49	7		42	Plehn, A. (1896).
43	16		27	Plehn, F. (1898).
14	1		13	Brem (1906).

Day 1. 200 c.c. of dark red urine passed drop by drop with intense burning. Plehn, A. (1896), 42.

Day 1. Rigor and intense air hunger; the urine is very scanty and micturition painful. 121.

Day 1. Acute strangury, urine passed in small quantities with intense pain. 132. Plehn, F. (1898).

There is discomfort, rarely amounting to pain in micturition. Daniels (1901), 57.

Miscellaneous

Pain was recorded in 21 of 39 cases. In 4 pain was absent. In 14 there was no record. Pain was in the back in 5, umbilical in 1, post-cervical in 1. Connal (1916), 11.

Muscular

D.N., aet: 16. Kasan, Russia.

25.5. a.m. T. 37·2°, urine reddish, pain in the region of the backbone, in the calf, and especially in the hip-muscles. Vomiting, hiccough, nausea. Urine 250 c.c. (48 h.), dark red, sp. gr. 1041, blood *P. vivax*.

26. Urine 550 c.c. (24 h.), sp. gr. 1028. Perekropoff (1926), 287.

Pectoral

Case 14. Day 3. T. 38·1°. Patient complains of a feeling of constriction in the chest, which makes it impossible for him to lie on the right side. Schellong (1890), 69.

Cases.	Present.	Absent.	No record.	Authority.
49	1		48	Plehn, A. (1896).
43	8		35	Plehn, F. (1898).
19	1		18	Barratt and Yorke (1909[a]).

Day 1. A very violent rigor lasting 2 hours with an extremely painful feeling of oppression over the chest. 131.

Day 1. Violent rigor, intense icterus, distressing nausea, great restlessness, praecordial 'anxiety,' pain in back and legs. 143. Plehn, F. (1898).

Perineal

May 96. Acute chill apparently after a journey. Since then shivering and perineal pain with flatus.

7.7. Q. 1 to 2 g., on account of slight fever and perineal pain.

9. Q. 1·0 g., 4 hours later shivering, and return of the acute perineal pain; 5 p.m. urine 100 c.c., dark red. Dempwolff (1898), 162.

Praecordial

Day 4. Patient complains of persistent insomnia and a sensation of suffocation and constriction in the precordial region, P. still rapid and at times irregular.

Day 8. Patient complains of the same precordial anxiety, heart beats regular, death. 25.

Day 4 (?). Dyspnoea and praecordial distress have increased. (An anti-spasmodic draught of ether and laudanum, a large blister on the epigastric region.)

Day 5. The cardialgia is more bearable. 21. Barthélemy-Benoit (1865).

Day 2. Persistent nausea and vomiting, much praecordial distress and restlessness, very little sleep, urine black, abundant. Pellarin (1876), 190.

Cases 48. Praecordial pain 3. No record 45. Plehn, A. (1896).

3 Oct. Sudan. Hgburia.

5. At about 7 p.m., contrary to orders, he got up to use a night stool and fainted; on coming round he was seized with a most severe attack of dyspnoea with acute anginal pain over the cardiac region. Crispin (1905), 358.

Day 1. 2 p.m. Hgburia, 4 p.m. marked praecordial pain and breathlessness. Christophers and Bentley (1908[a]), 188.

Renal

Cases 15. 4 pain, 1 tender, 11 no record. Crosse (1892).

Cases 48. In 1 the pain recorded as renal. Case 11. Plehn, A. (1896).

Day 1. Slight tenderness over left kidney.

Day 3. Tenderness over kidney absent. 'Africa' (1915), 11.

Scrotum and Testes

Retraction of the testicles is common. Daniels (1901), 57.

Has been passing Hgb for 5 days; pain in abdomen and scrotum. Deeks and James (1911), 89.

Splenic

Cases.	Present.		Absent.		No record.	Authority.
	p.	t.	p.	t.		
15	4	5			7	Crosse (1892).
49	1		1		47	Plehn, A. (1896).
43	3	12	1	9	18	Plehn, F. (1896).
14	1				13	Gouzien (1900[a]).
14		2			12	Brem (1906).
17	1				16	Arkwright and Lepper (1918[b]).
39	1				38	Connal (1916), 11.
14		2			12	Arkwright and Lepper (1918[b]).
7	2					Fairley and Bromfield (1934).

p = pain. t = tenderness.

Day 2. The whole abdomen, especially the splenic area, is tender. Plehn, F. (1898), 123.

Day 2. Acute tenderness, which persisted for several days, over the splenic area. Owen and Murgatroyd (1928), 503.

Strangury

Cases 49. Present 2. No record 47. Plehn, A. (1896).

Cases 43. Present 4. No record 39. Plehn, F. (1898).

Day 1. Urine blackish red, micturition painful, acute strangury. Only 20–30 c.c. passed at a time. Plehn, F. (1898), 144.

Dysuria and tenesmus are rare but occur. Daniels (1901), 57.

Parotitis

21 Nov. Bilious vomiting . . . urine brownish red . . . calomel 1·0 g. in 5 doses.

22. Algidity with great prostration. Urine, which was blackish, is clearer.

23. Urine normal, mercurial stomatitis.

29. The hiccough has ceased, the stomatitis persists, left parotitis.

30. The inflammation extends to the submaxillary.

2 Dec. 20 leeches applied to the angle of the jaw.

5. The left parotid is very hard, the right softening.

10. Behind the ear is a large slough extending to the angle of the jaw.

12. Death. P.M., both parotids are masses of pus. Bérenger Féraud considers that parotitis is very rare, and is inclined to attribute it to the calomel and resulting stomatitis. Bérenger Féraud (1874), 157.

Day 5. Double parotitis. Day 6, death. Stephens and Christophers (1900), 33.

16.4.1911. Hgburia, great abdominal pain. 'Bipalatinoid' of Sod. bicarb. and liq. hydrarg. perchlor. given every 2 hours.

17. 6 p.m. Calomel grains 3.

18. Complains much of colicky pains, numbness in legs. Palatinoids discontinued.

19. Faeces : blood and mucus.
20. Mouth and tongue very sore, bleed easily (mercurial poisoning).
21–22. Urine normal, 288 c.c.
5.5. Urine, about 960 c.c. daily, severe cramp in abdomen.
6. Both parotids enlarged and tender (teeth clean and good). Small abscess discharging pus near the anus. Later right parotid suppurating, left incised but no pus.
9. Patient discharged. 'Africa' (1912), 33.

Penis, priapism

Priapism and a frequent desire to micturate, together with a feeling of weight in the perinaeum, in the absence of an accumulation of urine in the bladder, point to a disturbance of uro-genital centres. Corre (1883), 193.

Penis, retraction

Day 1. 9 a.m., pronounced icterus, T. 100°, rising to 104·8°, bilious vomiting, marked retraction of penis; 12.30 p.m., passed bright red urine. Gray (1898), 23.

Pharynx

Day 3. The patient complains of great internal heat and dryness of the throat. Heart sounds and impulse feeble, no anaemic murmur. Pellarin (1876), 190.

Among unusual symptoms a septic throat. Connal (1916), 11.

Pregnancy

Two cases in pregnant women. Miscarriage occurred in both and both mothers died. Deaderick (1910), 197.

Bonnafin records the case of two sisters, who in the same room, at a year's interval, one from the other, had

b.w.f. when 6 months pregnant and aborted. Gouzien (1911), 48 (r.).

Prodromata

Absent

The onset was very sudden. The patient was, to the best of his knowledge, in good health, and was shooting at a target from his verandah when some abdominal discomfort caused him to go to the latrine, where he found that he was passing blackwater. Daniels (1901), 52.

Child, aet. 7. Togo. Fever 6 months ago. Spleen considerably enlarged, parasites negative. Feeling quite well, took in the morning, Q. 0·2 g. Three hours later rigor and Hgburia. Recovery. Rodenwalt (1911), 360.

26–28. Q. grs. 10 t.d.s. 10 a.m., 2 p.m., 6 p.m.

29. 10 a.m. patient in bed, apparently well; 10.30 a.m. still in bed, Hgburia, T. normal, no change in physical condition; 12 noon faint conjunctival icterus, spleen 2 inches. Urine subsequently normal. 346.

The onset of blackwater in these four cases was sudden and unexpected. . . .

The absence of any excessive urobilinogen in the pre-blackwater urines of Cases 1 and 2, the relatively low degree of Hgbaemia two days before the passage of Hgb in Case 4, the relatively slight degree of anaemia . . . a couple of hours before the first passage of Hgb in Cases 3 and 4, all appear to us to be against the hypothesis of a pre-blackwater state, if by this is meant a state in which haemolysis is greater than that in ordinary malignant tertian malaria. 354. Yorke, Murgatroyd and Owen (1930).

Chill

13 Aug. Patient thought he had caught a chill in the evening.

14 Aug. 2 p.m. without preliminary malaise, dark red urine, shortly afterwards a violent rigor, T. 39·3°. Gouzien (1900[a]), 49 (r.).

Case.	Fever, etc., Days 3ª–1ª.			1ª.	Fever, etc. Day 1. Before onset.	
	3ª.	2ª.	1ª.	Q.	Fever.	Q.
1		+	+	+		
2					+	+
3			Ill		−	+
4	+		+*		−	+
5			+	+		
6¹			+			+
6²					−	+
6³			+		−	+
6⁴			+		−	+
6⁵			+*		−	+
6⁶			+*			
7					+	+
8¹			Ill		−	+
8²					Less fit	+
9	Headache, vomiting	Headache, vomiting	+*		−*	+
10¹	+	+	+		+	+
10²	+	+	+		+	+
11	+	+	+		+	+
12		+	+	+		
13			+	+		+
15¹	Ill	Ill	Ill		+	+
15²					+	+
16	+	+*	−	+		
17³	Ill	+	+	−	+*	+
17⁴			Exhausted	+	−	+
18			+	+		
19		+	+		+	+
20						+
21					+	+
22			+		−	+
23¹			+		−	+
23²			+		−	+
24¹			+		−	+
24²			+		−	+
25			Chill		Ill	+
26			+*		−	+
27¹			+	+	−	
27²			+	+	−	+
28			+			+
29¹			+	+		
29²		+	+		+	+
30			+−		−	+
31¹					Depressed	+
31²					+	+
31³			+		+	+
32			+		−	+
33				−		−
34					+	+
35					Ill	+

* = Parasites present.

Cases 49. Summary

Day 3ª, fever 4. Day 2ª, fever 9. Day 1ª, fever 31, negative 1, no record 17. Parasites, positive 5, no record 44.

Day 1, fever 14, negative 19, no record 16. Quinine 40, negative 1, no record 8. Plehn, A. (1896).

Fever and indisposition

Case.	Fever for — days before attack.	Case.	Fever for — days before attack.	Authority.
3	Ill	17	3–4	Christophers and Bentley (1908ª), 57.
4	4–5	18	Some days	
5	10th day	19	7th and 1st days	
6	2	20	3	
8	2	21	14, ill	
9	3	22	A few	
10	14th day	23	1	

Case.	Before the attack has been ill for	Case.	Before the attack has been ill for	Authority.
1	Not for a fortnight	9	3 weeks	Barratt and Yorke (1909ª), 161.
2	A week	10	3rd and 2nd days	
3	5 days (rigors)	11	A week	
4	None	12	1	
5	1 day (2 days before)	13	None	
6	4	14	1	
6ª	1	14ª	None	
7	3	15	4	
7ª	10	16	4	
8	3	17	1 (?) 4 days ago	

General

22 Sept. 6 p.m., violent attack of fever, which lasts until

23 Sept. 3 a.m., patient takes Q. 1·0 g., admission 7 a.m., afebrile. Tongue, with a very adherent thick grey coating, frequent nausea, no vomiting, sharp epigastric pain, worse on pressure. Abdomen free, urine normal, ipecacuanha 1·2 g., vomit at first colourless, then deep green viscid bile.

11 a.m., fever, prolonged rigor, sharp pain in loins and

epigastrium, P. 120 full. Profuse leek green vomit, urine scanty, bloody—Malaga-coloured. Icterus absent. The cold stage lasted about 2 hours, i.e. until

1 p.m. icterus developing. Barthélemy-Benoit (1865), 13.

The beginnings of the condition are most variable. Usually there is general malaise with a very bitter taste in the mouth. Nearly always the beginning is a bilious attack; it is uncommon to have several attacks with clear intermissions, but sometimes there are as many as three remissions before the continuous vomiting and icterus; hepatic pain has not been observed at this prodromic period, and sometimes the first pain noted is hypogastric. Loupy (1858). Bérenger Féraud (1874), 25.

A day or so before the first attack of fever, the patient suffers from general malaise, characterized by muscular lassitude, indisposition, anorexia, and some constipation. 210.

The pronounced degree and persistence of the 'gastric disturbance,' the intensity and constancy and duration of the rigor, the persistence of lumbar pains between the attacks suffice to distinguish these attacks from those of ordinary fever and to constitute a premonitory stage. They do not differ absolutely however from ordinary relapses of fever. 379. Barthélemy-Benoit (1865).

Prodromal attacks are one or two in number. For a day or two preceding these attacks there is general malaise.

1st prodromal attack

The rigor is more defined and of longer duration than ordinarily, the stage of heat is greater and the sweating more profuse. The gastric disturbance is so pronounced as to indicate the necessity of an emetic.

2nd prodromal attack

Lasting 8–10 hours, more intense than the preceding attack, sometimes nausea or even vomiting. The urine is

free from albumen, but has the colour of Madeira wine. Sometimes also there is a tendency to faintness and syncope. Bérenger Féraud (1874), 112.

Prodromata precede the outbreak of the disease in the form usually of rapidly transient febrile attacks which repeat themselves every 8, seldomer every 14 days, on the same day of the week. Observed in 21 of 26 cases. Fisch (1896[a]), 272.

A quite definite form of fever lasting for a longer or shorter time always precedes the outbreak of blackwater; it is a fever recurring every 8 days, so on the same day of the week . . . perhaps in the majority of cases this fever is slight and indeed almost overlooked. A further peculiarity is its tenacity ; Q. has only a slight effect on it. If nothing special happens it may afflict the patient for months, but should he be subject to any considerable fatigue b.w.f. sets in mostly on the 3rd day. In other cases the patient is hardly aware that he is suffering from fever, as only 1 or 2 slight attacks precede the b.w.f. On the early recognition of the precursor of b.w.f. is solely based an effective prophylaxis. 83.

While the usual malaria parasites have an extremely delicate covering, those of 8-day fever and b.w.f. have a thick one. . . . Single doses of Q., even 2–3 g., have no noteworthy effect, but frequently repeated smaller doses are very effective. In addition to medium or small doses of Q. we strongly recommend arsenic (Fowler's solution). 86. Fisch (1894).

Vide Prophylaxis.

Sthenic type

About noon he was attacked by great pain in the back and loins and through the lower limbs and by intense frontal headache. He complained of a parching thirst and was seized with colicky pains in the abdomen, producing a desire to go to stool. 5.30 p.m. Hgburia.

Insidious type

10 March, 1892. Unwell, fatigued, nausea, anorexia, constipation, intense weariness, epigastric depression, skin cool and moist. Mag. sulph. Antipyrin, Quinine.

11. Worse, face of an unusual pallor, headache, slight oedema of eyelids. Bad night, passed urine perfectly black.

Pernicious type

Suddenly seized with piercing pains in the stomach and abdomen. He began to vomit and had a prolonged rigor. He was obliged to go to stool and noticed his urine was turned porter-coloured. Connolly (1898), 884.

Vide supra, Classification.

Two facts emerge from the histories (of 21 cases). One is that Hgburia may be the first sign of illness. The other is that both subjectively and objectively the initial manifestation may be indistinguishable from malaria. Connal (1922[a]), 7.

In 3 of 6 cases seen before the onset of b.w.f. there was a pre-blackwater stage showing low fever, nausea, vomiting, persistent headache, constipation, general malaise, rigor, a spleen invariably much enlarged and painful, a liver sometimes so, and urine showing traces of albumen and usually of urobilin.

In 2 cases the urine was examined before the onset. In one a trace of albumen was found; in the other, six hours before the onset, urobilen, urobilinogen, albumin, and granular casts.

The dominance of dyspeptic symptoms was stressed, leading in one case to a previous tentative diagnosis of gastric ulcer. Manson-Bahr (1926–27), 412.

Vide supra, Prodromata, *absent*.

The appearance of these patients before the onset is usually characterised by that lemon-tinted skin and conjunctiva so characteristic of pernicious malaria, and this

combined with occasional biliousness and jaundice and insufficient quinine put the medical man on his guard. Thomson (1924), 89.

This is a most definite condition and may be recognized by the following signs. The patient is one who has passed through several slight attacks of fever, or at any rate has been infected with the sub-tertian parasite for several months. The complexion is sallow, the conjunctiva icteric, the liver enlarged, congested and tender, the tongue furred, the spleen generally enlarged and constipation is the rule. Persistent headache is usually complained of. The urine is dark, due to the excretion of urobilin, and contains a slight amount of albumen. Manson-Bahr (1929), 50.

There was nothing in the general condition of the patient, in the clinical, biochemical or serological manifestations of malaria to demarcate such cases from many others, similar in their state of health and in their degree of malarial infection, in which blackwater fever did not develop. Ross (1932), 210.

Jaundice

The observation was made in this case of the occurrence of transient jaundice on two occasions before the severe attack of b.w.f., malaria parasites being present on the second occasion. . . . I would suggest, then . . . that still more frequently haemolysis with slight jaundice occur without noticeable Hgburia . . . and are mild forms of the same condition. Blacklock (1923), 83.

Pain

1 April, 1893. After taking a prophylactic dose of Q. distinct prodromal symptoms. Dragging pains in all the limbs, discomfort, nausea.

1–2. In the night, T. vomiting, acute headache, Hgburia. Plehn, F. (1898), 128.

Paresis

24 May, 1906. No history of fever at this time (T. 101° on admission, and parasites in the blood,

although this patient denied fever). Complained of loss of use of right arm.

26. Chill, Hgburia. Deeks and James (1911), 118.

Restlessness

10. Q. grains 15 t.d.s. A good night.

11. Q. grains 15, 10 a.m., 2 p.m., 6 p.m. Patient appeared to be well on the road to recovery (from malaria), T.N. since 9th; felt very much better. At night apart from slight restlessness nothing untoward occurred.

12. 6 a.m. T. 98°; 8 a.m. Hgburia, T. 100° F. There followed a severe attack lasting 4 days. Yorke, Murgatroyd and Owen (1930), 339.

Prostration (weakness)

Cases.	Present.	No record.	Authority.
32	22	10	Bérenger Féraud (1874).
48	14	34	Plehn, A. (1896).
43	21	22	Plehn, F. (1898).
10	2	8	Seyfarth (1918[b]).

13 Oct. Hgburia.

16–19. Profound prostration, stretched on his bed exhausted and so weak that he can hardly respond to questions. Great care taken to secure retention of nutritive enemata. 171.

Day 2. 9 p.m. high fever, skin burning and dry. Dorsal decubitus, limbs completely relaxed, away from the body, fixed gaze; prostration is great, for the patient replies with difficulty to questions. Headache, tongue thickly coated, vomiting, frequent nausea, epigastralgia. (Recovery.) 336. Bérenger Féraud (1874).

Quinine (action of)

Day 2. 7 a.m. T.N., Q. 2·0 g., directly afterwards T. goes up to 39·2°; 11 a.m. pulse very weak and

intermitting, R. laboured, feeling of suffocation, acute anxiety and restlessness, tinnitus and stupor. Plehn, F. (1898), 128.

Day 3^a. Q. grains 15.

Day 2^a. Q. grains 15 × 3.

Day 1^a. Q. grains 15, 10 a.m., 2 p.m., and 6 p.m.

Day 1. T. 98°. 8 a.m. urine 'black,' T. 100°; 3 p.m. Q. grains 15 I.M. This was quickly followed by a great acerbation of symptoms. Yorke, Murgatroyd and Owen (1929–30), 339.

Respiration

Cheyne-Stokes respiration

Cases.	No record.	Cheyne-Stokes.	Day of onset.	Day of death.	Authority.
48	47	1	16	16	Plehn, A. (1896).
43	40	3	5	5	Plehn, F. (1898).
			6	6	
			16	16	
			9	10	Dempwolff (1898), 160.
10	8	2	7	7	Seyfarth (1918^b).
			2	2	
9	8	1	2	3	Fairley and Bromfield (1934–35), 151.
		1	5	Recovery	Low, Cooke and Martin (1928).

Day 16. T. 96·1°. No urine. Breathing with sighing and groaning. Cheyne-Stokes. Breathing stops before the pulse. Death in the night. Plehn, A. (1896), 120.

Day 5. 6.30 a.m. P. almost imperceptible at the wrist, R. irregular and of the Cheyne-Stokes type.

10 a.m. R. 42. A mucus rattle appeared with R., the patient being too weak to cough. (Recovery.) Low, Cooke and Martin (1928).

Day 2. Cheyne-Stokes R.

Day 3. Ditto. 3.30 p.m. dyspnoea with grunting expiration and melaena. (Death.) Fairley and Bromfield (1934), 151.

Dyspnoea

12 Oct. Day 24. Violent epigastric pain, with great embarrassment of the respiration.

13. On several occasions has had acute epigastric pain with suffocation. Sinapisms gave prompt relief to the pain.

19. The acute pain in the epigastrium accompanied by dyspnoea has returned. (Recovery.) Bérenger Féraud (1874), 403.

Cases 48. Present 6. No record 42. Plehn, A. (1896).
Cases 43. Present 15. No record 28. Plehn, F. (1898).
Cases 14. Present 2. No record 12. Brem (1906).

Day 1. On examination, respiration was difficult, the patient had a sense of suffocation. Brem (1906), 1897.

Day 7. Hyperpyrexia and very rapid pulse towards the end, great restlessness, delirium and air-hunger. 'Africa' (1915), 69.

Rigors

Duration

Case 11. Day 1. An attack commencing with a very violent rigor, rapidly passing off in 2 hours (11.30 a.m. to 1.30 p.m.), immediately afterwards Hgburia noticed. 5 p.m. Q. 1·5 g.; all the same in the evening a paroxysm with a very violent rigor, again passing off in 2 hours (9–11 p.m.). Schellong (1890), 66.

Duration of rigor in hours.	Authority.
¼	Fairley and Bromfield (1934), 150.
¾	Plehn, F. (1898), 120.
1	Ibid., 129.
2	Ibid., 131.
2½	Kleine (1901[c]), 665.
3	Plehn, A. (1896), 27.
4	Ibid., 46.

Q. 0·5 g., T. 37·5°. Three hours later he could only pass a few drops of black urine. Severe rigors then set in lasting 4 days at intervals of 12 hours. Kleine (1901[c]), 666.

Frequency

Initial rigor.					
Cases.	Present.	Absent.	Shivers.	No record.	Authority.
32	14			18	Bérenger Féraud (1874).
48	38	2	5	3	Plehn, A. (1896).
43	33		7	3	Plehn, F. (1898).
14	5			9	Gouzien (1900[a]).
38	8	3	3	24	Panse (1902).
14	8	6			Brem (1906).
19	10	1	1	7	Barratt and Yorke (1909[a]).
34	30	4			Deaderick (1914), 873.
39	17	4		18	Connal (1916), 11.
162	114*	48			Ross (1932), 227.
9	4	1	1	3	Fairley and Bromfield (1934).
452	281	69	16	86	

* 10 after the Hgburia.

The mode of onset was with a chill in 30 of 34 cases. Two without chill. Two with pain in the epigastric region. One case, chill and Hgburia simultaneous. Average period between chill and Hgburia was 2 hours. Deaderick (1914), 873.

Interval between rigor and Hgburia

Hours.	Cases 66.	Authority.
0–1	23	Ross (1932), 227.
1–2	8	
2–3	7	
3–4	6	
4–5	5	
5–6	3	
6–12	1	
12–	13	

30.11. Had a violent rigor, teeth chattering; then a sudden violent abdominal pain and immediately afterwards Hgburia. Van Campenhout and Dryepondt (1901), 70.

8.11.1904. 6 a.m. Patient took as usual Q. 1·0 g. 9.30 a.m. violent rigor and a few seconds later 100 c.c. of red urine (39).

5.10.1903. 8 p.m. Q. 0·5 g.

6. 2 a.m. Intense rigor of long duration. A feeling of constriction in the epigastrium, as if he were choked. A few minutes later patient sees that he is passing black urine (45). Broden (1906).

Multiple

5.9. T.N. Q. 1·0 g., 1½ hours later rigor, fever, vomiting. 2 hours later T. 38°, rigor, T. 40°, Hgburia. 9 a.m. third rigor, urine yellowish-brown, icterus. 28.

4.12. T.N. 12 noon Q. 1·5 g., 3 p.m. cold bath, shortly afterwards rigor, uneasiness, dyspnoea, strangury, Hgburia. 7 p.m. T. 39·5°, sweating begins.

5. Rigor in the night. 9 a.m. rigor, precordial oppression, cardialgia, vomiting, very restless and weak. 12 noon, rigor, T. 39·1°. Towards evening 4th rigor. 47.

31.3.96. 9 a.m. Q. 1·0 g., 11 a.m. rigor, fever, vomiting; 2 p.m. Hgburia.

1.4. Rigor in the night. 9 a.m. third rigor, T. 40·6°. 51. Plehn, A. (1896).

In attacks of short duration the T. is quite that of an intermittent fever. It usually rises after 6, 12, and in some cases after 24 hrs., and at the same time the Hgburia increases, to fall again afterwards. The repetition of the rigor, 1 to

5 times, after 6 or a multiple of 6 hours is characteristic of the disease. Fisch (1896[a]), 273.

Intervals between rigors

Case.	Number of rigors.	Intervals (hrs.) between rigors.
1	1	
2		
3^1	3	6
3^2	—	—
3^3	2	6
3^4	2	6
3^5	—	6
4	2	12
5^1	3	?
5^2	3	
5^3	2	
5^4	1	
6^1	2	
6^2	3	
6^3	4	
7^1	3	12
7^2	2	12
8^1	2	24
8^2	2	6
8^3	2	6
9	1	
10	1	
11	2	24
12	2	12
13^1	3	6
13^2	3	6
14	1	
15^1	1	
15^2	1	
16	2	24
17	1	
18	1	
19^1	2	12
19^2	1	
20	1	
21^1	2	24
21^2	1	
21^3	1	
22	4	6
23	1	
24	2	6

Cases.	Intervals (hrs.).
10	6
5	12
4	24

Fisch (1896[a]), 275.

Post-Hgbic

14 Aug. 2 p.m. Hgburia, shortly afterwards a very violent rigor. Gouzien (1900[a]), 49 (r.).

13 of 17 rigors occurred an hour or two before, 4 shortly after the Hgburia. Connal (1916), 11.

Rigors 114. Post-Hgburic 10. Ross (1932), 227.

Rigor and sleep

Day 1. Evening Q. 1·0 g. 10 p.m. severe rigor awakening the patient out of sleep. 35.

Day 1. 1 a.m. wakened out of sleep through a violent rigor, then feels hot, headache, vomiting. 38.

Day 1. 12 midnight. Awakened by a rigor, vomiting, then sweating, 1 a.m., urine dark red. 29. Plehn, A. (1896).

Had not been feeling well for over a week. Onset sudden, during sleep, with severe rigor. Daniels (1901), 75.

Rigors and Temperature

10 Oct. 8 a.m. Q. 1·5 g. Violent rigor. T. does not begin to rise until ½ an hour after the onset of the rigor, then rises rapidly. 130.

3.9.93. 9 a.m. violent rigor, T. 36·9°; 9.20 T. begins to rise, and at 12 noon T. = 40·4°. 135. Plehn, F. (1898).

Time of onset

Time of onset of rigors (121).			
Time.	Rigors.	Deviation from average 15.	Authority.
12–3	8	— 7	Stephens (1915), 203. Note.—The protocols are not given in the original.
3–6	7	— 8	
6–9	14	— 1	
9–12 n.	38	+ 23	
12–3	22	+ 7	
3–6	10	— 5	*Vide* App. 26.
6–9	9	— 6	
9–12 m.	13	— 2	
	121		

Salivation

Day 1. Calomel 1·0 g.
Day 3. The gums are slightly swollen and covered here and there with a thin white pellicle but little adherent. Salivation moderate. 14.

Day 2. Calomel 1·0 g. in 5 doses. Tongue, a thick slimy coating.
Day 3. Calomel 0·6 g. in 3 doses.
Day 4. The tongue is less coated, some signs of gingivitis.
Day 5. The stomatitis extends to the whole buccal mucosa, which is covered with not very large patches of a thin white pellicle but little adherent. Salivation moderate. 16.

Day 1 (?). Purgative pills with calomel.
Day 3. Calomel 0·5 g. in 3 doses.
Day 4. Calomel 0·6 g. in 3 doses.
Day 5. The gums are swollen, hot and painful, some salivation; the buccal mucosa has irregular red patches. 20. Barthélemy-Benoit (1865).

Days 1–3. Calomel grains 20 (total).
Day 4. Incipient salivation. Easmon (1885).

5 a.m. Q. 0·5 g.; 6 a.m. Q. 0·25 g.
9 a.m. Continuous salivation with attempts at vomiting, urine deep red. Tomaselli (1897), 96.
Vide infra, Stomatitis.

Sequelae

Cholelithiasis

1920. Patient in New Guinea. *P. falciparum* infection. 1923 and 1926 b.w.f. after he had omitted to take Q. for some weeks on each occasion. 1929 (Melbourne). Gall bladder inflamed and adherent to bowel, completely filled by a calculus 5 × 2·5 cm., amorphous, consisting almost

entirely of bilirubin and some Ca bilirubinate. 1930. 2 pigment stones removed from the common bile duct which contained white bile. The stones consisted of bilirubin with a thin coating of cholesterol. Fairley, K. (1930), 1395.

30 Nov. 3 weeks after the b.w.f. had a series of typical attacks of biliary colic, each lasting 10 minutes and requiring morphia. Further attacks in Dec. and Jan. Manson-Bahr (1930), 106.

Haemorrhage (gastric)

Patient recovered from b.w.f., but died shortly afterwards from severe Hge from the stomach. Christophers and Bentley (1908[a]), 226.

Malaria (cure of)

The radical cure of chronic malaria subsequent to a single attack of b.w.f. has been observed. Gouzien (1911), 78 (r.).

Nephritis

The only sequela apart from a more or less prolonged anaemia is a kidney lesion which in the convalescent frequently cannot be recognized by examining the urine, but during subsequent febrile attacks shows itself by the albuminuria which in Cameroon fever is scarcely ever seen. Plehn, F. (1898), 188.

The only sequelae that I encountered were cachexia and renal lesions. In half the cases examined from a few months to several years since the attack (in Marianna, Arkansas, U.S.A.) abnormalities of the urine have been found. These consisted of albumen, cylindroids, or casts. Deaderick (1910), 198.

A grave attack may cause lesions of chronic nephritis, as in yellow fever. Gouzien (1911), 6 (r.).

The kidneys were examined in a few cases of b.w.f.

at a previous period, but who had died from some other illness. The interval between the b.w.f. and the examination of the kidneys varied from a few weeks to some months. In no case was there evidence of chronic nephritis. Dudgeon (1920), 221.

Spleen

Contraction

The chief exciting causes of this fever—namely, exertion, chill and quinine—have, therefore, this action in common, that they cause contraction of the spleen. Blacklock and Macdonald (1928), 9 (r.).

Diminution in size

28. Spleen 2½ fingers from costa.
29. Spleen 2 fingers from navel.
31. Hgburia cleared. Spleen back to 2 fingers from costa. Schellong (1890).

13.11.1891. Hgburia.
17. Spleen 3 fingers.
25. Spleen not palpable.
26. T. 40°. Two hours later T.N.
27. Spleen one finger.
30. Spleen not palpable. Kohlstock (1892), 428.

Soldier, aet: 23. Invalided from Madagascar to Marseilles.

7 Oct. Spleen 22 cm. long by 16 cm. broad. Liver normal. Urine, alb. neg.
8. p.m. Q. bihydrochloride 0·2 g. subcut. Pulv. quinquinae (yellow) 2·0 g.
9. 5 p.m. rigor, T. 40°, nausea. Evening, Hgburia.
10. Spleen 18 cm. by 13 cm., p.m. urine deep amber, no blood tint.
12. Spleen 13 cm. by 9·5 cm.
14. Spleen 10 cm. by 7 cm. Rendu and Poulain (1900), 1000.

Day 2. Spleen 2 fingers below the costa.
Day 3. 8 a.m. parasites scanty; 9 a.m. negative.
Day 4. Hgburia negative.
Day 7. Spleen not distinctly palpable. 7.

Day 2. Spleen 2 fingers below costa.
Day 24. Spleen gone back. 8. Panse (1902).

Day 1. 10 a.m. spleen neg., liver neg.; 3 p.m. spleen enlarged beyond costa.
Day 2. Spleen much enlarged.
Days 7–12. Spleen hardly perceptible. Amblard and Eschbach (1917), 814.

The enlarged and tender spleen rapidly decreased, ceasing to be palpable by the sixth day. Manson-Bahr (1926–27), 413.

Enlargement

Cases.	Positive.	Negative.	No record.	Authority.
15	5	4	6	Crosse (1892).
48	17	4	27	Plehn, A. (1896).
43	19	13	11	Plehn, F. (1898).
14	1	2	11	Gouzien (1900[a]).
38	24	4	10	Panse (1902).
14	13	1	0	Brem (1906).
20	14		6	Da Costa (1906).
33	20	1	12	Christophers and Bentley (1908[a]).
19	14		5	Barratt and Yorke (1909[a]).
39	3		36	Connal (1916), 11.
17	14	2	1	Arkwright and Lepper (1918[b]).
10	5	2	3	Seyfarth (1918[b]).
5	4	1		Yorke, Murgatroyd and Owen (1929–30).
162	40	3	119	Ross (1932), 230.
26	21	5		Ross (1932), 230.
9	8		1	Fairley and Bromfield (1934–35).

During the attack the spleen underwent considerable enlargment and was very painful. 187.

Day 1. 2 p.m. Hgburia; 4 p.m. spleen not palpable; 9 p.m. 2 fingers below the costa.

Day 2. a.m. spleen a hand's breadth below costa. 188. Christophers and Bentley (1908[a]).

The illness was severe in those attacks in which the enlargement of the spleen was greatest; in those in which enlargement was slight or not appreciable, the attack may be described as mild, except in one case. Barratt and Yorke (1909[a]), 153.

Friction

Day 11. There was a friction rub heard over the spleen—he complained of severe pain in this region for the following 12 days—and of flatulence and abdominal distension. Harsant (1921), 385.

Pain and tenderness

Cases.	Present.		Absent.		No record.	Authority.
	p.	t.	p.	t.		
48	2				46	Plehn, A. (1896).
43		13		11	19	Plehn, F. (1898).
	5		1		37	Ibid.
38	2				36	Panse (1902).
14		2			12	Brem (1906).
20	2				18	Da Costa (1906).
17		2		1	14	Arkwright and Lepper (1918[b]).
10	1	2			7	Seyfarth (1918[b]).
9		2			7	Fairley and Bromfield (1934–35).
199	9	21		6	163	

Stomatitis

Day 1. Calomel 1·0 g. in 5 doses.
Day 2. Calomel 1·0 g. in 5 doses.
Day 3. Commencement of mercurial stomatitis, salivation, foetid breath.
Day 4. Salivation fairly profuse.
Day 6. Enlargement of glands from the stomatitis, salivation profuse.
Day 8. Stomatitis less. 25.

Day 2. Calomel 1·0 g. in 5 doses.

Day 3. On the gums and on several parts of the buccal mucosa signs of mercurial stomatitis. Honey of roses, lemon juice, alum.

Day 4. The stomatitis has spread and is more defined. Pot. chlorate (4·0 g.), gargle. 18. Barthélemy-Benoit (1865).

Day 6. a.m. a little urine (in bladder), skin dirty grey, stomatitis, frequent vomiting, constipation relieved by enemata. T.N., P. 80, no urine. Plehn, A. (1896), 49.

Among unusual symptoms, sore lips and gums. Connal (1916), 11.

Day 1. Calomel 1·5 g. in 6 doses.

Day 2. Calomel 0·6 g. in 3 doses; calomel 0·5 g. in 4 doses.

Day 3. Mercurial stomatitis begins.

Day 4. The stomatitis is fairly acute.

Day 7. The stomatitis is healed.

Day 23. Relapse of b.w.f.

Day 24. Calomel 0·6 g.

Day 25. Stomatitis.

Day 26. Stomatitis very acute. Bérenger Féraud (1874), 224.

Sweating

Cases.	Present.	No record.	Authority.
32	10	22	Bérenger Féraud (1874).
48	12	36	Plehn, A. (1896).
43	7	36	Plehn, F. (1898).

Day 3. Noon. Severe rigor, headache, oppression at the base of the thorax, vomiting very frequent, profuse sweats. P. 120. Bérenger Féraud (1874), 363.

Profuse sweating lasting over 4 hours accompanied the fall in temperature. Plehn, A. (1896), 42.

Day 2. T. 36·6°. Much sweating, not offensive.

Day 3. T. below 37°. Better, much foul-smelling sweat. 155.

Day 2. T. N. persistent vomiting, constant sweat, in spite of frequent change of clothing. Restless night.

Day 19. Q. 1·5 g. Great sweating and vomiting, great weakness, urine clear. 159.

Day 2. T. 39·7°, P. 140. Patient lies restless and sweating. In hospital, T. below 38°, profuse sweating, some vomiting.

Day 3. Some sleep at night, T.N., much sweating, great weakness and restlessness. 159. Dempwolff (1898).

Day 1. 5 p.m. fall of T. Patient begins to sweat; 10 p.m. the urine is more abundant and begins to clear. The night passes quietly, the sweating continues. Plehn, F. (1898), 154.

The condition of the skin varies, but as a rule there is profuse diaphoresis even when the temperature is high. It is frequently intermittent. Daniels (1901), 55.

Literally *he sweats bile*. Guillon (1907[a]), 132.

Day 1. 12 noon Hgburia, 150 c.c.; 12.30 p.m. T. 105°; 1.30 p.m. T. 101°; then commenced to perspire freely (profusely, 161) and condition improved. Barratt and Yorke (1909[a]), 178.

Blood, *P. falciparum*. Noon Q. 0·5 g.; 2.30 p.m. rigor; 4 p.m. T. 40·2°; 8 p.m. Hgburia. At night diarrhoea set in and profuse sweating followed by great exhaustion and tenesmus of the bladder. Mann (1902), 528.

Sweats may occur with the decline of the fever or with collapse. Sometimes the perspiration is charged with bile pigment. Deaderick (1907–08), 30 (r.).

[In one recorded case] profuse drenching sweats were common every day. Connal (1916), 16.

Taste

Day 2. Patient better, Hgburia neg., nausea and a bad taste still exist after cessation of fever. Plehn, F. (1898), 131.

Day 3. Oliguria 190 c.c. Green vomit fairly profuse, headache, somnolence, mouth very bitter, *salty taste.* Gouzien (1900[a]), 76 (r.).

Temperature

Curve

Cases 38. Tertian 2. Quotidian 7. Irregularly intermittent or remittent 29. Plehn, F. (1898), 108.

3 Sept., '93. 9 a.m. Violent rigor. T. 36·9°.
9.20 a.m. T. begins to rise.
12 noon. T. 40·4°.
9 p.m. T. 37·9°.

4. 8 a.m. No rigor. T. begins to rise.
3 p.m. Intense feeling of heat. T. 39·4°.
10 p.m. Patient feels quite well. T. 36·6°. 135.

6 June, '94. 9 a.m. Violent rigor.
9.15 a.m. T. begins to rise.
11 a.m. T. 40·3°.
3 p.m. T. 41·0°.
5 p.m. Sweating.
10 p.m. T. 38·2°. 155. Plehn, F. (1898).

The temperature curve is (1) intermittent or (2) remittent or subcontinuous. The intermittent type is seen most commonly in the dry season (Dahomey). The remittent type is seen in the period of malarial reinfections, i.e. the winter. The intermittent quotidian is the prevailing type on the Ivory Coast and in Mayotta. The remittent form is the commonest in Tonkin, Soudan, and Mauritius, and almost exclusively so in Senegal, Dahomey and Congo.

Irregularly continuous atypical forms with typhoid or septicaemic symptoms indicate a secondary infection.

Gouzien (1911), 11, 18 (r.).

In Case 3 the T. was taken at hourly intervals. It reveals a truly remarkable, rapidly succeeding, series of more or less violent fluctuations. . . . Had we continued to record

the T. every four hours . . . the dramatic rises and falls of T. would have escaped observation.

1. One and a half hours before Hgburia T. was normal.

2. Coincidently with or possibly immediately before Hgburia T. rose suddenly.

3. During the first 3 days of b.w.f. T. exhibited 8 distinct elevations.

4. On Day 3, T. on two occasions rose 6 degrees within an hour or two.

5. The elevations were of short duration, and the fall was almost as sudden and as great.

6. A low type of fever persisted for several days after the urine had cleared.

Two of the sudden great rises of T. followed almost immediately on the intravenous injections of $NaHCO_3$ and NaCl respectively. 355.

A plausible explanation is that they resulted from the flushing into the circulation of some toxic substance from the spleen or other organ. 365.

Yorke, Murgatroyd and Owen (1930).

in Anuria

As anuria persists, the temperature, which at first is pyrexial, falls and eventually becomes, and continues to be, subnormal. Ross (1932), 216.

Duration

Cameroons. Cases 27.

The average duration was 21½ hours, that of the Hgburia 35 hours. The maximum duration of the fever was 48 hours, that of the Hgburia 72 hours. Plehn, A. (1896), 23.

and Euphoria

Day 6. a.m. T. 37·6°, 37·4°; p.m. T. 39°, P. 138, icterus decreasing. The feeling of well-being is always greatest with the highest T. Plehn, A. (1896), 43.

Hyperpyrexia

Vide supra, Types of Attack.

Pre-Hgburic, Hgbic, Post Hgbic fever

A[1]. Pre-Hgburic febrile attack. Parasites positive.					
Day.	*P. falciparum* per mm[3].	Q, grains.	Hgburia.	Temperature.	
				Min.	Max.
1			—	97·5°	100°
2	2600		—	98°	100°
3	80		—	96·5°	100·4°
4	1360	10	—	101·2°	97·2°
5	880	30	—	97·5°	96°
6	20	30	—	96°	97°
7	12	30	—	96°	
8	neg.	30	—	96·5°	98°
9	neg.	30	—	96·5°	103·7°
				100·2°	104·5°

The amount and type of fever, number of leucocytes, fall of Hgb (86–69%), amount of urobilin excretion and effect of quinine were precisely what we would have expected from the number of parasites counted; and the same thing may be said of the following apyrexial period (days 5–8). 310.

A[2]. Pre-Hgbic, Hgbic and Post-Hgbic fever. Parasites negative.								
Day.	Q, grains.	Red cells, m.	Hgb, %.	Hgb-uria.	Temperature.			
					Min.	Max.	Min.	Max.
9	30		60	—	96·5°	103·7°	100·2°	104·5°
10	30		50	+	97·7°	104°	100°	104·8°
11	0	2·6	42	+	97°	103·2°	98·5°	103·7°
					100°	103·5°		
12	0	1·15	30	—	98·4°	101°	98·4°	100·5°
			35	—	98·4°	101·4°		
13	0		30	—	97·2°	102·7°		
14	0		25	—	98°	101°		
15	0		25	—				100·7°
					99°	102·7°		
16	0		25	—	97·7°	100·4°		
17	0		25		97·5°	99·7°		
18	0	1·45	30	—	97°			

The attack was very serious. 308.

The fever consisted of several severe paroxysms on each day, accompanied by sharp rigors and profuse sweats.

Much bilious vomiting occurred on days 10 and 11. 310.

A³. Febrile attack from day 41 to day 54. Parasites negative. Hgburia negative.						
Day.	Q, grains.	Hgb, %.	Temperature.			
			Min.	Max.	Min.	Max.
40	1	90		97·7°	96°	96·7°
41	2		96·5°	98°		
42	2		96·7°	99·5°	98·5°	
43	2			99·7°	97·5°	100·5°
44	2	87	96·5°	97·5°		
45	2	78		100°	98·6°	
46	2	85	97·2°	101·5°	98·5°	101·8°
47	0	90	97·8°	102°		
48	0	83	96·5°	101·5°		
52	0		97·2°	103°	99·2°	

Day 55. T. remained subnormal.

The third (A^3) pyrexial period was very similar to the second one (A^2), except only that it was not so severe, and that Hgburia was entirely absent. 310. Ross, Thomson and Simpson (1910).

Post-Hgburic

Hgburia 3½ days, interval few hours; Hgburia 12 hours, interval 1 week; Hgburia 20 hours, interval 5 hours; Hgburia 10 hours, interval 9 days; Hgburia 24 hours. This fever lasted for over 5 weeks and left me prostrate. Banks (1900), 112.

Charts illustrative of post-Hgburic pyrexia: (1) very slight or moderate, (2) prolonged and severe, (3) more continuous type, (4) hyperpyrexia in the post-Hgburic period (2 fatal cases), (5) post-Hgburic pyrexia appears to be rare in suppression cases. Daniels (1901), 63.

Date.	Hgburia.	T.	Hgb, %.	Authority.
22.5	+	40·3°		Panse (1902), 11.
23.	+	High		
24.	+	High		
25.	—		50°	
26.5 until 7.6	Fever; on one occasion rising to 40·8°.			

Date.	Hgb.	C.c. of Urine.	Max. T.	Hgb, %.	Authority.
21 Dec.	+		103°		Brem (1906), Case 3.
22	+−	900	102°		
23	−		102°		
24	−		103·5° Death		
4 Jan.	+			(3 days critically ill)	Ibid., Case 5.
5	+				
6	+	240	101·5°		
7	+	570	101°		
8	−	1740	102°		
9	−	1530	101·9°		
10	−	1410	101·5°		
11	−	1530	102·8°		
15	−			24	
P.H.F. persisted for 5 days longer uninfluenced by Q.					
6 Feb.	+		103°		Ibid., Case 7.
7	+		100·4°		
8	+				
9	−			30 (17th)	
P.H.F. for 15 days.					
19 Apr.	+				Ibid., Case 11.
20	+−	2100	102·4°	42	
21*	−	2400	100·4°	28	
22	−	2310	103·1°		
23	−	1560	103·1°		
24	−	2370	102·1°	24	
25	−	2100	101·7°		
26	−	2670, 2670	102·2°		
27	−	2040	102·7°		
28	−	2040	102·1°		
29	−	1680	102·7°		
30	−		102°		
1 May	−		101°		
2	−		101·2°	19	
5	−			17	
Duration of P.H.F. from the 22nd was 18 days.					

* Jaundice clearing rapidly.

15 Oct. Hgburia.

7 Nov. Irregular pyrexia continued, and any extra exertion caused a rise of T. to about 101°. (Duration not stated.) Howard (1907), 81.

Very commonly there is even severe and continued fever lasting many days after the Hgburia is over. Christophers and Bentley (1908[a]), 67.

Date.	Hgburia.	T.	Authority.
2 Sept.	+	Rigors. 103°	'Africa' (1914), 23.
3	+	Rigors. 101°	
4	+	103·6°, 99·6	
5	—	99·6°, 100·8°	
6	—	Rigors. 97°, 99°	
7	—	Rigors. 102°, 103°	
8	—	Rigors. 99°, 99·6°	
9–15	—	Rigors.	
16–22	—	Rigors. T.N. 103°	
23–28	—	Rigors.	
29	—	No rigors.	
1 Oct.	—	T.N.	

This case is of interest on account of (1) the large number of rigors continued daily for more than three weeks, (2) the large doses of Q. injected with apparently very little effect on the T., (3) the non-recurrence of Hgburia in spite of high T. Blood negative throughout.

Date.	Hgburia.	Max. T.	Pain.	Vomiting.	Restlessness.	Authority.
21 Aug.	+	105°	Epigastric			'Africa' (1914), 24.
22	+	104°		+		
23	—	103°		+	+	
24		104°		+	+	
25		102°		Less		
26		100·4°			+	
27		102°		—		
28		100°		—+	+	
29		101°		+		
30		104·5°	++ Epigastric		+	
31		100·8°				
1 Sept.		103·8°		+	+	
2		98·6°		+	+	
3		99°		—		
4		99·6°				
5		100·4°			+	
9	From now onwards improves.					

1. Before Hgburia *P. falciparum*. After Hgburia, blood negative.

2. T. vomiting, cerebral and other serious symptoms

persisted long after cessation of Hgburia. Urine practically normal throughout.

3. Large doses of strychnine and digitalis given to prevent heart failure. Q. in considerable doses with slight effect on T. Ibid.

Day.	Hgburia.	Max. T.	Hgb, %.	Authority.
?	?	40°	79	Ziemann (1924), 540.
		39·4°, 39·4°	70	
		40°	59	
		39·4°	40	
		39·6°	31	
		39·4°, 40°	22	
		40°	17	
		39·7°, 40·4°	16	
		39·8°	14	
		Death		

Parasites, if present, disappear almost always on the first day. Hgburia can still persist for some days, and then be replaced by polyuria. Characteristic is the intermittent fever always with rigors, often twice a day, which begins in a few days. Icterus also disappears with the disappearance of the Hgburia.

Severe haemorrhages may occur as the result of the gigantic anaemia. Ibid.

Duration of Hgburia 4 days, followed by 8 days (or more) of a low type of fever: for the last 6 days below 100°. Case 3. Yorke, Murgatroyd and Owen (1929–30).

May continue for a considerable period, after Hgb has disappeared from the urine. It is most commonly associated with the relapsing type of case. Ross (1932), 228.

Day.	Hgb-uria.	T.	Urine, c.c.	Day.	Hgb-uria.	T.	Urine, c.c.	Authority.
6	+	102·8	2280	13	—	105·4	900	Penington (1931–32).
7	—	104·2	2250	14	—	105·6	1410	
8	—	105·4	1530	15	—	106·0	1920	
9	+	105·0	1530	16	—	102·4	2610	
10	—	104·6		17	—	102·4	2690	
11	+	106·8	1890	18	—	102·4	2430	
12	—	102·0	1560	19	—	103·6	1980	
				20	—	104·4	2100	

The case was that of a New Guinea native, aet: 29.

The initial Hgburia lasted 6 days, with a relapse of 12 h. duration on day 9 and one of 8 h. duration on day 11. Frequent rigors occurred during and subsequent to Hgburia (Parasites, negative). Polyuria occurred throughout. Recovery.

Thirst

Cases.	Present.	No record.	Authority.
32	13	19	Bérenger Féraud (1874).
15	1	14	Crosse (1892).
48	1	47	Plehn, A. (1896).
43	0	43	Plehn, F. (1898).
14	1	13	Dempwolff (1898).
71	69		MacMillan (1925), 59.
223	85	136	

On admission, extreme weakness. P. 100–110, skin cold and moist. Thirst is very intense, but each mouthful of fluid provokes nausea and very painful retching, which increases the pain in the epigastric region, which radiates to the right hypochondrium. Complete suppression in the afternoon. 15.

On admission . . . apyrexia, icterus general and very intense, tongue coated with a thick yellowish bilious very adherent deposit, red at the margin and tip, bilious vomiting at short intervals, thirst fairly acute, but each mouthful of 'tisane' is immediately vomited, causing great pain in the epigastrium. 20. Barthélemy-Benoit (1865).

Day 1. 5 p.m. Apyrexia, intense icterus, intense thirst, pain in the epigastrium and right hypochondrium.

Day 2. 7 a.m. Icterus very intense, pain in the epigastric and hepatic regions, intense thirst, nausea.

4 p.m. Restlessness of bad prognostic import, some nausea, no motions, urine black, patient worse at night, delirium, convulsive movements.

Day 3. 3.30 a.m. Death. 183.

14 Oct. (day 4). Fever for last four days, 7 p.m. P. 110, complains of great weakness, thirst intense, restless.

15. Complains of great exhaustion, pain in liver region.

16. Intense thirst, urine normal.

17. 1 a.m. Some effortless bilious vomiting, great prostration, burning skin; 1·15 a.m. loss of consciousness, P. 140., *subsultus tendinum*, *trismus*, difficulty in swallowing, respiration difficult and noisy. 1.45 a.m. death. 195. Bérenger Féraud (1874).

Day 2. Great thirst, but however little the patient drinks, the result is deep green bilious vomit. 190.

Day 2. T. fallen. P. 96–100. Tongue coated rather than icteric, nausea, vomiting, intense thirst. 209.

Thirst is one of the greatest torments of the disease, and the sole desire which the patient feels is for drinks, a desire acute, ardent, insatiable. 473. Pellarin (1876).

Day 3. Patient constantly craves for water, but always vomits it, also wine and champagne. ·01 g. morphia subcutaneously in the stomach region, of no effect. Schellong (1890), 70.

Day 1. Great thirst. Plehn, A. (1896), 40.

Day 3. T. 36·9°, P. 92, full, good. 10.45 a.m. gets up to stool. Directly afterwards, rigor. T. 39·5°, vomiting, inky urine, great exhaustion, terrible thirst; 11 a.m. patient is worse, throws himself about on the bed, and groans with irregular sighing breathing. Dempwolff (1898), 156.

Day 1. 7 p.m. euquinine grains 15; 10 p.m. delirious, vomiting incessantly, intense thirst, agonising pains in loins, epigastrium and legs, T. 104°, P. 100; midnight Hgburia. Urine cleared on day 4. Recovery. 'Africa' (1914), 61.

Tongue

Case.	Day.	
1	1	Before Hgburia. A thick greyish, very adherent coating. Calomel 1·0 g. in 5 hourly doses.
	2	Remains coated. Calomel 0·5 g. in 3 doses.
	3	Getting clean.
2	2	A thick slimy coating. Calomel 1·0 g. in 5 doses.
	3	Still heavily coated. Calomel 0·6 g. in 3 doses.
	4	Less coated. Signs of stomatitis.
3	1	Large, moist, a slimy greyish coating, bile-stained. Calomel 1·0 g.
	2	Dry, with a brownish coating. Calomel 1·0 g.
	3	Moist, far less adherent. On the gums and buccal mucosa, signs of mercurial stomatitis.
4	1(?)	Thick, yellowish, bilious, very adherent coating. Red at the edge and apex. Purgative pills and calomel.
	2	Cleaning. Calomel 0·5 g.
5	1	Covered with a thick slimy adherent greenish coating.
	2	Dry, brownish. Death.
6	1	Dry with a greenish bilious coating. Calomel 1·0 g. in 5 doses.
	2	Calomel 1·0 g. in 5 doses.
	3	Moister, very 'dirty.' Mercurial stomatitis, salivation.
	8	Cleaning.

Very severe cases: the coated tongue dries, becomes brown due to a dirty deposit, which also covers the gums. 218. Barthélemy-Benoit (1865).

Case.	Day.	
3	2	Tongue moist, broad furred and bile-stained.
	4	Tongue moist, less furred.
4	1	Tongue moist, furred, indented at the edges.
14	3	Tongue covered with moist fur of a brownish-yellow colour.
16	1	Tongue covered with foul white fur.
17	1	Tongue whitish-yellow coating, clean at the tip.
	2	Dry brown fur on tongue.
	3	Tongue dry, brown and furred.
	5	Tongue still dry and brown.
	6	Tongue moist and cleaning at edge and tip.
18	2	Tongue moist, furred and has a circular black patch behind the tip toward left side.
25	2	Tongue furred.
	3	Tongue less furred, but browner down the centre.
	7	Tongue moister, but still brown and rather dry down centre.

Crosse (1892).

The tongue throughout is moist and thickly coated with a greenish deposit. We have never seen the dryness so characteristic of typhoid and yellow fever. Clarac (1898), 56.

Day 5. 6.30 a.m. the patient showed signs of collapse. The mouth and tongue were very dry and sore.

7 p.m., transfusion . . . the tongue less dry and the patient succeeded in coughing up mucus from his throat. Low, Cooke and Martin (1928).

Uraemia

Distinct uraemia symptoms were absent even in almost complete anuria lasting many days. At most a slight headache frequently present could be ascribed to uraemia. Vomiting was not constant. I never observed oedema of the shins, nor cramps or impairment of consciousness. Prognosis is very bad, but not hopeless. Plehn, A. (1896), 14.

Day 7. Urine 3–5 c.c. twice. In the evening an uraemic attack, clonic cramps of 5 minutes duration, unconscious, later amnesia.

Day 10. Ceaseless hiccough; 7.45 p.m. after a hip-bath an uraemic attack, nystagmus, Cheyne-Stokes R. Ether, 2·0 g. Still five minutes' stupor, then cramps, and in spite of ether, 8 p.m., death. Dempwolff (1898), 161.

Some of the symptoms which the patient showed belong to the uraemic set—the vomiting, diarrhoea, profuse sweats, headache, restlessness, distress, and Cheyne-Stokes respiration. (Death day 5.) Ameuille, Sourdel and Marcorelle (1918), 558.

VOMITING, HICCOUGH, ETC.

Hiccough

Duration

Hiccough also is a very grave symptom, yet I have seen recovery after it had lasted for nearly a week in a very acute case. 307.

13 March (day 4). Vomiting less frequent, hiccough from time to time.
15. Vomiting has returned.
16. Vomiting during the day, hiccough almost continual.
18. Hiccough persists, but less frequent, vomiting constantly.
21. Vomiting less frequent, hiccough less acute.
28. Vomiting profusely. (Recovery.) Bérenger Féraud (1874), 391.

The most distressing symptom is the periodic outbreak of hiccough, and continuous vomiting; each effects with the other a certain interchange, as hiccough for a while ceases after violent vomiting. Schellong (1890), 70.

Hiccough has always been regarded as a symptom signifying a fatal outcome. In Rhodesia it was common in the anuric and toxic cases, and the gravity with which it was viewed was unfortunately always justified. Ross (1932), 229.

Onset and mortality

Anuria (A) or Oliguria (O).	Day of onset.	Day of death or recovery (R).	Authority.	
O	6*		157.	
O	?	11?	166.	
	4	5	168.	
	4	R	390.	Bérenger Féraud (1874).
A	2(?)	9		Crosse (1892), 70.
O	2	5		Küchel (1895), 447.
	3	20	33.	
O	12	16	41.	Plehn, A. (1896).
A	11	11	116.	
A	3	5	119.	
A	?	8	121.	
O	13	16	126.	Plehn, F. (1898).
A	3	10		Dempwolff (1898), 160.
	3	R		Gouzien (1900[a]), 16 (r.).
	4	R		Brem (1906), 1901.
O	3	9		Barratt and Yorke (1909[a]), 217.
O	2(?)	3		
	5	R		Fairley and Bromfield (1934–35).

Cases 18. Deaths 12.
* Ceased on day 9. Death (dysentery?) day 23.

Nausea

Day 2. Pressure not painful except in the epigastrium and right hypochondrium, where pressure as light as it could be induces nausea. 190.

Day 5. Nausea persists, although vomiting has not recurred. 191.

Day 2. Pressure on the right side over the anterior ends of the 7th, 8th, and 9th ribs painful and causing nausea. 205. Pellarin (1876).

Retching

Day 1. Great exhaustion and frequently distressing retching all through the night, but there was no actual vomiting. Crosse (1892), 67.

Vomiting

In Anuria

If the kidney infarct (suppression) is complete, then free Hgb is eliminated through the digestive tract. It is vomited in blackish-brown masses and in the same way is eliminated in the stools.

In incomplete anuria one often sees in the vomit deep green particles, probably small masses of Hgb, greatly changed by the gastric juice. Fisch (1896[a]), 273.

In anuric cases the vomiting may be of the uraemic type, though these cases rarely exhibit typical symptoms of uraemia. Ross (1932), 229.

Cases (illustrative)

11 March. Intense general icterus, frequent bilious vomit, almost black, deep green urine, malaga, copious and frequent.

12. But little rest in the night, vomiting less frequent.

13. Vomiting less frequent, icterus persists, urine a little changed, hiccough from time to time.

14. No vomiting since last night, urine normal, hiccough more frequent; 3 p.m. some vomiting during the day.

15. Vomiting returned, green in colour, urine normal.
16. Vomiting during the day. Hiccough almost continuous; the patient can take nothing. T. has fallen.
18. Hiccough persists, but not so frequently, always vomiting, no fever.
21. Constant nausea, vomiting and hiccough slightly less.
27. Vomiting from time to time.
28. Vomits anything he takes, very exhausted.

8 May. Discharged, cured. (Quinine prescribed throughout the attack.) Bérenger Féraud (1874), 390.

8 Aug. Feeling very unwell. Took a purge, several motions, repeated bilious vomiting. 8 a.m. deeply icteric; 11 p.m. urine dark-red chocolate colour, very turbid 30 c.c. Total Q. retained 4·5 g.

9. Uncontrollable vomiting. Icterus deep mahogany. Vomiting about every 10 minutes, the quantity out of all proportion to the fluid intake; at times 500 c.c. of watery matter streaked with green slime at a single vomit. Abundant liquid given in an attempt to make the continued retching accompanying the vomiting less distressing. To compensate for the colossal loss of water, enemata of water 500 c.c. × 5 given, quickly absorbed. At night hiccough, and so no sleep. Urine 132 c.c. Q. 4·0 g. (8 × 0·5 g. subcutaneously).
10. Vomit at times deep black or blackish green (blood). Fainted twice on standing. A hot moist pack for 2 hours gave great relief. Patient feels quieted and slept awhile. Enemata of water 750 c.c. × 3. The hiccough returns with the old frequency. Urine 20 c.c. Q. 3·25 g. subcutaneous.
11. After a pack, the most distressing symptom, the vomiting ceased, patient sleeping for a while, hiccough as before. Evening, instead of vomiting, diarrhoea at first induced by calomel, increased so greatly as

to exhaust the patient. Urine 8 c.c. Q. 1·5 g. (subcutaneous).

12. Icterus unchanged. No vomiting, ceaseless hiccough. A motion every half-hour, with great tenesmus, thin pulp, blackish green, at times dark reddish (abundant bile and blood). Intellect clear. Urine 19·25 c.c., clear greenish glistening. Q. 1·59 g. 7 p.m. death from cardiac failure. Küchel (1895), 447.

23.9. 8 a.m. Q. 1·0 g.; 11.30 a.m. rigor, T. 105·8°, violent vomiting, blood-coloured urine.

25. Only a few drops of urine with a motion.

26. Frequent vomiting; urine, a.m. 45 c.c., p.m. 25 c.c.

28. Nausea less, urine 47 c.c.

1.10. Vomiting. Urine 90 c.c.

2. The vomiting increases; morphia has no effect.

3. Continuous vomiting of large quantities of watery bile-stained fluid. Urine 71 c.c.

4. The vomiting persists, no food can be taken, nutrient enemata not retained. Hiccough, urine 320 c.c.

5. Diarrhoea, condition as yesterday, urine 71 c.c.

6. Condition unchanged, diarrhoea, urine 54 c.c.

7. Violent diarrhoea and vomiting.

8. *Facies hippocratica*, involuntary stool, Cheyne-Stokes breathing, death. Plehn, A. (1896), 41.

Colour

At first yellow when the vomit is not very plentiful, but usually it is green from the beginning, resembling a solution of arseniate of copper. Dutroulau (1868), 325.

The fluid is perfectly limpid except perhaps for a little mucus and for a slight foam; it is a beautiful green colour, like that in the ornamental bottles in chemists' shops.

Exceptionally it is greenish yellow.

In severer cases the fluid contains opaque solid matter.

Day 4. Some bilious vomiting, followed by colourless vomits with distressing nausea. 127. Bérenger Féraud (1874).

Day 3. In the afternoon a slight attack preceded by a rigor and ending in the evening with sweating. During the attack, vomit, black when seen in mass; a wet piece of linen is stained deep yellow-saffron, the bile mixed with water being neutral in reaction. 205.

Day 1. Leek green vomit, frothy.
Day 3. Return of the vomiting, yellow, watery, profuse, not frothy. 209.

Day 2. Nausea. Vomiting, which has taken on the characteristic green modification with a whitish foam. 212. Pellarin (1876).

In the worst forms of b.w.f. the vomit assumes a bluish-black colour, but this is as distinct as possible from the ' coffee-grounds ' of true yellow fever. Easmon (1885), 280.

Day 3. The patient ejected considerable quantities of viscid bluish fluid from the stomach. 593.

Out of 642 cases reported (in Alabama) only 14 presented this symptom (black vomit). 598. Cochrane (1885).

Day 2. The vomit, which had looked like green paint, was now a mixture of yellow and green, but never of a black colour. Crosse (1892), 72.

Day 2. Frequent vomiting, at first deep green, then gradually changing to golden yellow. Gouzien (1900[a]), 15 (r.).

Had an attack of high fever, jaundice, restlessness, black-coloured vomiting, etc. Death. Christophers and Bentley (1908[a]), 231.

1. At times limpid, grass-green, like an ammoniacal solution of copper with mucus floating on the surface.

2. More often a dark green, containing particles or clots resembling chopped greens (spinach vomit).

3. Rarely blackish coal-like or even speckled with black Hgic points.

4. A dirty yellow, brownish yellow, chestnut colour is of bad prognosis.

5. In the uraemic form the vomit is serous, bilious but not ' porracés ' leek green as it is initially. Gouzien (1911), 10 (r.).

Day 3. Vomited three times creamy-green fluid. ' Africa ' (1915), 21.

The vomited matter was usually deeply stained with bile. Ross (1932), 229.

1. Day 1 (?). T. 40·3°, P. 140, much delirium, black vomit, yellow sclerae, urine deep red. 301.
2. Day 5 (?). Early morning, coma, black vomit, high delirium, P. 120, hardly palpable, death. Naumann (1933).

Duration

19.12.94. Rigor vomiting Hgburia.
26. Uncontrollable vomiting.
27. Vomiting stops. Plehn, A. (1896), 25.

Day 2. Urine dark red colour. Vomited once.
Day 3. Urine clear. Barratt and Yorke (1909[a]), 186.

Vomiting was severe and lasted 12 days. Fletcher (1914), 43.

Distressing retching and bilious vomiting for 4 days. 65.

Vomiting began with the fever and continued all through the attack (9 days). 2nd day, suppression of urine. 67. ' Africa ' (1915).

Frequency

Cases.	Present.	Absent.	No record.	Hiccough.	Authority.
32	25		7	4	Bérenger Féraud (1874).
15	14	1		1	Crosse (1892).
48	31		17	2	Plehn, A. (1896).
43	24		19	4	Plehn, F. (1898).
14	7[1]	3	4	1	Dempwolff (1898).
17	10		7		Koch (1899).
14	11[2]		3	1	Gouzien (1900[a]).
38	3		35		Panse (1902).
14	13[3]	1		1	Brem (1906).
20	18	2		0	Da Costa (1906).
19	14	2	3	1	Barratt and Yorke (1909[a]).
23	14	3	6		'Africa' (1914), 60–65.
21	15				'Africa' (1915), 52.
39	33	2	4		Connal (1916), 11.
17	15	1	1	0	Arkwright and Lepper (1918[b]), 378.
10	7		3	0	Seyfarth (1918[b]).
7	6	1			Gaskell (1920).
150	By no means constant.				Ross (1932), 229.
9	6		3	2	Fairley and Bromfield (1934).

[1] In 1 the vomiting was initial.
[2] In 2 the vomiting was initial.
[3] In 3 the vomiting was initial.

The records refer to vomiting during the attack, and not merely initial vomiting at the onset.

General

Nausea, retching and vomiting. Usually begins in the paroxysmal stage of the attack. At first mucus and bile, then pure concentrated bile, yellowish brown or grass green. Occasionally a litre in some hours.

The vomiting at first at irregular intervals, and with noisy distressing retching, then more frequently abundantly and with less effort. A period of calm follows and then the vomiting returns. During the intermissions or remissions the vomiting is rarer or ceases.

Each bout of vomiting results in collapse and extreme general feebleness. 213.

The quantity of bile passed may be 1000–1200 c.c. in some hours. It is coloured an intense brown or green. It

is sticky, viscous, has a strong nauseating smell, and decomposes rapidly in the air. 217.

In severe attacks vomiting is intense; in still graver it becomes 'passive' or suddenly stops. 220. Barthélemy-Benoit (1865).

Hgic.

Day 1. 11 a.m. violent rigor, T. 41·3°, air hunger, oppression, abundant bloody vomit and much blood in the numerous diarrhoeic stools. The Hgburia, bloody vomit, and stools persist for 3 days. Plehn, A. (1896), 46.

17 Dec. Bloody vomit said to have accompanied the bloody urine.

19. Anuria.

22. Continuous exhausting vomiting of greenish-black masses. Anuria.

25. Urine. 120 c.c., dark blackish brown. Vomit, dark blackish green.

26. Anuria.

28. Exhausting vomiting of bile masses, partly mixed with blood. Anuria.

30. Retching continues. Incontinence of faeces. Anuria.

1 Jan. Death. Plehn, F. (1898), 118.

Day 12. Vomiting—not abundant—of blackish matter containing mucus, epithelium and altered red cells. 19 (r.).

1 Sept. B.w.f.

2. Incessant golden-yellow vomit; 3 p.m. vomiting subsiding; 5 p.m. renewed yellow vomit with black spots, haemorrhagic.

3. Urine clear; green vomit with haemorrhagic spots; icterus persistent. 48 (r.).

23 Aug. p.m. Hgburia (60 c.c.).

24. Bilious vomiting, urine scanty.

25. Green vomit with black haemorrhagic spots. 45 (r.). Gouzien (1900[a]).

This morning took four grains of Q. Remained well till mid-day. Became seriously ill at 1 p.m. when he vomited black material like coffee grounds. T. 104°. . . . Passed red urine . . . 'looking like blood.' Death. Barratt and Yorke (1909[a]), 225.

2 a.m. Hgburia. Vomited three times, bilious green fluid, with traces of blood. 11.

Vomiting occurred in 15 of 21 cases. It was bilious in 4 cases, and coffee-grounds in 1 case. 52. 'Africa' (1915).

Quantity

The quantity of bile passed may be 1000–1200 c.c. in some hours. Barthélemy-Benoit (1865), 217.

The quantity may attain to 2000 c.c. for 'one vomiting.' Dutroulau (1868), 325.

It is not rare for 800 or even 1000 c.c. of bilious fluid to be vomited in 2 or 3 hours. Bérenger Féraud (1874), 124.

Urea in vomit

Day 3. 1·5 g. per litre.

Day 6. 1·27 g. per litre. In diarrhoeic stools 0·24 g. per litre. Achard and Saint-Girons (1912), 756.

Weakness

15 in 48 cases. Plehn, A. (1896).

27 in 43 cases. Plehn, F. (1898).

Yawning

(*a*) 27.11.95. Midnight, Hgburia. 10 a.m. sweats, yawns much, but is mentally clear and free from pain.

(*b*) 25.7.96. 11 p.m. Hgburia.

26. 3 p.m. T. 38·2°, apathetic, yawns and sweats very much. Dempwolff (1898), 155.

Wau, Behr-el-Ghazal.

26 Oct. (day 2). T. 99°, skin moist and cool, pulse weak and scarcely perceptible, and his breathing

Summary of Initial (Day 1) Symptoms. Plehn, F. (1898).

Case.	7.	11.	12.	15.	16^1.	16^2.	16^3.	17^1.	17^2.	18.	20.	21^1.	21^2.	21^3.	24^1.	24^2.
Rigor	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
T.	40·5°	40·1°	40°		39·3°	40°	+	40·3°	41·2°	39·5°	40·3°	40·4°	+	40·1°	39·9°	
P.	112	110	100						120+		120	105			100	
Nausea							+									
Retching		+	+			+		+	+							
Vomiting	+			+	+		+			+	+	+	+	+		+
Icterus	+	+	+		−	−	+	+		+	+	+	+	+	+	+
Dyspnoea			+					+	+						+	
Pain, head				+	+	+						+	+	+	+	+
,, back						+						+	+	+		+
,, legs																
Oppression, pectoral	+	+							+							+
Tenderness, abdomen		+						+	+				+			+
Tenderness, liver	+		+		+											
Tenderness, spleen			+	+	+	−	p*	p	+		−	−				
Strangury			+		+					+		+	+			+
Sweating		+			+							+			+	
Agitation, anxiety			+													+
Unconsciousness.	+															
Stupor						+										
Delirium						+	+					+				+
Weakness		+							+				+			

* p = pain.

Case.	26.	27.	28.	29.	30.	31.	32.	33.	34.	35.	36.	37.	38.	39.	40.	41[1].
Rigor . .	S*	+	+	S	S	40·1°	S	+	+		+	+	+	S	+	+
T. . . .	39·1°	+	40·1°	40·1°	40·1°		38·2°	+	39·4°	40·6°	38·4°	39·3°	38·6°	38·0°	39·5°	41°
P. . . .																
Nausea . .				+							+					
Retching . .	+	+					+		+			+		+	+	+
Vomiting . .								+		+						
Icterus . .	+—	+	+	+	+	+	—	+	+	+	+	+		+	+	
Dyspnoea . .								+				+			+	+
Pain, head .	+										+				+	
,, back .		+														+
,, legs . .		+														
Oppression, pectoral . .		+	+													+
Tenderness, abdomen . .															+	+
Tenderness, liver										+	+					
Tenderness, spleen . .	—	—	+	+	—			—	+						+	
Strangury . .		+	+			+		+		+		+		+		+
Sweating . .										+		+			+	
Agitation, anxiety . .		+				+		+		+	+	+				
Unconsciousness.																+
Stupor . .						+									+	+
Delirium . .																+
Weakness . .				+								+				

* S = Shiver.

quick and shallow with occasional yawning. 6 p.m. the yawning . . . had entirely ceased. This yawning had been a well-marked symptom in the morning. Ensor (1906), 387.

Day 1. Rigor. T. 104°. Hgburia.

Day 2. 6 p.m. pallor marked. Yawning. Christophers and Bentley (1908[a]), 202.

Day ?. 2 injections of sodium bicarbonate solution. Patient's general condition improved. Urine 341 c.c. by catheter. The patient, after a few minutes of shallow sighing, yawned and fell asleep. Hanschell (1925–26), 490.

Short Summary of Cardinal Symptoms

Rigor and T.

Rigors occur most commonly at 9–12 n. An initial rigor ushers in the attack in some 60% of cases. Hgburia following within an hour in the majority of cases. Multiple rigors are common and the duration of a single rigor may be from $\frac{1}{4}$ to 4 hrs. In some 10% of cases the rigor is post-Hgburic.

T. may not begin to rise until 20–30 minutes after the rigor. Three exceptional types of T. are: (1) Hyperpyrexia (e.g. 109°) with fatal ending, (2) Subnormal T. of anuria, and (3) Post-Hgburic fever, at times with grave anaemia.

Icterus

Occasionally absent. Occasionally may precede the rigor and the Hgburia. May be universal on day 1. Usually disappears in a few days but may persist for weeks or even months. May also disappear before death. Bilirubin has been found in the sweat. Itching occasionally occurs.

Icterus sine Hgburia appears to be associated with bilirubinuria.

Hgburia

Hgb may be absent in the first urine passed after the rigor. The duration of Hgburia may be only a few hours (6). A duration of 1, 2, or 3 days is about equally common. A duration of 4 days is about $\frac{1}{2}$ as frequent as that of 3 days, of 5 days $\frac{1}{2}$ that of 4 days and so on.

Albuminuria persists for a variable period after Hgburia or may be " permanent."

Certain malaria cases give a positive guiac and turpentine or benzidine test for Hgb, but negative spectroscopically at least in the latter case.

Intermittent Hgburia occurs with a frequency of about 10%. One relapse is the commonest condition, but as many as 11 may occur. A clear distinction cannot always be drawn between a " relapse " and a " second attack."

The association of a relapse with a rise of T. is a frequent occurrence.

Bilirubinuria may occur subsequent to the Hgburia.

Death

The death rate is commonly about 20% +. In about $\frac{2}{3}$ of the cases it occurs in the first week and in about $\frac{1}{3}$ in the 2nd week. If we take the frequency of anuria as 10% and its fatality as 100%, then death from anuria is equal to that from all other causes. Cardiac failure is, however, commonly assigned as the cause of death.

CHAPTER 9

TREATMENT, PROGNOSIS, PROPHYLAXIS

Treatment, General

1865

A mild case

1. *Ipecacuanha :*—At the beginning of the febrile stage, 1·2 g. in ½ a glass of water, in 2 or 3 doses at 10 minutes intervals. When it acts, vomiting is aided by 4 or 5 glasses of warm water. The resultant vomiting can be checked by warm tea, flavoured with orange, in small doses, and then more freely, to promote diaphoresis and the general sedative action which follows ipecacuanha.

2. *Quinine sulphate :*—After the vomiting has ceased, 1·0 g. divided into two doses in capsules, with laudanum 5 drops to each dose.

3. *Lumbar pain :*—Poultices with laudanum to the loins; camphorated oil (with opium) embrocations. Repeat.

4. *Intermittent pyrexia :*—The vomiting and haematuria, usually in suspense during the apyrexia, return with the second rise of temperature. In these cases, as improvement has already set in, it is unnecessary to repeat the ipecacuanha, it is enough to give a hot aromatic, to promote sweating, then Q. sulphate 0·8 g. in 2 doses, given as above. Q. 0·6 g. is continued every 3rd and 4th day, and the aromatic draught replaced by barley water 2 litres + potassium nitrate (azotate potassique) 2 g. per diem.

5. *Icterus and constipation :*—If icterus has been intense and if constipation exists after the second attack, calomel 1·0 g. with jalap resin, aloes and soap, 0·5 g. of each. A purgative enema is also advisable to promote expulsion of bile and rectal contents.

6. *Prevention of relapse* :—If from the cachectic state of the patient and from the usual type of the prodromal attacks a relapse is anticipated on the 7th or 14th day, Q. 0·6 g. is given on the evening of the 6th and morning of the 7th days, counting from the date of the first attack.

A severe case

Ipecacuanha :—When the biliousness is pronounced a 2nd dose at the beginning of the 2nd paroxysm.

Quinine :—Is given during the remissions of T. or preferably

Calomel :—1·0 g. in 5 doses, 1 every hour. On the next day 0·6 or 0·5 g. in 3 doses, 1 every hour. A slight stomatitis is produced which coincides with the cessation of fever, the rapid return to normal of the urine and a distinct general improvement.

Stomatitis :—To check the spread of the stomatitis and salivation, astringent gargles and a mouth-wash of honey of roses and alum acidulated with lemon-juice.

Vomiting :—Sulphuric ether 1·0 g.
Laudanum of Sydenham 1·0 g.
Mucilage 120 c.c.

Small quantities at intervals or aerated waters, champagne, ice.

Blisters :—If these remedies fail, a blister covering the mesogastric region and $\frac{2}{3}$ of the anterior surface of the liver should be applied.

Epigastralgia :—If this does not cease with the blister, morphine hydrochlorate 0·025 g. is applied to the raw surface night and morning.

Lumbar pain :—Apt to be acute when the urine is scanty, very bloody and with sediment. A few leeches over the kidney or preferably wet cups, with slight scarification, to avoid too great depletion by leeches, often give prompt relief. Opium, belladonna, chloroform embrocations, large poultices, hip baths ought to be persevered with.

Quinine :—If not tolerated by the mouth is given as an enema. Q. 2·0 g.; water 120 c.c. + 5–10 drops of laudanum, 2–3 times at 4-hourly intervals, according to the gravity of the case.

A very severe case

If the case has reached the 3rd stage, if the vomiting has not been checked, if the prostration of this last stage has not been averted, emphasis must be placed on the revulsive action of

1. *Blisters* :—To the gastro-hepatic region and to the legs. A strong solution of quinine or Q. in powder 1 g. for each blister is applied and enemata of quinine every 4 hours.

2. *Hiccough* :—A large sinapism between the shoulders, ether capsules, or morphine may check it.

The timely administration of calomel up to the first signs of mercurial stomatitis is for us the essential basis of treatment. One can only reckon on the action of quinine when calomel has produced its double effect—alterative and purgative—obtained by fractional doses at regular intervals. What has induced us to adopt this treatment is the striking coincidence between the clearing of the urine and the appearance of stomatitis. Barthélemy-Benoit (1865).

1868

Evacuant treatment :—What impresses one from the first is the necessity of interfering with the abnormal secretory function leading to the excessive output of bile. Ipecacuanha, tartar emetic, and neutral purgative salts by the mouth or per rectum have an almost constant effect when they have time to act. Acidulated drinks help in this change, for they attack the Hgic conditions which often form part of the morbid condition.

Calomel :—Frequently used in our colonies, but it is not, as in the English colonies, made a panacea, a specific for bilious diseases.

Vomiting :—Vomiting and diarrhoea may be so frequent

that the evacuants are eliminated as soon as taken. To check this, and to give the evacuants time to act, it is necessary to act through the skin. Cold compresses to the epigastrium and hypochondria; sinapisms to the legs usually suffice, but a large blister is more certain.

Leeches, poultices, sudorifics :—When not only polycholia but circulatory disturbance or a continuous type of fever exist treatment should not begin with evacuants, but with numerous leeches and poultices, and when the inflammatory process is pronounced, leeches to the head, irritant foot-baths, sudorifics.

Quinine :—Taking advantage of periods of intermission or remission at least 2·0 g. should be given between the attacks. Even if the fever is continuous it should not be entirely omitted. Dutroulau (1868), 339.

1874. *Senegal*

1. *Prodromal period* :—

There are 2 sets of phenomena in this first period: (1) the bilious state or better the 'indigestion' of the *primae viae*, (2) the fever. For treating the first the great majority of physicians have recourse to

Evacuants :—(a) *Emetics.* Ipecacuanha 1·2–1·5 g. Some physicians add tartar emetic 0·05 g. With numerous glasses of warm water a considerable quantity of bile is expelled.

(b) *Purgatives.* Are far less distressing; I prefer them when the indigestive or bilious state is not too intense and secondly for debilitated patients. I use jalap, castor oil and purgative enemata and I often preferred the latter. I do not advise calomel.

Opiates :—Between emetic and opium treatment it is difficult to choose but most frequently I have used opiates where the tendency to vomit was less marked, but I have also used them when it was not only imminent but had begun. Syrup of opium 30–60 g., water 100 g., a spoonful

hourly. When sleep ensues the patient has not long absorbed a sufficient amount to be dangerous. In over 300 cases without any previous treatment I have seen the bilious state yield at least as rapidly as to emetics and purgatives. I have often combined the two modes of treatment. (1) An emetic followed by an opiate, (2) an opiate and an emetic the following day if the biliousness has not improved. 313.

Quinine :—

Time :—As soon as possible, at the remission of the first fever. If an emetic has been given, 1–2 hours after the last vomiting. If an opiate, 1–2½ hours after the beginning of the treatment.

Mode :—1. 1·0 g. in solution is usually given in the Senegal hospitals. Some physicians add 5–10 drops of laudanum, but I give it after tolerance has been prepared by opium treatment.

2. In powder in a little dough, in fractional doses every ½ hour.

3. As an enema. A large warm-water enema is first given. After the motion, Q. is injected through an anal obturator. Q. 1·5–2 g. in H_2O 150 or 200 c.c.

4. I regard Q. applied to the surface of a blister as useless.

Dose :—3–5 g. per diem as long as the fever lasts 3–5–8 days. If tinnitus and deafness are excessive, administration is stopped for 6–12 hours. 323.

2. *Febrile period* :—

Quinine :—However slight the attack may appear, active treatment is essential, at least 2–2·5 g. in the first 12 hours in mild cases and 2–3 or even 3·5 g. in severe cases. Continue until the fever is definitely cut short. All

possible means should be taken to see that Q. is really and completely absorbed. I am convinced that Q. by itself has been successful in many cases which appeared very serious.

Evacuants :—(a) *Emetics* are indicated in this first period, only, at most, if they have not been given already. They may aggravate the vomiting, which is already distressing and abundant, and lead to a condition of retching and hiccough.

(b) *Purgatives* :—Drastic purges like aloes, jalap and scammony, owing to their small bulk, are used by some physicians, but enemata appear to be more rational considering the intolerance of the stomach. 334.

Calomel :—Has been used, as, though small in bulk, it has a decided purgative action, and secondly for its alterative action—modifying the biliary function. 345.

(a) *Purgative* :—0·8–1·0 g. some hours after the initial emetic. If a severe case or if the evacuation has been scanty, as much as 2·0 g., repeated for 2–3 days. 345.

(b) *Alterative* :—1·0 g. in 4–6 fractional doses in 24 hours, repeated.

1. In the practice of some salivation is avoided.
2. Others endeavour to obtain salivation as rapidly as possible, regarding it as the precursor and not the result of improvement.
3. Others again hold that in mild cases the purgative action alone suffices, while in moderate or severe cases the alterative action—salivation—is necessary.
4. Others finally by giving the drug partly in big doses, partly in fractional doses, desire to embrace all sides of the

question, unaware really whether it is from the purgative or alterative action that they are going to get good results, using the drug because tradition favours it, not ascribing to it any other importance or not troubling about its real action. 347.

Calomel as a purgative :—In slight cases of b.w.f. when Q. has checked the fever, purgation is a secondary matter. Citrate of magnesia, manna, jalap, or aloes in powder, castor oil in emulsion—all are as easy to take as calomel, and there is no danger of salivation or super-purgation. 349.

Calomel as an alterative :—B.w.f. often ceases without any treatment, so that calomel is not indispensable, and it may be doubted whether calomel hastens the remission of symptoms. In over 30 cases, moderate or severe, the remission has occurred as rapidly, if not more so, in those treated without calomel. The remission is in direct proportion to the energy of use of quinine. 354.

Calomel not only profoundly weakens the patient, but it produces a stomatitis, sometimes serious. 355.

I have frequently had occasion to establish a connection between inflammation and suppuration of the liver with mercurial treatment. 360.

Pain (*epigastric, hypogastric, hepatic and lumbar*) :—

1. A large poultice to the affected parts. Difficult to retain in place when there is vomiting.
2. Oily embrocations, wrapping hot flannels lightly round the body.
3. A large blister extending from the epigastrium to the sides of the body may give complete relief from very acute pain in a few hours.
4. For the lumbar pain, a blister is contra-indicated owing to the dorsal decubitus. Instead a sinapism or oily embrocation is used.
5. For the hypogastric pain, a large poultice. 378.

Vomiting :—(a) Teaspoonfuls of water taken every minute is of all the methods suggested the preferable one, although it requires the constant attention of a nurse for whole hours.

(b) A blister to the epigastrium may be useful.

Quinine :—Given in the febrile period to fortify the patient against the adynamic period. When the vomiting is persistent, a large emollient enema is given and after an evacuation a quinine enema Q. 1·0–1·5 g. in water 150 c.c. If rejected an anal obturator should be used for a second enema. 380.

3. *Adynamic period* :—

Lumbar pain :—A sinapism, followed by a hot oily narcotic embrocation followed by a large poultice sometimes gives relief. Dry cups and leeches may be used where the anaemia is not too great and when the pain is acute and persistent. Cupping is preferred by some by reason of the greater irritation produced for the same loss of blood.

Hypochondrial pain :—The same treatment is applicable.

Epigastric pain :—The same treatment.

Vomiting and Hiccough :—A troublesome complication of the febrile period, and may persist after the cessation of fever. If aerated waters, ice, hot tea, aromatic or antispasmodic draughts fail, recourse may be had to enemata, giving nothing by the mouth for 3–5–8 days.

(a) A large simple enema of water in the morning and afternoon. In case the first enema is not passed in $\frac{1}{4}$ of an hour, a second is given immediately. Subsequently

(b) *Nutritive enemata* :—

(1) Beef tea 150 c.c.
Red wine 50 c.c. or

(2) Beef tea 60 c.c.
Brandy 30 c.c.
Red wine 30 c.c.

(c) *Quinine enema :—*

'Quinine' 0·5–0·75 g. in acid solution.
Brandy pure or diluted 150 c.c. 383.

4. *Convalescence :*—Eggs (soft-boiled), 1 at first, then up to 4 a day are preferable to soups or puddings, milk, etc., and nourishment is preferable to tonics such as quinquina, iron. 395.

Fever :—During convalescence requires Q. 1 g. daily. 397.

Gastric disturbance :—Ipecacuanha followed by a purge. 398.

Constipation, colic :—This, like the fever and gastric disturbance, is regarded as essentially malarial—larval malaria—and is treated by quinine. 404.

Tonics :—(a) *Vinum quinquinae :*—the tonic or febrifugal action depends on the character of the wine used and on that of the bark. If a febrifugal action is desired then yellow quinquina and white wine should be used. If, on the other hand, a tonic action is required, grey quinquina and red wine. The same results can, however, be got with quinine alone or tannin alone, and with vinum quinquinae there is the danger of alcoholism.

(b) *Extract of quinquina :*—As a tonic 2–4 g. per diem. Not on an empty stomach.

(c) *Tannin :*—0·3–0·5 g. with food.

(d) *Strychnine :*—0·05–0·10 g. in 1000 c.c. H_2O. 20–50 c.c., 20 minutes before food.

(e) *Arsenicals :*—8–10 milligrams per day. Intolerance occurs very rapidly in Senegal.

(f) *Iron :*—A more rapid and better tonic than the others. 406. Bérenger Féraud (1874).

1876

Between the treatment with massive doses of 10 grammes of sulphate of quinine and 4 grammes of calomel and the

treatment without any quinine or calomel there is an abyss which disturbs the reasoning faculties.

Transport :—Experience has shown that this should be avoided as far as possible, as it inevitably causes suffering and may aggravate the disease.

Quinine :—1–2 grammes in 24 hours if there is reason to believe it is being absorbed, otherwise by enema in fractional doses with tincture of opium to promote absorption.

Vomiting :—Nothing will check the vomiting at the onset in severe cases. Quinine pills, with extract of opium and tartaric acid sometimes appear to check it. After 1 or 2 days opium or morphine frequently checks or arrests it. But often this occurs spontaneously.

Fluids :—A much-discussed question—whether the patient should drink to quench his thirst in spite of the nausea and vomiting or whether he should take as little as possible in order to avoid these. I believe that abundant fluid taken prudently and in small quantities at a time is the most potent means at our disposal for treating the disease.

Ipecacuanha :—Sometimes useful when 'indigestion' is pronounced. 1–1·5 g.

Calomel :—Useful when constipation resists laxative enemata. 1 g.

Bleeding (local) :—In cases of very acute localized pain with high fever may be indicated where the patients are not too weak.

Convalescence :—Is always fairly long. Vinum quinquinae, iron, good food, departure to a healthy climate, exercise in the open air, cold baths, hydrotherapy, flannel next the skin are the best means of complete cure. Pellarin (1876), 474.

1886

Mild cases :—A few small doses of calomel combined with opium and bicarbonate of sodium . . . followed by efficient doses of quinine will very promptly . . . place the patient in a state of convalescence.

Grave cases :—

1. At once apply over the epigastrium and liver a blistering plaster.

2. Hypodermic of morphine $\frac{1}{4}$ to $\frac{1}{2}$ grain, and repeat after 1–2 hours.

3. If the stomach is not quieted . . . , calomel 3–5 grains, with sod. bicarb. every 2–3 hours . . . to act with certainty on the liver (generally 15–20 grains suffice).

4. If the bowels are not moved in 4–5 hours, give enemata of warm water containing a tablespoonful of camphorated oil, every 1–2 hours, until the bowels gently evacuate.

5. If the stomach is still troubled with nausea, give a drop of creasote, made into an emulsion with sod. bicarb. and a small quantity of morphine with aqua menthae, every 1–2 hours, p.r.n.

6. As soon as a bilious discharge has been had from the bowels, give quinine.

7. As soon as the function of the liver is restored, give the muriated tincture of iron 20–30 drops every 4 hours.

8. If the kidneys fail to act, a liniment of spirit of turpentine, tincture of digitalis, and whisky, rubbed in warm over the back, will often be found efficient. Sometimes spirit of turpentine inwardly, 3–5 drop doses, may be needed to supplement the liniment.

So well satisfied am I with the results, that I can with confidence commend the same to any physician. Day (1886), 83.

Gold Coast

In some cases it is necessary to use drugs—if not more than 300 c.c. of urine are passed in 6 hours and ' Romans-horner ' milk produces no increase.

Potassium acetate :—3–6 g. in water. If not retained it is given as an enema 6·0 g. in 250–500 c.c. H_2O.

Boracic acid :—2–3%. 1 litre is drunk in the day, but if used it is preferable to give it as an enema 5–8 g. in 500 c.c. of water. Patients will more readily drink pure water the

whole day than the rather unpleasant boracic acid solution. Fisch (1894), 96.

U.S.A.

Of 107 practitioners, 33 used calomel; 25 tr. ferri. chlor.; 23 arsenic; 18 ergot; 14 turpentine; 10 sodium hyposulphite in the treatment of b.w.f. in the United States. 26 other drugs used.

Calomel :—50 grains every 3 hours. 3 doses. Has never seen a case ptyalized by this large dose (Weight).

Tincture of chloride of iron :—Combined with arsenous acid the remedy *par excellence* (Guice).

Sodium hyposulphite :—The best remedy (Jones).

Turpentine :—To arrest the renal hemorrhage, the best remedy (Guice). Hare and Krusen (1895), 291.

Alabama. As soon as the diagnosis is made, a hypodermic of morphia and atropia is given, followed immediately by a ten-grain dose of calomel. 5 grains are repeated every 2 hours, 4 or 5 doses, . . . when so administered I have never seen it act as a drastic purgative, nor have I witnessed evidence of mercurial poisoning.

If the patient can be seen 2 or 3 times a day, Q. bisulph. gr. 5, Morphin sulph. $\frac{1}{8}$ gr., Atropin sulph. $\frac{1}{200}$, Aqua ℥ 30, for one injection, repeat every 8 hours.

If patient can not be seen frequently, Q. sulph. gr. 5, Camphor monobromate gr. 2, Morphin sulph. gr. $\frac{1}{12}$ to $\frac{1}{8}$, Atropin sulph. $\frac{1}{200}$–$\frac{1}{600}$, Capsicum pulv. gr. $\frac{1}{2}$, one capsule every 4–5 hours.

If the T. is above 102·5°, phenacetin gr. 3–5, caffeine gr. $\frac{1}{2}$ to 1, Sod. bicarb. gr. 1, one powder, repeat every 2 hours until T. is reduced.

Copious draughts of skimmed sweet milk and water. One to two large saline enemata daily. Sinapisms to the back, kidneys, and epigastrium. Ten successive cases without a death. I have such implicit faith in the above treatment that I no longer dread having charge of such cases. Du Bose (1899), 539.

The remedy which has given the best results is calomel.

If it does not act promptly, it should be followed by some active hydrogogue. In many cases it would be well to administer at the outset a large enema of warm water, as constipation is the rule. To encourage the action of the skin hot mustard footbaths should be given, and the body sponged with hot water and alcohol. I have also used with great satisfaction . . . phenacetin grains 5–10, with ipecacuanha grain $\frac{1}{4}$ to $\frac{1}{2}$ and caffeine citrate grains 1–2. Smith (1900), 189.

Dahomey

1. *Decoction of Cassia occidentalis* (Ahouandémé) :—15 g. of fresh dried leaves per 1000 c.c. water with sugar and lemon juice. 1–3 litres in 24 hours. 51.

2. *Hypodermic injection of saline :—*

(a) If the decoction is not well taken and if the urine is not definitely clearing after 24 hours, give a saline injection 200–300 c.c. of 0·79%. Repeat if necessary.

Indications :—Definite weakness as indicated by pallor, restlessness, dyspnoea, feeble pulse.

Contra-indications :—Renal disease (oedema or anasarca), hyperpyrexia 39·5°, as the injection itself may cause a rise of T. In this case endeavour to reduce the temperature by

(b) *Enemata :*—of cold water 200–300 c.c., every 2–3 hours, 1000–1500 c.c. in the day or

(c) *Wet pack or cold lotions :*—e.g. camphorated alcohol lotion. 58. While this treatment is in progress and if the urine is copious enough

(d) *Bromohydrate of quinine :*—·25 g. 1 or 2 injections. Apart from the question of a malarial infection, quinine is valuable from its antiseptic and antipyretic properties. It should be given in cases of hyperpyrexia, and provided the quantity of urine passed is about normal. If the temperature is not very high, 38°–39°, we do not give Q. 53.

3. *Saline enemata* :—When the case is not urgent and not requiring hypodermic injections, saline enemata 0·7%, 200–300 c.c., 5–6 per diem are very effective; they are stimulant diuretic and diaphoretic. 53.

4. *Ether and caffeine hypodermically* :—Especially caffeine where there is danger of syncope or in great weakness. An injection is valuable also before and after a saline injection. Caffeine is also the best treatment for headache and the enervation due to anaemia. 0·3 g. 1–4 injections, ether 1–6 injections.

Prescription :—3 injections of caffeine, 2 of ether. 16.

5. *Counter-irritation* :—

(a) *Dry cups* :—several (4), twice a day in the lumbar region, to be maintained during the acute stage. Wet cups except in very vigorous patients are injurious.

(b) *Ether spray* :—2–3 minutes to the epigastrium, for epigastralgia and vomiting. Repeat. Relief is immediate and patients often ask for the treatment.

(c) *Painting with iodine, dry cups, sinapisms* :—For the hepatalgia and splenalgia usually not very acute. Blisters are strictly prohibited owing to their irritative action on the kidneys.

Accessory drugs and treatment

Antipyrin :—0·5 g. may be tried for the initial hyperpyrexia, to induce sweating, followed by some cups of ' thé punché ' (tea with rum).

Diuretics :—Lactose (50 g. per litre), liquorice (1·0 g. per litre), mineral waters.

Diuretic and cardiac tonic :—Digitalis with or without caffeine.

Morphia :—If the history is negative in regard to past renal lesions, and if enough urine is being passed, morphia 0·01 g. hypodermically may be given to allay restlessness and insomnia among the most distressing symptoms of the initial period.

Purgatives :—

(*a*) If administration *per os* is possible, Hunyadi János, Carabaña, or castor oil.

(*b*) Calomel is injurious from the danger of hydrargyrism in debilitated patients, or those with bad teeth. (Gouzien (1911) 93. (r.).)

(*c*) A large simple enema, or with boracic acid 15 g., or glycerine 50 g., or salt 15–20 g., per 500 c.c., every morning.

Hiccough :—Ether-chloroform draught, sinapism between the shoulders, morphia.

Vomiting :—

(*a*) Saturated solution of chloroform diluted with twice its volume of sweetened water flavoured with orange-flower, a dessert spoonful every ½ hour, followed by a spoonful of Vichy water. (*b*) Cocaine hydrochloride 0·05 g. (*c*) Ice. (*d*) Iced champagne. (*e*) Ether spray. (*f*) 'Pointes de feu' (cautery). (*g*) Ice to the epigastrium. (*h*) Dry cups.

Convalescence

Laxative :—Rhubarb 0·5 g.
Calcined magnesia 0·25 g. 2–4 cachets daily.

Tonic :—Not earlier than 4th or 5th day.

Morning: hot black coffee, repeated in the afternoon if wished, quinquina, kola, nux vomica, Fowler's solution, etc. When convalescence is established

(*a*) Pot. ferric tartrate 0·1 g.
Ext. quinquinae 0·5 g.
3–4 boluses daily at meals or

(*b*) Pulv. nuc. vom. 0·015 g.
Ext. quinquinae 0·5 g.
Pulv. quinquinae 0·25 g.
3–4 boluses daily at meals. 50. Gouzien (1900[a]) (r.).

South Carolina

Mild cases :—Aromatic sulphuric acid acts well.

More severe :—Tinct. digitalis, Tinct. ferri. chlor. āā ℥vi; Ammon. chloride ℥iii; Aquae dest. ad ℥iv. One teaspoonful in water every three hours.

Sodium hyposulphite :—In drachm doses every 3 hours to keep the bowels open.

Nausea and vomiting :—Mustard plasters to the epigastrium. Brandy on crushed ice, or bismuth subnitrate, cerium oxalate and carbolic acid in mucilage of acacia.

Jactitation and sleeplessness :—Potassium bromide, spiritus aetheris nitrosi and chloral hydrate, adding acetanilide if fever be high.

Suppression of urine :—Acetate of potassium with inf. digitalis and high rectal injections of salt and water. This failing, salt solution hypodermically.

Hiccough :—' Hoffmann's anodyne,' or spirits of turpentine, or oil of amber.

Calomel I never use. Quinine I never use until my patient has passed 20–30 hours without any sign of Hge. Sparkman (1901), 290.

North Carolina

Cold baths :—Are not objectionable when the fever is high.

Counter irritation :—Over the kidneys may do some good.

Calomel :—Is used with much success when properly administered.

Nausea and vomiting :—Hypodermics of morphia and atropia are very serviceable.

Normal saline solutions :—A sheet anchor. Hypodermoclysis or as high rectal injections.

Bleeding :—In sthenic (more or less robust) cases. I sometimes bleed from one arm and infuse into the other. Of special service when suppression threatens.

Diuretic :—When the stomach can retain it, citrate of potassium, lactate of strontium and inf. of digitalis cannot be excelled. Parrott (1901), 293.

Louisiana

Calomel and bicarbonate of soda :—Of each two grains until bowels act freely.

Magnesia sulphate :—In hot water if unsatisfactory evacuations after 8 or 10 doses (of calomel). Often necessary to combine podophyllin and aloin with the mercurial.

Hyposulphite of sodium :—20 grains every 2 hours after the bowels have acted from calomel and magnesia.

Coma :—Calomel in large doses (60 grains if necessary) in fresh butter, placed in the mouth. Quinine bisulphate hypodermically.

Spirits of turpentine and ergot :—For antihemorrhagic effect.

High temperature :—Sponging with hot or cold water.

Sleeplessness :—Morphine and bromides.

Heart stimulants :—Strychnine and nitroglycerin. Watkins (1901), 291.

1911

1. *Hyperpyrexia* :—
   a. *Enemata* :—Cold or lukewarm, every 3 or 4 hours, or better
   b. *Hot baths* :—35°, 1 or 2 daily; the patient while still wet is wrapped (in sheet and blanket) to promote reaction. They are sedative and anti-thermic, and are the best means of averting typhoid symptoms, or
   c. *Warm sponging* :—Where there is a tendency to fainting. Cold hydrotherapy in any form should be avoided, as it may increase the renal lesions.

2. *Restlessness, pain, insomnia* :—
   Early stages :—
   a. *Hot baths* :—A valuable aid. b. *Morphia* :—In the initial stages only 0·005–0·01 g.—provided enough urine is passed—especially if pain is severe.

Later stages :—

c. *Caffeine.* d. *Saline injections.* e. *Chloral :*—2·0 g., yelk of egg 1, water or milk 250 c.c. in case of threatening uraemia or actual convulsions. f. *Sulphonal :*—0·5–1·0 g., or g. *Veronal :*—0·25–0·5 g. in cases of uraemic insomnia.

Headache :—a. Cold compresses, or *b.* ice-cap.

Hepatalgia, splenalgia :—a. Dry cups, or *b.* painting with iodine, or *c.* hot compresses with *tinct. opii.* 91.

Lumbago :—Dry cups to kidney region, repeated, hot sand bags, hot water bottle, warm baths, friction with ' balsam of Fioraventi,' [1] or spirit and lime juice.

Vomiting :—

a. Hot or cold drinks, frequently; though vomited in part, they are partially absorbed.

b. Frequent purgatives allay the gastric irritability.

c. Tinct. Iodi. a few drops in ½ wineglass of water or especially ' Rivières mixture.' [2] Though of use, are but little efficacious against the initial vomiting.

d. Chloroform 4 g.
Gum Arabic 8 g.
Water (sugar) 250 c.c.
Only efficacious 36–48 hours after the onset. In the case of alcoholics or those to whom chloroform is nauseous.

e. Chloroform 1–2 g.
Pulv. Gum Arabic 8 g.
Yelk of egg 1.
Water 125 c.c.
As an enema, 4 quarts [3] in 24 hours.

1 An alcohol turpentine liniment.

2 (*a*) An alkaline draught containing potassium bicarbonate, or (*b*) an acid draught containing citric acid.

3 A " quart " is about 250 c.c.

Contra-indication :—Cardiac or renal disease.

f. Sherberts flavoured with brandy or rum.

g. Ice sucked or ice-water sipped through a straw. 92.

Epigastralgia :—

a. Ether or ethyl chloride spray. Though giving real relief the effect is transitory. Repeat frequently.

b. Sinapisms, and compresses (with laudanum) alternately, or *c*. compresses (with chloroform), or *d*. hot water bottle, or *e*. ice-bag. *f*. An injection of morphine may be required for the agonizing pain.

Hiccough :—If not combated by the laxative and sedative treatment already begun at the start, try

a. Sinapisms between the shoulders, or *b*. Ether capsules.

Usually a complication of uraemia, and it is this latter condition which requires treatment. 92.

3. *Purgative treatment* :—

a. Calomel. Contra-indicated in oliguria, extreme malnutrition, and in cases of bad teeth.

Calomel
Jalap } ââ 0·6 g. 2 cachets.

b. Castor oil, yelk of egg and milk, followed by an enema of glycerin 50 c.c. If there is vomiting *c*. Castor oil enema or senna and sulphate of soda ââ 15 g. *d*. Large enemata of water are used only in the early congestive stage; later they may induce syncope.

4. *Collapse* :—

(*a*) In grave cases saline injections, 1% saline 200–400 c.c., 1 or 2 injections in 24 hours. Site of injection: the inguinal fold or inject upwards at a point about half-way down the thigh, in a line through the anterior superior

spine. The solution (not more than 300 c.c. at a given point) is allowed to gravitate in, 10–15 c.c. per minute. (*b*) In less severe cases, enemata of saline 0·7%, 200–300 c.c., 3 or 4 injections in 24 hours, the first preceded by a large plain or boracic acid enema. 97.

Saline injections are the basis of the treatment of b.w.f.

Contra-indications :—

1. Pronounced cardio-renal disease. In case of oliguria, facial oedema, signs of uraemia (contracted pupils, hiccough), it is not always necessary to omit them, but caution should be used.
2. If the temperature has not fallen to about 39°, enemata of saline or water or hot baths should be used instead.

Accessory treatment :—Ether, caffeine (before the saline injection in weak patients), camphorated oil, sparteine, digitalis (in cardiac arhythmia with typhoid symptoms), artificial respiration and 'le marteau de Mayor'* in grave cases. Envelopment of the limbs in cotton wool in cases of coldness of the skin.

5. *Maintenance of urinary secretion and prevention of uraemia* :—Saline injections, and dry cups are the best means available.

Diuretic infusions :—of the dried leaves of Ahouandémé (*Cassia occidentalis*) 15 g. per 1000 c.c. water, or Kinkélibah (*Combretum Raimbaultii*) 10 g., or stigmata of maize 20 g., or voa-fotsy (*Aphloia thæformis v. Madagascariensis*) 25–30 g., weak tea, or citronella.

Alkaline mineral waters :—provided there is no oedema. Lactose 50 g. per bottle increases the diuretic effect.

* Metallic hammer plunged in boiling water and applied straightaway to the cardiac region.

Saline injections, bleeding and theobromine

Date.	Symptoms.	Urine, c.c.	Bleeding, c.c.	Saline injection, c.c.	Theobromine, g.
26	Hgburia, T. 39°				
27	Icterus, vomiting, lumbago, prostration			300+ En. 500×2	
28		110		300×2	
29	Very weak, vomiting	35		300×2	
30		35			
31	Vomiting begins again	30	250	300	
				300	
1	Oedema of legs and face	45	225		0·5
2	Lumbago persists	50			1·0
3	Vomiting ceased	55	250		1·5
4	Evening T. 39·1°	80	100	300	
5	Apyrexia. Hiccough	250			2·0
6	Oedema less. No sleep	720			2·5
7		960			2·5
8	Oedema of legs gone	2650			
9		3500			
14		1945			
22	Discharged				

The bleedings were followed or not by saline injections according to the state of the pulse and the oedema . . . Theobromine once the renal permeability was partly established acted by completing the unblocking of the kidney. 103.

Convalescence :—Quinine (tonic doses), tincture nux vomica, powder of quinquina 0·50 g. with or without potassium ferric tartrate 0·10 g. (4 doses in 24 hours), Fowler's solution, or cacodylate of soda 0·05 to 0·10 g. Saline enemata (remineralisation of the plasma).

Spasmodic intestinal obstruction :—Warm baths, belladonna, morphine, and when the spasm has ceased oily enemata—olive oil 300–400 c.c. given with a long tube and the following day castor oil 30 c.c., followed if necessary by a glycerine enema.

Foetid stools :—Enema. Creosote, 20 drops.
Glycerine, 60 g.
Water, 500 c.c.

Hepatic congestion :—A glass of Vichy water every morning, fasting.

Albuminuria :—Alcoholic friction, massage, warm baths.

Clothing :—Flannel belt and underclothes. Fresh air.

Decubitus :—During first days of convalescence. There is danger of sudden syncope.

Diet :—When stomach tolerance established, milk in sips, milk diet as far as possible until albuminuria ended. If patient cannot tolerate milk, chicken broth, toast and water.

Liquids :—For weakness, temperature having fallen, black coffee, Vichy and champagne, or a ' cocktail ' of milk, eggs, sugar, rum; or ' American cream,' milk 250, yelk of egg (2), champagne 1 glassful. Red Bordeaux 100 c.c., sweetened water 1000 c.c.; Beer and Vichy to vary the list.

Nutritive enemata :—Milk and chicken broth, of each 60 c.c. Yelk of egg, 1. Red wine, 15 c.c. Pepsine, 2 g. Tinct opii, 2 drops, twice daily. Gouzien (1911).

U.S.A.

1. The bowels should be opened with calomel (3 to 5 grains is sufficient) followed by a saline cathartic; or if vomiting prevents, enemas may be used.
2. The most important general measure is the introduction of fluids by mouth, by rectum, subcutaneously or intravenously.
3. For vomiting and restlessness morphin in repeated small doses given hypodermically is harmless and by far the most useful and satisfactory remedy. Crushed ice, also, may be useful.
4. Quinine :—*Vide infra.*

It makes little difference whether or not white patients receive quinine, while from coloured patients it should be withheld. Brem (1911), 162, 168.

1. Anti-venom or horse serum, 1 ampoule, repeat in case of relapse. In asthmatics use crotalin (rattle-snake) $\frac{1}{100}$ grain if there is sensitivity to horse serum.

2. Abundance of fluids and caffeinae sodio-benzoatis 0·25 gramme.
3. Cantharides tincture 5 drops, water 2 ounces, sodium bicarbonate 1 dram. Stir well. Two tea-spoonfuls every ½ hour until urine is normal.
4. Calomel in small divided doses during icterus.
5. Iron tonics during convalescence. Trout (1925), 228.

1. Do away with the product of malaria saturation, viz. acidosis, normal saline 2 pints, sodium bicarbonate 1 oz. intravenously.
2. Do away with the primary cause, viz. malaria.

Habituation to Q. :—Tinct. cinchonae ℥ i–ii in water every 3 hours, then liquid extract of cinchona, then euquinine, then quinine. Burkitt (1926–27).

Dakar

1. Wet cups to the loins as a preventive against renal congestion.
2. Antivenomous serum 20 c.c. night and morning.
3. 300 c.c. of glucose solution (45 g. per litre) + 5 g. of calcium chloride drop by drop *per rectum* twice daily.
4. Saline solution cutaneous or rectal is absolutely avoided.
5. No quinine is given.
6. Not more than 2 litres of fluid in 24 hrs., in very small doses, and only cooled in cases of absolute intolerance for liquids at room temperature.

Cases 27. Deaths 1. Conil (1929), 739.

Rhodesia

Mild moderate type :—Promotion of diuresis by fluids by the mouth usually sufficient. If anuria threatens, saline or bicarbonate injections. If toxaemia threatens, blood transfusion. 244.

Anuric type :—The re-establishment of urinary secretion is beyond our resources in the majority of cases. The continuous exhibition of copious fluids may be dangerous, tending

to pleural and peritoneal effusions. Lavage of the pelvis of the kidney by ureteric catheters is suggested. 245.

Fulminating and toxic type :—It is in this type of case that blood transfusion is most urgently called for. If it has no effect on the haemolysis it is the best method of overcoming the anaemia and resulting anoxaemia. If transfusion cannot be done, the best substitute is 10–15% glucose in saline. Glucose saline is also given by rectum. Special attention should be given to the heart The most suitable stimulants are strychnine and adrenaline, preferably the latter, as the vasomotor centre may be depressed by the toxaemia. 246.

The relapsing type :—Fluids by the mouth in many cases suffice. If intravenous treatment required, transfusion is the most helpful in overcoming (if not the haemolysis) the acute anaemia. After cessation of Hgburia, raw meat juice and liver were used to stimulate the haemo-poietic system. Iron and arsenic were also used as tonics. Post-haemoglobinuric fever was not found to be amenable to treatment. 247. Ross (1932).

Jérémie, Haiti

1. The malaria was treated with atebrin alone. Atebrin + plasmochin in a large percentage of cases leads to spasm of the stomach.
2. Glucose and insulin. *Vide*, *Insulin.*
3. Campolon injections 1–2 ampoules daily. 171. Cardiac stimulants were unnecessary in the cases treated with campolon. 173.

Although atebrin alone can induce Hgburia, yet it appears to be the most neutral of all products. In a case of kypho-scoliosis it was quite easy, even with slight doses of quinine, antipyrin or plasmochin, to induce Hgburia or MetHgburia, but atebrin in very large doses, 0·4–0·6 g. daily, produced no result. 172.

Cases 18, deaths 0. Naumann (1934).

Treatment, Specific

Alcohol

Even in the case of alcoholics there should be complete abstinence during the attack. Plehn, A. (1896), 55.

Anaphylaxis (anti)

It is clear to me that b.w.f. is an anaphylactic accident due to Q. This theory explains why Q. *per os* produces b.w.f. more frequently than an injection. Absorption *per os* is more rapid than when Q. is injected. In the latter case the organism has usually time to set up disanaphylaxis.

To avoid anaphylaxis I thought one could use the disanaphylactic vaccination of Bezredka, i.e. some hours before giving the normal dose to inject a quite small quantity of Q. 0·05 g. in a few c.c. of water. David (1914), 509.

Antilysin

On the supposition that a serum haemolysin is at work in b.w.f. an anti-amboceptor serum was prepared for trial. Voigt and Voigt (1934), 240.

Arsenic (colloidal)

As soon as possible after Hgburia appears an ampoule of

Colloidal arsenic	0·34 milligrams
Colloidal iron	0·12 milligrams
Water	2 c.c.

is injected I.V. Repeat on day 2 and for safety on day 3. On day 4 or 5 adrenalin is prescribed for 8 days. If fever appears during convalescence, colloidal quinine is used as it never produces Hgburia.

Cases 23. Deaths 1, instead of 33%, the usual figure. Roux (1918), 390.

Arsenophenylglycine

The treatment was based on the assumption that although parasites were absent from the blood they might be present in the internal organs.

20th. Day 10. Patient appeared moribund. 15 c.c. of a 10% solution injected into the gluteal muscle. The injection caused considerable pain and alarming worsening of the general condition, but in half an hour considerable improvement, but there was no essential change during the next 24 hours.

21st. 11 a.m. 16·3 c.c. injected. Pain from the injection only slight; the condition remained unaltered, the fever moderate, but at night ensued long and deep sleep.

22nd. T. not above 38° for the first time. Recovery. Skrodzki (1910), 711.

[Nov]arsenobenzol

A case of Hgburia apparently determined by collosol quinine treated with injections of novarsenobenzol 0·3 g. Doré (1921), 79.

Autohaemotherapy

Blood withdrawn from a vein injected subcutaneously.

Case 1. 40 c.c. injected on 3 consecutive days. Recovery.

Case 2. 10, 20 and 20 c.c. injected on 3 consecutive days. Recovery. Fabre (1920), 337.

Blister

Vomiting was so severe that on the fourth day of the disease it appeared likely to bring about a fatal result. Sinapisms, ice, champagne, etc., had been used without the least benefit, but absolute relief was obtained within an hour by the application of liquor epispasticus over the line of the vagus in the left side of the neck. Marshall (1910), 1334.

Caffeine sodio-benzoate

The treatment is based on the observation made in a case of acute catarrhal jaundice that the icteroid hue and the bile from the urine disappeared, rapidly, on the fourth day following a daily dose of 3 grains of caffeine sodio-benzoate hypodermically.

Grains 3, intramuscularly, twice daily. If still jaundiced

on 7th day, once daily until 12th day. Temperature controlled by cold sponges and ice-cap to head. Enemas in lieu of purgatives. Then enema of sodium carbonate 2% and glucose 1%. About 45 drops per minute for 3 hours. Then 3 hours rest and so on until urine more or less normal. Vomiting and hiccough controlled by a single injection of morphine and atropine. Diet for first 3 days, liquid gelatine, soda water. When vomiting ceases milk may be given. 12 cases in 8 months, successfully cured. Facio and Rojas (1925).

Calcium chloride

$CaCl_2$ 4–6 g. daily *per os.* 1–2 g. in normal saline hypodermically. Has preventive anti-haemolytic and powerful curative action. Vincent (1905), 633.

1. *Normal saline* :—500 c.c. night and morning.

2. *Calcium chloride* :—2 g. to each 500 c.c. of saline or as calcium lactate (solubility 1 in 15). The calcium to be continued for 10–15 days.

3. *Quinine* :—None during the Hgburia. Subsequently tried carefully, while calcium is still being given.

28 cases. 0 deaths. de Chazal (1908), 118.

To increase the resistance of the red cells we give crystallised $CaCl_2$ 5–6 g. in water 150 c.c., a spoonful every hour, or in the case of vomiting, 2 enemata at 6 hours interval between each. We also give hypodermics of normal saline 250–300 c.c. every 6 hours, decreasing the dose by 50 c.c. every 6 hours from the third day. Also enemata 300–500 c.c. morning and evening. This treatment to be omitted if symptoms of uraemia appear.

To promote the functioning of the liver, an alkaline or laxative enema.

Hot compresses often renewed are applied to the liver region.

For uraemia, bleeding is advisable.

For anuria, hot moist compresses, prolonged hot baths, wet cupping and laxatives.

No Quinine.

Cases treated, 115. Deaths, 8. 6·9%. Cardamatis (1911[b]), 303.

Calcium—Peptone

Calcium chloride, crystallised, Merck, 5%. One injection daily for 3 days. Day 5, Calcium chloride 1·0 g. + Q. 0·5 g. for another 8 days. Injections of peptone (10 c.c. of a 5% solution) with a view to decreasing complement gave no satisfaction, but Calcium intravenously and peptone intramuscular (not more than three injections) were satisfactory. The combined effect is attributed to the fact that Calcium makes good the deficiency in Calcium which is responsible for the upset in ionic equilibrium, while the peptone counteracts the increase in complement caused by Q. and other agents. The Calcium injections produced a sensation of congestion and great heat in the head, arrest of respiration for some seconds and formication in the hands and feet. Weselko (1926), 659.

Cecropia spp.

Fluid extract, 10–20 g., in 24 hours, in 200–500 c.c. of menstruum, sweetened or not. (In Amazonas.) da Matta (1912), 357.

Chloroform

1. Chloroform 6·0 g.
   Gum arabic 8·0 g.
   Sugar water 250·0 g. To be well shaken before use.

Given in sips about every ¼ hour, until slight intoxication produced. 1. It allays the vomiting; 2. increases the quantity of urine; 3. decreases the albuminuria. Even if the first dose is vomited, enough chloroform is left in the stomach to anaesthetize it. After 2 or 3 doses, chloral per rectum is used instead. The number of doses of chloroform necessary also based on the quantity of albuminuria. Albuminuria is said often to disappear suddenly with this treatment.

2. Sulphate of soda 15·0 g.
   Senna 15·0 g.
   Water 250 c.c. enema, instead of calomel.

3. Sodium chloride 10·0 g.
   Water 1000 c.c. per rectum after the motions produced by the enema.

4. Quinine 1·0 g. hypodermically, on the first day. Quennec (1899).

Cholecystotomy

It seems to me that these cases (suppression) are *eminently* surgical emergencies. . . . In cases other than suppression, particularly fulminating ones . . . a large intravenous saline should be given. If no definite satisfactory result is seen in about four hours the gall-bladder should be opened. In suppression it should not be delayed more than 36 hours as a maximum. Hewetson (1929), 164.

Cholesterin

Cases in which already 1 or more relapses have occurred appear to me to be the only suitable ones to test the efficacy of cholesterin.

5 June. Evening, Q. 0·5 g.
6. Rigor vomiting Hgburia. Two further rigors with vomiting, T. followed by sweating. Rigors followed by darkening of the urine tint.
7. 4 p.m. a teaspoonful of cholesterol dissolved in 30 c.c. of hot olive oil and mixed with milk.
   6 p.m., Rigor 4, less violent than previous ones. No vomiting.
   8 p.m., 10 p.m., cholesterin about 2 g.
8. 3 further doses of cholesterin.
9. Hgburia —.
10. Alb. —.

The case was a severe one, and I regarded it as hopeless, but the prompt change in the whole picture after cholesterin was convincing. Külz (1910), 739.

Cholesterin as a powder is frequently badly absorbed. For lack of a better means, that of Külz (1910), 739, is the method of choice.

Cases 6. Death 1; anuria had set in before cholesterin treatment.

Case 4 (Hamann). After some doses of cholesterin Hgb —. At the wish of the patient cholesterin stopped, Hgburia returned. This occurred 4 times. Cholesterin now given for two days after the cessation of Hgburia. Q. 1·0 g. in small doses was now tolerated on the second day. Grimm (1910), 743.

10 March, 1911. p.m. T. 39·5°.

11. 6 a.m. Q. 0·6 g.; 8 a.m. 0·4 g.; 10 a.m. Hgburia. p.m. T. 39°, P. 110, *P. falciparum* ++. Cholesterin a teaspoonful hourly. After 4 hours urine clearer. General condition good.

12. a.m. T. 37·5°; noon, rigor T. 39°, cholesterin as before and liq. pot. acetat. Urine 1800 c.c. in last 24 h. Digitalis, intravenous saline 500 c.c.

13. T. 35·5°, P. 130, small, running. Saline injections, digitalis and camphor subcutaneously. Urine 200 c.c. Unconscious. Icterus +.

14. Death. Schäfer (1911), 793.

Cholesterin was without effect in a case of quinine intolerance. The ' threshold ' dose of Q. which induced Hgburia was between 0·6 and 0·8 g. Thus :

17.1.1911. Q. 1·0 g. (5 × 0·2, at 2-hourly intervals) + cholesterin 3·0 g. in olive oil given ' in the morning.' 8 p.m. Hgburia, T. 38°.

20. Q. 0·8 g. (4 × 0·2) + cholesterin 3·0 g. in olive oil. Transient Hgburia, T. 37·8°. Werner (1913).

Annam

Cases 14 (18 including relapses). Injections of cholesterin in oil without other treatment. Total quantity injected varied from 0·5 to 3·5 g. The duration of Hgb

was up to 24 hrs. in 3, 25–48 h. in 7, 49–72 h. in 8 cases. Mathieu (1931).

Choline chlorhydrate

Cases 5. Death 1. Treated solely with chlorhydrate of choline and abundant diuretic infusions. The urine cleared in 21, 2, 1, 1, and 3 hours respectively after the subcutaneous injection of choline. Dose 1 or 2 injections of 0·02 g. daily. De Raymond (1932), 218.

Electrargol

A case of malaria. (Parasites neg.)
Days 1–2. Plasmochin simplex, 0·02 g. × 3 daily.
Day 3. Plasmochin, 0·02 g. There followed a typical b.w.f. attack. Successfully treated with electrargol. Scharov (1932).

The physicians here (Haiti) have never seen a convincing result of this remedy either in malaria or in b.w.f. Naumann (1934), 173.

Glucose

Cases 6. Deaths 0.

Injections of lactose 9·25% and glucose 4·7% solutions subcutaneously and as enemata. They are more beneficial than saline solutions. Sorel (1913), 199.

Gum

In blackwater fever if bile could be made to contain more mucus the fever would surely be prevented because much mucus prevents the gastroenteritis. . . . We propose to use instead of mucus, Tragacantha or Gummi arabicum . . . in a solution as thick as possible and also in the greatest quantity possible. Kubo, Iba, Ichinose (1920).

Insulin and dextrose

Severe b.w.f. arises in malaria cases when an injury of the liver exists. Insulin 0·5 c.c. (10 units) subcutaneously and about 40 g. dextrose given daily. The dextrose given as far as possible *per os*, but also subcutaneously and as a

40% solution with Strophanthin intravenously. Cases 15. Deaths 4. Naumann (1933), 306.

Mercury chloride

23 July. 1 a.m. b.w.f.

8 a.m. T. 105·5°. Phenacetin grains 10 every 2 hours.

9 a.m. Hydrarg perchlor. 1 in 1000 ℥ 10. Repeated on 25th and 26th.

Salt solution (salt 1 teaspoonful to ½ pint of water) given 'continuously throughout.' No details given. Recovery attributed to salines, and the mercury injections. Greene (1920), 555.

Mercury cyanide

Intravenous injection of half a centigramme. A second dose after 20 hours interval and a third after the same interval. The temperature falls a few hours after the first injection. 5 cases cured. Muñoz (1920), 35.

6 cases cured with mercury cyanide injections, 1 centigramme every 24 hours. Pelletier and Quemener (1921), 227.

Methylene blue

As a drink :—10 drops of a saturated solution of methylene blue are given in ½ a glass of water, 'tisane,' or tea every hour.

Intravenously :—1 c.c. of a saturated solution in 4 c.c. of water (= approximately 0·05 g.). A second injection 10 days later.

Subcutaneous injections of saline, 50–100 c.c. (not more), are also used and intramuscular injections of strychnine (1 mgm.). 12 cases cured. Daniel (1921), 81.

Néphrine

4 cases treated with 'néphrine' (injectable néphrine, Chaix). 1 ampoule = 2–3 c.c.

1. No urine for 14 hours. Néphrine injection 9 p.m. 1–7 a.m. passed water 3 times.

2. No urine for 15 hours. 4 hours after the injection passed water.
3. No urine for 16 hours. 5 hours after the injection passed water.
4. No urine for 14 hours. 5 hours after the injection passed water. Ringenbach (1915).

Nephrotomy.

Nyasaland

Day 2. Suppression set in.

Day 4. Right nephrotomy, under chloroform anaesthesia, splitting the tense capsule from pole to pole, and incising the bulging grey kidney along the middle of the free border.

Day 5. 340 c.c. of brown fluid containing granular matter were withdrawn from the bladder.

During the next few days small amount of urine passed naturally or drawn off by catheter.

Day 9. A series of uraemic seizures, followed by coma and death. Stannus (1914), 38.

Guatemala

Day 1. Urine 28·4 c.c.

Days 2–4. Urine 0 c.c.

Day 4. Under local anaesthesia aided by a few whiffs of ether in closing (owing to the restlessness of the patient): the right kidney was decapsulated.

Day 6. 8.30 a.m. pituitrin 1 c.c. Patient afterwards voided about 6.2 c.c. of urine.

Day 8. Death.

At no time was the patient unconscious, nor was there any mental aberration; no clinical symptoms of uraemia, and no convulsions nor muscular twitchings. Patient received about 5200 c.c. of fluid intravenously, and in addition took fluids by mouth freely at times. Gage (1925), 125.

Kenya

Complete suppression for 3 days. Local, general, subcutaneous and intravenous medication had been tried. Incision of the capsule of both kidneys was then performed. There was considerable oedema in the perinephric tissue and the kidney itself was engorged and bulged when the incision was made. The capsule stripped easily. There was a certain amount of urinary secretion during the following 24 hours, but afterwards suppression again set in and eventually the patient died. Braimbridge (1926–27), 267.

Oxygen

Oxygen inhalations from the onset were continued during convalescence when this was too tedious. They have given remarkable results. . . . Patients that have used them ask for them again persistently. They produce an immediate sense of well being especially in uraemic complications. A serious case requires 2 or 3 cylinders of 30 litres daily. Clarac (1898), 110.

Quinacrine *

2 cases (*P. falciparum* present in one) successfully treated with quinacrine. Alain (1934), 93.

2 cases (*P. falciparum* in one, *P. falciparum* (gametes) and *P. vivax* in the other) successfully treated with tablets of (0·1 g.) quinacrine. It has a remarkable action on the schizonts of *P. falciparum* and the schizonts and gametes of *P. vivax* and *P. malariae*. Blondin and Riou (1934), 97.

Quinine

If it is correct that b.w.f. represents the acme of malaria infection, and if it is correct that Q. is a specific against malaria, then Q. must influence this disease favourably. . . . To my relief I found that the more I increased the dose the more certain was the result, and finally I concluded that in all early cases this treatment never failed. . . . The

* = Atebrin.

dose of Q. which suffices, and indeed is necessary, to abort an attack of b.w.f. amounts in the case of a robust man to 8 g. in 24 hours. That at times one can and indeed must give more cases 10 and 13 prove, which received 10 and 10½ g. in 24 hrs. . . . Occasionally the disease ceases after a single day's dose, but usually the large doses of 6–8 g. must be given daily for some time, and only when convalescence has definitely set in should the smaller daily doses, 4, 3 and 2 g., quite gradually decreasing, be given, and still must be continued for several weeks. In spite of these precautions, malaria relapses often occur during this period of dequininisation. 48.

Case.	Total days.	Total Q., g.	Recovery.	Remarks.
4	28(?)	52·5	R.	Day 1ª. Daily Q. 2·5–3 g.
6	58	121	R.	Day 3. Daily Q. 3·0 g.
7	27	75	R.	Day 1. Q. 5·5 g.
8	14	47	R.	Day 4. Q. only 3·0 g., owing to eye trouble yesterday.
9	16	56·5	R.	Day 9. Q. 5·5 g. partly by enema.
11	23 58	123 160	R.	Q. 6, 7, or 8 g. daily for 11 days.
13	3½ 25	29·5 73	R.	Day 6. Q. 10·5 g. in 24 hrs.

Steudel (1894).

Day 1. Hgburia, strongly foaming urine 800 c.c., vomiting about every half hour.

Day 2. No sleep, persistent sweating. In 24 hrs. Q. 6·0 g.

Day 3. Urine clearing, persistent sweating. In 24 hrs. Q. 5·0 g.

Day 4. Q. 4·0 g.

Day 5. Q. 3·0 g.

Day 6. Patient gets up, vomiting stopped. Q. daily 2·0 g. later 1·5 g. Apart from tinnitus no particular effect.

J., Congo pilot.

30 June and 1 July. Diarrhoea, about 10 motions daily.

2 July (day 1). Morning expecting an attack of fever took Q. 1·5 g. 4 p.m. the boat stuck fast on a sandbank. Unpleasant situation, great excitement; felt unwell and in 20 minutes Hgburia, persistent vomiting, Q. 1·5 g. retained.

Day 2, Q. 7·0 g.; Day 3, 5·5 g.; Day 4, 4 g., etc.

The course of the case was similar to that of case 1. The large Q. doses caused intense tinnitus but hardly any deafness. Küchel (1895), 447.

In 150 cases treated with Q. we have observed oliguria in 52 and anuria in 26.

J. Théophanidis in 22 cases treated with Q. observed fatal anuria in 10 cases. Cardamatis (1902[a]), 40 (r.).

Vide Symptoms. *Death, causes.* Shropshire (1903).

Cases 1932. Compiled from various sources :—

Treated with quinine. Cases 328. Deaths 57. 17%.

Treated without quinine. Cases 374. Deaths 57. 15%. Deaderick (1907–08), 37 (r.).

Treatment with Q. Cases 1347. Deaths 329. 24·4%.

Treatment without Q. Cases 1134. Deaths 83. 7·3%. Cardamatis (1910), 106.

Race.	Cases.	Deaths.	%.	Authority.
Treatment with quinine.				
Whites. . .	67	9	13·4	Brem (1911), 169.
Blacks . . .	28	9	32·1	
Total . .	95	18	18·9	
Treatment without quinine.				
Whites. . .	111	17	15·3	
Blacks . . .	33	5	15·2	
Total . .	144	22	15·3	

Race.	Treatment.	Attacks.	Deaths.	%.
Parasites present.				
Whites . . .	Quinine	25	5	20
Blacks . . .	,,	12	2	17
Total . . .	,,	37	7	19
Whites . . .	No quinine	46	7	15
Blacks . . .	,,	10	2	20
Total . . .	,,	56	9	16
Parasites absent.				
Whites . . .	Quinine	42	4	9
Blacks . . .	,,	16	7	44
Total . . .	,,	58	11	19
Whites . . .	No quinine	65	10	15
Blacks . . .	,,	23	3	13
Total . . .	,,	88	13	15

'The presence or absence of malaria parasites appears to make no difference in the mortality.' Brem (1911), 169.

Greece. Malaria, cases 3568. Blackwater 51. Deaths 7. Q. 1–1·5 g. intramuscular, twice daily for 4 days, until T. has fallen. Not given internally. Not when idiosyncrasy or tendency to renal Hge exists. Great weakness of the patient, a feeble and soft pulse, low blood pressure are also contra-indications. Trabadaros (1928).

The intramuscular injection of 15 grains of Q. (parasites neg.) given to Case 3 a few hours after he had first passed black water was followed by a remarkable exacerbation of the symptoms; and the further administration of Q. (parasites neg.) to Case 4 on the fifth day after the first attack of haemoglobinuria was followed by a second attack on the 6th day. Yorke, Murgatroyd and Owen (1930), 353.

Saline

Hypodermic

On my return to France (from Madagascar) in 1907 I wished to systematize the treatment of b.w.f. cases by sodium chloride 0·7% and I suggested this method to Dr. Gouzien principal medical officer of the colonial troops then in Dahomey. Reynaud (1909), 570.

Hypertonic

Two pints of hypertonic saline 1·2 per cent. to which had been added 0·03 per cent. of $CaCl_2$, intravenously. One case, recovery. Gupta (1916), 417. Nalini (1916), 417.

Intravenous

7th. Q. grains 10, less than 2 hours later, urine black.

8. Night. Admitted to hospital, very exhausted, T. 99·2°, warm saline per rectum, morphia grain $\frac{1}{4}$.

9. 3 a.m. morphia grain $\frac{1}{4}$, rigor T. 102°; 6 a.m. rigor T. 102°, vomiting almost continuous, jaundice, urine black; 12 noon intravenous saline 25 oz.,* calomel grain $\frac{1}{4}$ hourly, 3 doses; 7 p.m. intravenous saline 25 oz.; 10 p.m. morphia grain $\frac{1}{4}$, T. 101°.

10. 3 a.m. morphia grain $\frac{1}{4}$ owing to restlessness; 10 a.m. intravenous saline 25 oz.; 2 p.m. T. 102·4°; 10 p.m. T. 100·2°.

11. 2.45 a.m. patient somewhat collapsed, saline 1 pint per rectum, morphia grain $\frac{1}{4}$; 7 a.m. saline 1 pint per rectum; 10 a.m. intravenous saline, 25 oz.; 6 p.m. T. 102·6° (total saline intravenously 9th–11th, 4 pints); 8.40 p.m. saline per rectum with glucose and bicarbonate of soda every 6 hours; 9 p.m. digitalin grain $\frac{1}{100}$.

12. 12.40 a.m. saline and glucose per rectum; 3.20 a.m. strychnine grain $\frac{1}{30}$; 2.30 p.m. saline and glucose per rectum; 3·5 p.m. strychnine $\frac{1}{30}$; 8 p.m. saline and glucose per rectum; 11.30 p.m. digitalin $\frac{1}{100}$ grain.

* 1 oz. = 28·4 c.c. 20 oz. = 1 pint.

13. 3.30 a.m. saline and glucose enema; 9.45 a.m. ditto; 7 p.m. digitalin $\frac{1}{100}$.

I feel convinced that but for the intravenous injections he would have died. Bruce-Porter (1914).

There is ground for believing that the decrease in the urinary secretion is partly to be accounted for by the deposit of the brown amorphous material in the kidney tubules in such quantity as to obstruct them, or even to block them completely. . . .

One of the most important lines of treatment is to increase diuresis, and the speediest method of doing this is to inject a sodium chloride solution intravenously. Patrick (1918), 404.

Rectal

28 May. Hgburia.

30 May–2 June. Intravenous saline, 7 pints +.

31 May–2 June. Urine 53 c.c.

3 June. Condition seemed hopeless. Nothing could be given by the mouth or rectum. Marked oedema of face, chest and arms. High rectal double-current irrigation begun, 4 pints of hot saline every hour and later every 4 hours irrigated. Shortly after each irrigation the patient had a desire to micturate, at first teaspoonful amount, until 10 June 4004 c.c. passed. The change from a bloated puffy individual to one thin and washed out was very striking. It seemed as if the irrigations had a direct effect on the blocked kidneys. Wallace (1921–22), 129.

Serum

Anti-streptococcus

Dr. Cranford thought that the disease might be complicated by streptococcus septicaemia. . . . The rationale of the treatment seems to be: that normal blood contains both hemolytic and anti-hemolytic substances; in blackwater fever and in paroxysmal Hgburia the anti-hemolytic substance is at fault. Ruiz (1923), 61.

Anti-streptococcus serum given in 20 c.c. doses. In one

case there was 'a strong anaphylactic reaction,' but the serum was repeated next day without ill effect. 6 cases. 1 death. 65. 6 cases. 3 deaths. 69. United Fruit Company (1924), 69.

Antivenomous

Cases 4. Deaths 0. Boyé (1922).

Cases 2. Deaths 0. Reznik (1924).

Cases 3. Deaths 1. Thomson (1924[a]), 94.

Cases 29. Deaths 0. Cases where serum used after onset of anuria 2. Deaths 2.

If the urine has not cleared 24 hours after the injection of 20 c.c., inject a further 20–30 c.c. Tardif (1926).

Haemostatic

Quiriqua Hospital, Guatemala.

Haemostatic serum 'Lapenta' is given hypodermically or intravenously in doses of 2–5 c.c. every 4 to 6 hours. Generally 4 c.c. diluted with 20 c.c. of saline given intravenously.

The rationale of the treatment is based on the belief that in b.w.f. the anti-haemolytic substance in the blood is at fault and that normal horse serum supplies the defect. There were no symptoms of anaphylaxis or other ill effects from its use. 20 cases, 0 deaths. In 1924, 9 cases, 1 death. Aguilar (1926), 63.

Sodium bicarbonate

I was therefore led to abandon the use of this drug (Q.), and to substitute a modification of the Sternberg line of treatment adopted in yellow fever.

Sodium bicarbonate grains 10 and liquor hydrargyri perchloridi minims 30. Every 2 hours for the first 24 hrs. and subsequently every 3 hrs. until the urine is free of Hgb.

18 consecutive cases without a single death. Not a single case of suppression. Hearsey (1904), 545.

Day of onset? Passed 1 oz. of black urine 5 hours before first seen. 2 hours later, ½ oz. of urine by catheter. Patient unable to talk or move, vomiting stopped.

Treatment: Sodium bicarbonate grains 150, water 1 pint, I.V. Repeated 1 hour later. 15 minutes later, urine 12 oz. by catheter deep red; but little sediment. Recovery. Hanschell (1925–26), 488.

Calomel grain $\frac{3}{4}$ every $\frac{1}{2}$ hour, 3 or 4 doses.

Enema of soap and water at outset. Enemata of weak Pot. permang. solution twice daily.

All food is stopped. Nothing but boiled water until the urine is clear for 3 days and alkaline in reaction. Boiled water—some every $\frac{1}{2}$ hour.

Absolute rest is essential. Windows wide open to ensure pure air.

Sod. Bicarb. $2\frac{1}{2}$ oz.
Calc. Carb. 5 oz.
Mag. Carb. Pond. 5 oz.
Bismuthi Oxy. Carb. 10 drs.

A teaspoonful in water every 2 hours, 6 a.m.–10 p.m., when a double dose is given.

Antiphlogistine over the kidneys relieves the pain.

After treatment, Tinct. cinchonae 1 dr. t.d.s. If no recurrence of Hgburia Q. is added.

As the patient improves milk 1 part water 3 parts is given, then jelly, fruit juice and oatmeal porridge. Forbes (1929–30).

Aug 1. 6 p.m. Hgburia of 30 hours duration.
2. Suppression. $NaHCO_3$ grains 150 in 1 pint water, I.V.
3. 3 pints of same solution. Suppression complete (catheter, negative).
4. 6 a.m. urinary secretion recommenced. Normal saline 2 pints I.V.
5. Normal saline 1 pint.
6–9. Recurrent attacks of haemoptysis, moist râles at both bases; ascites, some general oedema.

During next fortnight very drowsy, condition resembling uraemic toxaemia. Convalescence slow. Yorke, Murgatroyd and Owen (1930), 339.

El Centro, Colombia, S.A.

1. Sodium bicarbonate, a teaspoonful in a pint of water or fruit juice ad. lib. by the mouth. Quantity reduced when urine alkaline, or

2. Sodium bicarbonate 10 g. Sterile normal saline 500 c.c. filtered and injected I.V. as soon as diagnosis made without further sterilisation.

3. Absolute rest, milk diet, intravenous saline when dehydration was present.

4. Plasmoquin in preference to Q. if parasites present after onset of b.w.f. (in 7 of 20 cases).

The intravenous injection had the almost immediate effect of making an acid urine alkaline. *Per os* this result only produced in 2 of 8 cases.

Urine acid at onset. Cases 13.					
Cases.	Treatment.	Urine after treatment.	R.	D.	Authority.
8	Per os	2. Alkaline 6. Acid	2 2	4	Paterson (1932–3), 539.
5	Intravenous	5. Alkaline	5		
Urine alkaline at onset. Cases 5.					
	Bicarbonate not given		4	1	

Bicarbonate and Glucose

Symptoms.	Treatment.
11.3.33. 11.30 p.m. Hgburia. 12. T. 103·9°, P. 96, R. 30. S/D = 90/40, Cheyne-Stokes breathing.	12. 4 p.m. Sodium bicarbonate (150 grains to pint) 17 ounces, glucose 5% 13 ounces, I.V. 9 p.m. Sod. bicarb. 1 pint. Glucose 17 ounces.
13. R. Cheyne-Stokes, S/D = 80/46. Urine 3½ ounces by catheter. 12 noon. Dyspnoea attack. 3.30 p.m. S/D = 108/52. 5.15 p.m. Collapse, death, 40 hours after onset.	13. 1½ pints of fluid per rectum absorbed. 1 pint glucose I.V. Dry cupping to lumbar regions.

Fairley and Bromfield (1934–35), 151.

[Di]-Sodium Phosphate

24 out of 25 ordinary urines examined had a complete or partial anti-haemolytic action on quinine bisulphate haemolysis in vitro. 69.

The anti-haemolytic effect of urines depends on the presence of K_2HPO_4 or Na_2HPO_4. 0·015 g. of crystallized water-free Na_2HO_4 neutralizes 0·04 g. Q. bisulphate. 130.

A 10 day Q. treatment had the effect of producing haemolytic urines in malaria patients and healthy subjects. 70.

200 c.c. of a 2·5% solution of Na_2HPO_4 intravenously. In a relapse 120 c.c. of a 6% solution of Na_2HPO_4 and NaCl was used. 130. Matko (1918[a]).

16 Mar., 1918. 2.30 p.m. typical attack of b.w.f. after Q.

17. 6 p.m. great pallor, icterus of conjunctiva and body, some bronchitis of both lower lobes, spleen enlarged tender, 14 c.m. beyond costal margin, 12 c.m. in breadth.

7.30 p.m. 150 c.c. intravenous of solution containing 3·0 g. NaCl and 3·0 g. di-sodium phosphate.

8.45 p.m. urine, only traces of Hgb. and Alb.

18. 6 a.m. abundance of cells and casts in urine, consequently 10.30 a.m. second injection. 20 hours later casts very scanty.

19. Third injection. Disodium phosphate 1·0 g. water 200 c.c. In 2 hours casts gone.

Effect on spleen: 16 hours after injection 1, decrease in length of 2 c.m.; 24 hours after injection 2, only 1½ fingers beyond costa. To this enormous early decrease of the spleen and the flooding of (toxic) products was attributed the persistent stupor of the patient after the 2nd injection. Matko (1918[b]), 398.

A case treated with 3% solution of disodium phosphate and salt in water I.V. Recovery. It is advisable to treat all cases, as we do not possess a more effective treatment. Loewenhardt (1918), 974.

Case 1. Treated by Matko's method. The Hgburia

not checked and a prompt regeneration of red cells not observed as described by Matko (1918). 398.

Case 2. The injection given previous to the giving of Q. in a patient in whom Q. 0·2 g. regularly produced Hgburia. The result was the usual one—Hgburia. Rusznyák and Weil (1918), 871.

Matko's method. The Hgburia ceased shortly after the injections. Rusznyák (1919), 943.

5 cases treated by Matko's method (intravenous injections of 100–200 c.c. of a watery solution containing 3% di-sodium phosphate and 3% sodium chloride). Patients cured in a few days. No great weakness, no great anaemia, the blood destruction soon ceasing. 5 other cases treated with 1 death (moribund when treatment begun). Beck (1922), 1381.

Stimulants

A case of acute blood destruction with all the symptoms of a septic fever. This was the only case (apart from choleriform cases) where the heart and pulse, most severely affected *ab initio*, required the use of stimulants. The rest of the cases only necessitated such treatment at times in the latest stages. The strength of the heart even in severe cases was relatively but little affected, and treatment was essentially limited to flushing the kidneys with mineral waters with the result of eventually increasing the thirst already great without it. Plehn, A. (1896), 55.

Terebene

Introduced by Dr. Kerr Cross has been extensively employed (in Nyasaland), and a considerable number of cases so treated have recovered. In the cases I saw, no effect seemed to follow its use or disuse. Daniels (1901), 59.

TRANSFUSION

12 July. German East Africa. Hgb 43%.

13. Shivering, indisposed, Q. in small doses, in the night Hgburia.

22. Hgb about 8%. Transfusion, 400 c.c. of blood taken from a negro servant, defibrinated and filtered

through sterilized linen; vein exposed, tied peripherally, and a canula inserted. After injection of about 300 c.c., sudden stoppage of the heart, then slow beats resumed. Owing to great anxiety and threatened collapse 2 ether injections. Thereafter fairly well and very confident. 2 hours later violent rigor lasting 1½ hours, the patient expecting every minute to die seeing red flashes and bodies in his eyes. Gradually regains strength.

23. Hgb 21% (19 hours after the transfusion). Recovery. Steudel (1894), 13.

Female aet: 37. Paris.

22 Ap. 1912. Day 4. Cell count 782,000. Hgb 15 %.

23. The left radial artery of the husband was anastomosed with the left internal saphenous vein of the patient. The operation fatigued the patient, who complained of the absolute immobility essential, got greatly excited many times. 5 c.c. of urine by catheter. Cell count (3 hours after the transfusion) 1·08 m., Hgb 23%.

24. Count and Hgb practically the same. Prostration, persistent anuria, death. Achard and Saint-Giron (1912), 751.

Patient moribund, dry tongue, dry teeth, deep somnolence, deep breathing, wax-like pallor, sunken features, icterus. P. 120, Count 1·30 m., Hgb 12%.

1.11.18. 7.55 p.m. the radial artery of the donor joined to the median vein of the patient; 8.39 p.m. operation ended.

3 hours after the transfusion, black urine passed on 3 occasions, so that a great part of his own or the transfused blood was destroyed.

2. 12 hours after the transfusion the count was 1·60 m. and Hgb 22%. Taking a count of 5 million as corresponding to a total volume of blood of 5 litres, the increase of ·30 m. corresponds to ·3 litre of

blood. But the increase of 10% in the Hgb value corresponds to ·5 litre of blood. The discrepancy between the two values was probably due to Hgbaemia.

5. Count 800,000, Hgb 13%, diarrhoea, increasing somnolence, fever.
6. Diuresis, death. Coenen (1919), 287.

Blood taken from median basilic vein of donor mixed with 100 c.c. of 1% citrate allowed to flow into vein of patient by gravity. Cases 2. Recoveries 2. Esquier and Godillon (1920). Esquier (1922), 44.

Day 5. 6.30 a.m. patient showed signs of collapse, P. almost imperceptible at the wrist, R. irregular, and of the Cheyne-Stokes type. Strychnine grain $\frac{1}{30}$, glucose 227·2 cc. I.V.

10 a.m. Rapid change for the worse, sweating, pain in the chest, R. 42, features pinched, eyes dull, mucus rattle with R., Strychine grain $\frac{1}{30}$. Camphor in oil 1 c.c., 1 hour later.

6 p.m. semi-conscious.

7 p.m. citrated whole blood 400 c.c. transfused. Visible improvement, patient succeeded in coughing up mucus.

10.45 p.m. sudden collapse. Strychnine.

11.20 p.m. another period of collapse, possibly due to pain of haemorrhoids on defaecation after an oil enema.

Day 8. P. quickened, R. laboured, drowsy and weaker. He was coughing up large quantities of sputum. He was obviously sinking.

12 noon, citrated whole blood 300 c.c. Immediate general improvement.

Day 9. Slept a little during night in spite of distressing cough, mentally brighter, normoblasts in blood, red cells 1 million, Hgb 30%. *Vide* Blood. Cell count.

Day 10. Slow but steady progress. Low, Cooke and Martin (1928).

Case.	Date of Hgburia.	Symptoms.	Date.	Transfusion.	
1	31.7.29	6 p.m., Hgburia, skin icteroid, mucosae pallid, P. soft compressible, count 2·0 m., blood pressure S/D = 80/50.	1.8.29 2 p.m.	Blood 625 c.c.	R.
2	9.11.29	1 p.m., Hgburia, vomiting, marked jaundice, count 3·2 m., Hgb 65%, S/D = 100/66.	11.11.29	350 c.c.	R.
3	5.2.30	2 p.m., Hgburia, very sick and drowsy, tongue dry and dirty, vomiting troublesome, count 2·8 m., S/D = 126/72.			
	6.2.30	Count 1·3 m.	6.2.30	700 c.c.	D.
4	13.5.31 6 p.m. (about)	6 p.m., Hgburia, skin yellow, mucosae pallid, count 1·7 m., S/D = 108/52.	14.5.31 12.45 p.m.	Citrated blood 660 c.c.	R.
5	1.11.30	2 p.m., Hgburia, 11.30 p.m., rigor, vomiting, tenderness over bladder and spleen.			
	2.	7 a.m., rigor, vomiting, cyanosis of nails, skin yellow, S/D = 110/75.	2.11.30 2.15 p.m.	Citrated blood 500 c.c.	
	3.	Restless, epigastric pain, sclerotics yellow, spleen palpable tender.			R.
7	13.12.33 17.	6 p.m., Hgburia. Gravely ill, dyspnoea, cyanosis, restlessness, photophobia, mental irritability, hiccough, vomiting. Pulse rapid, S/D = 98/ ?.	17–24.	Citrated blood 5 transfusions Total 3000 c.c.	R.
8	25.2.34	4 a.m., Hgburia. Admitted T. 102·8°, P. 128, R. 28, jaundice, vomiting, S/D = 108/55.			
	26.	Count 1·94 m., Hgb. 34%.	26.	170 c.c.	
	27.	Count 1·20 m., Hgb. 20%.	27.	227 c.c.	
	1.3.	Count 0·95 m., Hgb. 16%.	1.3	284 c.c.	
	2.	Count 0·88 m., Hgb. 17%.	2.	568 c.c.	
	3.	Count 1·09 m., Hgb. 18%.			R.

Fairley and Bromfield (1934–35).

Vitex peduncularis

Vitex peduncularis, var. Roxburgiana. India.

Infusions of the leaves, and fresh stem bark extract, used in the treatment of malaria and b.w.f. Vaughan (1921), 187.

Voa-fotsy

1. No Q. even if the temperature is high and parasites present.

2. Purgative enemata.

3. Infusion of Voa-fotsy. *Aphloia thæeformis* Dried leaves. 30 g.

Infuse 5–10 minutes in water 1000 c.c. Taken hot or cold with or without sugar. The patient should drink as much as possible. The remedy has been used for long by the natives of the East coast of Madagascar in cases of b.w.f.

1907. 27 (hospital) cases. 3 deaths, but all had taken Q. during the attack.

1907. Numerous private cases. 0 deaths. Fontoynont (1908), 577.

PROGNOSIS

Blood

There is immediate danger of death when the count falls to 1 million, even if there be no associated anuria. Menk (1927), 115.

General

When the icterus is generalized and not exaggerated, micturition easy and urine abundant, retaining its transparency, intermissions regular, or definite prolonged remissions (of fever), vomiting only at long intervals: all these are good signs. Suppression more or less complete, frequent vomiting, intense lumbar pain: all bad signs. Barthélemy-Benoit (1865), 388.

1. The gravity of an attack is very probably directly proportional to the amount of anaemia of the patient. 301.

2. A violent rigor a bad sign. 302.

3. An initial syncope, a severe attack. 302.

4. Initial profound weakness (and prostration): very dangerous. 302.

5. Initial restlessness, anxiety, fright, impatience, brief and jerky speech, as of drunkeness, disordered movements all indicate a severe attack. 302.

6. Throwing off the bed-clothes, tossing, sighing, groaning: a very serious condition. 302. Bérenger Féraud (1874).

Vide p. 161.

Bad prognostic signs were marked diminution in the amount of urine, excessive and uncontrollable vomiting, somnolence, coma and singultus. Deaderick (1910), 198.

Onset with violent rigor, acute pains, early icterus becoming intense and generalized are unfavourable signs. Gouzien (1911), 78 (r.).

Under this treatment, the only dangerous cases will be

1. Cases of uncontrollable vomiting.

2. Cases with intense pyorrhoea where suppression starts at once.

3. Cases complicated with tape-worms . . . if the worms are cleared out the cases may recover. Forbes (1929–30), 156. *Vide supra, Sodium bicarbonate.*

Heart

The second great danger (after anuria) lies in the formation—after the acute stage and in direct consequence of the blood destruction—of thrombi in the heart and great vessels. This often occurs without any notable diminution in the quantity of urine, generally in cases where the quantity is unusually large. Thrombi diagnosed with some certainty from the loud murmurs and irregular heart action make the prognosis very bad. They usually end fatally after 5–8 days through sudden heart weakness or embolus, frequently directly following a sharp movement of the patient in bed. 187. Plehn, F. (1898).

Hiccough

In the third stage of the disease is always fatal. Barthélemy-Benoit (1865), 388.

I have long thought that it was an almost certain sign of death, but I saw a patient recover after it had lasted nearly a week. Bérenger Féraud (1874), 307.

Hiccough is very common. It occurs in mild as well as in severe cases, and unless excessive is of no prognostic import. Daniels (1901), 56.

A grave but not hopeless sign. Gouzien (1911), 79 (r.).

Icterus

The intensity of the icterus is proportional to the gravity of the attack. Bérenger Féraud (1874), 305.

The degree of jaundice was a fairly reliable indication of the seriousness of the case. Of 30 fatal cases, in 13 jaundice was well marked, in 17 intense. Phear (1920), 5.

20 cases of icterus with bile pigment in blood plasma, 16 deaths. Dudgeon (1920), 209.

Severe jaundice is usually followed by death. Thomson (1924[a]), 89.

Kidneys

A nephritis following after the Hgburia is not on the whole very unfavourable. In most cases after a few days without dangerous symptoms, casts and albumen disappear. But I have seen a case of this kind end fatally. Plehn, F. (1896), 187.

I have often had occasion to state that patients who suffer from kidney diseases rarely survive an attack of b.w.f. Borle (1910–11), 240.

Persistent albuminuria, after the cessation of Hgburia, especially if there is progressive oliguria, necessitates a very cautious prognosis : nephritis thenceforward is certain. Gouzien (1911), 79 (r.).

Race

Creoles and mulattoes show the highest mortality. The mortality amongst the natives of Tonkin and Madagascar

is high compared with that of the natives of Africa. 77 (r.). In the case of the Tonkinese the frequent occurrence among them of distomatosis may influence the prognosis (*Clonorchis sinensis* itself is, according to some authors, accompanied by Hgburia). 78 (r.). Gouzien (1911).

Temperature

The continuous fever type is more dangerous than the intermittent. Hyperpyrexia, in itself without a secondary infection, is rarely the cause of death. A second infection adds to the gravity, and suppuration is almost certainly fatal. A sudden fall of T. with feeble P., dyspnoea, and prostration are all grave signs. Gouzien (1911), 79 (r.).

Urine

Anuria

Suppression more or less complete is a grave sign, but it is rare, and not so common as in yellow fever, but has the same prognostic value. Bérenger Féraud (1874), 306.

Persistent albuminuria (after negative Hgb) with diminution of urine indicates nephritis. Gouzien (1911), 79 (r.).

Anuria on the first day is not necessarily an unfavourable sign, as it may be due solely to a reflex spasm of the bladder muscle. In some cases I saw after an anuria of 12–20 hours' duration an abundant flow of almost normal urine and convalescence setting in without further incident.

When anuria lasts more than 1 or 2 days the condition is always to be regarded as serious.

It is fairly common in these cases even with composed courageous patients, to meet with a definite death premonition. Even in these cases the prognosis is not absolutely hopeless, as sometimes after many days the tubules again become pervious. Yet these cases are very few compared with those that go on to anuria and death. Plehn, F. (1898), 187.

Prognosis is absolutely unfavourable when anuria has lasted more than 24 hours. Two cases in which oliguria (a small quantity only of urine) set in on the first day. Then com-

plete anuria, which persisted until death in one case on the 7th, in the other on the 9th day. Werner (1902), 763.

Colour

From the depth of colour of the urine passed in the early stage the duration of the attack can be fairly estimated, unless relapses occur, irrespective of treatment. Daniels (1901), 59.

Ketonuria

Of the eleven cases in which ketones were present, 6 were fatal. The prognosis is particularly unfavourable in fulminating cases, where ketones appear early and progressively increase in amount. If the quantity diminishes as the case proceeds the prognosis is more favourable. Ross (1932), 185.

Polyuria

Abundant urine is a sign of gravity. Bérenger Féraud (1874), 305.

Urobilin

Urobilinaemia without urobilinuria is of grave prognosis; the reverse condition is rather favourable. Gouzien (1911), 79 (r.).

Vomiting

Frequency and persistence bad signs. 306.

When the vomited matter is green, yellow or saffron-coloured the case is not very severe. If the green matter is perfectly fluid there is no cause for anxiety, but if the green (not very deep) fluid contains in it solid matter resembling chopped spinach, it is more serious, and if the condition continues it is critical. Bérenger Féraud (1874), 307.

Vomiting is a common symptom, and is frequently severe and persistent; when excessive the prognosis is unfavourable. Daniels (1901), 55.

Intractable vomiting is a grave sign. Recurrence of the vomiting after a period of cessation indicates the onset of

uraemia. Sudden arrest with failing urine, and dyspnoea, is an indication of the onset of stupor and coma. It is said by Europeans in the Congo that so long as the patient vomits yellow bile he is in danger, but if green recovery is probable. Gouzien (1911), 79 (r.).

PROPHYLAXIS

Bicarbonate of Soda

' Après l'excellent résultat qui m'a donné le bicarbonate de soude en s'opposant si efficacement à la formation de la methémoglobinurie, en présence d'un corps aussi puissamment producteur de cette substance, que la quinine chez nos sujets prédisposés, je ne manquerai pas de conseiller également en temps d'épidémie amarile.' Carreau (1891), 63. Guillon (1909[a]), 35.

The administration of alkalies previous to giving quinine . . . has not led in my experience or in that of several medical men in Rhodesia to any diminution of the risk of Hgburia in these Q.-intolerant cases. Ross (1932), 236.

Cinchona

1. Girl aet: 11. Algeria.
Hgburia following Q. on four occasions from 6.9.17 to 4.10.17.
6.10.17. Treated with *Pulv. quinquinae* for 2 months. No Hgburia.
24.8.18. 7 p.m. Q. 0·25 g. × 2. Hgburia at night. Treated with *Pulv. quinquinae*. No fever. No Hgburia up to 10.11.18.

2. Boy aet: 7. Algeria. Brother of above.
Hgburia following Q. on 23 and 25.10.18.
26.10.18. Treated with *Pulv. quinquinae*. No fever up to 10.11.18. *Pulv. quinquinae flavae*, 2 heaped-up teaspoonfuls in water before each meal 50 g. in 15 days, or
Pulv. quinquinae flavae 50 g.
Ferri redacti 2 g.

A teaspoonful in water before each of 2 principal meals. Parrot (1918), 846.

Quinine

While a single large dose even of 2 or 3 g. has no particular effect, it must not be forgotten that smaller oft-repeated doses are very effective. In addition to these repeated medium or small doses we strongly recommend arsenic. With the appearance of the 8 or 14 day recurring fever, for 3 or 4 days in succession Q. 0·5 g. twice daily or in a single dose of 1·0 g. should be taken, and in addition thrice daily at meals 3 drops of Fowler's arsenic solution, increasing the amount by 1–2 drops on each successive day, so that on the 2nd day 4–5 drops are taken three times a day. Should at the right time repeated doses of Q. be omitted and then at the approach of one of the attacks a single large dose (2·0 g.) be taken, one will be startled with the occurrence straightaway of an attack of bile fever (blackwater). Fisch (1894), 86.

Q. 0·5 g. every 5th day. 1 Feb. 1897–1 Feb. 1899. Cameroons.

	Individuals.	Residence in months.	Attacks of malaria.	Attacks of b.w.f.	Deaths from b.w.f.	Authority.
P.	47	446	90	6	0	Plehn, A. (1902), 690; (1903[c]), 546.
N.P.	54	573	287	31	3	

Individuals who had gone home during the same period.

		Residence (average) in months.			Deaths from b.w.f.	
P.	22	19·2			0	
N.P.	23	14·6			3	

P. = Prophylaxis. N.P. = No prophylaxis.

For some years the missionaries and other European employees of the Basle mission on the Gold Coast have regularly taken Q. in gramme doses, at first 2–3 g. every month, latterly 1 g. every 12 days. Not a single individual who has carried out this course precisely has been attacked

with b.w.f., but, on the contrary, those who have neglected it for a longer, or at certain stations for a shorter period, or those who only take it irregularly, or at more or less long intervals. Fisch (1902), 10. Ruge (1902), 504.

Q. Prophylaxis.	Cameroons.	Kept fit.	Blackwater fever.		
			Cases.	Attacks.	Deaths.
Irregular	70	47	35	83	6
Regular	69	62	12	19	3

Complete details as to each case are given in the original. In the 12 cases of b.w.f. among those following regular prophylaxis, the dose was in the majority 0·5 g. every 5 days. Ziemann (1904), 370.

In every instance in which a sulphate (e.g. Q. sulphate) was given by the mouth a well-marked fall in the salt concentration of the serum was observed, and the rapidity of the fall varied directly with the amount of sulphate ingested. When, however, chlorides (in the form of Q. hydrochloride) were given, no such fall occurred—in some instances, on the contrary—a rise. The administration of sulphates in whatever form is dangerous, and the best form of administration in order to destroy the malarial parasites is the (quinine) hydrochloride in combination with sodium chloride. McCay (1908), 42.

Quinine prophylaxis twice weekly.	Persons.	Cases.	%.	Deaths.	Case mortality (%).	Authority.
None . .	94	49	52	16	32·6	Fisch (1914), 30.
Less than 0·8 g.	115	9	7·8	1	11·1	
More than 0·8 g.	175	4	2·3	0	0·0	

In the histories of 150 cases of b.w.f. investigated by me, quinine was in no instance used in a proper way, and I never encountered a single case in a person who took five grains daily. Thomson (1924), 103.

It is perhaps worthy of note that one of these patients, Case 4, asserted that he took as a prophylactic a daily dose of 5 grains of Q. with the utmost regularity during the ten years

he was in West Africa; and a similar statement was made by two other cases seen by one of us recently. Yorke, Murgatroyd and Owen (1929–30), 353.

It has also been demonstrated that—

1. Q. 10 grains for 5 days previous to and for 8 days after the bite of an infected mosquito does not prevent infection.

2. Q. 10 grains for 10 days after the bite prevents infection. 233.

In the present series of cases (150 ?) twenty individuals who suffered from b.w.f asserted that they had taken regular doses of Q. 234. Ross (1932).

Nyasaland

Five grains of Q. were taken daily, beginning on the day of the departure from Marseilles, and if any felt ill, tired, sickly or out of sorts, the dose was doubled for a few days. The success of this method has been marvellous. There are now more than 600 White Fathers serving under these malarious conditions, and for the past twenty-eight years, since the adoption of the regular 5 grains of Q. a day rule, not one single case of b.w.f. has occurred. Guillemé (1932), 2. Thomson (1934), 402.

Quinine habituation

1. Girl aet: 8. Spanish Jewess. With a history that every time she took Q. she had b.w.f.

27. *P. falciparum.* p.m. T. 99°.
28. 6 p.m. Q. grains 2 + Sod. bicarb. grains 2.
9 p.m. passed black water like stout.
29. a.m. T. 102·2°; p.m. 98·8°.
7. 12.30 p.m. Q. grains $\frac{1}{32}$ + Sod. bicarb. grains 2.
4.30 p.m. restless, feeling sick.
4.45 p.m. dark-coloured urine (like stout.) T. 100°.

2ª. M. S. aet: 10. Dutch boy. A distinct history of Q. producing Hgburia.

15. *P. falciparum.* p.m. T. 99·4°.
16. T. 97°, 98·4°.
17. a.m. T. 98°, Q. grains $2\frac{1}{2}$ (hypodermically); p.m. T. 99·4°.

18. a.m. T. 98°, Q. grains 2½; p.m. T. 100°, Hgburia (? when).
21. a.m. T. 97°, Q. grains 3; p.m. T. 99·4°, Hgburia (midnight).
23–29. Q. grains 3 daily. No further trouble.

2[b]. M. S. readmitted.
22. *P. falciparum*, T. subnormal.
25–1. Q. injections, beginning with grain 1 ending with grains 8.
6. Q. grains 2 + sod. bicarb. grains 7 *per os*, at 2, 6, and 10 p.m.
7. 1 a.m. rigor, T. 99·8°, Hgburia neg., Q. continued 4-hourly, i.e. at 10 a.m., 2, 6 and 10 p.m., Hgburia pos. (midnight). Thomson (1924[a]), 108.

Nor is there sovereign virtue resident in what may be called the 'desensitization' procedure in which extremely small initial doses of Q. are gradually increased until the patient is receiving full doses of the drug . . . during the period of the present work four cases developed under these conditions. Ross (1932), 236.

Summary

The treatments here summarized have been advocated with no more evidence of their efficacy than that the patients (or some of them) survived. In some cases only a single case has been treated! The fact that many cases recover without the use of any special drug or drugs—a fact over and over again ignored—invalidates the claims made.

Of the multitude of treatments used, perhaps saline has the best record, though it should be used cautiously. The evidence as to whether Q. should be given or not is conflicting. It would seem to be unnecessary unless there is evidence to the contrary.

Of modern treatments, transfusion in cases of grave anaemia would appear to be beneficial.

CHAPTER 10

THE BLOOD

Corpuscles

Agglutination

Very frequently, very marked clumping of the red blood corpuscles occurs. When these are below 2,000,000, this can be seen macroscopically in the drop before it is spread out. Krauss (1904), 64.

Case 7. Day 5. Pseudo-agglutination was marked and sedimentation rate rapid. 152.

Case 9. Day 3. Red cells 1·37 m. There was marked pseudo-agglutination associated with a rapid sedimentation rate. 154. Fairley and Bromfield (1934–35).

Coagulation time

Day 1. Coagulation of blood markedly increased.

Day 2. Coagulation not so noticeably rapid as yesterday. Case 20. Christophers and Bentley (1908[a]), 196.

In 6 of 36 cases clotting was imperfect. Cardamatis (1912[b]), 381.

Day 1. 12 noon. Blood, rapid clotting in spite of the oxalate. Barrenscheen and Glaessner (1923), 412.

Cases 49. The coagulation time was delayed (? in all). In 5 cases it was 25 minutes. Weselko (1926), 658.

Cell Count

Soldier aet. 24, invalided home from Madagascar Dec. 1895.

2, 10, 15, and 18 Feb. 1896. Hgburia.

19 Feb. Cell count 620,000. Ferrier (1896), 462.

Day 19. Hgb 45%. Cell count 1·03 m. (repeated, 1·00 m.). The disparity between the Hgb value and the cell count apparently due to Hgb in solution, derived from red cells laked during the taking of the blood. The blood had a peculiar reddish-yellow colour apparently due to Hgb in solution (perhaps also bile pigment). Plehn, A. (1896), 53.

Even in the severest cases the count is a not inconsiderable value above 1 million. Plehn, F. (1898), 10.

In a strong young merchant, in 2 days the count fell from 4·31 to 1·11 millions and the Hgb from 80% to 20%. Ziemann (1906), 574.

Case 3.				Case 4.				Authority.
Day.	Red cells, mill.	Hgb, %.	Leucocytes.	Day.	Red cells, mill.	Hgb, %.	Leucocytes.	
2	3·80	75	10,000	2	2·5	55	13,000	Grattan (1907), 242.
3	3·80	70	12,000	4	1·47	30	12,000	
5	3·70	70	9,549	8	1·10	25	13,800	
23	4·99	96	14,900	14	1·34	40	11,000	
				37	3·25	63		

1 Dec. *P. vivax*. Q. 1·5 g. in 3 doses, one every hour; 6 p.m. rigor T. 40°, epigastric oppression; 11 p.m. dark urine.
3. Red cells 1·13 m., Hgb 18%, leucocytes 5,400.
5. Red cells 0·44 m., leucocytes 22,000, death. Carducci (1907), 227.

In one case in S.E. Bulgaria the count fell from 4·5 to 1·2 millions after 4 days Hgburia. A fall of 1 m. in 24 h. is common. The lowest figures were 500,000 to 800,000. Seyfarth (1918[a]), 276.

Day 2. Red cell count 920,000. Schilling and Jossmann (1924), 1498.

31. *P. vivax.* Q. grains 10, Plasmoquine 0·01 g., twice daily.
4. Drugs stopped. Total given = Q. 100 grains, Plasmoquine 0·09 g.
5. Bilious vomiting frequent and severe, cyanosis distinct, icterus ++, Hgburia, cell count 562,500, leucocytes 3437, death. Amy (1934), 325.

Blood destruction had proceeded to the extent of leaving only 600,000 red cells per c.mm. and 10% Hgb. Manson-Bahr (1926–27), 412.

In a recent moribund case in whom the urine had cleared, but who was suffering from extreme anaemia (the blood count showing only 850,000 red cells per c.mm.), blood transfusion of 700 c.c. of blood was performed. Death. Manson-Bahr and Sayers (1927), 275.

Day 4. He was desperately ill, deeply jaundiced, anaemic, blood count 980,000, transfusions. Recovery. Low, Cooke and Martin (1928), 645.

Day.	Red cells, mill.	Hgb, %.	Hgb-uria.	Red cells, mill.	Hgb, %.	Hgb-uria.	Red cells, mill.	Hgb, %.	Hgb-uria.	Author-ity.
1	3·96	45	+	2·8	45	+				Seyfarth (1918[a]), 274.
2	3·65	45	+	1·78	30	+				
3	3·2	40	+				3·0	50	+	
4			+	1·4	15	+	1·9, 1·8	52, 31	+	
5	2·8	35		1·1	15	+	1·5, 1·8	31, 30	+	
6	2·8	35					2·4	28		
7	2·5	30					1·8	32		
8	2·5	30		1·1	15		1·7	30		
9	2·4	35					2·0	30		
10	2·1	40		1·7	20		2·0	30		
11							2·0	30		
12	2·5	40					2·0	35		
13	2·6	40		1·4	20					
14	2·5	40		1·4	30		2·5	35		

In cases 2 and 3 a fall in the count of over 1 m. has taken place in about 24 hrs.

Day.	Red cells, mill.	Hgb-uria.	Red cells, mill.	Hgb-uria.	Red cells, mill.	Hgb-uria.	Red cells, mill.	Hgb-uria.	Red cells, mill.	Hgb-uria.	Red cells, mill.	Hgb-uria.
1	1·56	+									3·62, 3·45	+
2	·98	−	4·10	+	4·20	+	4·88	+ −	2·38	+	2·77	+
3	1·01	−	3·82	+	3·90	+	2·60	−	1·90	−	1·58	+
4			3·12	+	3·55	− + −	2·23	−	·82	+	1·60	+
5			3·96	−		−					1·52	−
6			3·82	−		−						
	Plehn, A. (1896), 36.		Plehn, F. (1898), 124.		Brem (1906), Chart 9.		Deeks and James (1911), 126.		Dudgeon (1920), 211.		Yorke, Owen and Murgatroyd (1930), Case 3.	

In fatal cases

Days before death.	Red cells, m.	Days before death.	Red cells, m.	Authority.
4	5·00	5	1·22	Deeks and James (1911), 103, 93, 99, 94, 88, 127, 134.
6	2·69	2	1·18	
4	2·21	3	1·02	
4	1·88			
Hours.		Hours.		
1	·76			Stephens and Christophers (1900), 29.
7½	·80			'Africa' (1915), 21.
A few	1·33	A few	·99	Dudgeon (1920), 211.
,,	1·05	,,	·90	
,,	1·00	,,	·82	

In Oliguria

Day.	Red cells, m.	Urine, c.c.	Remarks.
1	3·17		Suppression continued till death on the 10th day. In early suppression cases, the anaemia and icterus continue to increase, although little or no Hgburic urine is excreted. Daniels (1901), 62.
2	2·36	120	
3	2·18		
4	1·74		
5	1·80		
6	1·63		

and Quinine

14 Oct. Hgburia, icterus, T. 39·8°.
15. 5 p.m. T.N.
22. Q. 0·5 g., well borne.
30. 11 a.m., T.N., cell count 6·00 m.

31. Q. 1·0 g.
2. (1 ?). 10.30 a.m., cell count 5·66 m.

The fall in the count of 340,000 on the day after the dose of Q. 1·0 g. is noteworthy. Pöch (1908), 597.

and Transfusion

Day.	Red cells, millions.	Hgb, %.	Transfusion, c.c.	Authority.
5	·98	30	400	Low, Cooke and Martin (1928), 646.
6	1·00	30		
7			300	
8	1·00*	30		
9	1·60			
10	2·21	40	(Liq. arsenicalis)	
13	2·80	40		
17†			(Q, Fe, As)	
21			(Liver, Plasmochin)	
21	3·23	70	Recovery	

* Normoblasts present. † *P. falciparum* present.

Case 1.*				Case 2.		
Day.	Red cells, mill.	Hgb, %.	Reticulocytes, %.	Red cells, mill.	Hgb, %.	Reticulocytes, %.
1	2·61	67	1·4	T. 2·17	50	2·2
2	2·33	45	·7	2·56	53	9·4
3	1·72	33	·7			9·0
4			·9	1·60	32	2·4
5	1·34	30	1·2	1·62	31	1·4
6	·97	22	4·4	1·60	31	6·6
7	1·20	25	1·0			6·9
8	Transfusion		2·8	1·26	27	12·6
9	1·18	29	2·4	1·10	26	16·6
10	1·43	28	3·4			14·2
11	1·45	29	6·0	1·04	28	18·6
12			13·4			20·0
13	1·57	28	23·4	1·23	28	20·0
14			35·0			18·8
15	1·34	26	30·2	1·44	24	25·0
16						39·6
17	1·58	31	53·6			
18						
19				1·73	32	52·2
20	1·90	40	50·0			
21	2·25	57	42·0			
22				1·91	43	42·0

* Transfusions of about 500 c.c. of citrated blood given (dates unrecorded).

Blackie (1934–35), 574.

Colour Index

Almost always I found the relationship (of Hgb to cell count) normal, especially if one considers that the Hgbaemia ought to shift the relationship in favour of the Hgb, and conversely, at the onset of most intense blood formation the cell count in relation to Hgb appears to be somewhat high. There are cases, however, where this explanation does not suffice and the disproportionally low cell count can only be explained by the lessened resistance of the red cells to the usual methods employed. 15.

Case 35. Day 19. Cell count 1·03 to 1·00 m. Hgb 45. The disproportionate fall of the count can indeed only be explained by a pathological lowered resistance to the operation of withdrawing the blood, etc. The cells which were actually counted showed no greater tendency to haemolysis than that of controls, although they altered their shape much more readily. 53.

Hgb % and the cell count are regularly reduced by a $\frac{1}{4}$ or a $\frac{1}{3}$, in Europeans in Cameroon, of that of normal European values. 59. Plehn, A. (1896).

The Hgb which after many months' stay in Cameroon is seldom normal falls to 60% or 40%. In an especially severe case it fell to 16% shortly before death. Plehn, F. (1898), 110.

Day.		C.I.	Count in millions.	Hgb, %.	Case.	Authority.
1	Max.	1·1	1·56	34	16	Plehn, A. (1896), 36.
	Min.	·58	5·00	58	9	Arkwright and Lepper (1918[a]).
2	Max.	1·5	1·18	35	200	Deeks and James (1911).
	Min.	·5	4·88	50	196	Ibid.
3	Max.	1·4	1·29	35	109	Ibid.
	Min.	·4	3·92	30	79	Ibid.
4	[Max.	1·2	1·36	32	6	Arkwright and Lepper (1918[a]).][6]
	Min.	·5	1·80	20	129	Deeks and James (1911).
5	Max.	·9	1·52	27	35	Plehn, A. (1896).
	Min.	·6	3·96	49	13	Plehn, F. (1898).
6	Max.	1·6	4·11	69	10	Ibid.
	Min.	·1	2·40	5	109	Deeks and James (1911).
7	Max.	·9	3·55	65	14	Brem (1906), 1904.
	Min.	·8	1·47	25	16	Plehn, A. (1896).

[ ][6] = 6th day.

Day.	C.I.	Count in millions.	Hgb, %.	Authority.
2	·87	1·94	34	Fairley and Bromfield (1934–35), Case 8, 145.
3	·8	1·20	20	
5	·8	·95	16	
6	·9	·88	17	
7	·8	1·09	18	
9	·9	1·06	19	

Colour Index. Volume Index. Volume Colour Index

Day.	Count. mill.	% Haema-tocrit.	Hgb.	V.I.	C.I.	V.C.I.	Authority.
1	3·62	32·5	72	1	1	1	Yorke, Murgatroyd and Owen (1929–30).
	3·45		70		1		
2	2·77		64		1·16		
3	1·58		36		1·1		
4	1·60	13	15	1	·47	·47	
5	1·52		21		·7		
7	1·42		27		·96		
12	1·84		40		1·1		Case 3.
1	4·20	31·5	82	·94	1	1·06	
2	4·25	29	81	·85	1	1·17	
6	4·26	30·8	81	·9	1	1·11	
8	4·40	26·4	77	·75	·85	1·13	
	4·41	28·6	77	·86	·94	1·09	Case 4.

Clot

Day 1. Serum separated from clot, deep yellow with a reddish tinge. No solution of the clot in serum, or deepening of red colour of serum took place even after many hours. Case 19. 194.

Day 4. Serum showed orange tint characteristic of Hgbaemia. No tendency for clot to dissolve in serum. Case 24. 203.

Day 5. Hgburia neg., serum yellow, Hgbaemia neg. Clot dissolved to some extent over night, though it did not do so in a control blood. Case 25. 204.

Day 2. Serum orange yellow. Blood received into citrate shows small amount of Hgbaemia. No solution of clot in serum. Case 26. 205. Christophers and Bentley (1908[a]).

Groups

Cases of the disease were found in Groups II, III and IV (Moss classification). The majority of cases either belonged to Group II or to Group IV, a result which one might expect in view of the fact that in European populations generally, these two groups include roughly 80 per cent. of individuals. Ross (1932), 102.

In 7 cases, 6 belonged to Group IV, I to Group II (Moss classification). Fairley and Bromfield (1934–35), 145.

Morphology

Basophilia

In our experience it is a late and somewhat rare condition, generally associated with polychromasia. Christophers and Bentley (1908[a]), 79.

A thick blood film shows a marked degree of basophilia in the advanced stage of the attack. Menk (1927), 115.

General

In 3 of 12 cases the red cells (under the microscope) changed extraordinarily quickly. They did not assume the typical crenated appearance, but appeared to be radially folded around the centre or swollen on the flat. Controls showed that the technique was not responsible. Plehn, A. (1896), 14.

In the blood films (48 in 19 cases) made during and immediately before Hgburia, the red cells were natural in aspect, no partially decolourised cells or stromata being seen. Barratt and Yorke (1909[a]), 153.

Achromia and ghost cells were observed several times. *Corps en demilune* and Cabot's rings were occasionally found as early as on the 2nd and 3rd days. Howell's bodies were sometimes frequent in the later stages of the disease. Menk (1927), 115.

Megalocytes

Megalocytes, microcytes and sometimes normoblasts are present when the increasing Hgb % shows that energetic blood formation is proceeding. 15.

Day 8. Hgb to 18·5%. Megalocytes, diameter 3 times that of normal red cells. Nuclei clearly visible in fresh film. 43. Plehn, A. (1896).

Macrocytes are abundant, as well as the so-called Ponfick's shadows. Less numerous on the whole are microcytes and poikilocytes. Plehn, F. (1898), 110.

Microcytes

Day 8. Hgb 18·5%. Microcytes $\frac{1}{3}$ of normal red cell diameter. 43.

Day 3. Red cells 2·69 m. Hgb 49%. Numerous microcytes. 52. Plehn, A. (1896).

In 10 of 36 cases there was microcytosis. The small cells stained more deeply than the rest of the cells. Cardamatis (1912[b]), 381.

Normoblasts

Nucleated red cells a sign of commencing regeneration are a regular find. Plehn, F. (1898), 110.

Nucleated red cells are not usually seen, if at all, until late in the disease. Christophers and Bentley (1908), 79.

Day 7. Death. The blood picture resembled that of advanced pernicious anaemia, except for the marked leucocytosis. A very conspicuous feature was the large number of nucleated red cells of all sizes showing signs of mitotic division. Coles (1913), 1230.

Day ?. Nucleated red cells formed no less than 13·7% of the corpuscles. Fletcher (1914), 51.

Nucleated red cells were generally not found earlier than on the 4th and 5th days. At the peak of the blood crisis they sometimes reached 20% of the number of the white-blood cells. They are not seen at all in some of the rapidly fatal cases. Menk (1927), 115.

Polychromasia

3.2.1902. Scanty polychromasia and basophilia.
4. Parasites positive.
5. Q. 0·3 g. subcutaneously.
6. 2–4 polychromatic cells, macrocytes, microcytes and shadow cells in every field. Urine normal.
7. Slight fever, parasites pos., polychromasia considerable.
8. Polychromasia, shadows and many macrocytes, anisocytosis marked. 4 p.m. Q. 0·3 g.; 8.30 p.m. Hgburia.
9. Noon, Hgburia neg. Polychromasia scanty, shadows few, Hgb 40%, cell count 2·1 million. Ruge (1902), 505.

28.7.1901. Hgburia.
3.8. Hgburia neg., Albuminuria neg., many large polychromatic cells.
4–6. Slight T. rises, parasites a few, very many polychromatic cells, also nucleated and basophilic (gekörnte), Hgb 35%.
14. Basophilic cells last found.
16. Polychromasia. Discharge. Panse (1902), 12.

During the early stages of b.w.f. polychromasia is rarely seen; it begins to be apparent after the second or third day, and reaches its maximum most often when the patient is convalescent, usually several days after the cessation of the Hgburia.

Case 20. Day 3. Polychromasia began to be conspicuous.
Day 6. An extraordinary degree of polychromasia, large polychromatic cells forming a considerable proportion of the total. Basophiles were also present. 79.

Case 21. At no time during the Hgburia in this primary attack did the blood show polychromasia, degeneration of the red cells or nucleated red cells. But five days later a relapse took place, and at this time polychromatic red cells were present in large numbers, together with numerous nucleated red cells of

various sizes, and a marked general poikilocytosis. 80. Christophers and Bentley (1908[a]).

The thin film during the first few days showed polychromatophilia and anisocytosis. Menk (1927), 115.

Reticulocytes

Day.	Red cells, millions.	Hgb, %.	Reticulocytes, %.	Remarks.
5·5·31	4·17	74		
11.	3·41	60		
				7 p.m. Hgburia.
13.	2·40	35		Counts 2.30 a.m.
14.	1·70	26	2·6	12.45 p.m. 600 c.c. citrated blood.
22.			33·6	Maximum reticulocyte rise.
12.6.	4·36	66		Case 4, 146. Recovery.
2	1·94	34		Blood transfusion 6 oz.
3	1·20	20		,, ,, 8 ,,
5	·95	16		,, ,, 10 ,,
6	·88	17		,, ,, 20 ,,
7	1·09	18		
9	1·06	19	10·5	
10			32·2	Maximum reticulocyte rise.
36	3·36	70		Case 8, 152. Recovery.
3	1·37	28	0·2	Case 9, 153. Death.

Fairley and Bromfield (1934–35).

Vide p. 365.

Shadow cells, etc.

Day.	Large shadows.	Small shadows.	Anaemic cells.	Poikilocytes.	Case.	Remarks.
1	15	20	35	105		20,000 red cells counted in each case.
2	51	35	35	48	20	
3	2	27	15	84		
1	156,[1] 0 [2]	33, 0	16, 0	129, 15	21	
2	12	6	6	21		
1	0	0	0	0		
2					24	
3	80 [3]	22				

[1] 6 hrs. after onset of Hgburia. [2] Several hours later. [3] Hgburia pos.

Christophers and Bentley (1908[a]), 79–81.

Spherocytes

26th. Urine dark reddish brown. Hgburia (?).

29th. Blood. Stained specimen. Besides the normal cells present in overwhelming majority, small red spheres $\frac{1}{2}$ to $\frac{1}{4}$ the normal diameter. Heuck (1880), 174.

1. Two hours after the onset no abnormality can be detected.

2. Four hours after the onset among 20,000 red cells 150 large shadow corpuscles, 129 small shadow corpuscles, 16 markedly anaemic cells. 75.

3. Small fragments of red cells, irregular, stellate or elongated, staining more feebly than normal red cell substance. 77.

4. 'Spherocytes.' Cells of small size, having a regular circular outline staining more deeply than red cells; in fresh films are darker than red cells. 77.

5. Cells with normal or irregular pear-shaped outline, and pale centres. 78. Christophers and Bentley (1908[a]).

Splenic blood

Large shadows, %.	Small Poikilocyte shadows, %.	Spherocytes, %.	Agglutination.	Phagocytosis.	Miscellaneous	Case.
·05	·2	·15	—	++		19
Not conspicuous		·7	—	++		20
·15	·15	·1	—	++	·7% large pale cells	22
Very numerous		6·6	++			24
·1	·05	·4	+	++	Pigment +	26

Christophers and Bentley (1908[a]), 88.

Thread-like structures

Day 7. (Death.) What I had not observed in other severe anaemias was the presence of long threads of a deep red colour (Giemsa stain) entering or coming out of lymphocytes or nucleated red cells. One thread measured 39 μ. Coles (1913), 1230.

Regeneration

Is rapid when the haemolytic process has ceased as shown by the presence of a large number of haematoblasts (nucleated red) and small red cells. Gouzien (1911), 19 (r.).

Rouleaux

In certain cases there is little tendency to rouleaux formation. Gouzien (1911), 19 (r.).

Sedimentation rate

The sedimentation time (Linzenmeier technique) is decidedly decreased (as) in any severe anaemia. The reading of the time is very difficult, as the upper level of the cell column, is a hazy zone of turbidity, made up largely of leukocytes and blood platelets instead of red cells. Menk (1927), 116.

5 April. 3.30 p.m. Q. urethane 0·05 g.; 7 p.m. Hgburia. (4th attack following Q. in the period 15 Feb.–5 April).

7. Sedimentation rate (Linzenmeier) 1 h. 8 min., resistance about normal, parasites positive. Mühlens and Knabe (1931).

Day 4. The sedimentation rate was rapid—a finding which is very characteristic of the anaemia of b.w.f. Fairley and Bromfield (1934–35), 311.

Viscosity

Day 3. Blood spreads very badly (i.e. does not adhere readily to the slide) in making a film. 17 (r.).

Guillon, in Guinea, observed in all cases a laked and oily appearance of the blood which is difficult to spread and fix. 20 (r.). Gouzien (1911).

Volume

Day 2. Anuria, 2 p.m. 100 c.c. of NaCl and Na_2HPO_4 (Matko).

Resistance of washed red cells: H. begins at 0·7% saline.

Blood serum : Hgb — Haematin ++ Bilirubin ++.
Serum corpuscle volume ratio $\frac{4{\cdot}5}{1}$. Barrenscheen and Glaessner (1923), 412.

Day.	Haematocrit, %.	Red cells. m.	Hgb, %. Fleischl.	C.I.	Case.	Authority.
8	20	2·61	30	·58	3	Barratt and Yorke (1909[a]).
7	14·8				11	
2	33				12	
5	33·3				14	
4	22·5		21·5		17	

N. aet: 25. Saigon. Oliguria, anuria. Intravenous salines.
Day 8. Hydraemia can be extreme, 145 c.c. of serum for 35 c.c. of clot.
Day 9. Death. Lahille (1915), 916.
Day 4. Red cells 925,000. The haematocrit showed only 6·8 per cent. of corpuscles by volume. Fairley and Bromfield (1934–35), 312.

Leucocytes

Absolute count

18.11.1891. (Day 5.) Red cells 1 m., leucocytes 2800. Kohlstock (1892), 428.

Day.	Red cells, m.	Hgb, %.	Leucocytes.	Authority.
1 9 a.m.	5·07	85		Murri (1896), 116.
3 p.	4·98	75	22,320	
6 p.	4·64	70	25,420	
2	4·38	70	26,040	
4	3·85	65	20,460	
5	4·09	65–70	24,180	
6	4·14	65–70	21,080	
8	4·36	70–75	19,220	
12	4·11	70–75	8,680	
15	4·15	70–75	12,400	
2	4·10	72	2,300	Plehn, F. (1898), 124.
3	3·82	68	2,600	
4	3·12	42	2,300	
5	3·96	49	2,800	
6	3·82	47	2,600	
7	Death			

The diminution in cells ranges within moderate limits. In the severest cases the values may range between 2500 and 3000. Plehn, F. (1898), 110.

Day.	Red cells, m.	Hgb, %.	Hgb-uria.	Leuco-cytes.	Authority.
1	4·00		+	22,000	Stephens and Christophers (1900), 34.
1[a]	3·43		—	2,000	Ibid., 37.
2	2·77		+—	2,000	
4	3·19		—	7,000	
3	3·09		—	6,000	Ibid., 41.
2	1·57	35		9,200	Achard and Saint-Girons (1912), 752.
4	·78	15		20,400	
5	1·08*	23		48,100	
6	1·09	24		60,800	

* 3 hours after transfusion.

In many cases of b.w.f. we have observed a considerable increase in the leucocytes, a fact which does not tally with the malarial nature of this disease. Cardamatis (1902[a]), 39 (r.).

The blood differs from that of acute malaria in the frequent leucocytosis, which may be quite transient and inconstant and bears no relation to the severity of the case. Krauss (1904), 64.

Day.	Leuco-cytes.	Hgb-uria.	Leuco-cytes.	Hgb-uria.	Leuco-cytes.	Hgb-uria.	Authority.
1	7,500	+	9,000	+			Seyfarth (1918[a]), 274.
2	9,500	+	12,000	+			
3	10,890	+			4,500	+	
4		+	16,000	+	5,200	+	
5	17,000		16,000	+	4,300	+	
6	9,900				2,900		
7	10,100				4,100		
8	12,300		18,000		5,700		
9	7,000				5,000		
10	7,000		20,000		5,000		
11					5,000		
12	6,000				4,000		
13	7,000		7,000				
14	7,000		8,000		4,000		

In the first stage of the disease the count is usually normal. Later, in the reparatory stage there is a tendency to leucocytosis and some of the severe cases may yield a count of 18,000 or more. Menk (1927), 115.

D.N. aet: 16. Kasan, Russia. 24.5. 6 p.m. rigor. T.

Day.	Red cell, m.	Hgb, %.	Leucocytes.	Hgburia.	*P. vivax.*
25·5	4·80	91	5200	+	+
26	5·12	78	5300	+	+
29	4·54	64	4800		+
31	3·67	50	480	+	+[a]
1	3·50	50	4600		+
2		42		+	+
3	3·12	45	3810		+[b]
4	3·50	28	4200	+	+
5	3·85	39	4650		+
6–11	5·20	72		—	+
17					—

a. Cortex cinchonae rubrae. 1·0 g. × 6 daily. *b.* Q. bihydrochloride 0·15 g. × 10 daily. Perekropoff (1926), 287.

Day.	Case 3.	Case 4.	Remarks.
	Leucocytes.	Leucocytes.	
1	4,000	4,700	Between the 2nd and 3rd days there was a fall of 1·19 m. in the red cell count. Possibly the leucocytosis of 18,200 on the 4th day may represent an attempt of the organism to deal with the stroma of haemolyzed erythrocytes.
	3,700		
2	4,400	3,500	
3	9,700		
4	18,200		
5	5,700—		
6		4,600—	
7	12,500		
8		4,300+	
		5,500	
12	7,300		

— = Hgburia neg. + = Hgburia pos.

Yorke, Murgatroyd and Owen (1929–30), 361.

Differential count

Day.	Hgburia.	Large mono-nuclear.	Small mono-nuclear, lympho-cytes.	Poly-nuclear.	Eosino-phil.	Death or Re-covery.	Case.
1	+	17	3	70			9
2	+	24	6	69			
3	—	19	15	65			
4	—	15	8	77		R.	
1	+	19	11	70			10
	+	27	19	54		D.^{2}	
1	+	21	16	61			11
2	+	11	12	75		R.	
1	+	6	4	89		D.^{2}	12
2	+	21	13	65			13
	+	22	17	61			
3		18	17	65		D.^{3}	
2	—	23	23	54		R.	14
2		25	14	61		R.	15
1	+	12	12	75			16
2	+	15	10	74		R.	

The values are given in ' round numbers,' and the total may not be exactly 100. D.^{2}, D.^{3} = Days of death. Stephens and Christophers (1901).

Day.	Hgburia.	Large mononuclear.	Small mononuclear, lymphocytes.	Polynuclear.	Eosinophil.	Death or Recovery.	Case.
6	—	15	15	69	1		17
7	—	16	19	64	2	D.[7]	
1	+	20	18	60	1		18
3	—	17	14	67	1		
4	—	18	10	70	2	D.[8]	
1	+	20	14	64	1		19
	+	18	22	60	1		
3	+	13	24	62	1	R.	
1	+	23	20	56	0		20
	+	18	12	69	0		
2	+	16	24	60		R.	

The values are given in ' round numbers ' and the total may not be exactly 100. D.[7], D.[8] = Days of death. Stephens and Christophers (1903).

	Day 13[a].		Day 2.	Day 17.	Authority.
Total per mm.[3] .	7,000		13,000		Pöch (1903), 597, 598.
Neutrophil . .	61		66·3	62·3	
Transitional . .	3·3		0·8	1·3	
Large mononuclear .	11·3		11·9	8·3	
Lymphocytes . .	23·8		15·1	27·4	
Eosinophil . .	0·6		5·9	0·7	
	Day 15[a].	Day 1.	Day 2.	Day 15.	
Total per mm.[3] .	7,400	10,800	9,200	6,400	
Neutrophil . .	44·8	76·5	51·4	50·3	
Transitional . .	1·3		2·7	2·4	
Large mononuclear.	10·2	2·8	7·5	10·0	
Lymphocytes . .	41·5	20·5	36·8	36·6	
Eosinophil . .	2·2	0·2	1·6	0·7	

[a] = before the attack.

Day.	Poly-nuclear.	Mono-cytes.	Lympho-cytes.	Eosino-phil.	Case.	Authority.
1	59	20	20	·5	4	Christophers and Bentley (1908[a]), 82.
2	54	27	18			
3	56	22	23			
4	54	17	24	6		
1	64	23	9	2	20	
2	62	29	9	2		
3	57	22	14	2		
4	49	25	20	3		
7	73	9	9	5		
1	83	10 + 1	6	0	19	
2	67	8	18	6		
1	74	18 + 2	6	·2	21	
2	62	10 + 7	21	0		
2	49	20 + 11	20	·2	17	
4	62	22	13	2		

The figures after + refer to cells of the macrophage type.

Day.	Poly-nuclear.	Mono-cytes.	Lympho-cytes.	Eosino-phil.	Case.	Authority.
2	49	27	24	1	10	Christophers and Bentley (1908[a]), 82.
2	61	33	6	0	11	
2	56	15	21	·4	16	
3	49	25	21	5	12	
3	59	26	9	6	14	
3	65	18			18	
3	57	13 + 5	23	·5	25	
3	57	25	17	1·5	1	
4	54	25	21	·2	15	
4	75	12	12	·3	24	

Cases 36. *a*. 15 examined 5–10 hours after the onset. T. 39°–40·2°. Polynuclears 71–90%.

b. 4 examined 24–32 hours after the onset. Polynuclears 65–71%. Cardamatis (1912[b]), 381.

Day.	Poly-nuclear.	Lympho-cytes.	Large lymphocytes (monocytes).	Eosino-phil.	Myclo-cytes.
1	74	12	12	2	0
2	68	19	12	1	0
2	65	21	13·5	0·5	0
3	63	10	27	0	0
4	61	15	23	0	1
5	64	14	20	0·5	1·5
7	47	20	28	1	4

Death on day 7 with a marked leucocytosis. Coles (1913), 1230.

Day.	Poly-nuclear.	Small lymph.	Large lymph.	Mono-nuclear.	Trans-itional.	Myclo-cyte.	Eisino-phil.	Mast cell.
1	74·4	10·2	1·8	9·6	2·4	0·8	0·6	0·2
2	55	14·8	3·6	19·2	2·4		5	
3	55·2	24·8	4·4	5·8	3·8		6	
4	72	9·4	2·6	13	2·2		0·8	
2	73·4	11	3·4	6·8	1·6	3·6	0·2	
3*	69·8	12·2	2·4	10·6	2·2	2·8		
4	55·2	15	3·6	18·6	4·8	2·4	0·4	
5	73	14	2	5	1·2	3·8	0·6	

* 2 erythrophages, 1 pigmented monocyte in 500 leucocytes.

Connal (1922[a]), 11.

Day.	Total leucocytes.	Monocytes.	Lympho-cytes.	Poly-nuclear.	Eosinophil.
4	17,000	1	24	75	
7	22,000	2	17	81	
8	26,000	3	20	77	
9	19,000	4	20	76	
10	12,000	4	20	75	1
11	7,320				
19	6,800	4	33	63	

Day 6. Considerable quantities of pus were present (in the urine) and culture gave a pure growth of *B. coli*. This was possibly a factor in the neutrophile leucocytosis which characterized the earlier stages of the disease. Fairley and Bromfield (1934–35), 312.

Endothelial plaques

Cells of very large size and plaques of 2 or more joined together are not uncommon, later in the disease.

Nucleus :—Irregular in outline, large and may stretch nearly across the cell.

Protoplasm :—Hyaline, often much vacuolated, and may contain débris, shadows, or red cells.

They resemble cells found in the splenic and hepatic veins *post-mortem*, and the endothelial cells of the visceral capillaries. Christophers and Bentley (1908[a]), 84.

Eosinophil

13.11.1891. Hgburia.

30. Convalescence set in with an initial leucocytosis and considerable increase of eosinophil cells. Kohlstock (1892), 429.

Regeneration is observed at once and is associated with marked relative increase of eosinophils (up to 14 per cent.). Krauss (1904), 65.

Frequent partial or total disappearance of the eosinophil cells during the early stages, followed by reappearance, sometimes in considerable numbers at a later stage. Christophers and Bentley (1908[a]), 84.

In 28 of 36 cases the eosinophils were increased from 2 to 5%. Cardamatis (1912[b]), 381.

Eosinophils were usually absent during the peak of the Hgburic periods. Menk (1927), 116.

Lymphocytes

At this stage (cessation of Hgburia) also true lymphocytes and eosinophils which have been reduced almost to the vanishing point (during Hgburia) once more reappear, sometimes in increased numbers. 81. A most interesting phenomenon, in a number of cases, is the great reduction of true lymphocytes. 84. Christophers and Bentley (1908[a]).

In nineteen counts made in the twelve cases, the small lymphocytes averaged 18%. The small leucocytes therefore show a slight reduction. Woldert (1912), 635.

Lymphocytosis (? relative or total) was at times found in cases with a low total count. Menk (1927), 116.

Macrophages

Appear usually within the first 24 hours and are still to be found when Hgburia has ceased.

Type 1 :—Resemble ordinary large mononuclear leucocytes. Diameter 15–25 μ.

Nucleus :—Oval, indented or kidney shaped, usually eccentric. May measure 15 μ in long diameter.

Protoplasm :—A large amount of hyaline or faintly granular protoplasm. May contain malarial pigment or occasionally red cell shadows. These cells form a marked feature in the blood.

Type 2 :—Irregularly circular. Diameter 15–20 μ or more.

Nucleus :—Compact roundish or rhomboidal, more or less central, 10–12 μ.

Protoplasm :—Often vacuolated, contains débris of red cells, with red cell shadows, or unaltered red cells in the smaller forms. They resemble small mononuclear leucocytes (lymphocytes) except in size.

Type 3 :—Large cells 20–30 μ.

Nucleus :—Irregular or polygonal, lateral or stretching across the cell.

Protoplasm :—Phagocytic, frequently containing débris, or altered red cells. Christophers and Bentley (1908[a]), 83.

Mast cells

An unusually high percentage of ' mast ' cells were present in 2 of 12 cases. Woldert (1912), 635.

Monocytes (large mononuclear)

During the leucocytosis (*q.v.*) the large mononuclears continue even with or in excess of the small lymphocytes. Krauss (1904), 64.

Very early after the beginning of the attack there is a large mononuclear leucocytosis. Christophers and Bentley (1908[a]), 81.

In all cases of my series the large lymphocytes (? monocytes) seemed to be increased from the time of onset to several days subsequently. In twenty counts made in the 12 cases, the large lymphocytes average 27%. Woldert (1912), 635.

In 15 of 36 cases the mononuclear leucocytes (? lymphocytes and monocytes) increased to 55–60%. Cardamatis (1912), 381.

Monocytosis not observed. Seyfarth (1918[a]), 276.

The mononuclear and transitionals showed wide variations in different cases. Excessive values, 17–24 per cent., were observed only in 2 severe cases during Hgburia. Menk (1927), 116.

Monocytes (abnormal)

The small mononuclear leucocytes (not lymphocytes) in one case on the 4th day showed deeply staining nuclear-like bodies 1–2 μ at the periphery of the cells. Probably nuclear extrusions associated possibly with cell proliferation. It is possible that they are analogous to ' Kurloff bodies ' in guinea-pigs' blood. Christophers and Bentley (1908[a]), 85.

Myelocytes (eosinophil)

Many of the polymorphonuclear neutrophile elements which have possibly shown diminished granular staining of their protoplasm during the attack, now (with the cessation of Hgburia) appear more densely granulated, a condition shared by a large number of the transitional and mononuclear elements, many of which latter approach the myelocyte type. Some of these also show a distinct tendency to

eosinophil granulation; and should perhaps be described as eosinophil myelocytes. Christophers and Bentley (1908[a]), 81.

Myelocytes and transitional cells

Towards the end of the attack a large proportion of the polymorphonuclear cells contain nuclei much less lobulated than normal and such cells appear to be immature forms of polymorphonuclear leucocytes. Other cells of similar nature are of more or less purely mononuclear type and appear to be neutrophil myelocytes. Christophers and Bentley (1908[a]), 85.

A high percentage of myelocytes were present in 5 of 12 cases. Woldert (1912), 635.

Polynuclear

During the leucocytosis (*q.v.*) the polynuclear leucocytes may increase to 85 per cent. or over. Krauss (1904), 64.

There is a reduction in the normal % of polymorphonuclear leucocytes, occurring within a few hours of the onset of Hgburia and persisting for several days subsequently. Average 49%. Woldert (1912), 635.

Even at the onset, a high percentage of immature neutrophils appears. They are not excessively increased in slight cases, but reach astonishing numbers in severe and fatal cases. They persist in large numbers until repair begins in the blood-forming organs. Menk (1927), 116.

Phagocytosis

Specimens of blood taken very early after the commencement of an attack exhibit a relative large mononuclear leucocytosis consisting chiefly of the ordinary typical large cells with kidney incurved and somewhat eccentrically placed nuclei.

A little later mononuclear cells of a different type appear, and it is coincident with the appearance of these new elements that phagocytosis of red cells and shadow corpuscles may be

observed. At a still later stage enormous irregular endothelial plaques appear. 81.

Some evidence of its (phagocytosis) occurrence can invariably be found on careful search, especially during the earlier stages of the disease. 84. Christophers and Bentley (1908[a]).

Case.	Day.	Hgburia.	Phagocytosis of red cells.	Pigmented leucocytes.	Authority.
1	3	—	+	+	Christophers and Bentley (1908[a]).
5	1	+	+	+	
7	3	—	+	+	
8	1	+	+	+	
	2	+	+	+	
11	2	+	+	+	
12	3	—	+	—	
14	3		+	+	
15	4	—	+	—	
16		—	+	—	
17	3		+	+	
18	5	—	—	—	
22	2	+	+	+	
23	4	—	+	—	
24	4	+	+		

In one of these cases the mononuclears and transitionals were vacuolated and presented a picture suggesting erythrocytophagia. Menk (1927), 116.

Phagocytosis of erythrocytes is a phenomenon frequently encountered in films both of the peripheral blood, and especially of the spleen pulp. Yorke, Murgatroyd and Owen (1929–30), 360.

Phagocytosis in spleen

14–16. Q. taken.

16. 2 p.m. Hgburia; 7 p.m. spleen puncture.

18. Hgburia +, —. As Hgburia continued for 41 hours after the spleen puncture, presumably blood destruction was in active progress at the time.

Peripheral blood: Parasites neg. Splenic blood: Parasites neg. Pigmented leucocytes pos. Phagocytosis was proceeding in 2 kinds of cells:—

1. Large macrophages: 1·7% contained red cells.
2. Small phagocytes: 1·3% contained red cells.

Phagocyted red cells were: (1) unaltered, (2) more or less decolourized, (3) replaced by vacuoles, the vacuoles representing a further stage of 2.

Phagocytic cells.	Unaltered red cells.	Decolourized red cells.	Vacuoles.
Large macrophages . . .	3	10	22
Small phagocytes . . .	37	9	5
Total in 'the field' . .	40	19	27

In the peripheral blood phagocytosis was not very conspicuous—chiefly in the form of vacuoles in macrophages. No small phagocytes were found. Christophers and Bentley (1908[b]).

Blood. The Plasma

Acidosis

Day.	Serum						
	P. g., per 100 c.c.	N.P.N. mgms. per 100 c.c.	NaCl, g. per litre.	CO_2, Vols. %.	Red cells, m.	Hgb, %.	Bile Pig., mgms. per 100 c.c.
2	4·4	140	5·4				18·5
4	4·8	158	5·3	66·6	1·06	23	0·4
6	5·0	168	4·9	64·8			0·2
8	5·2	188	4·8	60·3	1·56	22	
11	5·3	215	4·4	67·0	1·68	22	
15	6·8	170	4·7	79·4	2·15	28	
22	7·8	65	5·8	55·0	2·58	33	
Normal	7·0	35	6·0	65	5·0	90	0·2

Day.	Urine, c.c.	N.P.N., g.	N.P.N., g. per litre.	P., g.	P., g. per litre.	Sediment.
1	47	0·2	3·6	1·4	29·2	Black-red.
2	12	0·1	3·0	0·3	28·3	,,
			Complete anuria for 5 days.			
8	130	0·6	4·2	3·0	23·1	Dark red, 2%.
	45	0·1	1·7	0·2	9·0	Amber, red cells ++ and casts.
	35	0·1	3·3	0·2	5·4	
9	34	0·1	3·0	0·2	4·0	
10	290	0·9	3·2	0·5	1·7	
11	925	2·9	3·1	0·3	0·9	
12	1540	4·8	3·2	2·1	1·4	
13	2740	9·4	3·4	1·6	0·6	
14	4330	16·1	3·7	1·7	0·4	

Of particular interest is the lack of any acidosis, the very small amount of Hgb actually excreted by the kidneys, the extreme rapidity with which the Hgb from the destroyed red cells disappeared, the extreme degree of N retention in the blood, followed by recovery and the striking impairment of renal function.

Less than 2 grammes of Hgb were excreted in the urine before the onset of anuria (urine protein output), and the concentration of serum protein was even less than normal (Serum protein, day 2). During the first week after renal secretion was re-established the N.P.N. concentration in the urine did not exceed 4 g. per litre, although the N.P.N. of the serum was over 6 times normal . . . the most striking evidence of actual toxic injury to the secretory cells. Wakeman (1929), 170.

CO_2—Combining power

1. 2 hrs after onset, CO_2 C.P. 49
2. 22 hrs. ,, ,, 48·5.
3. 48 hrs. ,, ,, 35

Normal 50–75

Cuba. In two cases the values are just below the lower normal limit. In the third case there was definite reduction

in the CO_2 C.P., and in this case urinary secretion was re-established when alkali treatment was used. Whitmore and Roe (1929), 62.

Van Slyke gives the following values for CO_2 bound as bicarbonate (alkali reserve):

Normal 73–53 c.c. of CO_2 per 100 c.c. plasma.
Mild acidosis 53–40.
Moderate acidosis 43–30.
Severe acidosis below 30.

Normal.	Acute malaria.	Blackwater.	Authority.
66·4	71·1	67·3	Ross (1932), 129.
65·6	62·6	62·6	
60·7	61·7	57·9	
59·8	61·4	56·0	
56·7	60·7		
56·1	58·9		
	58·9		
	57·9		
	57·0		
	56·0		
	55·7		
	55·1		
	Convalescent, malaria.	Convalescent, b.w.f.	
	62·6	64·5	
	59·8	63·3	
		58·6	

18 Feb. Parasites ++, Hgb 70%, urine: alb. —, 6 p.m. Q. 1·2 grains.

19. 6 a.m. Q. 1·2 grains, shortly afterwards Hgburia; 1.10 p.m. sod. bicarb. 3·9 g.; 2.55 p.m. 3·9 g., total bicarbonate given 43 g.

Blood.	Hgb, %.	Haematocrit.	N.P.N. mgm. per 100 c.c. whole blood.	Cl as NaCl, g. per litre.	Serum proteins, %.	CO_2, vol. %.
19. 3.15 p.m. .	62	37	31·5	5·8	7·6	61·1
21. 9 a.m. .	70	39	31·4	5·6	7·7	71·2
Normal data	85–90	45	25–35	5·7–6·2	7–8	60–75

	Urine, c.c.	Re-action.	Total N, mgm.	N.P.N., mgm.	Protein, g.	NaCl, g.
19. 10.15 a.m. .		A				
19. 7 p.m. to 20. 2.5 a.m. . .	690	a	8,810	8,720	0·562	1·89
20. 7 a.m. .	215	a++	2,458	2,360	0·613	0·35
Total . .	905		11,268	11,080	1·175	2·24
20. 7 a.m. to 21. 6.30 a.m. .	2475	a	12,800	12,200	3·75	1·90
21. 7 a.m. to 22. 5.30 p.m. .	2000	a, A	10,700	10,650	0·312	1·10

A = acid. a = alkaline.

The notable aspects of this case of b.w.f. are the rapid disappearance of Hgb from the blood and the absence of either acidosis or functional injury to the kidney. The low excretion of NaCl may be due to dietary factors. Wakeman and Morrell (1929), 6.

	CO_2, c.c.							Authority.
Cases.	3.	4.	5.	6.	7.	8.	9.	
Day 1	58	60	65	51 57				Fairley and Bromfield (1934–35), 148, 319.
2	45		64	49 43				
3					33	48	22	
4					55	53		
5					62	70		
6					73			
7					79			
	D.	R.	R.	D.	R.	R.	D.	

The figures are given in ' round numbers.'

The plasma bicarbonate shows a definite decrease, being 45, 43, and 22 c.c. CO_2 per 100 c.c. of plasma and 48 and 33 in two gravely ill patients who recovered.

Bilirubinaemia

Besides blood colouring matter the blood plasma contains bile pigment at least some time after the beginning of the attack. Plehn, A. (1903[b]), 520.

B.w.f. at Rotterdam. Blood serum, Oxy-Hgb bands in

minimal quantity. The green colour of the serum was striking. Hymans van den Bergh (1904). Janssen (1904), 215.

Icterus is associated with the existence of an intense yellow colouring of the serum, but not with the presence of bile salts in the urine. Christophers and Bentley (1908[a]), 68.

Bile pigments appear to be present only after Hgbaemia has ceased. Le Moal found them together. Gouzien (1911), 21 (r.).

The blood serum gave a positive reaction for bile pigment during life in 4 cases, out of 7 examined. Arkwright and Lepper (1918[b]), 385.

Cases 49. Bile pigment 20. Deaths 16 of 20. Jaundice was also noted in other cases in which there was no bilirubinaemia. (Nitric acid test.) Dudgeon (1920), 209.

Bile pigment in 2 of 2 cases. The conjunctiva was icteric in one, the skin in the other. Paterni (1923), 544.

4 fatal cases with severe jaundice. Blood serum 4 of 4 positive, urine 2 of 4 positive. Thomson (1924[a]), 83.

Case.	Hours after onset.	Units (indirect).	Authority.
1	2	5·77	Whitmore and Roe (1929), 62.
2	22	11·19	
3	23		
4	6	5·19	
5	2½ days	4·17	
6	48		(Cobaltous sulphate standard.)
Normal		0–0·6	

The physiological maxima adopted by different observers vary from 0·6 to 2·0 units, i.e. 0·3 to 1·0 mg. per 100 c.c. Fairley (1930), 145.

Day.	Direct.	Indirect.	Units.	Authority.
1	+	+	3	Yorke, Murgatroyd and Owen (1929–30), 343.
	−	+	1·5	
2	−	+	1·2	
3	+	+	3	
4	+	+	3	
5	+	+	2	
	Recovery.			

Day.	Non-fatal cases.	Non-fatal, long continued, relapsing.	Fatal cases. Early toxic.	Fatal cases. Suppression.	Authority.
	Indirect units.	Indirect units.	Indirect units.	Direct units.	
1	4·4	6·2	6·5		Ross (1932), 143.
	5·7	11·4	11·1		
	7·4		13·0†		
	8·2		28·0*		
	9·1				
	10·1				
	10·4				
	11·6				
	16·0				
	21·6				
2	7·3	7·2		36·0	
	9·1				
	20·3				
3	5·1			18·4†	
4				27·0	
				36·0†	
5					
6				18·5†	
	14 cases	3 cases.	4 cases.	5 cases	

* Biphasic reaction.

† Approximately. Excess of Hgb in plasma interfered with test.

Cases.	2.	3.	4.	5.	6.	7.	Authority.
Days.	Units.						
1		27	7	10	20		Fairley and Bromfield (1934–35), 148, 319.
2	20	85	5	3	15		
3	24		2				
4	26			1·5		9	
5	9		3			9	
6	6					7	
7	2					4	
	R.	D.	R.	R.	D.	R.	

Bilirubinaemia (malaria)

Spleen not enlarged.			Spleen reaches costa.		Spleen ⅓ distance to umbilicus.		
Parasite.	Cases.	Average units.	Cases.	Average units.	Cases.	Average units.	
P. malariae .	2	·45	5	·8	1	·7	Table I.
P. vivax .	19	·9	20	1·4	5	1·8	
P. falciparum .	26	1·5	54	1·7	15	3·0	
P. malariae .			1	1·75			Table II.
P. vivax .	4	2·9	5	1·7			
P. falciparum .	4	·8	8	2·1	3	·9	

Table I. Bilirubin units are greatest for *P. falciparum*. The number of units in the case of each species increases with the size of the spleen.

Table II. The data of Table I are not confirmed. Kingsbury (1925–26), 462.

Units.					
0–1.	1–2.	2–3.	3–4.	4–5.	5+.
·25	1·0	2·0	3·1	4·0	6·0
·4	1·0	2·2	3·2	4·0	6·0
·6	1·1	2·5	3·2	4·0	6·4
·6	1·1	2·6	3·2	4·6	6·8
·75	1·2	2·6	3·2	4·7	7·2[d]
·9	1·2	2·8	3·5	4·8	8·8[d]
	1·4	2·8	3·6		
	1·4				
	1·4				
	1·5				
	1·5				
	1·6				
	1·8				
6 cases.	13 cases.	7 cases.	7 cases.	6 cases.	6 cases.

[d] = direct action.

1. Day after admission 3·5 units, parasites positive, Plasmochin given, parasites negative. Quinine

given, 10 hours later Hgburia, 6 hours after the passage of Hgburia 6·0 units.

2, 3, 4. As the bilirubin units were high, the urine was examined. Hgb *positive* in all (benzidine test), negative to spectroscope. Ross (1932), 139, 146.

Vide p. 218.

Bilirubinaemia (malaria) and Quinine

Case.	Initial units.	After 24 hrs.	After — days.	Days.
1	1·0	1·6		
2	1·7	2·1		
3	2·0	2·5		
4	0·6		0·3	3
5	2·5		0·7	4
6	0·6		0·2	9
7	2·4		0·6	8

Cases of *P. falciparum* (spleen *negative*) treated with quinine. There is an initial rise followed by a fall in the bilirubin values. It would appear that the initial rise is secondary to the haemolysis of infected corpuscles by the action of quinine. 468, 472.

In one example cited the Van den Berg units on admission were 3·5. After plasmoquin and quinine, Hgburia followed in 10 hours. The Van den Berg units rose to 6 +. 459. Kingsbury (1926–27).

In a small series of cases of malignant tertian malaria quinine was found to have the effect described by Kingsbury of first causing an increase in the degree of bilirubinaemia, which was later followed by a decrease. Generally speaking, it was found that results tended to be higher in those cases receiving quinine, but one case in which no Q. had been administered showed as much as 4 units of bilirubin. Ross (1932), 139.

Calcium

Case.	Calcium.		Authority.
	Hours after onset.	Calcium, mgms. per 100 c.c.	
1	2	10·4	Whitmore and Roe (1929), 62, 63.
2	22	8·7	
3	6	10·0	
4	60	9·5	
Normally		9–11	

Case.	Cholesterol.			
	Hours after onset.	Cholesterol, mgms. per 100 c.c.	Lecithin, mgms. per 100 c.c.	
1	2	178	282	Bloor's method for cholesterol.
2	22	114	149	
3	23	182	237	
4	6	150	195	
5	2½ (days)	125	171	
6	48	160	290	
Normal		160–200	240–300	

We do not attach any significance to the low lipid content of the blood in cases 2 and 5, as the other 4 cases are well within normal limits.

The blood was preserved in Cuba by addition of NaF. 10 mgms. per 100 c.c. blood, kept on ice, analysed 10–15 days later in Washington.

Cholesterol

Acute stage.	Total cholesterin	100	mgms.	per	100	c.c.
Convalescence.	,, ,,	116	,,	,,	100	,,
Present condition.	,, ,,	180	,,	,,	100	,,

Feyte (1932), 833.

Malaria.			Blackwater.			
Cholesterol, mgms. per 100 c.c.			Cholesterol, mgms. per 100 c.c.			Red cell count, m.
Case.	Blood.	Plasma.	Case.	Blood.	Plasma.	
6	200	148	1	234	200	
4	195	160	4	222	181	3·24
8	185	153	3	191	133	1·92
3	173	121	6	190		
2	166	129	5	178		
5	160	128	2	160	135	
7	153	106				
1	138	111	7	191	153	
10	132	114	9	121		
9	129	102	8	120		1·26
			12	210	186	
			11	173	128	
			10	143	108	
			10	114	75	2·74
			15	221	185	
			14	210	172	5·27
			13	186	166	1·91

Ross (1932), 132.

Cholesterol, mgms. per 100 c.c. Whole blood.						Authority.
Day.	2.	3.	4.	5.	6.	
1		68	81	71	77	Fairley and Bromfield (1934–35), 148, 319.
2		90	99	83	86	
3	102		109			
4	80		94			
	R.	D.	R.	R.	D.	

The average value of eighteen estimations of the whole blood cholesterol in five very typical cases of b.w.f. was 86·5 mgm. per 100 c.c., minimum 68·0, maximum 109. A persistent hypocholesterolaemia exists in both fatal and non-fatal cases, not obviously influenced by blood transfusion.

Normal values are taken by some observers as 150–170 mgms. per 100 c.c. Ibid

Tananarive.		
Type of case.	Cholesterin, mgms. per litre.	Average.
Moderate	870, 750, 700	773
Severe	370, 350, 300, 250, 200	294
Fatal	Traces or nil before death	
Dakar.		
Rapid recovery . . .	1000, 800	
Fatal (acute stage) . .	350 (trace only before death)	
Fatal	780 (not in the late period)	

During convalescence the values may reach 2000 to 2100, thus exceeding the normal values 1700 to 1500 mgms. per litre.

Relation to blood urea.	
Cholesterin, mgms. per litre.	Urea, mgms. per litre.
200–370	1700–7000
700–1000	400–600

With low cholesterin values high urea values are got. Dufour (1933), 521.

Case.	Day.	Hgb-uria.	Cholesterin, mgms. per litre.	Dakar. Remarks.
2	2	+	1200	No fall in value.
	5	—	1200	
3	2	+	1500	Normal values. Death 20 days from onset (cirrhosis of liver).
	7	—	1500	
4	2	+	1500	
	8	—	1800	Red cells 1·5 m.

The following values are taken:—Below, —1200; normal, 1200–1600; above, + 1600 mgms. per litre. Robert (1933), 522.

Complement

6 tests in 3 cases (Noguchi technique).

The duration of the intervals and the end of a Hgburic period are not primarily determined by the disappearance of complement. Menk (1927), 116.

Haemoglobinaemia

Patient at the height of the attack. T. 40·5°. Blood taken by a 'cup' applied to the thorax. To my astonishment I found not a single red cell unchanged. All that remained floated as pale discs of diminished size in the strongly stained plasma. The leucocytes also were very considerably diminished almost to complete extinction.

As regards the diminution in size, this was mainly observable in the thick edge of the cells, where were agglutinated with wonderful regularity. The same findings in 10 specimens. Heinemann (1885), 517.

3 Aug., 1894. 9.15 a.m. Q. 0·5 g.; 11 a.m. venipuncture, serum colourless, Hgb neg.; 12.15 p.m. T. 39·7°, P. 133, R. 60 (time of Hgburia ?); 5 p.m. blood serum reddish, Hgb bands positive. Murri (1896), 116.

Two cases of b.w.f. examined during the attack. Serum was obtained by applying 'cups' to the scarified lumbar region. The cups contained a little normal serum to prevent any alteration of the blood. The separated serum in each case appeared absolutely normal.

Case L. Oxy-Hgb bands of the same intensity as that of the serum of a control normal blood.

Case F. 1. Oxy-Hgb and Met-Hgb bands. 1st attack.
2. Oxy-Hgb. 2nd attack.

'There is then no Hgbaemia except the latent Hgbaemia which must accompany all malarial attacks.' 668.

The destruction of red cells can only take place in the kidney. 670. Berthier (1896).

Vide Pathology.

A case of b.w.f. at Rotterdam. Blood serum: Oxy-Hgb bands, Oxy-Hgb present in minimal quantity, the green colour of the serum was striking. Hymans van den Bergh (1904). Janssen (1904), 215.

Examination of the blood in b.w.f. has shown without exception the presence of true Hgbaemia, demonstrated by the centrifuging of blood received into hypertonic citrate solution; the serum after clotting has also always shown Hgb provided the Hgburia was still in progress, but in both cases the amount was usually small and more or less masked by the extraordinarily intense yellow coloration of the serum.

The amount of Hgbaemia in the serum exuded from the clot has not in our cases exceeded the amount shown by centrifuging the citrated blood.

Time after onset.	Serum.	Hgb Bands.
1. (*a*) 10 hours . . .	Deep yellow	+
(*b*) Next day . .	Lighter yellow	?
2. (*a*) 7 hours . . .	Deep orange	+
(*b*) Next day . .	Markedly yellow, orange tint	+
(*c*) Hgburia, neg. . .		—
3. 6 hours . . .	Markedly yellow, orange tint	+
4. (*a*) 4th day . . .	Characteristic orange tint	+
(*b*) 5th day . . .	Yellow	—
5. 2nd day . . .	Rosy red	+*

* Hgb = 3·75% (i.e. 3·75 c.c. of blood in 100 H_2O).

Christophers and Bentley (1908[a]), 73.

Day 3. Examination of blood on the slide showed very clearly an intense haemolysis. 17 (r.).

The absence or short duration of Hgbaemia is explained by some authors on the supposition that the Hgb is instantly fixed by the renal epithelium and only gradually eliminated. This would explain those cases where Hgburia persisted or was increasing while Hgbaemia was diminishing or absent. 69 (r.). Gouzien (1911).

Hgbaemia is almost never recognisable. Plehn, A. (1920), 322.

The blood withdrawn from a vein in a case of b.w.f. may show evidence of haemolysis ranging from a deep red coloration of the plasma to a faint tinging. The evidence of Hgbaemia rapidly disappears. Dudgeon (1920), 210.

The specimen of blood taken on admission (less than 12 hours after onset) was run into a dry tube and was allowed to clot. The serum which separated was dark red in colour. Patrick (1922), 452.

In 17 of 51 cases there was Hgbaemia. The colour of the serum varied in the positive cases from orange to faint pink, rose colour to deep rose red. The highest amount recorded was 3·2 per cent. (of normal blood?) the serum being a dark red in colour.

Examination of the same cases later on showed that the Hgbaemia quickly disappeared from the blood. Thomson (1924[a]), 76.

In two cases blood was withdrawn within two hours of the onset and showed Hgbaemia, the serum being bright rose pink; this condition rapidly disappeared. Manson-Bahr (1926–27), 413.

Day.	Case 2. Hgb % in terms of blood.	Case 3. Hgb % in terms of blood.	Day.	Case 2. Hgb % in terms of blood.	Case 3. Hgb % in terms of blood.	Authority.
1	2·1	·44, ·5	5	·5	·134[M]	Yorke, Murgatroyd and Owen (1929–30).
2	1·25	·44	6	·51		
3	·5	1·1[M]	7	·15	0	
4	·125	·25[M]				

M = Met-Hgb also present.

In severe cases of the disease there never was any doubt about the presence of Hgbaemia, but in the less severe cases it was, in many instances, difficult to satisfy oneself that Hgbaemia much in excess of normal was present. More-

over, the phenomenon was usually of short duration in uncomplicated cases. Ross (1932), 107.

In hepatic blood

1. Hgburia present.
   Peripheral blood: Hgb slight, undeterminable.
   Hepatic blood: Hgb 10% (Haldane Hgbometer). Brahmachari and Sen (1925–26), 340.
2. Hgburia present.
   Venous blood: Hgb very faint.
   Hepatic blood: Hgb distinct. Brahmachari (1925–26), 695.

Hgbaemia present in 5 of 5 cases at the beginning of the b.w.f. attack, but the duration was relatively short.

In 1 case, no greater Hgbaemia in liver blood. Kikuth (1927), 511.

and Met-Hgbaemia

The serum and citrated plasma were examined on the 1st and 2nd days. Both, on each day, were of a deep brownish crimson. The colour was due to methaemoglobin, probably with some oxyhaemoglobin and also to bile pigment. The patient was deeply jaundiced and died. Arkwright and Lepper (1918[a]), 140.

The spectrum obtained is oxy- or met-haemoglobin, or both may be present in the same sample of blood serum. Dudgeon (1920), 211.

Cases.	Oxy-Hgb.	Met-Hgb.	Oxy- + Met-Hgb.	Authority.
5	4		1	Arkwright and Lepper (1918[a]), 140.
18	6		12	Ross (1932), 109.
5	3		2	Yorke, Murgatroyd and Owen (1930).
7			7	Fairley and Bromfield (1934), 144.

Hours after onset.	Oxy-Hgb %.	Met-Hgb %.	Total Hgb %.*	Colour of Plasma.
4	1·4	1·3	2·7	Deep brownish red.
21½	1·35	2·26	3·61	
46	1·0	2·3	3·3	
4¾	0·83	1·33	2·16	Dark turbid brown.
16¾	0·20	1·66	1·86	Less brown and more yellow.
23	0·36	1·0	1·36	
40¾	0·13	1·0	1·13	
63¾	0·13	0·66	0·79	
22	0·26	1·33	1·59	Golden red to pale yellow.
47½	0·07	1·33	1·40	
15	2·48	2·66	5·14	Deep port wine colour.
19	2·15	2·66	4·81	
24	1·75	2·66	4·41	
35	1·16	3·33	4·49	
39¾	0·76	3·33	4·09	

* The Hgb of an oxalated blood in which the 'O capacity' = 18·5 c.c. is taken to be 100 % with a Hgb value of 13·8 g.

Fairley and Bromfield (1934–35), 146.

and Hgburia

Hgbaemia can exist for hours without a trace of Hgburia. We established the presence of 'ghosts' many hours before Hgburia and established also that the serum may have a reddish colour after the Hgburia has ceased. Murri (1896), 139.

Although the urine contained Hgb for 12 hours after the experiments were made, the patient's serum did not show any Hgb on separation from the blood clot. 25.

Observations were made on the 22nd, and there was still Hgburia on the 23rd (a few ounces only passed, showing Met-Hgb), though on both the 22nd and 23rd no Hgbaemia was to be detected by the spectroscope. 63. Stephens and Christophers (1900).

Day.	Hours after onset.	Colour of serum.	Hgbaemia.	Hgburia.	Authority.
1	10	Deep yellow	+	+	Christophers and Bentley (1908a), 74.
2		Lighter yellow	?	—	
1	7	Deep orange	+	+	
2		Yellow (orange)	+	+	
3		Less yellow	—	+—	
1	6	Yellow (orange)	+	+	
2				+—	
4		Orange	+	+	
5		Yellow	—	—	
2		Rosy red	+,3·75%*	+	
3		Ruddy yellow	+,1·5%*	+	
4				—	

* In terms of normal blood.

Day-time.	Hgb-aemia.	Urine, c.c.	Hgburia c.c. of red cells.	Remarks.
1. 11.30 p.m.	·65	285	4·1	The Hgbaemia appears to rise to a maximum (·95%) and then fall, and similarly the excretion of Hgb (calculated as red cells) rose to a maximum and then fell. Case 17.
2. 9 a.m.	·67			
3.15 p.m.	·95	1167	17·9	
3. 10.30 a.m.	·48	2207	4·2	
4.	·18	2535	1·8	
5.		1397	·8	
1a.	·16			The excretion of Hgb in the urine was rising while the Hgbaemia was falling. Case 3.
1. 6 p.m.	·57			
10 p.m.	·40	344	4·1	
2. 11.45 a.m.	·08	630	7·5	
3.	·08	1294	0·2	
4.	·08	1480	0·0	

Barratt and Yorke (1909a).

Hgburia.	Colour of oxalated plasma.	Hgb %* Varied from	to	Authority.
Before . . .	Dark orange	·16	·13	Barratt and Yorke (1909[a]), 73.
During . . .	Reddish tint	·95	·40	
During . . .	Dark orange	·30	·13	
Towards end . .	Dark orange	·20	·13	

* 1 % = 1 c.c. of red cells in 100 c.c. H_2O.

Case.	Time after onset.	Hgb-aemia.	Plasma or serum.	Authority.
8	Few hours after onset	—	S.	Arkwright and Lepper (1918[a]), 140.
9	Day 1	+	S.	
15	Day 1	+	P. + S.	
18	Day 1	+	S.	
6	Day 2	+	S.	
14	Day 4	+	P. + S.	
16	During an intermission	—	P. + S.	
1	A few hours before Hgburia ceased	—	S.	
7	,, ,, ,, ,,	—	S.	
10	,, ,, ,, ,,	—	S.	
4	After Hgburia	—	S.	

Day.	Colour of plasma and serum.	Colour of urine.	Day.	Colour of plasma and serum.	Colour of urine.	Author-ity.
1	Red-wine	Black	2	Red wine	Black	Menk (1927), 117.
1	Yellowish red	Black	2	Brown	Black	
1	Brown slight	Amber	2	Brown slight	Red	
2	Dark red	Black	2	Brown slight	Almost clear	
2	Brown-red	Black	2	Brown	Brownish	
2	Red wine	Black	2	Normal	Normal	
2	Red brown	Black	3	Brown slight	Black	

Cases 14. The urine sample was that most recently passed. In a fulminating case (death on the first day) the plasma and serum about 15 hours before death were of a dark red or ruby-red colour.

The benzidine test was positive for both plasma and urine in a dilution of 1 : 5200. Two controls were negative in 1 : 40 dilutions. Ibid.

Case 2.

Day.	Hour.	Hgb-aemia % in terms of blood.	Hgb-uria % in terms of blood.	Hour.	Hgb-uria, c.c. of blood.	Spec-tro-scope.	Remarks.
1			1·9		3·3	+	The Hgburia % increased up to nearly the end of day 2, when the total c.c. of blood fell to 1·3 c.c. and the percentage to 1·1 (112 c.c. of urine).
			1·9		5·0	+	
			2·6		3·7	+	
	10 p.	2·1	3·8	9 p.	5·5	+	
2			6·6		3·9	+	
			7·3		3·1	+	
	2 p.	1·25	10·7	4.30 p.	10·6	+	
			1·1		1·3	+	
3	5 p.	·5	Suppression				The Hgbaemia % fell from 2·1% to 1·25% while the Hgburia % was increasing.
4			·53		·6	—	
	2 p.	·125	·40	4 p.	·45	—	
			·35		·6	—	
5	4 p.	·5			1·2	—	
6	6 p.	·51			1·6	—	
7	6 p.	·15					

Case 3.

Day and hour.	Hgb-aemia. %.	Hour.	Hgb-uria, %.	Hgb-uria, c.c.	Day.	Hgb-aemia, %.	Hour.	Hgb-uria, %.	Hgb-uria, c.c.	Authority.
1			3·8	14						Yorke, Murga-troyd and Owen (1929–30).
10 a.	·44	11.15 a.	3·7	6·8	3			4·1	11·3	
			2·5	3·0				7·6	12·6	
			·5	1·5				6·4	14·1	
			·8	2·1				5·6	23·8	
9 p.	·50	8.40 p.	4·1	8·8	3.30 p.	1·1	4.30 p.	4·8	12·3	
								4·8	10·1	
2			2·2	2·7				2·6	6·3	
			1·8	1·7						
			5·7	10·4	4			1·4	4·9	
			3·0	5·1				1·6	6·3	
			3·2	4·9				1·0	3·2	
8 p.			3·2	4·4				·7	1·1	
8 p.	·44	7.45 p.	3·3	6·1	3.15 p.	·25	3.30 p.	·5	1·9	
			2·0	3·3				·3	·9	
								·2	1·1	

Summary.		
Hgburia, %.	Hgburia, c.c. of blood.	Remarks.
(1) 3·8 to ·8 (2) 4·1 to 1·8 (3) 5·7 to 2·0 (4) 6·4 to ·2	14 to 2·1 8·8 to 1·7 10·4 to 3·3 14·1 to 1·1	The Hgburia as judged by the % and the total c.c. of blood excreted shows a series of rises and falls.

Case 4.					
Day and hour.	Hgb-aemia, %.	Hour.	Hgb-uria, %.	Hgb-uria, c.c.	Remarks.
1 10.30 a. 7 p.m.	·21 ·1	10.30 a.	1·1 0	4·3 0	Day 1. Transient Hgb-aemia and Hgburia.
6	·2				
7			·2	1·2	Day 7 and 8. Relapse.
8 11 a. 6 p.	 ·57 ·25	 10.30 a. 8.20 p. 9 p.	·3 1·5	23·4 3·8 0 0 0	Day 8. 11 a.m. Hgbaemia ·57%, but no Hgburia up to 9 p.m.
9 Noon	 ·14	 Noon	·3 ·1	2·2 ·6 0	Day 9. Second relapse.

Yorke, Murgatroyd and Owen (1929–30).

Hgburia sine Hgbaemia

The serum was free from Hgb, but the Hgburia continued for 12 hours later. Stephens and Christophers (1900), 25.

While the urine in the bladder still contained haemoglobin, an increased amount of dissolved Hgb in the blood plasma was observed in most but not in all cases. Barratt and Yorke (1909[a]), 76.

Hgbaemia sine Hgburia

Hgburia present, a few hours later absent, but Hgbaemia present. Parsons and Forbes (1919), 379.

Day.	Case 1.		Case 2.		Case 3.		Case 4.		Remarks.
	Blood.	Urine.	Blood.	Urine.	Blood.	Urine.	Blood.	Urine.	
1			2·1	+	·5	+	·21	+	Hgbaemia as percentages of normal blood. S. = Suppression.
2			1·25	+	·44	+	·3, ·14	—	
3	·22	+	·5	S.	1·1	+			
4		—	·125	—	·25	+			
5			·5	—	·134	—			
6			·51	—					
7		—	·15	—					
8	·15	—							
9	·2	—							

Yorke, Murgatroyd and Owen (1929–30).

Case 4.			Case 5.			Authority.
Hours after onset.	Hgb-uria.	Hgb-aemia.*	Hours after onset.	Hgb-uria.	Hgb-aemia.	
43¼	+	1·13%	22½	+	1·59%	Fairley and Bromfield (1934–35), 147, 150.
47¾	—	+	38½	—	+	
63¾	—	·79%	47½	—	1·4%	

* 100% Hgb = 13·8 g. Hgb.

Hgbaemia and cell count

Case 3.				Case 4.				
Day.	Count in mill.	Hgb, %.	Hgb-aemia.	Day.	Time.	Count in mill.	Hgb, %.	Hgb-aemia.
1	3·62	72	·44	1	10.30 a.	4·20	82	·21
	3·45	70	·5		7 p.			·1
2	2·77	64	·44	2	2 p.	4·25	81	·3
3	1·58	36	1·1[M]		5.30 p.			·14
4	1·60	15	·25[M]	6	10.30 a.	4·26	81	·2
5	1·52	21	·134[M]	8	11 a.	4·40	77	·57
7	1·42	27	0		6 p.	4·41	77	·25
12	1·84	40	0	9				·14

M = Methaemoglobin also present.

Hgbaemia is expressed as c.c. of blood in 100 H_2O, e.g. 1 c.c. = 1%.

Case 3. The greatest destruction of red cells takes place between day 2 and day 3, viz. 1·19 millions. The highest Hgbaemia value, 1·1%, occurs on day 3.

Case 4. Day 1. Hgburia for about 2 hours. Days 7 and 8, Hgburia for about 10 hours. Day 9, Hgburia for about 5 hours.

There is a discrepancy between the cell count and Hgbaemia values. Yorke, Murgatroyd and Owen (1929–30).

Indican. *Vide* p. 668.

Lecithin. *Vide* p. 394.

Lipase

Various sera (? number) were examined for their lipase content, but no striking departures from the normal were found. Voigt and Voigt (1934), 235.

Meinicke turbidity reaction (*M.T.R.*)

No strongly positive, non-specific reaction was found in the 16 cases examined. Menk (1927), 117.

Non-Protein-Nitrogen (*N.P.N.*)

Case 1.		Case 2.		Case 3.		Case 4.		Authority.
Day.	Mgms. per 100 c.c.	Day.	Mgms. per 100 c.c.	Day.	Mgms. per 100 c.c.	Day.	Mgms. per 100 c.c.	
8	98	3	111[A]	1	39	1	30	Owen and Murgatroyd (1928), 509. Yorke, Murgatroyd and Owen (1929–30).
9	105	7	174	2	37	8	30	
15	72	11	207	3	56			
		14	206	4	65			
		20	148	5	66			
				7	41			
				12	40			

A = Anuria.

The blood and the urinary urea of Cases 1 and 2 show definite renal inadequacy. Ibid.

Case.	Hours after onset.	Mgms. per 100 c.c.			
		Non-protein N.	Urea, N.	Uric acid.	Creatinine.
1	2	61	40	3·6	1·1
2	22	71	38	6·0	1·3
3	23	49	23	4·5	
4	6	64	32	4·3	
5	60	149	72	10·4	3·0
6	48	182	125	9·1	6·0
Normal		25–35	10–15	1–4	1–2

An elevation of the non-protein nitrogen constituents of the blood might result from an increased catabolism of protein or a reduced capacity of the kidneys to excrete nitrogen. When the urinary secretion is fairly good, the nitrogen retention is mild; when the urinary secretion is scant, or there is urinary suppression, the nitrogen retention is more severe. These observations indicate . . . inflammatory changes in the kidney which interefere with excretion, and that an acute nephritis therefore exists. While Whipple (1927) says that acute nephritis (post-mortem) is not a constant finding, our studies indicate that there is always N-retention, even in cases in which the further progress is to recovery. Cuba. Whitmore and Roe (1929), 63.

Phosphorus (total blood)

Case.	Hours after onset.	Mgms. per 100 c.c.	Remarks.
1	2	35	Compare the two low whole blood values of Cases 5 and 6 with the high values for N.P.N. etc. of the same two cases. *Vide supra.*
2	22	34	
5	60	22	
6	48	24	
Normal		25–40	

Whitmore and Roe (1929), 62.

The inorganic phosphate content of the serum was not lowered in any of the cases investigated (? number). Voigt and Voigt (1934), 234.

Pigments

Brown pigment *

One of the peculiar features of the illness was the leaden grey colour of the skin and the mauve tinting of the lips and ears; another was the persistence in the plasma until the 11th day of a brownish pigment. Fairley and Bromfield (1934–35), 152.

The naked-eye appearances of the blood and plasma, Case 7 (not 8), was chocolate coloured and the plasma brown.

The samples of serum (on day 5 and day 9) contain a peculiar Hgb derivative with a normal prosthetic group, but the globin portion of the molecule is undoubtedly modified. The spectrum has the general appearance of Met-Hgb, with the bands shifted, however, about 60 Angström units towards the short wave end of the spectrum. Although it does not reduce with Stokes' reagent, the compound contains a trivalent iron. It is easily reduced with sodium hyposulphite and gives a typical haemochromogen (globin-protohaemochromogen). It has no properties of Met-Hgb when tested with alkali, H_2O_2, H_2S, azide, etc.

The pigment at no time appeared in the urine. Fairley and Bromfield (1934–35), 308.

Greenish yellow

During the Hgburic period of a case of b.w.f. a greenish-yellow pigment found in the blood, suggesting bilirubin, but giving none of the known chemical reactions of bile pigments. Giemsa (1908), 81 [181].

* Pseudo-Met-Hgb. *Vide* App. 26.

Reaction (*p*H)

Various sera (? number) at various stages examined as to their *p*H. In many cases there appeared to be a tendency to an acid reaction.

Acidosis appears to be a secondary development dependent on the intensity of the haemolysis and not a primary factor. Voigt and Voigt (1934), 236.

Sugar

In one instance sugar was present in the urine and amounted to 0·16 per cent. in the blood. Dudgeon (1920), 220.

Case.	Hours after onset.	Mgms. per 100 c.c.	Remarks.
1	2	57	* Was receiving intravenous glucose.
2	22	112*	The values in Cases 2 and 6 are not considered significant.
3	23	82	
4	6	113	Estimation by Benedict's new method.
5	60	107	Cuba.
6	48	128	Whitmore and Roe (1929), 62.
Normal		65–110	

Day.	Mgms. per 100 c.c.		Day.	Mgms. per 100 c.c.		Authority.
	Case 3.	Case 4.		Case 3.	Case 4.	
1		70	5	138		Yorke, Murgatroyd and Owen (1929–30).
2	148		7	118		
3	183		8		55	
4	228		12	117		

Urea

Day 3. Blood serum : Urea 0·53 g. per litre.
Day 4. ,, ,, ,, 2·04 ,, (Urine 17 c.c.)
Achard and Saint-Girons (1912), 753.

N. aet: 25. Saigon. Oliguria and Anuria. Death day 9.					
Day.	Serum.	Chlorides.	Urea, g. per litre.	Alb.	Sugar.
3	Deep green	5·85	3·78		
4	Green	4·91	4·67	78·90	
5	Less green	4·79	5·10		
8	Straw	3·27	5·77	82·70	1·0—
L.A. aet: 30. Saigon. Duration of Hgburia about 4 days. Recovery.					
2	Red	6·58	1·08		
4	Yellowish green	7·13	1·77		
6	Normal	7·21	0·47		
	Urine.				C.c.
2	Red	2·44	18·00	9·20	1400
3		2·04	23·00		1300
4	Clear	1·63	31·00	+	1400
5	Amber	3·96	24·50	+	1350
7	Brownish	5·72	14·00	Cloud	2000

Lahille (1915), 909, 913.

84 mgms. per 100 c.c., less than 12 hours after the onset of Hgburia. Patrick (1922), 453.

Cases.	2.	3.	4.	5.	6.	7.	8.	9.	Authority.
Day.	Mgms. per 100 c.c.								
1		175	66	79	180		124		Fairley and Bromfield (1934–35), 148, 319.
2	54	311	62	71	224				
3	44		41				150	372	
4	49		26	42		120	130		
5	30					219	98		
6	26					340			
	R.	D.	R.	R.	D.	R.	R.	D.	

An increase in the blood urea was observed in all patients varying from 54 to 79 mgms. per 100 c.c. in the three less severe cases and from 150 to 372 in the five severe ones.

Urobilinaemia

15 June, 1894. p.m. Hgburia.

16. 160 c.c. blood withdrawn from vein. Bilirubin and urobilin present in considerable quantity. Murri (1896), 116.

Day 2. Jaundice was marked. The serum was intensely yellow coloured and showed absorption bands similar to urobilin. Christophers and Bentley (1908[a]), 213.

Urobilinaemia has been recorded. Gouzien (1911), 21 (r.).

Xantho-proteic reaction

Vide p. 460.

Summary

Corpuscles

Red cell count : May fall to a million or less, and a fall of a million may occur in 24 hrs.

Regeneration : Among other signs is indicated by the appearance of normoblasts and an increase in the reticulocyte count.

Leucocytes : Much discrepancy exists in the values given for the absolute and relative counts, possibly dependent on the varying clinical condition.

Monocytes : An increase in the relative count is not uncommon but not always observed.

Lymphocytes : On the contrary, may be reduced.

Eosinophils : A low or negative value in the early stages is commonly noted.

Phagocytosis : Is a common early phenomenon.

Endothelial cells and plaques : Appear later.

Plasma

Acidosis : The plasma bicarbonate (alkali reserve) expressed in terms of CO_2 c.c. (liberated by acid) may in

certain cases show a definite decrease, e.g. CO_2 c.c. = 40, but again may be within normal limits.

Bilirubin : The values may range from normal to 80 + units in a fatal case.

Cholesterol : Hypocholesterinaemia is common, but not always observed.

Hgbaemia : The plasma may be deep port wine colour, or rosy red with a value of 3·75% expressed as c.c. of "normal blood," but again there may be little evidence of Hgbaemia. Nor is the relationship of Hgbaemia to Hgburia always a simple or parallel one.

Met-Hgb : Is commonly, but not always present with Oxy-Hgb, and may exhibit a higher % value than the latter.

N.P.N. : May attain a value of 200 + (mgms. per 100 c.c.) in cases of anuria, and in other cases a value above the normal, 25–35 mgms. per 100 c.c., is not uncommon.

CHAPTER 11

THE URINE

Albuminuria

Varies from 3·0 g. to 16·0 g. per litre. Bérenger Féraud (1874), 278.

Urine of the attack. 15 June.
Peptone, serum albumen 9 g. per litre, globulin, haemoglobulin.
Pigment: urobilin, no bile pigment.
Sediment: some hyaline casts, renal cells, leucocytes, no red cells. Murri (1896), 116.

The coagulum got by boiling urine—which an hour previously was free from albumin—with a few drops of acetic acid may fill more than $\frac{2}{3}$ of the test tube, and may fail completely in another ten hours. Its colour varies from that of dark café-au-lait to that of deep black coffee grounds.

Day and hour.	Urine, c.c.	Sp. gr.	Alb., g. per litre.	Hgburia.	Authority.
1					Plehn, F. (1898), 123.
2		1016–1020	2·5	+	
3	2021	16–18	3·0	+	
4	2260	15–16	0·9	+	
5	3428	9–11	0·6	+−	
6	2120	8–10	—	—	
7	(Death)				
1 8.30 a.	(Rigor)		+	—	Subsequent to the rigor two specimens of urine free from Hgb. passed. 129.
10.0 a.	151	1016	+	—	
12 n.	138	1012	1·2	+	
1 p.	150		1·2	+	
7 p.			—	—	
2 2 a.	(Rigor)			+	
6.45 a.	670	1014–1021	+	+	
6 p.			—	—	

The duration of Hgburia can be longest followed, by the brownish tinge of the precipitate got by boiling with acetic acid. A part of the coagulum collects on the surface of the urine and on cooling forms a solid plug.

Occasionally, too, the abundant coagulum will dissolve again readily on adding more acetic acid or by longer boiling. Plehn, A. (1896), 12.

Albumen, g. per litre.					
Day.	22.	28.	37.	41.	42.
1	2, 3	2	1	2, 0·5, t	1·2
2	8, 5, 3·25	1·75, 0·40	2	0	t, 0
3	3, 1·25, 0·25	t, 0	4, 0·5, 2·5, 2		
4	0·25, t				
5	t				
6	0				
	44.	73.	73.	15.	41.
1	1·5, 2·2, 1·3, 0·5	2, 3	4		2, 3
2	t	3, 3, 2	1·5	2·5	3·5, 3, 2
3		2, 1, 0·3, 0·2, t	1, 0·75	·75, ·50	1, ·30, ·20, t
4		t	0·5	t, ·20	t
5		t	0·4	t	t
6		t	t		t

t = trace.

Gouzien (1900[a]), 22–73 (r); (1911), 15, 41 (r).

The albumen varies from a heavy trace to 75% by volume. Krauss (1904), 61.

Cases 14. The lowest maximum albumen was 15%, the highest 95% by volume. Brem (1906), 1996.

Case 7[a]. Suppression 9 days. Average urine 28 cc. Coagulable proteid, $\frac{1}{4}$–$\frac{2}{3}$ of a column.

Case 11. Suppression 6 days. Average urine 66 c.c. Coagulable proteid, $\frac{2}{5}$–$\frac{1}{2}$ of a column. Barratt and Yorke (1909[a]), 106.

Cases 24. In some instances 50% of the entire bulk of the urine. In one instance . . . it solidified. Woldert (1912), 636.

Cases 34. The average variation of albumen was from 0·5 to 2·5 g. to the litre . . . two with 14 g. to the litre. Deaderick (1914), 874.

Cases 17. In the darker specimens of urine, the coagulable protein . . . after standing 24 hours often occupied quarter to half of the test tube. Arkwright and Lepper (1918[b]), 386.

Albuminuria and Hgburia

	Case 10.	Case 11.	Case 12.	Case 13.	Case 14.
Fluid urine. Haemin crystals obtained when Alb. % was					
Alb. % . .	14	23	15	11	32
Sediment. Haemin crystals obtained when Alb. % was					
Alb. % . .	6	12	No sediment	No sediment	28

The supernatant urine usually fails to give a positive test before Hgb has disappeared from the sediment (Cases 10, 11, 14). In two other cases (Cases 12, 13) the reaction was obtained from the urine when no sediment was present after standing.

Albuminuria . . . always persisted for a variable time after the disappearance of Hgburia.

I have obtained a positive test for Hgb in only 1 case (Case 10) when the albumen was under 11 per cent., the sediment yielding the reaction when albumin was 6 per cent. 1996.

At times in a clear straw-coloured urine there was a small reddish-brown sediment which yielded abundant hemin crystals, practically all the Hgb being in the sediment. 1901. Brem (1906).

Day of Disease.	Case 10.		Case 12.		Case 13.		Case 14.		Case 11.	
	Hgb.†	Alb., %.	Hgb.†	Alb., %.	Hgb.†	Alb., %.	Hgb.†	Alb., %.	Hgb.†	Alb., %.
2			+	25						
3	+ + +	32 25 20	+ — —	15 10 5	—	10			+	50
4	+ + +*	14 7 6	+	50	— — —		+	50	— —	 10
5	+ — +	10 5 10	— —	5 10	— — —		+	70	—	5
6	— —	1 10 2			— +	 43	+ — +	30 22 40		
7					— — —		— + —	22 30 20		
8					—					
9					+ +	11 46				
10					—	10				

* In the sediment. † Formation of haemin crystals.

Brem (1906).

Day.	Alb., g. per litre.	Hgb, % in terms of normal blood.	Authority.
1 2 3	1·05, ·6 ·5, ·7, ·7 ·5, ·3	10, 6·6 6·6, 6·6, 6·6 ·5, 2·5	Christophers and Bentley (1908[a]), 71.

Day.	C.c.	Re-action.	Oxy-Hgb bands.	Alb., total g.	Alb., g. per litre.	Remarks.
1	154	Acid	+	1·69	11	Case 1 was more acute and severe than Case 2, which was more chronic and with a slower recovery period.
	84	,,	+	1·18	14	
2	280	,,	+	2·8	10	
	280	,,	+	1·4	5	
	196	,,	+	0·29	1·5	
3	392	,,	+	0·39	1	
	280	,,	—	0·21	0·7	
	236	,,	—	0·12	0·5	
	560	,,	—		t*	
1	168	Alkaline	+	0·67	4	Case 2. On the sixth day 8 p.m. a trace of alb. only was present, but this continued until the 24th day of examination. For the treatment of this case *vide* Sodium bicarbonate, p. 344.
	252	Neutral	+	1·51	6	
	142	,,	+	0·71	5	
	142	,,	+	0·85	7	
2	56	Alkaline	+	0·44	8	
	42	Acid	+	0·25	6	
	98	,,	+	0·20	2	
	112	,,	+	0·17	1·5	
3		Suppression				
4	112	Alkaline	—	0·11	1	
	112	,,	—	0·11	1	

t* = a trace which continued up to the 24th day of examination.

Owen and Murgatroyd (1928), 523.

Ammoniacal urine

18.11.93. Hgburia, urine passed in drops with acute pain, slightly alkaline, total urine 75 c.c.

19. 340 c.c.

20. 800 c.c., alkaline, yellowish-brown, turbid, much sediment of swollen fatty epithelium and mucus.

The cystitis lasted for 3 days, as shown by the ammoniacal smell and distinct alkaline reaction, convalescence being thereby retarded. Plehn, F. (1898), 141.

Case 15. Day 3. 100 c.c. by catheter, dark urine, smelling strongly of ammonia. Schellong (1890), 70.

Anuria

1. *Colour :* greenish straw yellow, frequently distinctly fluorescent.

2. *Albumen :* may be quite scanty, although barely 50 c.c. of urine passed in the day.

3. *Specific gravity :* is subnormal, once as low as 1005.

4. *Sediment :* structural elements of possible kidney origin are completely absent until eventually a freer flow results. An abundant sediment is usually rare also in oliguria.

5. *Mucus :* occasionally present, in the scanty secretion, arising in part from the epithelium of the lower urinary tract, and glands belonging thereto. Plehn, A. (1896), 13.

It is noteworthy that in spite of the small amounts of urine passed, not only does it become free from Hgb, but even that it may be free from albumen. This shows that the products of the haemolysis, failing a passage by the kidneys, are removed in some other way. Daniels (1901), 57.

8. Admission. Urine (by catheter), Hgb+, Alb 55%.

9 and 10. By catheter, minimum 30 c.c., maximum 450 c.c. in 24 hrs.

15. Hgb neg., Alb 2%, ranging between 2% and 10% until

19. Death. Brem (1906), 1899.

Day.	Case 7a.				Case 11.				Authority.
	Urine, c.c.	Sediment.	Oxy-Hgb.	Met-Hgb.	Urine, c.c.	Sediment.	Oxy-Hgb.	Met-Hgb.	
1	350	1/30	+		225	Much	+		Barratt and Yorke (1909a), 119, 220.
	45	1/15	+		140	,,	+		
	30	1/30	+						
	12	1/30	+	+					
2	15	Very slight	+		10	,,	+		
	1·5	,,	—						
3	3	,,	—		10	,,	+	+	
	15	,,	—		12	,,	+	+	
	3	,,	—						
4	11	,,	—		8, 40	Slight	+	+	
5	17	,,	—		72	,,	—	—	
6	33	,,	—		73	,,	—	—	
7	48	,,	—		92	,,	—	—	
8	41	,,	—		84	,,	—	—	
9	23·5	,,	—		8	,,	Death		
10	43	(Catheter)	Death						

1. *Colour :*—Pale yellow or amber.

2. *Coagulable proteid :*—Case 7a, $\frac{1}{4}$ to $\frac{2}{3}$ column. Case 11, $\frac{2}{5}$ to $\frac{1}{2}$.

3. *Specific gravity :*—Remarkably low. Case 7a, 1010–1015. Case 11, 1008–1009.

4. *Sediment* :—Extremely small in amount. Case 7a, consisted (1) chiefly of dark granular casts, just visible to the naked eye, 100–150 μ long, 40–60 μ broad. The granules were coarse, 5 μ in diameter, dark reddish brown, in their aggregated condition somewhat resembling blood clot. No fine or medium-sized granules. The casts frequently had an external epithelial envelope. (2) Masses of epithelial cells and single epithelial cells presumably of renal origin. (3) Red cells in small numbers in both cases. The casts continued for 8 and 5 days respectively. Barratt and Yorke (1909[a]), 104.

A history of urine ' red like blood ' on the previous day. On admission no urine passed. 36 hours later 4 oz. drawn off by catheter. The colour was dark greenish brown. It gave no bands, but on boiling with strong caustic soda gave the bands of haemochromogen (reduced alkaline haematin). Arkwright and Lepper (1918[a]), 136.

Day 5.

Colour : Hgb neg., cloudy amber; contained fibrin-like shreds.

Protein : On boiling went solid.

Sediment : Leucocytes and red cells.

In general, it resembled lymph or serum. Ross (1932), 183.

Bilirubinuria

Cases.	Positive.	Authority.
14	2	Crosse (1892), 89, 92.
35	1	Plehn, A. (1896), 14.
16 [5]	2 [1]	Plehn, F. (1898), 112.
7	1 [2]	Arkwright and Lepper (1918[b]), 385.
8	5	Gouzien, P. (1900[a]).
14	1	de Chazal (1908), 121.
?	1 [3]	Thomson (1924), 85.
86	4 [4]	Ross (1932), 191.

[1] Bile acids also present.
[2] Intense jaundice and suppression present.
[3] Severe jaundice present.
[4] All cases of suppression. Positive direct van den Bergh + 4 units.
[5] Cases with well marked icterus.

The urine of b.w.f. does not contain a trace of blood, but its very remarkable colour is due to a large quantity of biliary matter—bilirubin, bilifuscin and bile acids. This biliary matter is also found in blood flowing from the liver (blood obtained post-mortem from the vena cava above the entry of the vena portae). Bérenger Féraud and Trouette (1872), 1156.

I will not maintain that there is never bile as opposed to blood in the urine, I only have the right to state that for my part I have never found a trace of these colouring matters and cholesterin. Louvet (1876), 267.

Santiago de Cuba.

Case.	Blood.	Bile.	Casts.	Epithelial cells.	Pus.
1	+	+	+	+	
2	+	+	+	+	
3	+	+	+	+	+
4	+	+	+	+	
5	+	+	+	+	

Case 6. Diagnosis. Acute nephritis. The casts were not discoloured by bile as they are in malarial haematuria. Smith (1900), 190.

Day.	Case 1.	Case 2.	Case 3.	Case 4.	Case 5.	Case 6.	Case 7.	Case 8.
1	—	+	+	t, +	+	+	—	—
2	—	+	+	t	—	+	—	
3	—	+—	+		—		+	—
4	—	—	+				—	
5	—	—	t				—	—
6	—	—					—	

+ = present, — = absent, t = trace.

Gouzien (1900[a]).

Much more difficult of explanation is the fact that in spite of severe icterus and bile pigment in the blood plasma, bile pigment is usually absent in the urine. Plehn, A. (1903[b]), 521.

Bile colouring matter is always found; bile acids later. Krauss (1904), 61.

Usually present in small quantity and transitorily. Gouzien (1911), 24 (r.).

Bile pigment was only found in the urine in one of 7 cases examined (a fatal case of suppression), but the presence of a large amount of Hgb may have prevented the detection of a small amount of bile pigment by the ordinary tests (HNO_3 and iodine). Arkwright and Lepper (1918[b]), 385.

Case 38. Admitted with b.w.f. In extremis. Very severe jaundice with bile pigment in the urine. Death. Dudgeon (1920), 225.

Bilirubinuria and suppression

No. of cases.	Plasma units (direct).	Icterus.	Colour of urine.	Hgb.	Bile pigment.	Authority.
1					+	Arkwright and Lepper (1918[b]).
1*	+4			+	+	Ross (1932), 191.
3	+4	Increasing	Deep olive green	—	+	Ibid.
2†		Disappearing	Colourless	—	—	Ibid.

* Before oliguria became an urgent symptom.
† A few days before death.

Bile pigment has only been demonstrated in the urine in those cases of b.w.f. where the plasma has given a positive direct van den Bergh reaction of more than 4 units. Ross (1932), 192.

Bile acids

17.11.1891. Day 4. Icterus.

18. Hgb+, Bilirubin+, Bile acids—.

21. Hydrobilirubin++, Leucin and Tyrosin—, Bile acids—, Acetic acid—. Kohlstock (1892), 428.

In 2 cases with very intense icterus I have found bile acids as well as bile pigment. Plehn, F. (1898), 112.

Bile salts

Absent in urine. Gouzien (1911), 24 (r.).

Day 1. Hgb, Alb, Bile salts and pigment.
Day 4. Hgb+, Alb—, Bile pigment—. Mathieu (1931), 41.

In only one instance was an unequivocal positive reaction obtained. This occurred in one of the cases showing bile pigment in the urine. Ross (1932), 192.

Chlorides (g. per litre)

Day.	Case 1.	Case 2.	Case 3.	Case 4.	Case 5.	Authority.
1	3·2–2·3	3	2·8	3	5·4	Gouzien (1900[a]), (1911).
2	3·2	1·5	1·7	2·5	2·8	
3	1·5–0	0·5	1·8			
4	1·8–0	1·0				
5	0·6	0·7	3·4			
6		1·2				

Day.	Case 6.	Case 7.	Case 8.	Page 15 r.	Page 41 r.	
1	8·5	5	5		5·5	
2	11	1·2		1·53 *	1·2	
3		·75–·55	3·2	1·65, 2·30	·75, ·55	* NaCl.
4		·50		1·45	·50	
5		·55	1·7	2·16	·55	
6		·50		2·26	·50	

During b.w.f. and subsequent fever up to day 23, chlorides were markedly diminished and the sp. gr. was rather low. Ross, Thomson and Simpson (1910), 310.

The fall is very great. It is rapid, and the first analysis may show it, but usually the fall is at a maximum about the 3rd or 4th day. In two cases the value was 0·5 g. per litre. It rarely rises again to its normal value. Gouzien (1911), 23 (r.).

Case 1. 3 g. per litre. Case 2. 4·2 g. per litre. Paterni (1923), 543.

Chlorides (as NaCl) in early samples of urine.								
%	No. of cases.	%	No. of cases.	%	No. of cases.	%	No. of cases.	Authority.
0–·05	1	·21–·3	7	·51–·6	1	·81–·9	0	Ross (1932), 188.
·05–·1	2	·31–·4	5	·61–·7	0	·91–1·0	0	
·11–·2	11	·41–·5	3	·71–·8	1			

The highest value was NaCl 0·72%. The majority lay between 0·1% and 0·4%.

Restriction in diet and the taking of abundance of fluid of low chloride content are factors which might be expected to influence the chloride content, at least towards the end of the Hgburic stage. In the earlier stages the conditions may be different.

Percentage and total chloride (as NaCl) in 24 h. samples.										
Day.	Case 1.			Case 2.			Case 3.			Author-ity.
	Hgb.	NaCl, %	NaCl, g.	Hgb.	NaCl, %	NaCl, g.	Hgb.	NaCl, %	NaCl, g.	
1	+	·16	1·28	+	·17	1·38	+	·11	1·65	Ross (1932), 189.
2	+	·15	5·67	—	·26	·94	+	·09	2·2	
3	—	·42	5·98	+	·06	·68	—	·05	1·75	
4	—	·25	9·06	+	·06	·56	—	·06	1·37	
5	—	·44	9·5	+	·06	·50	—	·21	3·92	
6	—	·56	10·49	+	·04	·24	—	·51	10·38	
7	—			+	·04	·41	—	·54	11·12	

The low initial values are probably to be ascribed partly to the pyrexia and partly to restricted diet.

Urine immediately before oliguria developed.

Case 1. *p*H 6·2. Chloride ·42%.

Case 2. *p*H 5·6. Chloride ·50%.

These values are above the average, but higher values have been found in cases without oliguria.

Colour of Urine

Black

Seen in bulk appears to be black, but by transmitted light blood red. Barthélemy-Benoit (1865), 21.

It is quite black by reflected light, but in a glass by refracted light it is red. Pellarin (1865), 474.

Day 1. The urine looked almost black in bulk, bright red by transmitted light. Crosse (1892), 75.

Day 1. Urine 50 c.c. inky black. Boiling with acetic acid, deep black coagulum filling almost the whole tube. Plehn, A. (1896), 33.

The black colour is only seen by reflected light and in thick layer. If these black urines are freed by filtration from mucus and sediment they appear dark ruby red. Plehn, F. (1898), 110.

The change in colour of the urine from red to black may likewise be due to some action of the renal epithelium on Hgb. Gouzien (1911), 69 (r.).

Brown

The first urine passed may be light red or quite dark. In the latter case it often shows on the removal of the Hgb by acidifying and boiling a considerable amount of dark brownish pigment. The same brownish-yellow colour is sometimes seen in the urine passed at the height of the attack. 68.

22.1.08. After several days' convalescence, T. rose this afternoon to 100° and the urine became brown, but no urobilin could be detected. 197. Christophers and Bentley (1908[a]).

When a solution of Hgb is added to urine in amount sufficient to produce a light red coloration, . . . ultimately the whole of the Hgb is broken up, a brown soluble pigment remaining which gives no absorption bands. 51.

Red blood cells in urine whose sp. gr. exceeds 1·009 become, on standing, poorer in Hgb, and assume a darker somewhat brownish aspect, but are ultimately decolorised

and form a brownish-white precipitate. . . . If such urine is centrifugalised and the supernatant fluid examined, it is found that no Oxy-Hgb bands are at first seen, the red blood cells becoming decolorised without any laking of their Hgb. When, however, the red cells have lost 75 per cent. or more of their Hgb, Oxy-Hgb bands make their appearance in the urine, which is now brownish in colour. It is thus seen that in the red cell the Hgb is broken up and does not leave the cell until it has become completely converted into brown pigment. 51.

In red cells, whose Hgb has been largely destroyed, Met-Hgb is found, on laking, to be present. When the destruction exceeds 85 per cent. it is generally readily recognisable, though it is still found in much smaller amount than Oxy-Hgb. 57.

Day 1. On centrifugalising the first specimen of urine the supernatant liquid was found to be quite clear, of a dark brown colour without any reddish tint, and on acidifying and boiling gave about $\frac{1}{20}$ column of a light brown flocculent precipitate. 195. Barratt and Yorke (1909[a]).

Dark

Urines secreted after the administration of Q.

Out of 854 specimens analysed, 126 (i.e. 14·76%) were dark-coloured, which suggested the possibility of some disintegration product of Q. in the urine. They were therefore investigated for kynuric acid, since the latter is supposed to cause the dark colour of the urine of the dog, and also since the formation of kynuric acid from Q. could have been expected. 53 of 126 dark-coloured urine examined, in none was kynuric acid found. Nierenstein (1919[b]), 215.

Green

Day 5. Urine still deeply coloured with a greenish tinge suggesting the presence of bile; 1000 c.c. in 24 hours; treated with nitric acid showed presence of bile, not observed on previous days. Bérenger-Féraud (1874), 332.

Day 2. Greenish-brown red. 4 p.m., dark ruby red. 29.

Day 1. By reflected light black, by transmitted light dark ruby red, with a green fluorescence. 32.

Day 4. Urine 4 c.c. yellowish pale green. Boiling: $\frac{9}{10}$ coagulum. Casts negative. 33.

Day 4. Urine 45 c.c., greenish yellow. 41.

Day 6. Urine 24 c.c., greenish yellowish brown. Boiling: $\frac{1}{3}$ coagulum. 49. Plehn, A. (1896).

Day 3. Micturition very frequent. . . . Two of the specimens had a greenish reflection. Gouzien (1911), 14 (r.).

Day 8. Urine 17 c.c. greenish brown. Ross (1932), 218.

Opalescent

During convalescence, the urine sometimes becomes milky, while the deposit is reddish, resembling uric acid. Barthélemy-Benoit (1865), 125.

At the critical phase they may be opalescent or 'turbid,' due to phosphates or urates. Gouzien (1911), 8 (r.).

Porter-coloured

Day 4. 650 c.c., sp. gr. 1030, reaction slightly alkaline, colour porter-coloured, deposit $\frac{1}{6}$ column dark brown, no Oxy-Hgb bands. 195.

The first specimen of the urine (of the rabbit) after intravenous injection of dissolved Hgb was . . . porter-coloured in a layer two inches or more in thickness, and dark red or reddish brown in a layer one centimetre thick. 80. Barratt and Yorke (1909[a]).

It will be noted that two samples showed no absorption bands. This was in spite of the fact that the urine in both instances was porter-coloured. Ross (1932), 175.

Purple

In one case it was remarkable that the coagulum kept for some days in a plugged tube, took on a bright purple red colour. Plehn, A. (1896), 13.

Case 2. Boiled with soda, on cooling, the urine gave deep haemochromogen bands, indicating, probably, the existence of reducing substances in the urine. Stephens and Christophers (1900), 30.

After addition of strong NaOH a purple-red colour, due to haemochromogen or reduced alkaline haematin, appeared, which gave the characteristic bands in the spectrum. Arkwright and Lepper (1918[a]), 136.

Yellow

The urine in returning to its normal amber colour sometimes has a golden-yellow or a very pale greenish-yellow colour recalling that of serum. Gouzien (1911), 8 (r.).

Decomposition

Often shows little or no tendency to putrefaction and can be kept with but little change for a long period. Christophers and Bentley (1908[a]), 72.

Bonnafin and Firket have emphasized the fact of the length of time the urine remains unputrefied. Gouzien (1911), 22 (r.).

I have kept specimens of the urine, for several weeks, if not for months, apparently without a fetid odour occurring. Woldert (1912), 636.

The urine kept for 24 hours in bulk without turning putrid at all. The daily quantity was from 2100–2700 c.c. all along. Connal (1916), 15.

A notable feature is that the urine keeps fresh for a long period. Thomson (1924[a]), 86.

That the urine keeps fresh for a long period was certainly not true of the majority of urines examined. Ross (1932), 170.

Foam

At times it is sparkling and frothy, as if composed of pure blood. Barthélemy-Benoit (1865), 124.

Case 12. Beer-brown urine, strong foam, much albumen, Hgb. 67.

Case 13. Day 2. Urine porter-coloured, opaque, foaming. 68.

Case 15. Day 1. Urine porter-coloured, opaque, strongly foaming. 70. Schellong (1890).

Day 1. The urine in bulk looked nearly black, the froth had a dirty red tinge. 71.

Day 2. By transmitted light the urines all looked bright red, in bulk they looked nearly black, the froth being of a pinkish colour. 76. Crosse (1892).

Evening 8 p.m. icterus; bordeaux red, strongly foaming urine. Küchel (1895), 447.

The duration of Hgburia can be followed longest by the light brown colour of the precipitate got by boiling with acetic acid or by the finely vesicular froth. Plehn, A. (1896), 12.

In two cases the urine had a greenish tinge with yellow foam; the reaction for bile was positive. Brem (1906), 1996.

On shaking the urine readily produces a persistent reddish foam. Gouzien (1911), 8 (r.).

Freezing point

$\Delta = -6{\cdot}23°$. The salt content was 0·3%. The urine was non-haemolytic for the red cells of the patient or for those of a normal person, so concluded that the Hgburia was not a false one due to laking of red cells (haematuria) by the urine. van den Bergh (1904). Janssen (1904), 205.

Day.	Δ.	Chlorides, g. per litre.	Urea, g. per litre.	Urine, c.c.	Authority.
2	−0·68°	6·5	1·5	150–200	Achard and Saint-Girons (1912), 754.
4	−0·63°	3·5	7·2	17	
5			6·2	5	
6			6·2	5	

Haemoglobinuria

From this examination (formation of crystals with salt and acetic acid) one can conclude with Vogel and Neubauer that the urine contains dissolved blood or liquid haemato-

globulin, a mixture of haemoglobin and methaemoglobin. Monestier (1873), 820.

Je viens de faire un second examen sur des urines noires que m'a procurées M. Sérez et en presence de ce collègue. L'examen ne nous a laissé aucun doute : deux bandes de réduction très-nettes ont été constatées entre les lignes D et E de Fraunhofer, l'une plus large dans le vert, presque dans la limite du vert et du jaune; l'autre plus étroite dans le jaune, en se rapprochant de l'orangé. Ces deux bandes se rapportent bien à l'hémoglobine.

Les urines de la fièvre bilieuse hématurique, dans lesquelles les globules sanguins se rencontrent (morphologiquement) en si faible quantité, renfermaient donc la matière même de ces globules à l'état de dissolution. Corre (1878), 393.

Le 13 février jai soumis à l'examen spectroscopique et microscopique des urines bilieuses hématuriques qui m'avaient été procurés par le docteur Lartique : 1°. Au spectroscope, ces urines donnent, d'une manière nette les deux raies d'absorption de l'hémoglobine, plus une troisième raie d'absorption dans la partie du spectre comprise entre les raies B. et F. de Fraunhofer, et que je crois due à l'urobiline. Venturini (1880), 62.

The pathogenic agent inducing this form of malaria does not act primarily on the liver or kidneys, but on the blood, leading to a considerable destruction of red cells and liberation of Hgb, followed either solely by hemospherinuria (haemoglobinuria) or, when the destruction of red cells is greater, by haemospherinuria and haematogenous or haemapheic icterus. Consequently the fever called *bilieuse hématurique* represents only a more intense form of the fever commonly called *hématurique* (in all probability a malarial form truly haematuric does not exist), and therefore forms with this latter only a single form which rather should be called *fièvre hémosphérinurique palustre*. In regard to hemospherinuria as the principal cause of the characteristic colour of this fever, the author relies on these facts : the urine contained Hgb when it was black, blackish-red, or bloody;

and the quantity of Hgb varied with the depth of colour. The urine of the majority of his patients contained not the least trace of bile during the whole course of the disease, although the urine of one of them became totally black. As regards the rest, for the most part the urines showed least bile actually when they were blackish-red or black. Karamitsas (and Abstract) (1882), 969.

This absence of blood corpuscles is in my opinion satisfactory evidence that the colour of the urine is not due to Hge from the kidneys. . . . That the colour is due to the presence of Hgb is proved by spectrum analysis. Sternberg-Cochrane (1885), 596.

Day 2. Spectroscopic exam. Oxy-Hgb, urobilin, and a large dark band in the red indicating hematin. Boisson (1896), 376.

Day.	Case 21.			Case 20.			Authority.
	Urine, c.c.	Hgb as blood, %.	Hgb as blood, c.c.	Urine, c.c.	Hgb as blood, %.	Hgb as blood, c.c.	
1	310	2	62	60	10	6	Christophers and Bentley (1908a), 69.
	630	3	18·9	750	6·6	50	
	280	5	14·2				
	570	5	28·5				
	510	3	15·3				
	280	3	8·4				
	650	3	19·5				
2	510	3	15·3	550	6·6	37	
	310	2	6·2	550	6·6	37	
	300	5	1·5	350	6·6	23	
3				450	5·0	22·5	
				300	2·5	8	
			189·8			183·5	

The Hgb in the urine was estimated (1) by comparing the colour with that of a solution of known strength of red cells in water or (2) by boiling the acidified urine and comparing the bulk of the precipitate obtained on centrifuging with that obtained from normal urine containing a known quantity of red cells and similarly boiled and centrifuged.

By this latter method can be estimated both unaltered Hgb and also Hgb which had been broken up by the action of the urine. Barratt and Yorke (1909[a]), 137.

Day.	Case 3. Recovery.				Authority.
	Urine, c.c.	Hgb as red cells, %.	Hgb as red cells, c.c.	Oxy-Hgb bands.	
1	62	1·4	·86	+	Barratt and Yorke (1909[a]), 185.
	86	1·2	1·03	+	
	86	1·2	1·03	+	
	110	1·3	1·43	+	
2	105	1·3	1·36	+	
	165	1·3	2·14	+	
	125	·73	·91	+	
	82	·73	·59	+	
	210	·1	·21	+	
	203	·1	·20	+	
	135	1·0	1·35	+	
3	140	·1	·14	+	
	148			—	
			11·25		

Note.—The figures in column 4 have been calculated from the figures in columns 2 and 3. The figures in the original are slightly different. If it be assumed that corpuscles form about 40% by volume of normal blood—to convert the above values into normal blood, multiply by $\frac{5}{2}$, or by 2, if it be assumed that corpuscles form 50% by volume of normal blood.

Case 7a. Death on day 10. Ibid., 199.							
Day.	Urine, c.c.	Hgb as red cells, %.	Hgb as red cells, c.c.	Ppt. as red cells, %.	Ppt. as red cells, c.c.	Oxy-Hgb bands.	Met-Hgb bands.
1	350	·41	1·43	1·8	6·3	+	
	45				·99	+	
	30	1·1	·33	2·5	·75	+	
	12	1·2	·14	3·5	·42	+	+
2	15	·8	·12	3·5	·52	+	
	1·5					—	
			2·02		8·98		

Case 10. Recovery. Ibid., 211.

Day.	Urine, c.c.	Hgb as red cells, %.	Hgb as red cells, c.c.	Ocy-Hgb bands.	Met-Hgb bands.
7	285			−	
	257	·82	2·10	+	+
	198			−	
	198			−	
	198			−	
8	370	·8	2·96	+	+
	114	·8	·91	+	+
	171			+	+
	198			−	
	170			−	
	86	·3	·25	− ?	
	142			−	
	198			−	
9	198			−	
	114			−	
	142			−	
	142	·8	1·13	+	
	84	1·0	·84	+	
	98			−	
	57			−	
	170			−	
	170			−	
	114			−	
	85			−	
10	120			−	
	130			−	
	180			−	
	320			+	
	40	1·4	·56	+	+
	140	2·1	2·94	+	+
	60	1·0	·60	+	+
	200			−	
	150			−	
11	860 (total)			−	
12	150			−	
	170	·8			
	180			−	
	200	·6		+	
	940 (total)			−	
13	150			−	
	120			−	
	150			+	
	70	·6	·42	+	
	150	·6	·96	+	
	140	·4	·56	+	
	240			−	
	140			−	

Case 11. Death on day 9. Ibid., 220.							
Day.	Urine, c.c.	Hgb as red cells, %.	Hgb as red cells, c.c.	Ppt. as red cells, %.	Ppt. as red cells, c.c.	Oxy-Hgb bands.	Met-Hgb bands.
1	225 140	2·0 2·0	4·5 2·8	2·6 2·6	5·85 3·64	+ +	
2	10	2·0	·2			+	
3	10 12	1·5 0·5	1·5 ·06	2·1 1·0	·21 ·12	+ +	+ +
4	8 40					+ —	+
			9·06		9·82		

Case 14. Recovery. Ibid., 228.					
Day.	Urine, c.c.	Ppt. as red cells, %.	Ppt. as red cells, c.c.	Oxy-Hgb bands.	Met-Hgb bands.
2	86 710 460	4·5 4·25 3·0	3·77 30·17 13·80		
3	370 310 400 170	3·0 3·0 ·35 ·50	11·10 9·30 1·40 ·85	+ + +	+ + +
4	114			—	
			70·39		

Case 14a. Recovery. Ibid., 230.				
Day.	Urine, c.c.	Hgb as red cells, %.	Hgb as red cells, c.c.	Oxy-Hgb bands.
1	480	1·8	8·64	+
2	770	1·2	9·24	+
3	440 50 120	·5 ·25 ·40*	2·20 ·12 ·48*	+ + —
			20·68	

* Dark brown precipitate.

Case 17. Recovery. Ibid., 241.

Day.	Urine, c.c.	Hgb as red cells, %.	Hgb as red cells, c.c.	Ppt. as red cells, %.	Ppt. as red cells, c.c.	Oxy-Hgb band.	Met-Hgb band.
1	285	1·45	4·13			+	+
2	28	3·0	·84	3·5	·98	+	
	85·5	1·9	1·62	3·0	2·56	+	
	28	1·5	·42	2·5		+	
	171	1·3	2·22	1·3	2·22	+	+
	142·5	1·4	1·99			+	+
	142	1·4	1·98	2·5	3·55	+	+
	171	1·5	2·56	2·5	4·27	+	+
	228	2·0	4·50	2·5	5·70	+	+
	171	1·6	2·73	2·5	4·27	+	+
3	85·5			2·3	1·96	+	+
	70			2·3	1·61	+	+
	114	·5	·57			+	+
	57	·4	·22	2·0	1·14	+	+
	28·5	·3	·08	2·0	·57	+	+
	285	·25	·71	1·5	4·27	+	+
	142	·36	·51	2·0	2·84	+	+
	114	·25	·28	1·7	1·93	+	+
	256	·2	·51	1·7	4·35	+	+
	285	·15	·42	1·2	3·42	+	+
	228	·15	·34	1·2	2·73	+	+
	228	·10	·22	0·7	1·59	+	
	114	·10	·11	1·0	1·14	+	
	200	·10	·20	0·5	1·00	+	
4	342	0·1	·34	0·5	1·71	+	
	314	0·1	·31	0·5	1·57	+	
	400	0·1	·40	0·5	2·0	+	
	456	·06	·27	0·5	2·28	+	
	285	·07	·19	0·5	1·42	+	
	228	·05	·14	0·4	·91	+	
	170	·06	·10	0·4	·68	+	
	340	·05	·17	0·3	1·02	+	
5	170	·06	·10	0·4	·68	+	
	430	·05	·21	0·4	1·62	+	
	228	·06	·13	0·4	·91	+	
	256	·10	·25	0·4	1·02	+	
	85			0·3	·25	+	
	228			0·3	·68	+	
						−	
			29·75		68·85		

We have employed two methods of determining the Hgb in the urine, viz. firstly, the method depending on the estimation of iron, and secondly Arkwright and Lepper's (1918[a]), acid haematin method, which, provided that certain precautions are taken and that the readings are made in a colorimeter and not in tubes as recommended by these authors, appears to us to be useful and simple. Yorke, Murgatroyd and Owen (1929–30), 357.

Case 1. Recovery.						
Day.	Urine, c.c.	Hgb, mgms. %.	Hgb, mgms.	Hgb as blood, %.	Hgb as blood, c.c.	Oxy-Hgb bands.
1	154 84	2362 1964	3630 1650	16 13	25·4 11·6	+ +
2	280 280 196	1200 5400 300	3360 1512 588	8 3 2	23·5 10·6 4·1	+ + +
3	392 280 236 560	152 81 22 15	597 228 53 84	1 0·5 0	4·2 1·6 0	+ — — —
4 5 6 7	1316 1708 1316 1344	12 23 30 15	262 409 434 214			— — — —
					81·0	

The percentage of iron in Hgb is remarkably constant, . . . and it appeared therefore that . . . the degree of Hgburia might be derived from the chemical determination of the iron in the urine, due allowance being made for its normal iron content.

The Hgb of normal blood can be taken as 15 per cent. (15 g. per 100 c.c. of blood). Owen and Murgatroyd (1928). Yorke, Murgatroyd and Owen (1929–30).

Case 2. Recovery. Ibid.

Day.	Urine, c.c.	Hgb, mgms. %.	Hgb, mgms.	Hgb as % of blood.	Hgb as c.c. of blood.	Hgb bands.
1	168	220	471	2	3·3	+
	252	280	717	1·9	5·0	+
	142	370	526	2·6	3·7	+
	142	548	788	3·8	5·5	+
2	56	100	560	6·9	3·9	+
	42	1031	433	7·4	3·1	+
	98	1534	1514	10·8	10·6	+
	112	168	189	1·1	1·3	+
3	Suppression					—
4	112		84			—
	112		64			—
	168		86			—
5	870		169			—
6	784		228			—
					36·4	

Case 3. Recovery. Ibid.						
Day.	Urine, c.c.	Hgb, mgms. %.	Hgb, mgms.	Hgb as % of blood.	Hgb as c.c. of blood.	Hgb bands.
1	360			3·8	14·0	+
	180			3·7	6·8	+
	120				3·0	+
	300				1·5	+
	240				2·1	+
	210			4·1	8·8	+
2	120				2·7	+
	90				1·7	+
	180			5·7	10·4	+
	165				5·1	+
	150				4·9	+
	135			3·2	4·4	+
	180			3·3	6·1	+
	165			2·0	3·3	+
3	270			4·1	11·3	+
	165			7·2	12·6	+
	217			6·5	14·1	+
	420			5·6	23·8	+
	255				12·3	+
	210				10·1	+
	240				6·3	+
4	330			1·4	4·9	+
	390			1·6	6·3	+
	300			1·0	3·2	+
	150				1·1	+
	360				1·9	+
	300				·9	—
	420				1·1	—
					184·7	

The curves representing the amount and concentration of Hgburia show definite indication of at least four or five critical periods during the first three days of the disease. . . . This affords further support to the conjecture reached from study of the temperature chart, namely, that the attack of b.w.f. in this patient was built up of a series of crises, each of which was manifest by a sudden haemolysis. Yorke, Murgatroyd and Owen (1929–30).

Case 4. Ibid.						
Day.	Urine, c.c.	Hgb, mgms. %.	Hgb, mgms.	Hgb as % of blood.	Hgb as c.c. of blood.	Hgb bands.
1	360			1·1	4·3	+
	525				0	—
	165				0	—
7	510				0	—
	600				0	—
	600				1·2	+
8	780			3·0	23·4	+
	240				3·8	+
	180				0	—
	180				0	—
	360				0	—
9	720			0·3	2·2	+
	360				·6	+
	240				0	—
	480				0	—
	600				0	—
					35·5	

Time.	C.c.	Hgb, grams.	Hgb, %.	Remarks.
12.15 p.m.	140	1·15	·82	The % increases to the 4th specimen, then falls and rises again in the ninth specimen, then falls and rises again in the twelfth specimen. Ross (1932), 181.
1	230	2·53	1·10	
2	180	1·25	1·08	
4.30	155	1·81	1·16	
5.30	170	1·0	·60	
7.30	225	1·01	·46	
8.50	340	1·26	·37	
9.45	397	1·49	·37	
11.5	340	1·87	1·55	
12 mid.	342	1·22	·36	
1.30 a.m.	350	1·14	·33	
5.30 a.m.	511	2·75	·53	
17¼ h.	3380	18·48		

Hgb absent in first urine

12 Jan. 5 p.m. T. 102·8°. Q. grains 10 (+ grains 4 previously).

13. 7 a.m. very ill, jaundiced, urine bright yellow.
9 a.m. vomit bright green. Urine 9 oz. (255·6 c.c.), dark red. Crosse (1892), 95.

METHAEMOGLOBIN

Cases.	Oxy.	Met-Hgb.	Oxy- + Met-Hgb.	Authority.
21		20†		Broden, A. (1906).
11	3		8	Barratt and Yorke (1909[a]).
18	16	2	4	Fletcher, W. (1914), 33.
104*	56	6	40	Ross (1932), 174.
2			2	Paterni (1923).

* 2 specimens, porter-coloured, showed no bands.
† Not stated whether Oxy-Hgb present also.

Some c.c. of urine were boiled, giving a coagulum sufficient to colour a light brown an equal volume of sulphuric alcohol raised to a very high temperature. This reaction, according to Neubaüer, indicates methaemoglobin, and I do not think it could be interpreted as indicating bilirubin. Louvet (1876), 267.

The examination of the urine which I carried out at home (in Vera Cruz) using Heller's test, and inspection with a Zeiss micro-spectroscope, showed the presence of methaemoglobin. Heinemann (1885), 518.

30 Dec., 1895. 11.30 a.m. rigor; 1.30 p.m. T. 41·8°, icterus, vomiting, diarrhoea; 4 p.m. urine: micro-spectroscope, bands of Oxy- and Met-Hgb.

31. 7.30 a.m. death. Ferrier (1896), 323.

When fresh urine passed early in the disease is examined by the spectroscope the bands of Oxy-Hgb are well marked and can easily be reduced and reinstated by shaking, but the band in the red indicative of Met-Hgb is often very faint, and only becomes pronounced after the urine has remained

standing for some time. The condition in b.w.f. seems therefore to be essentially an Oxy-Hgburia, the formation of Met-Hgb being to a large degree a secondary process. Christophers and Bentley (1908[a]), 69.

Met-Hgb was also usually observed in the urine in relatively small amount. 176.

Present in 8 of 10 urines examined. A negative examination may be followed by a positive and *vice versa*. Oxy-Hgb persists longer than Met-Hgb. Barratt and Yorke (1909[a]).

Day.	Case 3.	Case 7[a].	Case 10.	Case 11.	Case 12.
1	$+^{O}$	$+^{O}$, $+^{OM}$	$+^{OM}$	$+^{O}$	$+^{OM}$
2	$+^{O}$	$+^{O}$, $-$	$+^{OM}$	$+^{O}$	$+^{OM}$, $+^{O}$, $-$
3	$+^{O}$, $-$		$+^{OM}$	$+^{OM}$	
4			$+^{OM}$	$+^{OM}$, $-$	
5			$+^{OM}$, $-$, $+^{O}$		
6			$-$, $+^{O}$, $-$, $+^{O}$		
7			$+^{O}$, $-$, $+^{OM}$, $-$		
8			$+^{OM}$, $-$, $+^{O}$, $-$		
9			$-$, $+^{O}$, $-$		
10			$+^{O}$, $+^{OM}$, $-$		
11			$-$		
12			$-$, $+^{O}$, $-$, $+^{O}$, $-$		
13			$-$, $+^{O}$, $-$		

Day.	Case 14.	Case 14[a].	Case 15.	Case 16.	Case 17.
1		$+^{O}$	$+^{OM}$		$+^{OM}$
2		$+^{O}$	$+^{OM}$	$+^{OM}$	$+^{O}$, $+^{OM}$
3	$+^{OM}$	$+^{O}$, $-$	$+^{OM}$	$-$	$+^{OM}$, $+^{O}$
4	$-$		$+^{OM}$, $-$		$+^{O}$
5					$+^{O}$, $-$

O = Oxy-Hgb. M = Met-Hgb. $-$ = No bands.

Barratt and Yorke (1909[a]).

A further band was usually seen in the red, but with the means at our disposal it was seldom possible to be certain whether this was due to Met-Hgb or acid haematin, for in acid urine Oxy-Hgb is soon converted into acid haematin. Arkwright and Lepper (1918[a]), 136.

When Hgb solutions were mixed with phosphate solutions of varying *p*H it was found that at a *p*H below 5·5 the solutions after 1 hour at 37° were brown in colour and contained Met-Hgb only, whereas at a *p*H above 6·5 the solutions were red and contained Oxy-Hgb only. Baker and Dodds (1925), 256.

*p*H.	Oxy-Hgb.	Oxy + Met-Hgb.	Met-Hgb.	No. of Specimens.
4·6	1			1
4·8	1	1		2
5·0	1			1
5·2		1		1
5·4	1	2		3
5·6		1		1
5·8	2	3		5
6·0	3	3		6
6·2	3	5		8
6·4		4		4
6·6	4	2		6
6·8	2	2		4

The table shows the *p*H values of 42 specimens of urine *freshly* passed and the pigments therein.

*p*H 5·4 or lower, 4 specimens show Oxy-Hgb, 4 Oxy + Met-Hgb. Above *p*H 6·0, 9 specimens show Oxy-Hgb, 13 Oxy + Met-Hgb. The figures show a degree of irregularity in striking contrast to the regular and graded results got when Hgb solutions are tested in various *p*H concentrations. Ross (1932), 175.

Haemolytic bodies

There was isolated from the urine in 12 of 13 cases of b.w.f. a quinine derivative, 'haemoquinic acid,' which haemolysed sheep and human red cells.

Cases.	Haemoquinic acid, g.	In — c.c. of urine.	Authority.
Malaria, with rigors .	·18	21,000	Nierenstein (1919[a], 1919[b]).
,, without rigors .	0	8,400	
B.w.f.	·36	5,090	
,, ...	·28	1,840	
,, ...	·32	3,370	

In 16 of 27 cases extracted from the urine by means of alcohol or acetone, haemolytic bodies active in dilutions of 1 in 10 and on three occasions in dilutions of 1 in 33, 1 in 40, and 1 in 50 respectively. (More potent extracts were obtained from the tissues, but the tissues of Malaria cases did not yield such haemolytic bodies.) Dudgeon (1920), 223.

Ketones (acetone)

19.3. Urine 150 c.c. black, then anuria.
24. By catheter a few c.c. of rosy urine, alkaline, albumen 8 g. per litre. Bands of haematin. Odour of acetone.
24/25. Death. van Campenhout and Dryepondt (1901), 78.

Days 2 and 3. An enormous quantity of acetone and showed the aceto-acetic reaction very markedly.
Day 4. Hgb negative.
Day 5. Acetone negative. Burkitt (1915), 1138.

The urine at times had a peculiar odour similar to acetone. Connal (1916), 16.

In 6 of 43 cases during height of Hgburia. Dudgeon (1920), 238.

In 2 fatal cases (oliguria-anuria). Paterni (1923).

Di-acetic acid

In 4 of 43 cases during height of Hgburia. Dudgeon (1920), 238.

Ketonuria most common in the toxic and fulminating type of case.

Example 1. 12 samples of urine passed in 17 hours. Samples 1–3 neg., samples 4–12 pos.
Example 2. Sample 1 neg., Sample 2 onwards until death pos.

A case of almost complete suppression lasting 9 days: A few hours before death urine pos.

Cases of moderate severity: Some samples of urine pos., some neg.

Of 11 cases of ketonuria, 6 were fatal.

Cases 94. Urine specimens 164. Ketonuria, 11 positive (28 specimens). Ross (1932), 185.

Osmotic tension (haemosozic index)

Case 19. First urine 1·25% (in terms of NaCl). Towards end of attack ·83%.

Case 27. First urine 1·28%.

These values are far above those at which red cells are haemolysed, viz. about 0·5% NaCl. Christophers and Bentley (1908[a]), 72.

Pigments

Abnormal pigment

Day 1[a]. Q. sulphate grains 15 at 10, 2, and 6 p.m.

Day 1. Q. sulphate grains 15 at 10 a.m. and 2 p.m.; 5·45 p.m. Hgburia. Duration of Hgburia 4¾ h., of urobilinuria 21 h. As the urobilin was disappearing an abnormal pigment not further investigated made its appearance, and coloured the ppt. produced in Schlesinger's urobilin test . . . a salmon pink—this phase lasted 32 h. Acetone and diacetic acid were absent. Ramsden, Lipkin and Whitley (1918), 247.

Blue pigment

A pigmented substance soluble in chloroform and exhibiting a dark band between C and D of the spectrum, in much the same position as the band of alkali haematin in the red, was frequently found in the urine of patients taking quinine. If the pigment was present, it was always found so long as the patient was excreting Q.

Whether its appearance depends on the presence of picric acid (used in the estimation of Q.) or not, is not known.

In the case of experiments on a healthy man it was found after intravenous, but not after oral or intramuscular Q. Present in one case of b.w.f. 2 months before and 10 days after the attack. Hele (1922), 266.

Haemochromogen

Vide p. 428.

Indican

All tests for indican were negative. Schellong (1890), 63.

Day 7. Urine brownish. Contains a considerable quantity of indican. Lahille (1915), 914.

Urobilin

During the blackwater period there was a marked degree of urinary urobilin, viz. day 1, 340 mgms.; day 2, 300 mgms.; day 3 (Hgb neg.), 115 mgms.; after which it fell to the low level of 30–60 mgms. a day. Ross, Thomson and Simpson (1910), 309.

Generally present, at least traces. Gouzien (1911), 25 (r.).

Malaria: When there was a heavy malaria infection . . . the urine had the characteristic colour of urobilinuria, that could be recognized from a distance. . . . From the naked-eye appearance . . . it would be possible at once to pick out cases with a heavy malaria infection. Hele (1922), 265.

The urine was diluted until the urobilin band (Schlesinger's reagent) was still just visible. If the urine had been diluted 10 times, its urobilin value was called 10.

Malaria: The value was 2–8, seldom 12. With the cessation of fever in 2–4 days, the reaction was negative or only a trace. If the value rose again to 2–3, a relapse could be predicted with fair certainty.

Hgburia: On the view that urobilin stands in relation with red-cell destruction, 16 cases with high urobilin values were regarded as suspicious of blackwater. No more quinine was given them. They all developed Hgburia after 10–20

hours. In 1 case the value was 250, in 14 cases 40 or more, and in 1 case 25. The attacks were all slight, lasting ½ to 1½ days. Icterus was present in all, but besides feeling ill and weak there were no other symptoms. Sörensen (1914), 159.

Day.	Hgb.	C.c. of urine.	Urobilin present in a dilution of *n* times.
3	+	135, 411, 295	640, 320, 320
4	−	300, 88	160, 320
5	−−++	350, 235, 150, 235	320, 320, 320, 320
6	+	60, 295, 175, 295	320, 10, 10, 10
7	+	325, 115, 295	80, 40, 40
8	+	95, 145, 295	40, 80, 40
9	+	235, 235, 350	160, 160, 10
10	+	200, 295	40, 20
11	−	165, 235, 165, 115	20, 20, nil, nil
12	−	589	nil

Marcussen and Hansen's test was used and the dilution at which the green fluorescence disappeared, determined. Ross (1932), 194.

The figure 640 in the last column signifies that the urobilin tint was still positive when the urine was diluted 640 times, and so on for the other figures.

Urobilinogen

Qualitative test :—Gives with Ehrlich's aldehyde reagent a red colour.

Quantitative test :—10 c.c. of urine are placed in each of two test tubes of equal diameter, and so chosen that the column of urine in each measures 7 c.m. To one tube is added 1 c.c., and to the other tube 0·2 c.c. of reagent. Warm slightly and allow to stand for about 5 minutes. To determine the 'end point' make dilutions of the urine, until a faint pink colour is just discernible on adding the reagent to the urine. Thus if this point is reached when the urine has been diluted 200 times, the quantity of urobilinogen is stated to be 1 in 200.

Normal data :—Varies from hour to hour and day to day,

from 0 to 1 in 30. Usually in greatest concentration in the afternoon. 464.

Urobilinogen and malaria

Parasite.	How infected.	Cases.	Urines.	Urobilinogen in excess.	%.
P. malariae	Naturally infected	2	23	6	23
	Induced	2	113	0	0
P. vivax	Naturally infected	5	27	10	37
	Induced	6	167	10	6
P. falciparum	Naturally infected	38	181	63	35
	Induced	2	47	29	62

Patients with parasites in the blood may pass urine free from urobilinogen. 486. Owen (1928).

Urobilinogen and blackwater

Day.	Case 1.		Case 2.		Authority.
	Oxy-Hgb.	Max. value.	Oxy-Hgb.	Max. value.	
		1 in 50*		1 in 50†	Owen and Murgatroyd (1928), 523.
1	+	1 in 250	+	1 in 10	
2	+	1 in 450	+	1 in 40	
3	+	1 in 300	Suppression		
4	—	1 in 100	—	1 in 175	
5	—	1 in 150	—	1 in 75	
6	—	1 in 30	—	1 in 60	
7	—	1 in 50	—	1 in 30	

* Max. value 1–3 days before b.w.f. † Max. value 1–2 days before b.w.f.

Urobilinogen and quinine

Parasite.	Cases.	No. of cases showing increase after Q. treatment.	Max. rise.
P. malariae . .	4	2	1 in 15 to 1 in 25
P. vivax . . .	7	6	1 in 10 to 1 in 750
P. falciparum . .	8	7	1 in 60 to 1 in 1000

The increased output (in the case of malignant tertian) occurs from 6 hours to 68 hours after the Q. treatment. In normal patients Q. does not produce a rise in the urobilinogen output. Owen (1928), 496.

Quinine in Urine

Case.	Date and time.	Q., g.	Hgb.	Urine, Q.	Date and time.	Hgb.	Urine, Q.
1	13 Oct. 5.30 a.	0·5			13 Oct. 11 a.	+	
	7		+	t	2 p.	+	
	8		+	t +	4–7.30 p.	+	Less
	9		+		8–7.30 a.	+	Very little
	10		+	Ppt.	9–8.30 a.	—	Neg.
2	6 Aug. 8.40 a.	1·0			6 Aug. 4.0 p.	+	t +
	9.40	1·0			5.0	+	
	10.20				6.0	+	
	11.25				10.0	+	t —
	11.35		+	—	7 Aug. 2.30 a.	+	t
	1.0 p.		+	t	4.35	—	—
3	11 Aug. 7.0 a.	0·25			11 Aug. 2.0	+	More
	8.0	0·25			4.30	+	More
	8.45				12 Aug.	—	—
	11.20		+	t			

Tomaselli (1897), 96, 119, 122.

Day.	Q.	Hgburia.	Q. in urine.	Remarks.
1[a]	+			The conclusion was drawn that Q. is not excreted during, but only subsequent to Hgburia.
1		+	—	
2		+	—	
3		—	+	

Marchoux (1904), 215.

I have never observed the complete cessation of excretion of Q. during Hgburia, but in many cases I have observed that the elimination of Q. was slight during the Hgburia, but rapidly increased as the urine cleared. Le Moal (1907), 280.

Day of Hgb.	Q., % excreted.						Remarks.
1ª		28	22			25	Q. hydrochloride 1·0 g. was given daily before the onset of Hgb-uria. In 3 instances the Q. excretion was determined on the day before (1ª) Hgburia. In b.w.f. the excretion of a given dose of Q. is on the average somewhat higher and lasts longer than usually is the case.
1	19+	4	8	21+	20+	3	
		21+	12+			19+	
2	5+	5+	6	5+	9+	11	
	7	4		6+			
3	3	5	4	t	4	3	
4	—	t	—	—	—	—	
Total	35	39	31	32	33	36	

+ = Hgburia present. — = No quinine. t = trace.

Giemsa and Schaumann (1907), 71, 83.

Day.	Time.	Q.	Hgb-uria.	Reac-tion.	Q. in urine.	Day.	Time.	Q.	Hgb-uria.	Reac-tion.	Q. in urine.
						1ª		+			
1	a.m.	0·5 g.				1	a.m.		+—		
	p.m.		+			2			+	A	
2			+	A	+	3			+	a	+
3			+	A	—	4			—+—		t

A = acid. a = alkaline.

Gouzien (1911), 15, 17 (r.).

Date and time.		Hgburia.	Q. grains.	Blood, Q. mgms. per litre.	Urine, Q. mgms. per litre.	Ratio : $\frac{\text{Q. urine}}{\text{Q. blood}}$
Attack 1.						
12.4.18.	2 p.m.		15			
	4 p.m.	+				
	6 p.m.	+	15			
	10 p.m.	+	15			
13.	12.30 p.m.	+—		13·3	12·5	0·94
Attack 2.						
24.5.18.	10 a.m.		15			
	2 p.m.		15			
	6 p.m.		15			
25.	10 a.m.		15			
	2 p.m.		15			
	5.45 p.m.	+				
	10.30 p.m.	+—				
26.	1 p.m.	—		1·19	18·68	15·6

The points of special interest in these two attacks are the low $\frac{\text{Urine Q.}}{\text{Blood Q.}}$ ratio during the first attack and the fact that even on the day after a second milder attack, this ratio, although showing a considerable return of the secretory power of the kidney, is still much less than it would be in any normal patient. Ramsden, Lipkin and Whitley (1918), 246.

	Hgburia.	Quinine in urine.	Authority.
26.*	+	+	v. d. Hellen (1919).
27.	+	+	
28. 5 a.m.	+	+ 1.40 p.m.	
11.45	—	— 4.45 p.m.	

* 24.1.19. a.m., last dose of Q.

Q. was excreted for 5 days (only a few hours longer than the duration of the Hgb), suggesting the possibility of Q. being stored by the red cells.

Blackwater fever.				Malaria.			
Case.	Alkaloid mgms. per 100 c.c.	Case.	Alkaloid mgms. per 100 c.c.	Case.	Alkaloid mgms. per 100 c.c.	Case.	Alkaloid mgms. per 100 c.c.
1	1·5	7	9	1	3	6	10
2	4	8	17	2	8	7	17
3	5	9	29	3	9	8	40
4	5	10	29	4	10	9	40
5	6	11	46*	5	10	10	60
6	9						

* Sample taken immediately the urine was free from Hgb.

The malaria cases were taking Q. 30 grains thrice daily.

The amount of Q. given previous to or during the Hgburia varied.

The samples of b.w.f. urine were samples of the mixed urines of 24 hrs. taken at the height of the Hgburia.

The quinine concentration may be sufficient to excite haemolysis of human red cells (in vitro). Dudgeon (1920), 233.

Case.	Q., g.		Q. given, hours before urine collected.	Q. found.	Expected, from normal men data.	Authority.
1	·79	O	23	·085	·108	Hele (1922), 262.
	1·06	O	14			
2	1·06	S	During collection	·232	·256	
	1·06	S				
3	·53	O				
	1·06	M	30	·228	·239	
4	·64	V	14			
	1·06	M	12	·217	·274	
5	1·06	M	9	·079	·092	
6	·53	V	(first 6 hours)	·013	·032	
7D	2·12	M	72	t	?	

O = oral. S = subcutaneous. M = intramuscular. V = intravenous.

Cases 7. In 5 the excretion of Q. was only a little less than normal. In 1 the excretion was less than half the normal. In 1 (suppression for 3 days) only traces of Q. in the urine in the bladder post mortem. Ibid.

500 mgms. of quinine injected just before the attack.

Sample.	Amount of urine in c.c.	Specific gravity.	Albumen.	Mgms. of quinine per 100 c.c.	Total mgms.	Hgb.	Bile.
1	80	1010	0·18	10	8	+	—
2	?	?	?	?	?	+	—
3	150	1010	0·36	50	75	+	—
4	420	1009	0·24	3	12·6	+	—
5	333	1008	0·12	2	6·6	+	—
6	400	1008	0·12	0	0·0	+	—
					102·2		

Kligler (1923), 205.

Day.	Time	Q. grains.	Hgb-uria.	Reaction.	Q. in urine (Tanret).	Day.	Time.	Q. grains.	Hgb-uria.	Reaction.	Q. in urine (Tanret).
1a	6 p.	15									
1	10 a.	15				1	10 a.	15			
	2 p.	15					2 p.	15			
	6 p.		+	A	−		6 p.		+	a	t
	8 p.			,,	+		7 p.		+	N	t
2			+	,,	+−+		8.30 p.		+	N	+
3			+−	,,	+		9 p.		+	N	t
4			−	,,	+	2			+	a, A	t − t −
5			−	,,	+−	3		Suppression			
6			−	,,	t−	4			−	a	−

A = Acid. a = alkaline. N = neutral. t = trace. 1a = 1 day before Hgburia.

Owen and Murgatroyd (1928), 523. Yorke, Murgatroyd and Owen (1929–30).

Day.	Case 1.			Case 2.			Case 3.		
	Q. *per os.*	Hgb.	Q.† in urine.	Q. *per os.*	Hgb.	Q. in urine.	Q. *per os.*	Hgb.	Q. in urine.
2a							15+15+15		
1a	15						15+15+15		
1	15+15			15+15					
		+	−+		+	t + t		+	+
2		+	+−+		+	t − t −		+	+ t − t + t
3		+−	+		Suppression			+	− t +
4		−	+		+*	−		+−	+−
5		−	+−		+*	−			−
6		−	−t−		+*	−			−
7									
8									
9									
10									

a = Before (ante). * = No bands. Case 2, Day 4 (Hgb as blood = 1·65 c.c. Day 5 = 1·2 c.c. Day 6 = 1·6 c.c. The figures o, o, o in the text are erroneous. Cp. Owen and Murgatroyd (1928), 524. t = trace. † = Mayer's test for Q.

Yorke, Murgatroyd and Owen (1929–30).

Day.	Q. *per os.*	Hgb.	Q. in urine.	Day.	Q. *per os.*	Hgb.	Q. in urine.	Authority.
3[a]	10+10+10			5		−	−	Yorke, Murgatroyd and Owen (1929–30), Case 4.
2[a]	10+10+10			6	10×2	−	t−	
1[a]	10+10+10			7	10×3	−+	+	
1		+−	+	8	10×3	+−	+	
2		−	+−	9	10	+−	+	
3		−	−	10		−	t−	
4		−	−					

Quinine and Mayer's reagent

In alkaline urine Mayer's reagent may fail to detect quinine present at a concentration well within its 'quinine end-point.' Field and Kandiah (1935), 384.

Quitinine

Is found in the urine *in the early stages* of the excretion of Q. Nierenstein (1919[c]), 218.

Q. in tissues

Date.	Total Q., base given, g.	Liver, g.	Q., mgms. per 100 g.	Hours after death.
4–7 Nov.[1]	11·13	2140	37 15	3 24
3–4 Nov.[1]	5·30	1640	15·6 12	3 24
23 Oct. (26 D.)[2]	2·12	1450	2·8	3

1 = malaria. 2 = b.w.f.

Hele (1922), 265.

Reaction

Usually acid, becoming neutral as the haematuria decreases. Barthélemy-Benoit (1865), 126.

When the urine contains much Hgb it is always alkaline, apparently due to admixture of blood salts. Plehn, A. (1896), 13.

The acidity is high, from 40 to 180%, expressed in terms of decinormal NaOH solution. Krauss (1904), 61.

Day.	Case 2.	Case 3.	Case 6a.	Case 7.	Case 7a.	Case 8.	Case 10.
1		a, n, a		a, a, a	a, n, a		A
2	n	a, n, a, n	A	A	a	A	,,
3	,,	A	A		a	,,	,,
4	,,	A	A		,,		,,
5					,,		,,
6					,,		A, n
7					,,		a, A, a
8					,,		A, a, A
9					,,		a, A
10					,,		a
11							A*
12							a, A, a, A
13							a, A, a, A
14							a, A, a

Day.	Case 11.	Case 12.	Case 14.	Case 14a.	Case 15.	Case 16.	Case 17.
1		a		a	A		A
2		a, A, a, A		a	A		A, a
3	a		A	a, n, a	n, a	a	a, A
4	,,		A		a, A	A	A
5	,,		A			,,	a, A

Transverse lines = cessation of Hgburia. A = acid. a = alkaline. n = neutral.

* No bands on this day. On other days also, the bands were intermittent.

Barratt and Yorke (1909a).

Day.	Case 1.	Case 2.	Case 3.	Case 5.	Case 6.	Case 13.	Case 14.	p. 15.	p. 41.	Authority.
1	a	a	a	n	A	a	n		a	Gouzien
2	a	a	a	A	A	a, A	a	A	a, A	(1900a),
3	a, A	n, A	a, A, a			A	A	A	A	(1911),
4	A, n	A	n, a, A				A	A		15, 41 (r.)
5	n	A	A				A	A		
6	A									
7		A								

a = alkaline. A = acid. n = neutral.

Usually acid, often hyper-acid, sometimes neutral or alkaline, especially at the decline of the crisis. Gouzien (1911), 22 (r.).

Cases 49. Neutral in 38, acid in 11. Weselko (1926), 658.

Day.	Case 1.	Case 2.	Day.	Case 1.	Case 2.	Authority.
1	A	A, n	8	A	a	Owen and Murgatroyd (1928), 523.
2	,,	a, A	9	,,	,,	
3	,,	Anuria	10	,,	,,	
4	,,	a	11	,,	,,	
5	,,	a, A, a	12	,,	,,	
6	,,	a	13	,,	,,	
7	,,	,,	14	,,	,,	

Rhodesia. When cases were excluded which were receiving alkali treatment it was found that the reaction was invariably acid or neutral to litmus.

Of 42 urines examined 33 had a *p*H value of between 5·8 and 6·8. The lowest value observed was 4·6. Ross (1932), 170.

El Centro, Colombia, S.A.

Cases 22. On admission. Acid, 16. Alkaline, 5. Neutral, 1. Paterson (1932–33), 542.

Specific gravity

During the attack 1014–1035, during remission 1012–1018, during early convalescence 1012, during established convalescence 1008. Bérenger Féraud (1874), 276.

Day.	Case 7.	Case 8[1].	Case 9.	Case 10[1].	Case 16.	Authority.
1	18			28	10, 9, 4	Plehn, A. (1896).
2	19	28, 24	6–7⁻	24⁻		
3	18	28⁻			9⁻	
4	18					

Day.	Case 17[3].	Case 18.	Case 22.	Case 23[1].	Case 24[2].
1	22, 12, 7	17, 6		11	20
2		24⁻		3⁻	12
3	19, 22⁻	29⁻	13		12
4			12		13⁻
5			11		12⁻
6					13⁻

Day.	Case 25.	Case 30.	Case 31.	Case 32.	Case 35.
1			12, 2⁻		15
2	17, 10, 12	22, 7, 12		10	8, 13
3	13, 14⁻				13, 11, 13
4					12
5					9

— = Hgb absent, but it is not always clear when Hgb ceased.
The last one or two figures only are given, thus 4 = 1004, 24 = 1024.

The sp. gr. varies within wide limits according to whether abundance of fluid has been taken previously or whether owing to vomiting this has been impossible. It does not exceed normal limits, with 1016 as a mean. Plehn, F. (1898), 110.

Cases 8. Sp. gr. ranged from 1006–1030. van Campenhout and Dryepondt (1901).

After the urine has begun to clear it may become colourless, with a specific gravity as low as 1002. Krauss (1904), 63.

Cases 18. Sp. gr. ranged from 1016–1028. Broden (1906).

The sp. gr. varies inversely with the quantity. Deaderick (1907–08), 29 (r.).

Day.	Hgb % in terms of blood.	Alb, g. per litre.	Sp. gr.	Authority.
1	10	1·05	1018	Christophers and Bentley (1908a), 71.
	6·6	·6	1018	
2	6·6	·5	1017	
	6·6	·7	1018	
	6·6	·7	1020	
3	·5	·5	1018	
	2·5	·3	1020	

Day.	Page 185.	Page 192.	Page 199.	Page 204.	Page 211.	Page 220.	Page 224.	Page 228.	Page 233.	Page 237.	Page 241.
1	10–13		20–32		22	17	15		15–26		20
2	13–23	15	10	8–14	16–24	17	6–15		16–20		12–15
3	12–16	15		5–22	18			14–26	15–18	16	5–14
4	16	15			3–22			14–20	26	15	9–12
5		17	12		2–20	8		16–24		15	10
6			10		10–20						
7			15		12–20						
8			14–15		13–22						
9			15–18		11–18						
10			15		2–16						
11					11–13						
12					10–13						
13					12–15						
14					8–15						

The last one or two figures only are given, e.g. 2 = 1·002, 20 = 1·020.

The transverse lines signify cessation of Hgburia. Barratt and Yorke (1909[a]).

May.	Hgb.	Sp. gr.	May.	Hgb.	Sp. gr.	May.	Hgb.	Sp. gr.	Authority.
16	— — + ?	1028 1033 1030	17	++ + +	1028 1025 1023	19	−+* —	1023 1022	Brem (1911), 179.

Hgb test = guiac and turpentine.

* Supernatant fluid neg., sediment pos.

It is usually a little raised during Hgburia and oscillates between 1020 and 1040 (normal 1018–1020). It falls on the contrary during convalescence. Gouzien (1911), 22 (r.).

Day 1. Urine very dark red, almost black. 6 p.m. to 6 a.m. 500 c.c. sp. gr. 1005. Alb. 1·75‰. Oxy- and Met-Hgb. Chlorides 3‰. Urea 19‰. Urobilin marked traces. Acetone abundant. Death (oliguria-anuria). Paterni (1923), 544.

24.5. 6 p.m. rigor T.

25. Vomiting, hiccough, nausea. Urine 250 c.c. (48 h.), dark red, sp. gr. 1041.

26. Urine 550 c.c. (24 h.), sp. gr. 1028. Perekropoff (1926), 287.

Cases 49. Sp. gr. 1012–1016 in 23, 1008–1009 in 15, 'normal' in 11. Weselko (1926), 658.

Cases 164. Sp. gr. corrected for T. 15° C. The range was from 1005–1033. In 9 cases less than 1009, viz. 5 cases 1008, 1 case 1006, 3 cases 1005. Ross (1932), 167.

Sugar

In 1 of 8 cases, a trace on day 2. Gouzien (1900[a]), 22 (r.).

Alimentary glycosuria present, indicating disturbance of liver function. Van den Bergh (1904). Janssen (1904), 216.

Exceptional. Present in 2 very severe cases, one of whom had alcoholic cirrhosis of the liver. Gouzien (1911), 24 (r.).

Urine, sp. gr. 1010, neutral, much albumen and some sugar. Boogher (1913), 1292.

In one instance (? of 49 cases) sugar was present in the urine. Dudgeon (1920), 220.

Toxicity

Haemoglobinuric urine is hypotoxic. Vincent (1900). Gouzien (1911), 23 (r.).

Urea (g. per litre)

Day.	Case 1.	Case 2.	Case 3.	Case 4.	Case 5.	Authority.
1	26–13	16		35–26	8	Gouzien (1900[a]), (1911), 15, 41 (r.)
2	15–12	14–8	22	37	6	
3	12–13	10–14	32–10		14	
4	20	14	11–13			
5	22	11	22			
6						
	Case 6.	Case 7.	Case 8.	p. 15.	p. 41.	
1	14–22	22–24	9		22, 24	
2	46	19	9	3·5	19	
3		17–26	10		17, 26	
4		24	11	17·93	24	
5		21	15	20·54	21	
6			17			

The values are given in round numbers. Two entries = max. and min. values for the day.

C.c.	Sp. gr.	Alb., g. per litre.	Urea, g. per litre.	Chlorides.	Hgb.	Authority.
	1020, 1025	12	32·34	Scanty	11%	van Campenhout and Drye-pondt (1901), 55, 58.
600	1021	7	7·32	Scanty	Oxy+Met.	
1100	1016	0·25	24·5	Less scanty	Neg.	
1170	1015	0·25	24·4	Abundant	Neg.	
Scanty	1021	4	14·44	Scanty	14%	
600	1021	1·5			Oxy+Met.	
500	1019	0·25	14·44	Abundant	Oxy	
1000	1023	0			Trace	
900	1023	Trace		Abundant	0	

The ordinary output of urea varies with the nitrogenous intake, and may range from 10 to 40 grammes per litre per

24 hours, but ordinarily it is about 30 grammes. Owen and Murgatroyd (1928), 520.

Day.	Case 2.		Case 1.	
	C.c.	Total urea, grammes.	C.c.	Total urea, grammes.
1	704*	4·36	238†	2·13
2	308‡	1·73	756	9·40
3	Suppression		1468‡	19·15
4	392	2·57	1316	20·57
5	870	7·71	1708	23·09
6	784	6·20	1316	16·98
7	980	8·32	1344	17·48
8	1222§	11·10	2123	24·57
9	1061§	12·57	1599	20·46
10	1473	15·73	2214	33·10
11	1008§	10·86	2214	24·60
12	1010§	12·48	2436	31·12
13	1516	20·08	2044	32·38
14	1428	20·28	2800	32·50
15	1904	28·56	2940	29·40
16	2128	31·92	2604	26·04
17	1848	30·50	2464	24·64
18	1680	30·24	2380	22·71
19	1792	28·67	2828	26·16
20	1400	21·00	2072	20·72
21	2380	34·51	2968	25·23

* Urine from 6–9 p.m. † Urine from 6–8 p.m.
‡ Last day of Hgburia. § Incontinence.

In view of the fact that fluids alone were allowed for the first week, the output for the first 30 hours (day 1, 6 hours; day 2, 24 hours (Case 2)) is the only one that can with certainty be said to be low. Owen and Murgatroyd (1928), 520.

Urea concentration test

Case 2.			
Four weeks after onset of Hgburia.	C.c.	% urea.	Total urea.
Immediately before urea, 15 g. . .	70	1·2	0·84
½ hour after	84	1·2	1·008
1 hour after	84	1·2	1·008
2 hours after	56	1·5	0·840

In Case 2 as the output of urea remained below 10 g. for the first 7 days, the above test was consequently done. It shows delayed and impaired renal function. Owen and Murgatroyd (1928), 521.

Normally, 1 hour after 15 g. of urea in 3 ounces of water the urine will contain 2–4% or more of urea. Maclean (1925), 1215.

Day.	Blood urea, g. per litre.	Urine, c.c.	Sp. gr.	NaCl, g. per litre.	Urea, g. per litre.	Uric acid, g. per litre.
4	5·85	15				
5	5·85	750	1006	2	7·51	0·27
6	5·35	1200	1005			
7	5·50	2200	1005		6·50	
8	5·85	3200	1005			
9	5·30	4550	1010	2	11·25	0·21
10	4·40	4450	1008		10·25	0·48
11		2780	1008			
12	4·60	2800	1008	2	17·54	0·46
13		4100	1006	1·6	15·33	0·44
14		4300	1005	·60	12·33	0·29
15		3250	1005	1·50	14·00	0·31
21	0·50					

Day 4. Blood: Indican and Xanthoproteic test (Becher) ++, Non-protein N 3·25 g. per litre, Uric acid 0·095. Urine: Hgb +, Bile pigment +.

Day 5. Urine: Hgb —, Bile pigment —, Indican —.

Day 7. Blood: Indican and Xanthoproteic test +.

Day 9. Blood: Indican and Xanthoproteic test weakly +. *Vide* p. 668. Georgopoulos (1933).

Water elimination

Day 10. 9 a.m. Patient drank 1500 c.c. of water.

Time.	Urine, c.c.	Sp. gr.	Time.	Urine, c.c.	Sp. gr.	Authority.
9.30	300	07	11.30	95	05	Georgo-poulos (1933). *Vide* p. 668.
10	60	07	12	50	06	
10.30	95	08	12.30	150	06	
11	90	06	13	100	06	
			13.30	100	06	
				1040		

Uric acid and Urea

In one case 1 part of uric acid to 10 of urea.

In another case 1 part of uric acid to 63 of urea. Woldert (1912), 636.

Viscosity

Forms a foam in the upper layers and froths easily when stirred with a glass bead. Stains the linen intensely reddish brown and the colour adheres to the chamber owing to the viscosity of the urine. Barthélemy-Benoit (1865), 21.

Day 1. p.m. urine rather darker in colour and of a thick consistence, frequent desire to pass water and some difficulty in micturition. Crosse (1892), 67.

Day 1. 7 oz. of a very dark and somewhat viscid urine. 'Africa' (1914), 7.

Day 3. I was passing only a very small quantity of urine and that of the consistency of thick jelly. 'Africa' (1914), 53.

Sediment

If the demand on this excretion (of haemoglobin) is somewhat increased or prolonged, there appears at once in the urine—up to this time a clear ruby red—peculiar flecks, forming a slimy sediment, of a brownish or greenish colour, and when the animals were killed, the same material was found in the tubules of the kidney. They are granular-glandular masses, precipitates, the substratum of which is passed partly through the glomerular vessels, partly through the epithelium of the tubuli contorti, and which, as soon as it has clotted, forms within the labyrinth a quantity of large casts. It is in this that we meet the chief danger of every intense Hgbaemia, viz. in the blocking of the numerous renal tubules with semi-solid masses, a damage to the tubules hardly with a parallel so far as I am aware, in human pathology. The tubes are filled, so to speak with wedged-in clots, threatening a sudden occasionally inevitable standstill of the whole excretory process. Ponfick (1883), 391.

Absence of

Day 2. 225 c.c. still darker; sp. gr. 1017. No visible deposit in reagent glass or on filtering. Boiling: coagulum ½. Plehn, A. (1896), 38.

Day 1. Urine black, Ox-Hgb ++, no deposit.

Day 2. Night urine clear, Alb. neg. Van Campenhout and Dryepondt (1901), 77.

Case 12. The test for Hgb was positive when there was no sediment.

Case 13. 10 a.m. Urine pale red, Alb. 11%, Hgb positive, no sediment. 2.40 p.m. Urine, dark portwine colour, Alb. 46%, heavy brownish red sediment. Brem (1906).

Amoebae

Day 1. Urine Bordeaux red, abundant, weakly acid, sp. gr. 1019–1023; in the sediment, swollen bladder epithelium and pigment masses, and small unpigmented amoebae which do not take the usual methylene blue stain. Plehn, F. (1898), 142.

In Anuria

The urinary sediment of the first urine passed after 5 days of anuria was made up almost entirely of large masses of a black amorphous tarry material yielding haemin crystals on boiling with acetic acid. Following this for a few days the urine contained many formed red cells and large Hgb casts. Wakeman (1929).

Bacilli

Case 1. ♀. Nossi-Bé, Madagascar. Urine scanty, blackish red, collected in a flamed glass. Microscopically renal débris (glomerular, tubular), epithelial cells and albuminous casts. Some few red cells. In the cells and renal débris there was also in enormous quantity, in pure culture, a very small bacillus. Gram positive, often showing bipolar staining. Cultured on gelatine.

Case 2. Nossi-Bé. Creole child. Sediment scanty,

formed chiefly of albumen casts and a pure culture of a small bacillus. Q. 0·75 g. given, 3 hours later rigor, high fever, black urine and a larger quantity of the bacillus, red cells in fair number.

Case 3. Officer at Val-de-Grâce, home from Monteil (Kong region). Hgburia. Urine showed the small bacillus in the epithelial cells and albuminous débris, forming small colonies. Yersin (1895[a]), 448.

Cases 2. A very small bacillus in compact masses in the glomerular cells and tubular débris. Pathogenic for rabbits and mice; giving rise to a septicaemia. Yersin (1895[b]), 51.

In the urine of 5 cases (recovery) and in the liver of 1 case (death) a cocco-bacillus found possessing all the characters of *B. coli*. Bréaudat (1896).

In 1 of 20 cases during and after the attack. Barratt and Yorke (1909[a]), 180.

In 1 (Case 4) of 18 cases. The deposit was composed of blood débris, bacteria and numerous desquamated cells. Fletcher (1914), 41.

Streptococci: present in the majority of urines. Ross (1932), 196.

West Africa.

Cases.	Stage.	Organisms.	Staphylo-cocci.	Strepto-cocci.	Various.
8	Active	8	8		1
13	Recovery	12	11	1	4
44	Controls	34	30	7	6

The concentration of bacteria was generally found to be higher in the b.w.f. than in the control cases. Gordon and Davey (1935).

Bilirubin (*haematoidin*)

Occasional Hgb clumps and dark brown Haematoidin crystals. Schellong (1890), 62.

Microscopic examination of the sediment shows abundance of swollen epithelium, sometimes fatty, from the urinary

passages, granular cells, détritus, Hgb masses, haematoidin crystals. Plehn, F. (1898), 111.

Case 3. Day 1. Attached to some of the casts were small masses of reddish crystals (? haematoidin). 34.

Case 4. Day 2. A few minute reddish crystals present (? bilirubin). 36. Stephens and Christophers (1900).

I frequently found bright red crystals of haematoidin. Woldert (1912), 636.

In some (of 18) cases needles of haematoidin were seen mixed with the yellow globules 1–2 μ in diameter, which gave the same staining reactions as red blood corpuscles. Fletcher (1914).

Calcium salts

Calcium phosphate, calcium oxalate crystals, granules of calcium phosphate rendering the urine alkaline and opalescent. Gouzien (1911), 26 (r.).

As regards the altered (decomposed ?) urine, it showed abundant crystals of calcium oxalate, probably in relation with the 'hyperlithie,' and *colourless* triple phosphates. 'In a urine which contains bile pigment, Beale, p. 252, says that crystals of ammonium magnesium phosphate have a yellow colour.' Louvet (1876), 260.

In one case of jaundice I found a vast number of dumb-bells of oxalate of lime in the urine. These dumb-bells were of an intense yellow colour, but the octohedral crystals which were also present were colourless. Beale (1864), 211.

Calculus

Day 3. Sediment slight; fatty granular casts. 'Calcul biliaire.' Gouzien (1911), 15 (r.).

Casts, etc.

1. Granular epithelial cells.
2. Granular epithelial casts.
3. Red cells, decolorized, deformed, most numerous in

first specimens, but scanty and not in proportion to the colour of the urine.

4. Phosphate crystals, but only in the last specimens.

5. Innumerable granules, some opaque and blackish, some colourless and transparent (bacteria).

6. Large nucleated granular spherical or oval bodies (algae).

7. Fusiform and septate spores of yeasts. Corre (1883), 148.

I am inclined to think that the broken-down products of the blood can be excreted without inflammation of the kidney, while in other cases, viz. by ineffective reaction on the part of the patient, severe nephritis can occur.

1. It can occur early—the urine has then a normal or raised sp. gr. and the sediment contains casts, or it occurs

2. Later, when the Hgburia has ceased or almost ceased; then the quantity of urine, up to this time perhaps abundant, diminishes, the sp. gr. rises to normal or higher, the volume of the yellowish-white proteid ppt. rapidly increases, and casts previously absent appear in the sediment.

This could be called ' Secondary Nephritis.' This usually clears rapidly under suitable treatment, and in a few days abundant quantities of protein-free urine of low sp. gr. show that complete convalescence has set in. Plehn, A. (1896), 13.

Day.	Case 1.	Case 2.	Case 3.	Case 4.	Case 5.	Case 6^1.	Case 6^3.	Case 7.	Case 10^2.	Case 11.
1	+			−+	−	−		−	−	
2										
3	+	+	−		+			−	−	
4			−				−	+		−
5			−							
6		−	−							

	Case 17^3.	Case 18.	Case 22.	Case 23^2.	Case 24^2.	Case 25.	Case 30.	Case 32.	Case 35.
1	+				+				+
2	−				+	+	+	−	+
3		−					−		+
4				−					+
5			+	−					
6				−					

Cases 40. Casts: present 13, absent 12, no record 15. Urinary epithelium: present 6, no record 34. Mucus: present 1, no record 39. Plehn, A. (1896).

1. Swollen tubular epithelium, partly fatty.
2. Granular cells.
3. Détritus.
4. Hgb clumps.
5. Casts covered with pigment masses—a regular occurrence.
6. Round cells, frequently.
7. Red cells, never found. When they occur they signify an accidental complication due to Hges in the pelves of the kidney.
8. Haematoidin crystals. 110.

A normal urine may show the above constituents in less than half an hour, and in the same time become normal again except for a trace of albumen. 112. Plehn, F. (1898).

	Present.	Absent.	No record.
Casts	4	12	14
Epithelium covered casts	5	0	25
Granular casts	4	1	25
Hyaline casts	8	0	22
Pigment covered casts	2	0	28
Granular cells	1	0	29
Epithelium	5	0	25
Bladder epithelium	12	0	18
Renal epithelium	4	0	26
Hgb crystals	1	0	29
Hgb débris	1	0	29
Hgb granules	1	0	29
Hgb masses	3	0	27
Pigment clumps	11	0	19
Pigment débris	1	0	29
Pigment granules	2	0	28
Granular débris	1	0	29
Amoebae	1	0	29
Mucus	9	0	21
Red cells	0	7	23

Plehn, F. (1898).

Casts persist longer (than the albumen) and an occasional one may be found weeks after the attack. Daniels (1901), 57.

Cases 16. Casts: present 7, no record 9. Epithelium: present 10, no record 6.

1. Granular casts.
2. Hyaline casts.
3. Casts covered with the brown granular substance.
4. A few leucocytes.
5. Epithelial cells.
6. No red corpuscles were found. Brem (1906).

1. Granular casts (so-called haemoglobin casts) and an occasional granular cell increasing in number later.
2. Amorphous débris.
3. Degenerated granular cells ; in many cases at the height of the Hgburia the deposit consists mainly of these (without doubt from the kidney). Christophers and Bentley (1908[a]), 71.

1. *Granular casts* 15–200 μ long by 3–25 μ broad. The granules are brown and imbedded in a hyaline matrix and in size equal 0·5 μ–4 μ. The casts may be hard and dry or soft and swollen.
2. *Granular débris* and casts together form up to a fifth of a column on sedimentation.
3. *Hyaline casts.* Less frequent than granular casts.
4. *Casts with one or more nuclei.*
5. *Epithelial casts.*
6. *Free cells* and *masses* from the uriniferous tubules.
7. *Red blood cells*, in 10 of 20 cases. 102.

In three cases they appeared only as the Hgburia was passing off. All these disappeared in 3–4 days after the Hgburia.

8. *Squamous epithelium* occasionally.
9. *Pus cells* in two cases; persisting after the Hgb cleared.
10. *Bacilli* in one case. 181.

Case.	Colour.	Quantity.	Renal casts.	Hyaline casts or masses.	Granular casts and masses or free granules.	Renal cells.	Red cells.	Pus.
3	Whitish	$\frac{1}{6}$	+		+ fine		+	
4	,,	Small			+			
9	,,	$\frac{1}{40}$			+			+
10	,,	$\frac{1}{10}$			+	+	+	
11	,,	Abundant			+	+	+	
12	,,	,,		+	+	+		
14	,,	Small	+		+	+		
16	,,	,,			+	+		
14[a]	Brownish white	$\frac{1}{40}$	+		+ coarse			
5	Brownish	Small		+				
6	,,	,,			+	+	+	
6[a]	,,	,,			+	+	+	
15	Brown	$\frac{1}{60}$	+	+	+			
7	Dark brown	$\frac{1}{6}$			+ fine	+		
7[a]	,,	$\frac{1}{15}$			+ coarse	+	+	
8	,,	Small			+	+	+	
2	Chocolate	$\frac{1}{4}$			+	+	+	+
17	,,	$\frac{1}{12}$	+		+	+	+	
1							+	

The amount of deposit diminishes with the Hgburia, but after the urine has remained free from Hgb as long as 3 days, casts may still be found in it. 100.

All the above formed elements disappeared completely within 3 or 4 days after the disappearance of Hgburia, except in two cases of suppression; in these casts or plugs continued for 8 and 5 days respectively until death occurred. 103. Barratt and Yorke (1909[a]).

Casts : epithelial, fatty granular, fibrinous infiltrated with granules, haemoglobin brownish, hyaline or mucous.

Epithelium : renal, ureteral and vesical.

Red cells : amorphous débris.

Leucocytes : abundant in cases (v. rare) of renal suppuration. Gouzien (1911), 26 (r.).

1. Granular casts cemented by some hyaline substance.
2. Granular détritus consisting of minute Hgb bars.

3. Hyaline casts.

4. Epithelial casts. Deeks and James (1911), 72.

Hyaline and granular. Cases 17. Present 7. Absent 10. Woldert (1912), 636.

1. Hgb casts, brownish yellow *always* present.

2. Débris in form of minute yellow globules, 1–2 μ.

3. Renal pelvic cells in some cases.

4. Haematoidin needles in some cases. Fletcher (1914), 33.

1. In the first specimens, deposit consisted chiefly of small yellow granules. In some cases larger yellow granules or globules 1–4 μ were also present.

2. About the second day renal cells containing yellow granules and casts packed with large yellow globules were often seen.

3. Cells and granules were usually found in decreasing numbers for 2–3 days after the urine had become normal.

4. The scanty urine of suppression contained no renal cells or casts as a rule. Arkwright and Lepper (1918[b]), 387.

	Present.	Absent.	No record.	Authority.
Granular casts . . .	2	1	4	Seyfarth (1918[b]).
Hyaline casts . . .	3	1	3	
Hgb casts . . .	2	1	4	
Bladder epithelium . .	2		5	
Kidney epithelium . .	1		6	
Yellow Hgb granules . .	2		5	
Yellow Hgb clumps . .	6		1	
Detritus	6		1	
Leucocytes . . .	3		4	

1. *Granular amorphous matter:* more frequent in early specimens than,

2. *Granular casts:* become more numerous as the disease progresses, persist for some time after the urine has cleared, when the granular matter is absent.

3. *Epithelial casts:* common.

4. *Hyaline casts :* occasionally, especially after Hgburia has ceased.

5. *Epithelial cells :* from various parts of the renal tract.

6. *Red cells :* 3 times only in several hundred urines.

7. *Spirochaetes :* absent.

8. *Streptococci :* in majority of cases. Ross (1932), 196.

Clots

Day 1. Passed bright red urine with considerable difficulty, probably owing to the fact that several stringy clots were present. Gray (1898), 23.

Crystals

Triple phosphates : Cases, 20. Positive, 7. Negative, 2. No record, 11.

Case 7[a]. Day 1. Present in first specimen of urine only.

Case 10. Present on days 6, 7 and 12.

Case 11. Present on days 6, 7, 8, 9. Barratt and Yorke (1909[a]).

Crystals of phosphate and oxalate of calcium. Gouzien (1911), 26. *Vide* p. 464.

Cystin

The surface of the urine has occasionally an iridescent pellicle, attributed to cystin. Gouzien (1911), 8 (r.).

Formation of sediment

On standing, the urine gave a copious deposit of grey mucous matter. Microscopically : irregular fragments of epithelium, fatty globules mixed with other globules of irregular outline. 14.

The urine was of a deep reddish-brown colour, at first transparent, but rapidly forming a sediment of grey mucous matter. 20. Barthélemy-Benoit (1865).

18 Sept. Urine very black, having the appearance of very dark malaga (wine).

19. A thick sediment forms after passing.

22. Urine normal, much flocculent matter.

26. Urine pale, flocculi and sediment shortly after passing.
30. Violent rigor lasting about 2 hours, much nausea, copious bilious vomit. The urine straightway becomes black, giving immediately after passing a fairly abundant deposit. 363.

The urine is fairly commonly transparent when passed, but on cooling a multitude of particles appear, which gradually settle and form a deposit. This deposit is ashy grey or greyish red, and forms a mass occupying $\frac{1}{10}$ to $\frac{1}{3}$ of the height of the conical urine glass. 275. Bérenger Féraud (1874).

Haemoglobin

Case 10. At times in a clear straw-coloured urine there was a small reddish-brown sediment which yielded abundant haemin crystals, practically all the haemoglobin being in the sediment. No red blood corpuscles were found.

Case 11. Haemoglobin persisted in the sediment after the supernatant urine failed to yield haemin crystals. No red corpuscles were observed. Brem (1906).

'The deposit of granules in late cases when the urine was of a normal colour gave haemochromogen when dissolved in sodium hydrate.' 154.

All the blood pigments in solution could be turned into acid haematin (by adding HCl) and the granular deposit of altered haemoglobin was also taken up into solution by this means. 138. Arkwright and Lepper (1918[a]), 137.

Hgb granules

If a Hgb solution is added to a medium, of not more than about *p*H 6, containing 1% NaCl or over, the Hgb is precipitated in the form of granules.

These granules are soluble in normal NaHO, and on reduction give the bands of haemochromogen.

If the granules are dissolved in acid alcohol the spectrum of acid haematin is obtained. Baker and Dodds (1925), 258.

Haematoidin

Vide supra, Bilirubin.

Hippuric acid

Day 2. Urine 480 c.c. Sediment slight, reddish. Crystals of hippuric acid. Fatty, granular and hyaline casts. Gouzien (1911), 15 (r.).

Hyaline material

Day 4. The deposit consisted of granular masses and casts, the granules being fine, apparently refractile, and brown in colour, held together by hyaline material. Barratt and Yorke (1909[a]), 195.

Indican

Louvet found little blue masses in the urine of b.w.f., and Venturini and Corre observed a line in bF of Fraunhofer which they attribute to indican. Corre (1883), 189.

Indigo

The sediment of the urine of 5 October hardly differed from the previous specimens except in the absence of 'tubes protéiques' and in the presence of a great number of little masses of urinary indigo. Louvet (1876), 260.

Leucin and tyrosin

May appear, indicating grave liver changes. Krauss (1904), 61.

Leucocytes (pus)

Appear to exist in greater number than red cells (when present) even in the absence of suppuration. Gouzien (1911), 10 (r.).

In 3 of 7 cases. Seyfarth (1918[b]).

In 1 of 28 cases suppression of urine on the 3rd and 4th days, and thereafter had polyuria and a considerable deposit of pus in the urine. Connal (1922[a]), 7.

Day 6. Considerable quantities of pus were present and culture gave a pure growth of *B. coli*. Fairley and Bromfield (1934–35), 312.

Mucus

Is occasionally mixed with a mucoid material. Brem (1906), 34.

A case cited in which the Hgb coloured a cloud of mucus, the urine itself being yellow. Gouzien (1911), 8 (r.).

Red cells

Cases.	Positive.	Authority.
21	1	Broden, A. (1906).
9	0	Brem, W. (1906), 1996.
20	10	Barratt and Yorke (1909).
2	2†	Owen and Murgatroyd (1928), 511.
?	10	Thomson (1924), 86.
100*	3	Ross (1932), 196.
12	3	Dempwolff (1898).

* 'Several.'

† Case 1 : in one specimen on day 4. Case 2 : on days 2 and 4.

Having taken urine just after it was passed, and having examined it microscopically, we found intact red cells. Duchassaing (1850), 743. Pellarin (1876), 381.

A drop of urine placed under the microscope (× 80). shows neither red cells nor any trace of them. Daullé (1857). Dutroulau (1868), 308. Pellarin (1876), 118.

Using Heller's test, 'blood' found in the urine in one of 3 cases. Legrand (1859). Pellarin (1876), 386.

Hugoulin found in the urine some agglutinated red cells, but in minimal amount. The quantity of blood in the samples examined would amount at least to 4–5%. Bories making later similar researches found crenated red cells in the midst of amorphous material. Loupy (1862). Pellarin (1876), 120.

Microscopically red cells cannot always be found. They are not found (1) when the red colour is slight, (2) when the urine though deeply coloured is alkaline when passed. Pellarin (1865), 133.

No blood cells but some deformed whitish globules soluble in ether. 21.

At first not found, but later some deformed cells may be found in non-alkaline urine. 126. Barthélemy-Benoit (1865).

Hugoulin (1865) at Bourbon, adding sulphate of soda to the urine and examining it microscopically, stated that he had seen on one occasion a few red cells stuck together, but on another he was less successful.

Bories, also at Bourbon, found red cells irregular in shape with jagged outline amidst a mass of amorphous matter. He did not hesitate in putting forward the view that in b.w.f. the colour of the urine is due to a considerable quantity of red cells. Hugoulin (1865). Bérenger Féraud and Trouette (1872), 1155. Bérenger Féraud (1874), 279.

We have examined . . . a large number of urines . . . but have never found red cells. Bérenger Féraud (1874), 280.

I once found numerous red cells over the whole microscope field, either isolated or agglutinated in confused rouleaux. 85.

I have been able to find red cells only once in 4 cases examined microscopically, but the urine in the other cases contained the colouring matter of the blood. 381.

The urine of 'fièvre bilieuse à urine noire ou rouge' always contains blood, though it may well be that it does not always contain intact red cells. 387.

A distinction has certainly to be made between urine which contains all the elements of blood excepting intact red cells, and that which contains all, including red cells. This distinction is made in medical writings by the terms *false haematuria* and *true haematuria*. 313. Pellarin (1876).

In four cases that I examined carefully I found blood four times as shown by the red cells. 264.

Case 1. Deeply coloured with blood, did not show a great number of red cells. On the day after admission it was only in the fourth specimen that 3 red cells were found in a field, but leucocytes and platelets were abundant.

Case 2. The urine had lost its characteristic colour; 2 red cells quite intact were found in the first specimen examined.

Case 3. 9 red cells in the same field.

Case 4. Came next in abundance of red cells, although examined some hours (after passing).

There can be no longer any doubt of the presence of a great quantity of *dissolved blood* and a small quantity of *natural blood* in the majority of cases. 267. Louvet (1876).

Light greyish-red deposit in which from very few to enormous numbers of red cells or phantoms, leucocytes, various casts, urates, and other elements are found. Krauss (1904), 61.

In 10 of 20 cases, usually in very small numbers. 102.

In 3 cases not present at first, but as the Hgburia was passing off. 102.

In Case 2 the number was considerable.

1st urine: Abundant deposit consisting chiefly of red cells and stromata. Dark brown granular ppt, a few epithelial cells and bacilli.

2nd urine: Contained in addition pus cells (1 to 8 red cells) and a few blood casts and brown granular casts.

3rd–6th urines: Chiefly pus cells, in small amount red cells, and granular brown pigment and casts, some hyaline casts, squamous and columnar epithelium and bacteria in abundance. The urine had no odour of decomposition.

A week after recovery the urine still contained pus cells and bacilli. 180.

It is more probable, since cystitis was present that the red cells came from the bladder. 150. Barratt and Yorke (1909[a]).

Day 2. Urine of night and morning c.c. 150–200. Centrifuged. Deposit dirty brown. It is clear then that this deposit consists of red cells more or less altered by the haemolysis to which they have been subjected. Achard and Saint-Girons (1912), 754.

In 8 of 17 cases *entirely* absent. In 7 and 2 doubtful instances in which red cells were found, they were *never* present in sufficient quantity to give a red colour to the urine. In some specimens I would occasionally find 2 or 3 red corpuscles. In one case I found 9 or 10 red cells present in each microscopic field. Woldert (1912), 636.

1. Depleted red blood cells (eight per cent) and the plasmodium of malaria.

2. Thirty-five per cent. of blood—red and white corpuscles, malarial plasmodia, streptococci and staphylococci.

3. Urine was of the true blackwater type and contained fifty per cent. of blood, microscopically as in No. 2. Boogher (1913), 1292.

Note. These 3 cases appear to be cases of haematuria.

Case 1. Day 3. A few red cells. Case 2. No red cells. Case 3. Day 1. Very few red cells. Day 6. Absent. Parsons and Forbes (1919), 376.

Red cells (agglutinated)

Agglutinated red cells (which may be seen in the lumen of the convoluted and other tubules *post-mortem*) were demonstrated in 4 of 43 cases. These red cells showed great resistance to haemolytic agents (e.g. water, bile salts). Calcium did not intensify the haemolytic action of bile salts, but induced an opposite effect. These cells were found in 3 rapidly fatal cases with hemorrhages and in one case that recovered. Dudgeon (1920), 237.

Unidentified bodies

Day 4. Urine. 400 c.c. less dark, very turbid; the sediment, besides some detritus and red cells, consists almost entirely of short bright yellow needle-like structures. Teichman and Murexide test neg. Heller and boiling tests positive. Dempwolff (1898), 155.

Small clusters of oval transparent bodies . . . some kind of torula . . . not the common yeast plant. Mackie (1898), 1470.

A number of peculiar bodies resembling cylindroids tinged yellowish green having circular knot-like structures placed at varying intervals and from the circumference of which a number of fine wavy fibres of similar colour radiated in various directions. Mallamnah (1904), 246.

Urination painful and in the urine were found 12 black particles bullet-shaped about 1 mm. long by ·5 mm. broad. Brown when crushed, rather friable. They did not yield hemin crystals. Insoluble in HNO_3, which turned them green. Brem (1906), 1904.

Vide supra, Calculus.

Day 1. In last specimen of urine passed bodies of various size up to that of a red cell. They did not appear to be crystalline, but were homogeneous and spherical. Owen and Murgatroyd (1928), 511.

Urate of ammonia

Day 1. Met-Hgb, deposit: Hgb débris in globular form, casts of the same material, a few epithelial cells and some ammonium biurate; later it contained more ammonium biurate.

Day 2. Hgburia, —. Ammonium biurate crystals present. Fletcher (1914), 50.

Urate of soda

Case 25. Day 2. Urates. Plehn, A. (1896).

Especially at the crisis granules of urate of soda forming a cloudiness or covering the sides of the glass with a rosy grey or brick red layer. Gouzien (1911), 26 (r.).

Day 2. The sediment shows grains of urate of soda, pavement epithelium, small cells circular or bent, some leucocytes, but no red cells. Lahille (1915), 914.

Uric acid

Day 4. Mucus in suspension. Some crystals of uric acid. Gouzien (1911), 15 (r.).

In some specimens of urine, I repeatedly found certain

round and concentrically arranged bodies, from ten to forty micra in diameter, often containing a darker brown dot or apparent nucleus . . . in my opinion were composed of uric acid. Woldert (1912), 636.

Day 7. Sediment, numerous small round cells, some cylindrical epithelium and crystals of uric acid. Lahille (1915), 914.

Faeces

Bile

Day 1. Calomel 1·0 g.

Day 2. During the night 3 or 4 bilious stools, blackish, composed almost entirely of very thick bile adhering to the sides of the vessel.

Day 3. Several bilious stools during the night.

Day 4. Several diarrhoeic bilious stools. 14.

Bilious diarrhoea occurs in some cases; the faeces are composed in part of dark brown or black bile, adhering to the sides of the vessel and with a very offensive bilious odour. 217. Barthélemy-Benoit (1865).

Day 13. 1 motion composed almost entirely of brown bile. Béranger Féraud (1874), 401.

The faeces in spite of icterus are extraordinarily rich in bile pigment, and when diarrhoea coexists, appears to consist of pure bile; the hypercholia is extreme. Plehn, A. (1903), 521.

Bile salts

Bile salts were only looked for in cases 1 and 3, and they were detected in considerable amount. Green stools appeared on the first and second day. 216.

Day 3. Faeces so dark as to resemble melaena. Water added, filtered, heated with HNO_3; the colour became brown, red, blue, green and then mahogany from below upwards in the test tube in a few seconds. 186. Pailloz (1901).

Much bilious vomiting occurred on days 10 and 11

(those of Hgburia) and unaltered bile was present in the faeces up to day 15. Ross, Thomson and Simpson (1910), 310.

The stools can also be blackish like tar. It is a pseudo-melaena, for bile only is the cause. Moreover it occurs in considerable quantity, not only as pigment, but also as bile salts, as Pailloz (1901) observed. Gouzien (1911), 27 (r.).

Colour

In 3 of 4 cases the normal colour was preserved, in 1 bilious. Kohlbrugge (1899), 103.

(1) Usually a very dark green, or (2) blackish, tarry (pseudo-melaena), or (3) chestnut or apparently bloody, suggesting admixture of urine, but really due to bile, or (4) truly melaenic or haemorrhagic when an intercurrent infection is present, or (5) rarely clay-like. Gouzien (1911), 27 (r.).

Black

Not uncommonly diarrhoea occurs, which, in spite of the intense icterus, is bile stained, in many cases, indeed, of a brownish-black bloody colour, due to the passage of Hgbous serum into the gut. Seyfarth (1918[a]), 272.

Clay-coloured

16 Nov. Calomel grains 1½. Q. grains 50.

17. Urine ' becoming red in colour,' jaundice, diarrhoea with light clay-coloured motions. Yorke, Murgatroyd and Owen (1930), 346.

Green

Three concentrated bilious stools, viscid, deep green. Barthélemy-Benoit (1865), 23.

Red

In severe cases the bile in the stools is so concentrated as to resemble blood. Barthélemy-Benoit (1865), 218.

6 Oct. Stools reddish, urine the colour of blood.

7. Stools red as if they contained blood.

8. Death. 248.

Day 4. 2 bilious stools, brownish red; 3 p.m. a liquid bilious stool brown chestnut, without faecal odour. 337.

Day 1. Calomel 1·0 g. in 4 packets.

Day 2. Calomel retained, 7–8 motions containing matter like pure blood. 399.

The faeces often so closely resemble urine, that it is difficult to distinguish them; no smell, perfectly liquid, frothing readily on shaking, the foam being of a beautiful orange or reddish colour. They give the reaction for bile (Cunisset's reagent). 286.

Day 2. 4 bilious stools of the same colour as the urine. 328. Bérenger Féraud (1874).

Yellow

Case 14. Day 2. Patient very restless; has passed (in spite of the icterus) a pronounced coffee-coloured stool covered with foam, of a soft sticky consistence. Schellong (1890), 69.

Day 2. Urine: alb. neg., faeces golden yellow as in a baby, apparently extraordinarily rich in bile pigment. Case 16.

Day 5. Following an enema large masses of pure golden yellow stools. Case 24[2]. Plehn, A. (1896).

Day 2. Bilious stools, deep yellow. The pallor of the skin merging into a slight icteric suffusion. Gouzien (1900[a]), 24 (r.).

28th. Six loose motions, bright yellow.

29th. Hgburia. 'Africa' (1914), 68.

Consistence

In uraemic cases the stools are liquid and if not profuse are a favourable symptom, eliminating waste products. Gouzien (1911), 27 (r.).

Urobilin

Commencing from day 10 (Day 1 of Hgburia) there was a urobilin excretion of 32,500 mgms. during 6 days,

falling after this to the low figure of 100 mgms. per diem. Ross, Thomson and Simpson (1910), 309.

Summary

Fluid

Albumen : May have a value of 16 g. per litre. The urine on boiling may give a volume of 75% or "set solid." Albuminuria persists after Hgburia. In anuria alb. may be slight or the urine on boiling may set solid.

Bilirubin : As a rule absent. Its presence may be associated with a positive direct van den Bergh reaction in the plasma.

Chlorides : Low values are commonly recorded.

Colour : A black or porter-coloured urine does not always give bands of Hgb—the nature of the blackness in these (and possibly other cases) is undetermined.

Decomposition : 'The urine often shows little or no tendency to putrify,' but no exact observations on this point appear to have been made.

Hgb : A maximum percentage of about 10% (in terms of blood) and about 200 c.c. (often much less) is the maximum amount of blood passed. The percentage and total blood values may rise and fall during the Hgburia.

Met-Hgb : Usually present, but it comes and goes, and does not persist as long as Oxy-Hgb.

Ketones : Present in some 10% of cases.

Pigments : Urobilin perhaps always increased; urobilinogen also may show a large increase.

Quinine : Conflicting data as to excretion. It may be irregular; thus we may have t + t − t + t, etc.

Reaction : Acid, alkaline, neutral may follow one another in no definite order.

The *p*H is usually between 5·8 and 6·8.

Specific gravity : May range from 1002–1033.

Urea : Low values occur, associated with imperfect response to the "urea concentration" or "water excretion" test, indicating a damaged kidney.

Sediment

Sediment : May be absent. Hgb while absent in the fluid may be present in the sediment.

Bacilli : Staphylococci or streptococci are commonly present.

Casts, renal : Absent in perhaps half the cases but records are very incomplete.

Casts, granular Hgb : Present in the great majority if not in all cases. They may be absent in anuria.

Red cells : Conflicting data; present in a negligible percentage or in 50% of cases.

Faeces

Bile : Numerous general statements as to its presence but very few actual determinations of bile as such.

Hgb : Whether present as distinct from red cells is doubtful.

CHAPTER 12

PATHOLOGY

Acidosis

The organs most affected are the kidneys, liver, heart and spleen. These changes are what we would expect in an acidosis, and according to Professor Bartlett of Capetown were exactly of the degree and type one gets with severe acidosis from other causes. Thomson (1924), 73.

Adrenal Glands

Frequently congested and softened. Barthélemy-Benoit (1865), 123.

To the naked eye appear to be normal. Bérenger-Féraud (1874), 97.

Poor in spongiocytes. Porak (1918), 561.

Fat Lipoid (cortical): A reduction of the content was one of the commonest pathological changes . . . as in pernicious malaria. In a few instances no chromaffine was detected in the medulla. Fatty change in the cells of the medulla of both adrenals in one case. In some cases congestion of blood vessels, Hges, masses of agglutinated red cells in the vessels and necrosis of gland tissue. In one instance colloid-like bodies were numerous in the medulla.

Anaphylaxis

The tissue changes in b.w.f. are absolutely distinct from what is met with in anaphylaxis, viz. *Lungs:* sub-pleural Hges, marked congestion of alveolar walls, Hges into lung tissue and bronchi. *Thymus:* enlarged, and showed scattered Hges. *Spleen:* likewise. No changes in liver, kidney or other tissues. Dudgeon (1920), 216.

Blood

From the skin and viscera, excepting the spleen and kidneys, is always black, of a deep icteric colour, more or less fluid and mixed with bile. When the proportion of bile is great, the blood is oily and leaves a grease spot on paper or linen and rings of reddish blood and yellow bile separate out. Barthélemy-Benoit (1865), 129.

Gall Bladder and Bile

Gall bladder

Nearly always distended. The mucosa is deeply stained and sometimes shows marked vascular networks, but no petechiae or interstitial Hges. The ducts are permeable. 113.

Bile

The duodenum and colonic flexure are stained by it.

Colour : deep black or brown (much more rarely green), so that there is no correspondence between the leek-green colour of the vomited bile and that in the gall bladder. 114.

Consistence : in colour and consistence it recalls exactly those of Norwegian tar. Sometimes thick and clotted like resin or syrupy or even solid like wax, softening with heat. 114.

Quantity : 40–100 g. Usually 50–70 g.

Smell : stale, nauseous, '*sui generis*' as of the bile vomited by the mouth.

Case 5. 40 g. thick viscid bile resembling tar. 24.

Case 6. Only a small quantity of green bile. 27. Barthélemy-Benoit (1865).

Gall bladder always distended, usually projecting beyond the edge of the liver. The walls are normal. The bile duct is patent. 92.

Bile

Quantity always considerable. As a rule 60–70 g., but there may be 100 g. The colour and likewise that of

intestinal and even faecal bile is black, brown or yellow, varying with the thickness of the layer or when diluted, never green, while vomited bile is an intense leek green, not yellow. Bile from the bile ducts—on section—is yellowish. 93. Bérenger Féraud (1874).

Case.	Distension of gall bladder.	Bile : quantity, colour, etc.	Authority.
7	+	Thick blackish.	Bérenger Féraud (1874).
9	+	Very abundant, thick viscous.	
11	+	Deep green.	
p. 50	? b.w.f.	Smallish quantity, brownish.	
13	+	Black, clotted, resinous.	
17	+		
18	+(−)	30 g. black. Two green waxy masses almost filling the cavity.	
19		Black (decomposed).	
22	+	Fine deep green, viscous.	
23	+	45 g. black, like ' bitter.'	
24		Bladder 75 g., bile 50 g. black, pea-like concretions, friable.	
25	+	Black jelly-like.	

Cases 6. Bile : 20, 30, 40, 80 c.c. (all thick); 24 c.c. (tar-like), 150 c.c. (thin fluid). Colour dark green in all. Plehn, F. (1898).

Cases 12. Distension : in 4. Bile : black in 6, yellow and slimy in 2. Consistence : granular in 3, curdy or ropy in 3. Whipple (1909).

Gall bladder more or less distended. Average 50–60 c.c. May reach 200 c.c.

Bile usually blackish green, sticky, resembling tar. It may be clotted resembling grape or pear jam or prepared spinach. Calculi are not uncommon. Gouzien (1911), 71 (r.).

Anuria and oliguria. Death, day 9. Liver 2550 g. Spleen 520 g. Kidneys 290, 280 g. Bile : Iron 0·048 g. per 1000 c.c. Lahille (1915).

In the case 15 (one of three fatal cases) there was a high degree of jaundice, the bile capillaries of the liver were

blocked with inspissated bile, and dilatation of bile capillaries was also seen.

Bile: great inspissation, which in the gall-bladder was almost solid and of the consistency of very thick porridge. Arkwright and Lepper (1918[a]), 139.

Gall bladder in some instances was distended and the bile passages in the liver blocked, with thick tenacious bile.

Bile very thick—in some cases almost solid and of a deep green or orange colour. Dudgeon (1920), 219.

Gastro-Intestinal tract

Duodenum: Inflammation of the duodenum, progressing even to gangrene. Once in 3 cases obliteration of the duodenum by an extravasation of blood between the mucosa and muscular coats. Lebeau. Bérenger Féraud (1874), 77.

Stomach: The mucosa of the greater curvature is sometimes bile-stained, and this portion may be very markedly injected and soft.

Retiform or petechial Hges of the pylorus, cardia, and intervening area may occur. They are circumscribed and of little extent.

Hges below the mucosa are not seen. Nor are the stomach contents black as in yellow fever. Most of the patients were addicted to alcohol.

Duodenum: Similar changes. The staining with bile is more intense. 108.

Day 2. Death. Stomach contains 300 g. of a bright green fluid. Reddish-brown patches of congestion—chiefly on the lesser curvature—alternating with purple networks of no great extent. No softening. 24.

Day 6. Death. Stomach and intestine: nothing of note 27. Barthélemy-Benoit (1865).

The dependent parts are those most stained by the reflux of bile into the stomach. When death has occurred late and after a putrid diarrhoea which enables the liver to dispose completely of its excess of bile, the latter no longer flows into

the stomach, and the yellow or green colour of the mucosa is completely absent. 73.

Softening and vascularisation more or less marked of the mucosa is the result of alcoholic gastritis, and is not pathognomonic of b.w.f. for the following reasons: (1) B.w.f. cases occur in the great majority of cases in alcoholics, (2) identical lesions are found in other diseases, (3) non-alcoholic b.w.f. cases do not show these lesions. 75.

Contents :—

Yellow fever: Blood, or a fluid the colour of ink or coffee, or a brown liquid having in suspension black granules or flecks or sometimes a pultaceous coating resembling soot in mucus, staining linen dark brown and never yellow.

Blackwater: Definitely green, clear like the vomited liquid, or turbid like the water in which spinach has been boiled. 76. Bérenger Féraud (1874).

Stomach :—

Case 9. Inflamed, filled with bilious matter.

Case 13. Externally yellow, internally covered with clear green mucus. Alcoholic petechiae present, hardly defined.

Case 18. Well-marked alcoholic lesions. Externally Hgic arborisations on the greater curvature. Internally Hgic petechiae a hand's breath in corresponding position.

Case 22. Distended, 250 g. green bile, no alcoholic petechiae.

Case 23. Distended, contains a green granular fluid like the juice of chopped spinach.

Case 24. Distended with gas, contains no fluid. On scraping the mucosa a thimbleful of pure green bile is got. Here and there bright red petechiae. Bérenger Féraud (1874).

Cases 11. Normal in 5 except for sub-mucous ecchymoses of the ileum in 2 and necrosis of the follicles of the appendix in 1. Dilatation of the capillaries of the jejunum, presence

of melanin, and abundance of eosinophil cells in 4. Necrosis of follicular lymphoid tissue in 4. Whipple (1909).

The stomach fairly commonly shows arborisations or haemorrhagic petechiae, especially at the cardiac orifice. Gouzien (1911), 70 (r.).

Intestine (small): Shows arborisations or petechiae. In certain cases has a psorenteric appearance. Gouzien (1911), 70 (r.).

General

Case 8^2. Nothing of importance. 30.

Case 11. 'Lung embolus presumably.' 33.

Case 22. Besides extreme anaemia of all organs, a red area of softening in right optic thalamus. Spleen $18 \times 11 \times 4{\cdot}7$ cm., nephritis, Hgic gastritis, heart degeneration. 40.

Case 23^2. Extreme general anaemia, kidney changes, heart degeneration, numerous Hgic extravasations in mucosa of stomach, jejunum and ileum. Spleen $10 \times 8 \times 2{\cdot}8$ cm. 42.

Case 31^3. General anaemia, kidney changes, spleen $18 \times 11 \times 4{\cdot}2$ cm. Hges on the right side of the whole extent of the slightly thickened pleura, oedema of the lung, degeneration of the heart muscle. 50. Plehn, A. (1896).

Clinical symptoms and pathological lesions are essentially referable to intravascular haemolysis.

The initial vomiting, like the chill and T., resembles the symptoms that follow intravenous injection of any foreign protein. The cause of the subsequent vomiting is not clear. Oral administration of fluids in the face of vomiting may only wash more salt from the body. Parenteral saline and glucose solutions may, in these circumstances, put an end to vomiting.

No support has been found for the theory that acidosis occurs in b.w.f. and offers an indication for alkaline therapy.

Anuria seems to be referable primarily to occlusion of the renal tubules with coagulated blood débris.

Vomiting and shock may play an important secondary rôle. Wakeman et al. (1932), 436.

Glands (portal, mesenteric, pancreatic)

Are usually enlarged, and are soft, moist or juicy. Pigment, black, green or greenish black, may be present.

The marginal sinus is dilated or oedematous, and may be full of wandering monocytes (polyblasts of Maximow) or epithelioid cells. These cells usually exhibit phagocytosis, as evidenced by the presence of pyknotic nuclei, red cells, melanin, etc.

The lymph cords also may contain melanin. Necrosis of the follicles is common. In some cases eosinophil cells are abundant. Whipple (1909).

Haemorrhages

Petechiae : Seen only once. Scattered over the lower limbs, abdominal wall and the inner side of the fore-arm. In the same case the dermis that had been blistered was infiltrated with blood and the blisters were filled with a bloody fluid. Barthélemy-Benoit (1865), 106.

Especially in pleurae, stomach and gut. Pericardium 1; subcutaneous tissue 1; optic thalamus 1; retinae 1. In 2 of 35 cases extensive stomach and gut Hges during life, one ending fatally in 36 hours. Plehn, A. (1896), 16.

Pancreas : No Hgic pancreatitis. *Kidneys :* Hges in some cases and intense engorgement of cortex and medulla. *Lungs :* Sub-pleural Hges in a few cases. Hge into the alveoli and considerable congestion of alveolar walls on many occasions. In some instances pulmonary Hges widespread. *Heart :* Sub-pericardial, in cases with an acute course. Dudgeon (1920).

Heart and vessels

Day 2. Death. Pericardium 180 c.c. of reddish fluid. Heart voluminous. In the aorta and pulmonary artery voluminous organized clots, elastic and firm and prolonged far into the vessels and their branches. Auricles

empty, ventricles with soft diffluent clots. The early death might be attributable to these clots. 23.

Day 6. Death. A very resistant fibrinous clot extends from the orifice of the aorta into the left subclavian, right primitive carotid and right subclavian, filling $\frac{2}{3}$ of the lumina, and being 35 cm. long in the case of the left subclavian. Sudden death during convalescence attributed to the clot. 26. Barthélemy-Benoit (1865).

Heart

Cases 17. *Fatty degeneration :* Diffuse in 3, localised in 5, absent in 9.

Hges : Sub-pericardial in 3, intramuscular (with necrosis) in 1. Dudgeon (1920), 215.

Cases 6. *Pericardial fluid :* Yellow, in excess ; in one case about half a pint.

Oedema : of interstitial tissues with isolation of muscle fibres, considerable.

Lipochrome : Golden brown, increased at either pole of the muscle fibre nuclei. Thomson (1924), 70.

Case 7. Right heart empty, left heart has several clots.

Case 13. Right heart distended by a bulky black clot; left heart by a fibrinous clot.

Case 18. Small, strongly contracted. No clots.

Case 22. 600 g. contains bulky clots. Pericardium contains a bloody fluid.

Case 23. Icterus of cardiac tissue, chordae tendineae, and of tricuspid and mitral valves. Ventricle contains a fibrinous clot.

Case 24. Right cavities : gorged with black blood, with non-organized clots. Left heart : numerous fibrinous clots. The largest, in the ventricle, penetrates the aorta for 8–10 cm. and almost obstructs its lumen. A bulky black clot occupies the left auricle penetrating the aorta and pulmonary veins. Bérenger Féraud (1874).

Fibrinous clots common, especially on the right side. Pericardial fluid is non-icteric. Pellarin (1876), 323.

Cases 8. Normal 2, dilated 5, fluid blood in 3, clots in 2.

The serum, clots, or froth, greenish in 3. Fragmentation of muscle 1, fatty degeneration 1. Whipple (1909).

Hypostatic congestion

Hypostatic congestion—subcutaneous ecchymotic patches—is only seen where the death agony is prolonged, and more especially where the heart has been gravely involved, otherwise it is less common and less deep in colour and more diffuse, sometimes hardly appreciable. Barthélemy-Benoit (1865), 106.

Hypostatic streaks and ecchymotic patches are fairly common. They are due to the action of gravity on the cadaver. Best seen in robust individuals and when death has been early. Almost completely absent in anaemic patients with death occurring in, say, a fortnight. They are not constant as in yellow fever. Bérenger Féraud (1874), 68

Lividity suffusions are always superficial, but little developed, limited to dependent parts.

In yellow fever they are deep, extensive, occurring on the anterior surface of the cadaver, which is marbled with various colours.

I have not seen ecchymoses, still less deep infiltration of blood, in the muscles or affecting a whole limb—these are vital phenomena characteristic of yellow fever—a Hgic disease.

In b.w.f. the face is pale, slightly icteric with no trace of Hgic congestion. In yellow fever the buccal and nasal mucosae show evidence of Hge, as also often the neck and the anterior plane of the body in the form of yellowish-red, bluish or purple patches. These distinctions are more or less lost when yellow fever occurs in anaemic subjects. Pellarin (1876), 320.

Icterus

Sometimes more distinct after death. If at the time of death the skin is only sub-icteric, the colour is deeper in the fatty and connective tissues, as is the case in yellow fever. 105.

The brain substance and membranes are more or less icteric, less frequently the ventricular fluid. 107.

The pericardium, endocardium and the intima of the two main arteries are sometimes more deeply coloured than other tissues. The pericardial fluid is sometimes icteric and bile pigment is easily detected. 108.

Day 2. Death. All the soft tissues, including the costal cartilages, are deeply icteric. The endocardium is icteric, and more intensely so the internal coat of the aorta and pulmonary artery. The aortic orifice shows a deeper yellow ring sharply defined. 25. Barthélemy-Benoit (1865).

Icterus of the skin is uniform (not so in yellow fever), a light or deep yellow, but if death has taken place towards the end of the 2nd week or later, it may be indistinct. 68.

It is seen in the pleurae, peritoneum, pericardium, meninges, and sometimes in the ventricular fluid of the brain and sometimes in the intima of the arteries and veins. 71. Bérenger Féraud (1874).

I have never observed the development of icterus after death; on the contrary, in one case it was less pronounced after death than during life. In yellow fever icterus is often more apparent after death. Icterus takes the place of blood which passes to the dependent parts. Pellarin (1876), 320.

Kidney

Weight in grammes :

342	130, 125	160, 190	260, 220	310
342	150, 148	160, 190	250, 245	320
342	155, 160	360	244, 254	320
342	160, 160	360	350, 165	320
380	160, 160	170, 190	550	325
770	160, 160	180, 200	550	350
800	160, 160	230, 220	295, 275	350
1000	160, 180	230, 220	630	380
	170, 175	230, 220	630	405
	170, 175	240, 235	320, 370	415
			370, 400	510
			410, 390	
Barthélemy-Benoit (1865).	Bérenger Féraud (1874), 79.			Whipple (1909).

Weight : Increased in 6 of 10 cases.

Capsule : Sometimes thickened.

Colour : A constant feature is the deep reddish-brown colour almost always spotted with black ecchymotic patches, sometimes covering $\frac{4}{5}$ of the surface. They occupy not only the cortical layer, but penetrate more or less deeply into the tubular substance.

This colour is due to a vascular stasis or hyperaemia—observed in 9 of 10 cases—the essential pathological lesion.

In the severest cases the condition is one of a general apoplexy, but when there has been no profound functional trouble such as anuria the patches are then limited to the cortex. The black colour is due to an interstitial suffusion of blood sometimes resembling an actual Hgic focus or apoplectic node.

Consistence : In the ecchymotic patches, the parenchyma is reduced to a purple pulp on pressure.

Pelves : Usually empty. On 3 occasions a few drops of muddy fluid resembling pus, but containing not pus cells, but fragments of epithelium and broken-down blood.

Haematuria : Is directly due to the apoplectic condition. Barthélemy-Benoit (1865), 120.

Case 5. No apparent enlargement. Externally marbled with purple patches which extend more or less deeply into the cortical layer. Tubular area deep brown, soft, blending in colour with the cortex. 24.

Case 6. *Left kidney :* pale, almost bloodless. *Right kidney :* a general purple colour, cortex reduced to a pulp. On section the tubular substance shows large blackish ecchymotic patches. 27. Barthélemy-Benoit (1865).

Renal ecchymosis is not constant; on the one hand it occurs in other diseases, and when it exists, it is only the ultimate degree of a venous congestion. Serez (1868). Pellarin (1876), 375.

Congestion : The colour of the parenchyma—a deep reddish brown is evidence of the congestion. Here and there are ecchymotic patches—varying in size from that of

a lentil to four-fifths of the organ. Chiefly in the cortex, but they may extend to the collecting tubes. Sometimes there is an actual apoplexy. When death has occurred late there is an appreciable pallor of the cortical substance, indicating a lesion of the parenchyma. 99.

Congestion explains the haematuria up to a point, and if the black colour of the urine is due to an excess of biliary substances, one must attribute haematuria to their irritant action. 101.

Abscess : Has been noted. 99.

Case 13. Purple ecchymotic patches. (Congestion in process of absorption.) On section evident congestion, especially in the cortex. Petechial Hges of the pelves and calices. Large veins gorged with fluid black blood.

Case 17. Nil.

Case 18. Slightly congested.

Case 19. Cortex bright red bleeding. Tubules show clear signs of destruction.

Case 22. (Suppression.) From the left kidney on section a yellowish fluid escapes, but not from the right.

Case 23. Ecchymotic patches. On section here and there small apoplectic nodules.

Case 24. Matter resembling pus in the pelves and calices. It is not pus, but urates. Bérenger Féraud (1874).

Death during the attack :—

1. One or more ecchymoses, definitely circumscribed, occupying at most $\frac{1}{5}$ of the surface.

2. A sub-ecchymotic infiltration or apoplexy, limited to the cortex, and not extending among the tubular bundles.

3. A relative anaemia of the cortex—whether ecchymotic or not and congestion of the tubular portion.

Death following an attack but due to some other form of pernicious attack or to some other disease :—

An ulcer or phlyctenular abscess of one or both kidneys, also limited to the cortex and to be regarded as an extension of the Hgic process. 84.

1. Ecchymosis with Hgic infiltration has occurred in all fatal cases. Its black colour marks it off very clearly from the surrounding more or less pale areas. On the surface it shows as a black ecchymosis. In form it is conical, with the base peripheral and the apex towards the hilum. The tubular portion of the kidney is highly engorged but with no appearance of Hgic infiltration or infarct.

2. The abscess or phlyctenular ulcer—seen in 4 cases. Its position and form are the same as those of the Hgic infiltration.

A brown, black or purple bleb forming a slight projection covered each abscess. The cavities contained a deep brown liquid—once some drops of pus. 328.

The essential change is the anaemia of the cortex, the deep red colour of the tubular area, the circumscribed ecchymosis covering a Hgic infiltration limited to the cortex; later the abscess or phlyctenular ulcer equally limited to the cortex, i.e. a peculiar form of localised nephritis. 376. Pellarin (1876).

Case 2. A large ecchymosis occupying about ·03 of the surface. Not recorded in Pellarin (1862), but recorded in Pellarin (1865) and Pellarin (1876), 192.

Case 3.* Cortex pale grey with a rosy tint. Tubules and pyramids reddish brown, much congested.

Left kidney. 2 brown blebs, one a little more, the other a little less than 1 cm. in diameter. On incision a brown fluid escapes. The walls of the cavities smooth, injected. Encrusted on them 3 or 4 white granules the size of a grain of rice. On crushing them these formed a semi-fluid oily matter. The cavities are conical with their base at the periphery and apex at the base of the pyramids—thus occupying the thickness of the cortex. 200. Pellarin (1876).

Case 6. *Right kidney.* An ecchymosis, 2–3 cm. of surface covering a blackish Hgic infiltration of the cortex.

* No record of Hgburia.

Left kidney. 1. On the periphery an ecchymosis, somewhat less in extent, not projecting like the former, covering a recent Hgic infiltration limited to the cortex.

2. On the anterior surface a superficial ecchymosis with a subjacent infiltration of only 1–2 mm. in depth. 208.

Case 11.[1] *Left kidney.* 1. On the anterior surface, an ecchymosis 2–3 cm. broad, stretching from the convex almost to the concave border. The Hgic infiltration is confined to the cortical substance. The infiltrated parts are black and the kidney around is engorged.

2. On the convex border a brown bleb containing a reddish-brown mixture of urine and serum.

Right kidney. On the convex border an ecchymosis 1–2 cm. in extent. 302.

Case 13.[2] Each kidney showed on the lower half of the posterior surface a large ecchymosis 5 mm. in thickness. 315. Pellarin (1876).

1 case. Hgburia neg. day 4. Death day 10. P.M. 4 hours after death.

Glomeruli : Haemosiderin reaction, diffuse blue. Scanty blackish-brown granules present.

Tubuli contorti : only in isolated spots necrotic.

Contents : a gray crumbling granular mass.

Haemosiderin reaction : numerous blue granules, especially on the surface of the epithelium, partly intracellular, partly in the lumen.

Loops of Henle : scanty blue granules in the ascending limb.

Collecting tubules : scanty blue granules.

Vessels : scanty blackish-brown granules. Fe-reaction, negative. They often lie in close proximity to the blue-staining lumps.

[1] Recorded also in Pellarin (1865), 475. [2] ? Hgburia.

Interstitial tissue : Isolated collections of round cells. Here and there small Hges. Stieda (1893).

Death, day 2. Fixation in Müller's fluid.

Malpighian capsules : slightly thickened, peripherally connective tissue is thicker than normally.

Contents : no exudate.

Tubuli contorti : dilated.

Epithelium : narrower than normally, containing numerous fine greyish-black granules. The cells fused at their base are jagged towards the lumen.

Contents : (1) a reticulated exudate; (2) granular détritus; (3) red cells agglutinated into the form of amorphous blocks.

Tubuli recti : the masses of granules form actual casts. The largest granules are the size of red cells, greyish in colour, and the largest of these have a slight yellowish Hgb colour. Peripherally the masses are continuous with normal red cells, while the largest of them are larger than red cells. Ferrier (1896), 324, 458.

1 case. Death within 24 hours.

Glomeruli : intact, moderately swollen. The cavities do not contain blood.

Tubuli contorti : relatively few contain extravasated blood.

Collecting tubes : a great number, often the majority are filled with blood. The blood has the following appearances :

1. Masses of red cells, almost normal except that their outline is not sharply circular, and intermediate conditions passing into
2. Finely granular casts staining like red cells with eosin.
3. Casts of fragmented red cells $\frac{1}{3}$–$\frac{1}{4}$ or less, of the diameter of a red cell.
4. Casts of agglutinated red cells, with their outlines still visible, forming refractile incompletely homogeneous masses.

Haemorrhages : Extravasated blood is found mainly under the capsule and in the region of the collecting tubes, much

less so in the labyrinth. The process is one of venous stasis and of multiple Hges into the uriniferous tubules. If the process were due to Hgbaemia and filtration of red cell débris, the latter should be found especially in the convoluted tubes—in the secretory region—and the lesions should be more uniform. Berthier (1896), 672.

1 case. Death 18 hrs. after the rigor.

Kidneys. Right, 160 g. Left, 170 g.

Glomeruli : intact.

Tubuli contorti : desquamation of epithelium which is infiltrated by a diffuse rusty coloured matter.

Lumina : 1. Filled with casts composed of degenerating epithelium and a fine dust of the same colour as the protoplasm. 2. Some contain red cells.

Collecting tubes : similar casts, but of a deeper colour. Boisson (1896), 374.

Kidneys in Anuria

A blocking of the tubules with corpuscular fragments or parasite pigment could not be seen in fresh razor-cut sections, and both were absent in the fluid passed from time to time. Plehn, A. (1896), 14.

Scattered here and there in the sections, some of the tubules were found to contain peculiar granular masses which took on special (eosin and picric acid) staining. They were a peculiar product of the disintegration of the epithelial cells. The cells are found lying in masses in the tubules; then they begin to agglomerate into a reddish mass in which no nuclei are visible. This mass finally takes on a granular character, and in its ultimate stage is composed of a great number of minute rounded granular bodies simulating micrococci.

In some parts comparatively few tubules are diseased, whilst in others many of them are affected. Thin (1899).

Oliguria. Death, day 4 :

Enlargement : slight. No marked congestion. *Cortex :*

dark brown, soft. From the cut surface a brownish fluid resembling urine was expressed, but no visible blood.

Glomeruli : changes were absent.

Tubuli contorti : the cells were in process of active disintegration, had lost their striation, were very granular, many of the nuclei also showed signs of degeneration.

Contents : a granular mass.

Tubuli recti : filled with shed epithelium and masses of granules. The larger collecting tubes were also filled with granules resembling, but rather larger than, those seen in the urine.

Capsule : adherent in patches. Under the capsule were patches of young fibrous tissue with large multi-nucleated cells containing yellow pigment. Stephens and Christophers (1900).

Cases 5.

Glomeruli : occasionally desquamated epithelium and within the capsule a granular mass with colourless hyaline spheres. No imbibition of Hgb or granules of Hgb within Bowman's capsule.

Tubuli contorti : 1. Degenerative changes in the portions of the cells bordering the lumen, sometimes necrosis.

2. In one case (*a*) greater part of the tubules greatly changed, with only finely granular amorphous détritus in the lumen, or (*b*) preserved and flattened with Hgb cylinders in the lumen.
3. Cells loaded with light yellow granules (Hgb).
4. Cells infiltrated with Hgb.

Casts : consisted of

1. Granules or blocks of Hgb or filaments stained with Hgb.
2. As the preceding, but mixed with small uninuclear cells stained with Hgb.
3. Spherules the size of a red cell, indistinct greenish-yellow when stained with eosin and haematoxylin.

4. Hgb détritus and altered red cells.
5. Leucocytes (lymphocytes) stained with Hgb or bile.
6. Epithelial cells impregnated with Hgb.

Loops of Henle: Epithelium well preserved and not infiltrated with pigmentary substances. Casts as in the convoluted tubes, but more numerous in the medulla and pyramids—whence the brownish-red or black striae with a low magnification.

Tubuli recti:

1. Epithelium disintegrated and mixed in the lumen with Hgb granules.
2. Many tubes dilated, forming pouches filled with the above détritus.
3. Proliferation of the epithelium around the central pigment masses.

Interstitial substance: Intense hyperaemia. In one case interstitial Hges. In one case accumulation of epithelioid cells and leucocytes forming nodules—only among the tubules of the pyramids. Marchiafava and Bignami (1900), 500.

Cases 2.

Glomeruli: in some, slight swelling of the epithelium.

Capsule: finely granular material.

Tubules: dilated and separated from one another by swelling of the interstitial tissue. Between the tubules there is in places a moderate or extensive accumulation of leucocytes.

Tubuli contorti: epithelium is more or less granular, turbid, and in the portions bordering the lumen shows a ravelled appearance. In parts the epithelium is necrotic.

Contents: 1. An amorphous, finely granular (at times thread-like) matter.
2. Hgb casts of fine packed granules or coarser lumps, often somewhat hyaline.
3. Granular casts.
4. Hyaline casts.

Desquamated epithelium is more or less mixed with the casts.

Tubuli recti : epithelial changes less pronounced than in the tubuli contorti, but broadly of the same kind. The number of casts, especially Hgb casts, is relatively greater in the straight tubes, and most so in the collecting tubes. de Haan (1905).

Cases 6.

Glomeruli : tufts no change.

Capsules : abundant exudate in 1, slight in 5. Exudate, Fe-reaction positive in 4.

Tubuli contorti :

Dilatation : considerable in 2, slight in 4.

Degeneration : great in 1, moderate in 2, absent in 3.

Fe-reaction : cells, negative, basement membrane positive, and surrounding connective tissue frequently positive.

Loops of Henle : descending loop, finely granular, ascending loop coarsely granular matter. Whether this brownish-yellow coarsely granular (Fe-reaction negative) comes from the finely granular (Fe-reaction positive) material, or whether it is excreted by the tubuli contorti is uncertain.

Tubuli recti : dilatation occurs to a greater or less extent. Degeneration of moderate extent may occur.

Contents : coarse material Hgb-colour (Fe-reaction negative). The amount is so great as to block a great part of the tubules.

Malaria pigment : chiefly in the vessels, but here and there in the lumina and in the epithelium.

Case 2. *Epithelium* of tubules. No blue reaction. *Contents* of convoluted tubes and glomeruli blue. *Contents* of tubuli recti and collecting tubes, no blue or only faintly.

Case 3. (a) *Contents* of tubuli contorti give the most intense blue reaction. (b) The basement membrane (reticular tissue) of tubuli contorti and the adjacent connective

tissue less intense blue. (c) *Epithelium* of tubuli contorti still less intense blue.

Case 4. *Contents* of tubuli contorti most definitely blue. *Contents* of tubuli recti, no blue. Basement membrane and adjacent connective tissue of tubuli contorti a positive reaction in many parts.

Case 5. Only the contents of the tubules give a slight reaction.

Case 6. Tubuli contorti contents very distinct blue, the cells and the connective tissue negative. Tubuli recti contents negative. Werner (1907).

Cases 12.

Glomeruli : Normal in 5 cases.

Capsule : thickened or hyaline degeneration in 1 case. *Dilatation* in 2 cases. *Contents :* granular albuminous matter, sometimes very slight, in 6. Small globules or grains of Hgb, staining as the red cells in the tufts in 2.

Glomerular vessels : In the vessels entering the hilum intact red cells and Hgb granules in the plasma in 1. In this case Hgb granules also found in capillaries of the liver.

Tubuli contorti : Dilatation in 3 cases. *Degeneration :* swollen and granular in 6, granular and colloid degeneration in 1, degeneration and necrosis in 4.

Contents : coagulum of albuminous material in 10, Hgb granules in 12, desquamated epithelium in 4, polynuclear leucocytes (a few) in 3.

In 1 case the Hgb granules were so closely applied to the surface of the epithelium as to suggest secretion there. The granules in the loops of Henle also showed this peripheral arrangement.

Tubuli recti : Hgb casts in 7 (these appeared to be hollow in 2), Hgb in coarse masses or only a few grains in 4, epithelium, more or less, in 7 (stained with Hgb in 2).

Connective tissue : oedematous in 5, with many wandering cells in 4. Whipple (1909).

Cases 2. (*a*) Suppression of 8 days. Death, day 10. (*b*) Suppression of 5 days. Death, day 9.

Enlargement : $5 \times 3 \times 1\frac{1}{2}$ inches in (*a*), nearly as great in (*b*).

Medulla : dark brown, almost black, due to fine brown radiating lines.

Cortex : stippled with brown dots.

Glomerular capsules : distended, occasionally containing a finely granular deposit.

Tubuli contorti : distended, diameter 40–50 μ, epithelium flattened but otherwise normal. No granules in the cells.

Uriniferous tubules : granular plugs 30–80 μ in diameter, sometimes present, frequently absent. They give rise to the stippling of the cortex.

Collecting tubes : Smaller : plugs 30–40 μ in diameter.

Larger : plugs 40–80 μ in diameter, giving the striae of the medulla. In some cases the epithelium is detached leaving the basement membrane bare, or a plug covered with epithelium may have been detached (proximally) and partly fill the lumen.

Composition of Casts : 1. Usually of granules of large size 3–5 μ, staining darkly.*

2. In a few tubules, granules 0·5–2 μ, almost black, or sometimes lightly tinted.
3. Lightly stained débris, fine granules 2–5 μ, presenting every transition to No. 2.
4. Amorphous flocculent material.
5. Epithelial cells common.

Case 16. Death 7 days after Hgb ceased. Urine 640 c.c. daily during this period.

Naked eye : slight enlargement.

Tubules : dilated, but not sufficiently to flatten the epithelium as in the 2 previous cases. Epithelium throughout more or less detached. Some of the collecting tubes completely bare of epithelium, having the basement membrane exposed.

* With iron alum hæmatoxylin.

Composition of casts : 1. Large darkly-staining granules, 3–5 μ.

2. Small darkly-staining granules, ·5–2 μ.
3. Frequent lightly-staining granules, ·5–1·5 μ.
4. Flocculent material.
5. Epithelial cells.

Differences from previous 2 cases: (1) less distension; (2) more detachment of epithelial cells; (3) frequency of small granules. Malarial pigment absent in all. Barratt and Yorke (1909[a]), 120.

Weight (combined) : 380–1000 g. (Normal 340 g.).

Congestion : if death has occurred early, gorged with black blood.

Colour : the surface is covered with bistre-coloured (dark brown) spots or ecchymotic marbling, corresponding on section to similar zones extending into the cortex and medulla.

Glomerular nephritis : frequently shown on section by a red punctation.

Tubuli contorti : usually blocked by Hgb masses or even intact red cells. Adhering to this globular débris—haematic dust—are epithelial cells, the whole forming casts sometimes completely blocking the lumen.

Tubuli recti : sometimes blocked by hyaline casts or with haematic casts covering epithelial nuclei.

Haemosiderin : the dark epithelium of the tubuli contorti and the ascending loop of Henle is more or less cloudy and filled with yellow granules, sometimes giving the cortical substance a yellow colour. The granules give the iron reaction.

Melanin : the capillaries are very often filled with malarial pigment, as also the tubuli recti.

Abscesses : small serous cysts formed by the accumulation of red-cell débris in the glomeruli. They are the '*abcès phlycténoïdes*' of Pellarin. They indicate advanced malarial cachexia.

Suppuration : in the form of (1) miliary abscesses or (2) extensive cavities (*renal infarcts*) or (3) diffuse infiltration.

Sclerosis : usually with degeneration of heart and liver in alcoholics.

Atrophy : the result of constant chronic nephritis is rare. Gouzien (1911), 72.

B.w.f. Bulgaria. Formol fixation.

Glomeruli : many contained broad crescentic reddish-brown, partly finely granular, partly homogeneous, Hgb masses.

Tubuli contorti :—

Epithelium : of many tubes much swollen and in the portions bordering the lumen filled with tightly packed reddish granules and larger homogeneous masses. Other cells have a clear, more vesicular appearance.

Contents : finely granular clotted matter, in which occur larger Hgb drops and clumps.

Tubuli recti :—

Contents : almost completely filled with drops arranged like a string of pearls, which in the kidney pelvis form a thick blackish coating.

Interstitial tissue : in the boundary zone of the medulla occur thick masses of large cells containing brown pigment, giving the Fe-reaction. This unusual appearance probably results from an earlier attack. Marchand (1918), 441.

Days 3–4. Oliguria (100 c.c.). Day 4. Anuria. Death 1 p.m. P.M. day 4.

Glomeruli : normal.

Tubuli contorti : almost everywhere well preserved. Cellular outlines more distinct than usually.

Tubuli recti : hyaline casts very scanty. They sometimes showed a concentric stratification and often were rose-coloured. Granular casts exceptional.

'Pigment': some granules occurred in epithelial cells and some in the lumina of tubules, free or included in the casts.

There are insufficient changes to account for death, which is attributed in the main to anaphylaxis. Porak (1918).

Oliguria. Death day 4. P.M. day 6.

Weight 170, 170 g. Uniform deep red with blackish Hgic zones in the medulla.

Glomeruli : normal.

Tubuli contorti : the striated border of the cells almost everywhere intact. Here and there the cells are hypertrophied and full of Hgb granules. Some of these cells desquamate and form with the granules which fill the lumina here and elsewhere cellular haemoglobinous casts.

Tubuli recti : voluminous casts occur. Most often the epithelium of the excretory tubes has largely or completely disappeared.

Everywhere the tubules are full of Hgb granules (poussière hématique) uniformly distributed or forming dense blocks, in section giving the Hgb cast. Ameuille, Sourdel and Marcorelle (1918).

Glomeruli : Tufts : slightly or very intensely congested. Endothelium sometimes shed.

Capsules : Endothelium sometimes shed, and with blood débris present in the capsules, where death had occurred in the acute stage.

Tubuli contorti : Degeneration : the cells are large, swollen, vacuolated. They may lie free or be collected into casts.

Contents : blood serum, granular débris and agglutinated red cells, when death occurred during the acute stage. The débris is found in the cells, and obstructing the lumina.

Fe-reaction : The granular matter may show traces of free-iron or iron in large quantities. It is especially in the epithelium of the convoluted tubes that the iron granules are found.

Necrosis : large tracts of necrosis of the tubules were met with in some instances.

Interstitial tissue : acute inflammatory changes absent in uncomplicated cases. Dudgeon (1920), 220.

Cases 13.

Glomeruli : Tufts unchanged, blue Fe-reaction in 3.

Capsules : exudate in small amount in 8. Blue Fe-reaction of epithelium, basement membrane and exudate in 5. Desquamation in 2.

Tubuli contorti : Dilatation : in 6. *Degeneration :* in 2 (i.e. about 15%). *Contents :* granular material in 13. Hyaline plugs in 1. *Hgb drops :* in the cells in 1, on the surface of the cells in 10, in the lumina in 3.

Intercalary piece : shed epithelium uncommon in the lumina. Hgb in the masses plugging the lumen in 13.

Loops of Henle : Hgb drops on the surface of the epithelium in 10, in the cells of the ascending limb in 6, in the cells of the descending limb in 3.

Tubuli recti : shed epithelium commoner than in the intercalary pieces. Isolated cells or in masses on the surface or in the clotted matter if not too dense, normal in appearance, appear to have been shaved off by the coarse material, leaving the basement membrane *in situ.* Hgb in the clumps in 13.

Casts : Granular material in the lumen in all. This material is denser and coarser the more distal it is, and the coarser it is, the less intense is the blue Fe-reaction.

Haemosiderin

Tubuli contorti : In 12 cases the cells and basement membrane blue. In 3 cases fine deep blue-granules in the cells. In 9 cases contents of the lumen diffuse blue. In 2 cases deep blue granules in the lumen.

Loops of Henle : In 6 cases contents of lumen blue or blue granules. In 4 cases deep blue granules in the cells.

Schaltstücke and collecting tubes : In 3 cases contents blue or deep blue granules. In 4 cases coarse yellow or eosinophil masses, no Prussian blue reaction.

Glomeruli : In 3 cases blue. In 5 cases the epithelium and basement membrane of the capsule and also the exudate blue.

Haemoglobin reaction

Convoluted tubules: In 3 cases in lumen; Hgb in form of minute drops lying on surface of the cells. In 2 cases in the cells.

Loops of Henle: In 10 cases small drops in the lumen on the surface of the cells. In 7 cases in the cells.

Schaltstücke and collecting tubes: In 13 cases in the lumen. In 13 cases in the lumen generally in the form of compact masses. The contents are always more compact and coarser in the distal than in the proximal tubules. Salvioli (1922).

Case 1. Death day 2. Oliguria-Anuria.

Tubuli contorti: necrosis. The necrosed cells often impregnated with Hgb.

Loops of Henle: numerous casts of Met-Hgb granules.

Tubuli Recti: the same, here and there.

Interstitial vessels: engorged.

Glomeruli: the epithelium covering the tufts enlarged, rendering many of the capillaries impermeable. Capsule oedematous. Capsular space contains cellular débris and granular albuminous matter.

Case 2. Death. Day 7. Oliguria-Anuria.

Glomeruli: In part enlarged. Capsular epithelium in part swollen. In parts shows adherence of tuft to the capsule. In parts capsule slightly thickened.

Tubuli contorti and *Loops of Henle:* Hgb casts.

Tubuli recti: Hgb granules, and necrotic epithelium stained with Hgb forms large plugs.

Lymphocytic infiltration: in parts around vessels and tubules.

Case 3. Death. Day ?.

Glomeruli: spaces for most part normal. In some an increase in the nuclei of the tufts.

Tubuli contorti: for most part necrotic.

Tubuli recti: very few Met-Hgb casts. Paterni (1923).

Cases 8.

Enlargement: and congestion in most. In 2 cases of suppression, length just over 5 inches.

Colour : 2 cases of suppression. Medulla, dark brown to almost black, due to fine radiating dark lines visible to the naked eye.

Cortex : fine dark dots.

Malpighian capsules : distended.

Tubuli Contorti :

Lumina : distended in all cases.

Epithelium : cloudy swelling, degeneration or necrosis, especially in first convoluted tube and ascending loop of Henle. Some of the cells lie free in the lumen or form casts. The cells are swollen, vacuolated and the nuclei fragment and disappear.

Contents : albuminous débris sometimes tinged with Hgb in many.

Tubuli recti : Epithelium for the most part intact. In the largest collecting tubes (ducts of Bertini) granular casts occur, consisting of granules of various sizes, which may coalesce into large masses. The casts are sometimes coated with detached epithelium, leaving the basement membrane bare. Epithelial cells also occur in the casts. Many of the large granules of Hgb may approximate in size and appearance to red cells. 86.

In the smaller collecting tubes casts of débris also occur, but in the tubuli contorti are rarer. Agglutinated red cells in one case.

Malaria pigment : in the endothelial cells of the glomeruli occasionally.

Agglutinated red cells : in the collecting tubes in one case. 86. Thomson (1924), 68.

Cases ?

Tubuli contorti : necrosis of the epithelium.

Tubuli recti : epithelium for the most part retained.

The process of destruction of the epithelium extends to the basement membrane and eventually to the capillary walls, permitting the contents of the tubules to escape into the vessels. Oliguria and anuria are attributed to a primary

deficiency of water excretion. The formation of plugs is a secondary process following on this deficiency. It is supposed that the excretion of NaCl may also be defective through the injured epithelium, and that consequently a strongly hypotonic fluid arises which can haemolyse red cells in the kidney vessels. This secretion may not be passed as urine, but it often is, as evidenced by the low specific gravity of the urine.

Plugs : All transitions are found from shed epithelium to homogeneous and coarse clumped casts. Plehn, A. (1926).

In one case there was profound haemolytic jaundice, all organs being intensely bile stained; in another there was concomitant multilocular cystic disease of both kidneys. Forbes (1926–27), 417.

1 case.

Glomeruli : changes insignificant. Rarely, inconsiderable desquamation into the capsule. The red cells in the tufts showed no change. It was not possible to detect Hgb by any stain in the capsule.

Tubules :

Dilatation : for the most part widely dilated and frequently forming broad hollows.

Degeneration : especially conspicuous in the *tubuli contorti.* It takes the form of cloudy swelling or complete necrosis of the cells, and their loosening from the basement membrane in the form of a structureless nucleated albuminous mass. Desquamation can also occur of strips of almost unaltered epithelium without any necrosis. The necrotic process can extend further and involve the basement membrane so that by fusion of two adjacent tubules a wide cavity is formed. Further, the process extends to the thin wall of the capillary now traversing the hollow so that the contents of the blood can pass into the (wide) tubule and *vice versâ* the contents of the tubule into the capillary.

Casts : in proximal tubules fine granular, in distal coarsely and in the tubuli recti in clumps. They are strongly eosinophil—bright brown to orange red. These casts arise

from desquamated cells (79). Their eosinophil reaction being due to imbibition with Hgb.

Blood : blood cells unchanged and in different stages of transition to shadows occur in quantity in the lumina. Also various leucocytes. The haemolytic process takes place in the tubules, blood having entered through the communication between the capillary and the tubule which can be shown in many parts of the sections. Rapaport (1928).

Glomeruli : some engorged, others absolutely devoid of blood. Glomerular Hges occur, but not commonly. Swelling of the epithelium investing the loop, necrosis and desquamation occur. In some cases Hgb granules occur in the lumen.

Tubuli contorti : In some, granular degeneration in others, partial necrosis of the cells which may or may not contain Hgb granules. The lumina are in part empty, in part filled with Hgb granules not very large, in others they are filled with granules of a dirty red tint not staining with eosin.

Loops of Henle : Degeneration and Hgb inclusions less evident. In the lumina discrete Hgb casts may occur.

Tubuli recti : epithelium not markedly altered. Numerous casts stained with Hgb and bile pigment occur.

Capillary congestion : is noticeable in some areas. Paterni (1928), 670.

Cases 9.

Glomeruli : nothing noteworthy in 6. A slight amount of clotted material in the capsules in 3.

Tubuli contorti : Dilatation : in 4. *Degeneration :* slight in 2, extensive in 7. *Contents :* finely granular matter and shedding of epithelium in varying amount in all cases.

Loops of Henle : epithelium intact. Casts made almost exclusively of epithelium (shed proximally) in 3 cases. Otherwise casts of coarse material, brownish or yellowish-brown, in contradistinction to the finely granular material proximally.

Collecting tubes : casts of brown, reddish-yellow or blackish coarse material or in clumps, with in some cases imbedded epithelium.

Red cells : in scanty amount in the tubules in 4 cases. In the interstitial tissue in 1 case. Hoeppli (1929).

The view that anuria is due to the blocking of the tubules by Hgb masses is based on the fact that except for this blockage and dilatation of the tubules only insignificant changes occur in the parenchyma. This negative finding does not appear to me to justify us in considering the mechanical factor as the sole cause of oliguria.

1. In many cases the block alone is not sufficiently extensive to account for complete anuria.
2. In many cases when the anuria ceases there follows a relatively good flow, although the Hgburia persists.
3. The rarity of anuria in other Hgburias (Cold, March).
4. Of much greater significance is the impairment of function—diluting and concentrating power of the kidney—observed in all my cases, justifying an assumption of injury to the parenchyma—functional—and not an actual nephritis which might often be expected to become chronic, but this is not the case, even when the insufficiency has persisted for a long time. Georgopoulos (1933), 71.

Liver

Weight in grammes :

1620	1520	2030	2350	1610
2000	1580	2045	2430	1750
2100	1620	2140	2450	1750
2250	1750	2180	2450	1800
2270	1750	2240	2450	1970
2300	1800	2250	2450	2020
2350	1850	2300	2670	2080
2450	1930	2300	2720	2100
2795	1950	2300	2770	2240
	2005	2320	2880	2300
				2350
Barthélemy-Benoit (1865), 110.	Bérenger Féraud (1874), 79.			Whipple (1909).

Weight : nearly always increased.

Colour : deeper than normally, deep reddish-brown, purple, slatey, marbled with irregular patches of a deeper colour. These correspond to areas of engorgement more or less deep.

Engorgement : of portal system and sub-hepatic veins.

Consistence : friability greater than normally. When the colour is purple, pressure reduces the parenchyma to a pulp like splenic mud. 110.

Case 5. Globular. 2250 g. Nothing abnormal in colour or consistence.

Case 6. 2200 g. Deep reddish-brown colour, marbled with blackish or purple spots. A general hyperaemia. Barthélemy-Benoit (1865).

Enlargement : is due to the b.w.f. and not to prolonged residence in Senegambia.

Engorgement : The portal system is distended with blood. A venule has become a vein of average diameter and so on. On incising the liver in several places there is a notable loss in weight. The turgidity does not affect all venules, nor if a vein is carefully dissected, is its diameter uniform—it varies here and there.

1. Death during first week. The surface colour is less uniform than normally. It is marbled with little patches of congestion as is seen also in the parenchyma on section.
2. Death in 2nd or 3rd week. Congestion has diminished. Only a certain number of veins of fairly large diameter exude blood on section, while surrounding areas are completely empty.

The blood whenever death has occurred is fluid, black and being mixed with a fairly large quantity of bile has a peculiar violet colour. It is also more oily. Bérenger Féraud (1874), 81.

Case 7. Hypertrophied, slightly decolourized, grates (*crie*) under the scalpel.

9. Not inflamed.

11. Greatly hypertrophied, deep red, soft, penetrable by the finger.
13. 1900 g. chestnut-colour. Here and there small Hgic networks and somewhat redder spots—local congestions.
17. Enlarged, greyish, smooth, firm.
18. Not much enlarged, deep chestnut-colour, smooth.
19. Red, congested. The red and yellow colours of the hepatic granules are confused. Bleeds on section. Bile ducts portal-hepatic and sub-hepatic vessels red not icteric.
22. (Suppression.) 2950 g. lemon-colour. Slightly injected, firm slatey patches.
23. 2045 g. Mahogany-colour, smooth. Patches of clear yellow more extensive, and small bright red Hges, here and there forming ecchymoses, less so. Only the large vessels contain blood. Consistence less than normal, easily torn by the finger.
24. 2430 g. On the under side of the right lobe, a mahogany patch 4–5 cm. square. Bérenger Féraud (1874).

Guadeloupe.

1. Enlarged, yellow, pale, bloodless ; or
2. Enlarged, highly congested, deep brown, with grey and red punctations and a punctiform blackish pigmentation of the fine superficial vessels ; or
3. Congested and brown with pale yellow patches (combination of 1 and 2).

This fatty infiltration and icterus are less developed than in yellow fever. The nutmeg liver—brown area with yellow surrounding zones—of yellow fever is not seen in b.w.f. Pellarin (1876), 324.

Cells : no degeneration, brown shining granules for the most part small, giving without exception the blue Fe-reaction.

Vessels : 1. Larger irregular clumps giving a brighter blue reaction; 2. blackish-brown granules singly, or in masses of 3 or 4, not giving the iron reaction.

Bile ducts : here and there blue-staining granules. Stieda (1893).

Capillaries : dilated, containing some melanin granules.

'Embryonic proliferation' : in portal spaces and sub-hepatic veins.

Hepatic cells : swollen, protoplasm cloudy; nuclei stain fairly well.

Leucocytic infiltration : of the lobular capillaries. Ferrier (1896), 324, 460.

Oliguria. Death, day 4.

Enlargement : slight, surface smooth, blood flowed freely on incision.

Colour : pale, rather waxy-looking on section.

Necrosis : small necrotic foci lateral to the intra-lobular vein occasionally extending to the periphery of the lobule. The cells in these areas were shrunken, stained badly, nuclei distorted and staining diffusely.

Thrombosis : in considerable amount in the sub-lobular veins. Here and there pigmented cells occur in the thrombi.

Pigment : 1. Yellow pigment in the centre of the liver cells.

2. Greenish-black pigment in large swollen cells in the capillaries. It occurs in spherical clusters as in the spleen and is frequently surrounded by a clear area. In the swollen endothelial cells this pigment occurs in spherical masses and is found here together with yellow pigment.

3. In leucocytes in the small vessels.

The yellow pigment with HCl and K_4FeCy_6 gives a uniform blue reaction which is also given by the black pigment of the endothelial cells, but much of the black pigment is unchanged. Stephens and Christophers (1900), 31.

Cases 5.

Enlarged, congested and rich in bile. *Gall bladder:* filled with bile.

1. In some cases isolated necrotic cells or rather little islands of necrosis.

2. In other cases the cells contained yellowish pigment or granules of Hgb.

3. In three cases the bile capillaries greatly injected and distended with bile, especially in the centre of the lobule.

4. Atrophy, vacuolation, in some parts necrosis, or complete disappearance of cells, leaving only the vascular network with Kupfer's cells.

5. Many cells contain yellow granules. Marchiafava and Bignami (1900), 499.

The accumulation of pigment (yellow) and of ferruginous materials, in the liver as found post-mortem, indicates the alternative method (other than renal) of eliminating the haemolytic products from the blood. Daniels (1901), 58.

Cases 12.

Hepatic cells: swollen and granular in 2, degeneration in 4. *Necrosis:* 7 positive, 4 negative. *Haemosiderin:* 8 positive, 3 negative.

Capillaries: dilated in 6.

Bile canaliculi: dilated in 8, with hyaline plugs in 5, colloid plugs in 3.

Gall Bladder: dilated in 2. The bile is thick, granular, curdy or slimy.

Malaria pigment: 10 positive, 1 negative. Whipple (1909).

Enlargement: usual, may weigh 2–3 kilos.

Engorgement: if death has been rapid, with a bronze or slate colour; if death has been late, it is often bloodless, fawn or chamois-leather colour.

Degeneration fatty: much less frequent than in yellow fever. Gouzien (1911), 71 (r.).

Oliguria. Death, day 4.

Hepatic cells : normal, nuclei of unequal size. Pigment only in the cells at the periphery of the lobule.

Biliary canalicui : dilated.

Portal Spaces : infiltration of young cells, hypertrophy of elastic fibres, some giant cells, abundant pigment free or in mononuclear cells ; one schizont found. Porak (1918), 561.

Hepatic cells : normal.

Capillaries : blood more or less normal, and in addition abundance of Hgb granules some tenths of μ in size. Iron reaction negative.

These granules are of the same kind as those in the kidney. Hence either a post-mortem phenomenon or the granules are formed in the circulation, and so excreted by the kidney. Ameuille, Sourdel and Marcorelle (1918).

Enlargement : in all cases.

Congestion : common, and there may be Hges, subcapsular or in the liver itself.

Necrosis : one of the commonest lesions, either central or wide-spread, with polynuclear leucocyte reaction, but on the other hand the changes in the cells may be slight.

Sinuses : may be dilated and contain agglutinated red cells or at times numerous mononuclear cells.

Melanin : in the sinus cells or free. Together with melanin there may be free-iron granules or a diffuse iron staining of the sinus cells.

Fe-reaction : may be intense in the liver cells, either in the central or peripheral areas or in both.

Iron-free pigment : a yellow iron-free pigment may fill the liver cells.

Bile ducts : distended with thick bile. Dudgeon (1920), 220.

Case 1. Death, day 2. Oliguria-Anuria.

Gall-bladder : full of bile.

Liver : 1720 g. Spaces of Kirnann thickened by new connective tissue. Central lobules rich in bile pigment. Kupfer's cells enlarged pigmented (malarial). Haemochromatosis (haemosiderin) chiefly in areas where Kupfer's cells less developed.

Case 2. Death, day 7. Oliguria-Anuria.

Gall bladder : full of thick bile.

Liver : 1980 g. Bile canaliculi injected, Kupfer's cells pigmented (melanin).

Case 3.

Liver : full of macrophages with brown pigment. Kupfer's cells : brown pigment. Connective tissue : brown pigment. Hepatic cells : ochreous pigment. Paterni (1923).

Cases 8.

Enlargement : in all, congested in all.

Sub-capsular Hges : in one case, visible to the naked eye.

Oedema : general oedema with isolation of the cell columns in some.

Parenchyma cells : severe degeneration and necrosis of cells of the central area. A good deal of bile pigments in this area.

Fibrosis : absent. No increase of collogenous fibrils.

Gall bladder : distended with thick viscid dark bile and the bile capillaries choked with thick bile in all cases.

Haemosiderin : in cells of central zone in all cases.

Malarial pigment : in endothelial cells of blood capillaries in 5. Not abundant in 2. Doubtful in 1.

Haemolysis : red cells seemed to be haemolysed in many. Thomson (1924), 67.

Glisson's capsule : in parts considerable collection of lymphoid tissue.

R.E.S. : cells filled with malaria pigment and red cells slightly changed or in the form of fragments.

Bile canaliculi : considerably dilated, desquamation of epithelium. Rapoport (1928), 70.

1 case ♀. Death 16 May. P.M. 18 May.

Weight : 1920 g. Gall bladder almost empty.

Liver cells : normal.

Vessels : no distension. All the capillaries contain more or less normal blood and an abundance of Hgb granules, like those in the renal tubules. They give no iron-reaction. Lemierre and Rudolf (1931), 723.

Lungs

Cases 10.

Normal in 2, patches of broncho-pneumonia in 3, oedema in 3, slightly bile-stained in 1. Whipple (1909).

Hges : subpleural in a few cases, alveolar in many, in the bronchial lumina in many. Hges may be widespread.

Oedema : common.

Thrombosis or *embolism* of *pulmonary artery* in 2. Dudgeon (1920), 221.

Pleural cavities : several ounces of fluid invariably present. In one case (that had received a considerable amount of saline intravenously), both cavities absolutely filled with clear fluid, and collapse of both lungs. Excess of pleural effusion also seen in another case treated with 2 pints of normal saline intravenously. Thomson (1924), 71.

Marrow

Case.	Colour.	Hyper-plasia.	Increase of eosino-phils.	Mal. pig-ment.	Numer-ous nu-cleated red cells.	Author-ity.
2	Deep red	+	+	+		Whipple (1909).
3	Dark green	+	+	+	+	
4	Mottled, red and fatty		+	+	+	
5	Deep purple	+	+	+	+	
6	Deep red	+	+	+	+	
7	Mottled, reddish-pink	+	−	+	+	
8	Jaundice	−	+	+		
9	Red	+	+	+	+	
10			+	+		
11	Chocolate or red		+	+ (crescents)		
12	Reddish-brown		+	+ (crescents)		

Nervous System

Brain : Nothing characteristic. Epicranial tissues and meninges anaemic. Congestion only occurs when there have been pronounced cerebral symptoms. If the membranes are washed they never show an icteric tinge. In yellow fever

the epicranial tissues and membranes are always congested. Pellarin (1876), 322.

Brain : Cases 11. Normal 2, pale in 8, waxy in 3, ecchymosis in cerebellar cortex in 2, ecchymosis in pons and corona radiata in 1. Parasites: positive 2, negative 5. Pigment: negative 4. Whipple (1909).

Sympathetic ganglia : degeneration of ganglion cells and intense neuronophagia. The changes still more pronounced in the Gasserian ganglion with lymphoid infiltration.

Medulla oblongata : perivascular lymphoid infiltration and circumscribed miliary granulomata. Rapoport (1928), 71.

Pancreas : Fat necrosis or Hgic pancreatitis: not found. *Hges :* common. *Islets of Langerhans :* degeneration in 2, glycosuria ·16% in the blood in 1. Dudgeon (1920), 220.

Rigidity : absence is probably due to climatic causes (heat and moisture). Barthélemy-Benoit (1865), 106.

Rigidity is not absent. The degree depends on the interval between the beginning and end of the attack. The shorter, the greater, and *vice versâ*. Bérenger Féraud (1874), 69.

Always present in b.w.f., as in other tropical diseases, but begins later and ends earlier, so that the duration is shortened. Pellarin (1876), 319.

Spleen

Weight in grammes :—

350	280	525	850	185
380	280	600	870	200
380	350	600	875	260
600	380	620	1000	300
780	380	750	1000	340
870	425	772	1050	520
900	450	780	1065	600
950	465	780	1120	700
1000	520	780	1140	890
1680	520	850	1290	990
			1320	1100
			1680	1260
Barthélemy-Benoit (1865), 110.	Bérenger Féraud (1874), 79.			Whipple (1909).

The consistence varies much. In those who have taken much Q. and who have died at a fairly long time from the febrile attack it is fairly dense; when the patient dies quickly it is diffluent. Bérenger Féraud (1874), 96.

Case 7. 1300 g.

9. Normal.
13. 685 g. Slate-colour with blacker patches indicating a preceding Hge (raptus). The parenchyma is a red chestnut with white points. On pressing the characteristic crackling is felt. Tears easily.
18. 465 g. Diffluent.
19. 520 g. Normal.
22. 1000 g. In a mush.
23. 1290 g. Diffluent.
24. 1050 g. In a mush. Bérenger Féraud (1874).

1. Black, voluminous, soft, more or less engorged (as in pernicious malarial fevers), or

2. Grey externally, red internally, containing little blood.

In yellow fever the spleen may be slightly congested but is usually normal. Pellarin (1876), 324.

Malpighian bodies : enlarged, like semolina grains.

Venous sinuses : dilated and full of masses of rusty pigment turning black with $(NH_4)_2S$.

Melanin : scattered fine granules in the lymphatic sheaths of the arteries. Boisson (1896[a]), 373.

Fibrous trabeculae : thickened and containing granules of melanin in their substance, much less than in malarial spleens.

Haemosiderin : scanty. Ferrier (1896), 324, 460.

Cases 12.

Malpighian follicles : Enlarged appearing as white milky spots (1–3 mm.) in 8, not enlarged in 3. *Central necrosis :* to a greater or less extent in 11, degeneration in 1. Surrounding necrosed areas, are phagocytes containing nuclear débris (and in one case red cells), collections of polynuclears and a fibrinous coagulum.

Pulp : Sinuses : distended in 4, hyaline plugs in 3, areas of fine fibrin or in coarse clumps in 3, areas of necrosis in 3, collection of eosinophil cells in 4, polynuclears in 5, phagocytes containing nuclear débris and red cells in variable number in 11, phagocytes containing melanin in 12, yellow pigment in 1. Whipple (1909).

Oliguria. Death, day 4.

Follicles : Development of young lymphocytes, around the follicular artery which shows peri-arteritis. In parts patches of epithelioid cells surrounded by lymphocytes. Hyperplasia of supporting tissue.

Cords of Billroth : Numerous pigmented macrophages and free pigment. Hyperplasia of supporting tissue.

Venous Sinuses : Empty. Annular fibres hypertrophied

Malaria : Schizonts present. Porak (1918), 561.

Cases 17

Enlargement : In every case.

Perisplenitis : Recent or chronic in every case.

Malpighian corpuscles : Frequently prominent—a striking feature. The enlargement is due to endothelial cell proliferation with partial necrosis of many of the cells. Large coarse free-iron granules occasionally present.

Splenic stroma : Necrosis localised or less commonly diffuse.

Sinuses : 1. Distension and congestion of their walls.

2. Phagocytosis of red cells by the lining endothelium or the phagocytes were free in the lumen. The endothelial proliferation of the sinuses enlarging them at the expense of the lymphoid tissue.

3. Agglutination of red cells in the lumen.

Vessels : Thrombosis in 2 cases with infarction of the tissue.

Melanin : In the sinus cells or free and also a true iron-free pigment. In some cases the apparent melanin granules gave a free-iron reaction. This was not seen in malaria.

Free-iron : In some cases a very marked free-iron reaction

in the stroma, as granules or as a diffuse staining of tissues or cells. Dudgeon (1920), 218.

Case 1. Death day 2. Oliguria-Anuria.

530 g. Follicles but little visible.

Sinuses: Contain few red cells, polynuclears and occasional large pigmented macrophages.

Pulp: infiltrated with red cells and macrophages containing malaria pigment and red cells.

Follicles: Pigment and red cell débris. Paterni (1923).

Cases 8

Size: From one half to three times the normal.

Consistence: Soft and pulpy. One of the most constant and marked features of the disease.

Perisplenitis: In all, recent or chronic. In two, capsule adherent.

Malpighian corpuscles: Enlarged, in some giving sago grain appearance.

Venous sinuses: Endothelial proliferation, giant cell formation and phagocytosis of red cells. Some sinuses contained very little blood, most of the red cells being deformed and badly stained; in others there seemed to be agglutination of red cells with evidence of haemolysis.

Malarial pigment: In 5 cases readily demonstrated in macrophages. In 3 cases a remarkable absence of pigment, but crescents found.

Free-iron: In all in the cells.

Bile-pigment: In one case.

Thrombosis: Of the larger vessels with congestion and oedema. Thomson (1924), 65.

Malpighian follicles: Much enlarged.

R.E.S.: Great hyperplasia, especially in the follicles.

Melanin: In excess present. Rapaport (1928), 71.

Thrombosis

Day 4, red cells ·82 millions. Day 6, death. At the autopsy the man was jaundiced and most of the internal viscera showed the effects of arterial thrombosis. Dudgeon (1920), 211.

Thyroid

Normal. Porak (1918), 561.

Considerable diminution in the colloid content of the thyroid vesicle was demonstrated, and in one instance active multiplication of the cells lining the vesicles had occurred. Dudgeon (1920), 222.

Summary

Kidneys

Glomeruli : often normal. The capsules may at times show distension and desquamation, and their contents may consist of granular matter, or blood débris or Hgb granules.

The exudate, the epithelium and the basement membrane may give a blue haemosiderin reaction.

Tubuli contorti : May be dilated. The epithelium may be normal flattened or show degeneration or necrosis. This latter may be local or may affect large tracts. Granules are described as occurring in the epithelium itself or closely applied to its surface. These granules may give a deep blue Fe-reaction which also may be given by the epithelium and basement membrane.

The contents of the lumina comprise: (1) albuminous matter tinged with Hgb, sometimes reticulate or fibrillar; (2) Hgb drops, blocks, granules, casts (coarse or fine); (3) red cell débris, red cells, agglutinated red cells; (4) epithelial casts, granular casts, hyaline casts, leucocytes.

Tubuli recti : Some dilatation and much of the epithelium may be shed, exposing the basement membrane. The contents consist of casts of granular matter or masses as large as red cells not sharply defined peripherally, from fragmented or agglutinated red cells. The blue Fe-reaction may be positive as a diffuse staining or pick out individual granules.

Interstitial tissue : Intense hyperaemia may occur, with here and there actual haemorrhages, and the passage of blood into the tubules through fusion of the necrotic capillary and tubular wall is described.

Some observers consider that in some cases (of anuria) the changes found are too slight, or at any rate not sufficiently uniform to explain the anuria by a mechanical block.

Liver

Necrosis of the hepatic cells is a common lesion, but also the cells may be normal. Yellow pigment giving the blue Fe-reaction is commonly present.

Spleen

Malpighian follicles : Hyperplasia, giving the "Sago-grain" appearance is common.

Venous Sinuses : Usually dilated, frequently with evidence of phagocytosis by the lining cells, or as free macrophages.

Stroma : May be necrotic in parts. In some cases an intense blue Fe-reaction, diffuse or as granules.

APPENDICES

APPENDIX 1

SYNONYMY

1. Maladie paludéenne ictérique (title) (Fièvre Jaune, typhus ictérode, fièvre rémittente bilieuse, fièvre rémittente pernicieuse mélanurique). Duchassaing (1850).

2. Fièvre pernicieuse ictérique. Daullé (1857).

3. Fièvre bilieuse grave des pays chauds (title). Dutroulau (1858).

4. Résorption biliaire. Loupy (1858). Bérenger Féraud (1874).

5. Miasmatic haematuria. Cummings (1859–60).

6. Fièvre ictéro-hémorrhagique, pernicieuse ictérique, accès jaune, fièvre jaune des acclimatés et des créoles (253), fièvre rémittente bilieuse, fièvre bilieuse hématurique (253), fièvre bilieuse grave. Dutroulau (1861), 605.

7. Fièvre ictéro-hémorrhagique. Loupy (1862).

8. Accès jaune, fièvre bilieuse de la Guadeloupe et de la Martinique, fièvre bilieuse grave, bilieuse hématurique, pernicieuse ictérique, fièvre rémittente bilieuse, fièvre jaune des créoles, fièvre bilieuse hématurique (title), fièvre bilieuse rémittente, hématurique. Barthélemy-Benoit (1865), 9, 11.

9. Fièvre bilieuse néphrorrhagique (title). Pellarin (1865).

10. Fièvre pernicieuse ictérique. Dutroulau (1868).

11. Haemorrhagic malarial fever (title). Michel (1869).

12. ' Haemorrhagic malarial fever . . . Syn *Haemorrhagic* Malarial fever [Michel]. Black jaundice [Ghent]. Cachaemia [Osborn]. Icterode Pernicious Fever [Mc-

Daniel]. Malignant Congestive Fever [Osborn]. Purpuraemia [Riggs]. Yellow Remittent [Sholl]. Yellow Disease. Cane-brake Yellow Fever. New Disease.' Boston (1869).

13. Malignant congestive fever. Osborn (1869).

14. Cachaemia Haemorrhagica; Malignant Congestive Fever; Icterode Pernicious Fever; Purpuraemia; Yellow Remittent; Yellow Disease; Cane-brake Yellow Fever, etc. Michel (1869). American (1870).

15. Malignant malarial fever. Michel (1869). Deaderick and Thompson (1916).

16. Haematemesic paludal fever. Faget (1870). Deaderick and Thompson (1916).

17. Malarial catarrhal haemorrhagic fever. Faget (1870). Deaderick and Thompson (1916).

18. Haemorrhagic intermitting fever (title). Mabry (1870).

19. Fièvre bilieuse mélanurique (title), fièvre bilieuse uro-hématique, fièvre jaune des créoles et des acclimatés, fièvre bilieuse hémato-poïétique. Bérenger Féraud (1874), 2.

20. Double tièrce subintrante ictérique (Campet, Pagnet, Le Vacher), maladie paludéenne ictérique (Duchassaing), accès pernicieux jaune (Guillasse), fièvre pernicieuse ictérique (Daullé (1857)), fièvre (bilieuse) ictéro hémorrhagique (Loupy (1862)), fièvre ictérique (Laure), fièvre jaune des créoles, fièvre jaune sporadique, fièvre atrabiliare ou atrabilieuse (Schott), fièvre bilieuse hématurique (Dutroulau et d'autres), accès bilieux grave (Lebeau), fièvre mélanuriquo (Bérenger Féraud), fièvre à urines noires, fièvre bilieuse néphrorrhagique (title). Pellarin (1876), 181.

21. Fièvre *hémosphérinurique* palustre. Karamitsas (1882).

22. Ictérique, jaune sporadique, jaune des créoles et des acclimatés, pernicieuse ictérique, fièvre hématinurique (Maurel) (233), fièvre bilieuse hématurique ou mélanurique (233), erythrurie (158), fièvre hémoglobinurique (144), fièvre atrabilieuse, fièvre bilieuse grave, fièvre hémosphérinurique, fièvre ictéro hématurique ou néphrorrhagique, fièvre rémit-

tente bilieuse avec hématurie, fièvre uro-hémorrhagique Corre (1883), 144.

23. Swamp yellow fever. Bailey (1883).

24. Malignant haematuria. McDaniel (1883).

25. Blackwater fever (title). Easmon (1884).

26. Highland yellow fever, Haematuria miasmatica (title). Stubbert (1886).

27. Haematuric cinchonism. Barton (1890).

28. Blut-fieber (1890). Fisch (1894), 80.

29. Lipaemia or malarial haematuria. Martin (1891–2).

30. Malarial haemoglobinuria. Jones (1892).

31. Febres tropica intermittens biliosa haemoglobinurica. Kohlstock (1892).

32. Fièvre bilieuse de Madagascar. Dutroulau (1868), 311.

33. Perniciosem Sumpffieber. Le Nobel (1892).

34. Yellow malarious fever with haemoglobinuria. Davidson (1892).

35. Pernicious malarial fever. Dock (1894).

36. Schwarzwasserfieber. Plehn, F. (1895).

37. Hémosphérinurie. Kanellis (1895).

38. Lysaemia or malarial Haematuria. Martin (1896).

39. Malarial haematinuria Woldert (1896).

40. Haemoglobinuric fever (title), yellow chills. Field (1899).

41. Black jaundice, bronze jaundice, lead jaundice, etc. Smith (1900).

42. Pseudo-yellow fever (Stone). Jones (1900).

43. Malarial methaemoglobinuria or haematuria. Goltman (1904).

44. Malarial hemoglobinuria, malarial hematuria, hemorrhagic malarial fever, hemoglobinuric fever, bilious hematuric fever, icteroid malarial fever, tropical bilious malaria, bloody chills, black jaundice, swamp fever, blackwater fever, lysemia, yellow chills, country yellow fever, Dressler's disease, Tomaselli's disease. Krauss (1904).

45. Fièvre bilieuse hématurique, fièvre bilieuse mélanu-

rique, fièvre bilieuse hémoglobinurique, f. ictéro-hématurique, f. ictero-hémorrhagique, f. hémosphenurique,* f. ictero-hémosphenurique,* f. pernicieuse ictérique, accès jaune, Perniciosa emoglobinurica, Emoglobinuria dei malarici, Albumina-emoglobinuria parosistica, febbre itero-emoglobinurica, f. ittero-ematurica, f. emoglobinurica, f. biliosa-ematurica, emoglobinuria da Chinina, malattia del Tomaselli, black-water fever, bilious hemoglobinuric fever, icteroid pernicious fever, haematuric fever, haematuric remittent, black jaundice, Schwarzwasserfieber, hamoglobinurische malaria-Fieber. Castex, González and Poletti-y-Roque (1928).

* *Sic.*

APPENDIX 2

HIPPOCRATES. CASE HISTORIES

Hippocrates, Epidemics, Book I (14 cases)*

Case 1.* *Philiscus.*

Day 1, acute fever. Day 3, acute fever, *black urine*, delirium. Day 4, *black urine*. Day 5, epistaxis, round particles resembling semen suspended in the urine which varied . . . *black urine*. Day 6, death. Spleen raised in a round swelling. 187.

Case 2. *Silenus.*

Day 1, pain in the loins. Abundant bilious frothy unmixed stools, *urine black with black sediment*. Day 2, urine *black*, slight delirium. Day 3, 'tightness' of the hypochondrium, stools thin, *blackish*, urine *blackish*. Day 6, urine *suppressed*, acute fever. Day 7, *no urine*. Day 8, an eruption of small red acne-like spots persisting. Day 10, passed a thickish urine which on standing left a white farinaceous deposit. Day 11, death.

From the start continuous throbbing in the hypochondrium. 189.

Case 3. *Herophon.*

Acute fever, scanty stools, tenesmus, afterwards thin and bilious, *urine black* and thin. Day 5, deafness, spleen swollen, tension of the hypochondrium, scanty black stools. Day 8, urine of a better colour. Day 9, crisis. Five days later relapse, at once the spleen swelled, return of deafness. Crisis about day 17. 191.

* The page references throughout refer to Jones (1923), but Littré (1839 and Fuchs (1897) have also been consulted.

[*Case* 5. *Wife of Philinus.*

2nd day after delivery acute fever, stools bilious, urine *thin and blackish.* Day 15, profuse bilious yellow vomit, urine thick white sediment. Day 20, scanty bilious black vomits. Day 80, complete crisis. 195.]

Case 6. *Cleanactides.*

Irregular fever. Day 24, several bilious yellow vomits later green. Day 40, *urine reddish*, abundant *red deposit.* Day 60, urine, abundant white homogeneous deposit. 197.

Case 7. *Meton.*

Fever, painful heaviness in loins. Day 4, slight epistaxis from the right nostril, urine rather blackish, with a blackish cloud (enaiorema) floating in it. Day 5, violent epistaxis from left nostril, urine *thin and blackish.* 199.

Case 8. *Erasinus.*

Fever. Day 2, delirium at night. Day 5, *urine suppressed*, death. The fever throughout accompanied by sweating, hypochondria swollen, painful. Urine black with round clouds (enaiorema) in it. 201.

Case 12. '*Anon*'

A man dined when hot and drank too much. Vomiting during night, acute fever, pain in right hypochondrium, urine at first *thick and red.* Day 5, much oily urine. Day 7, urine similar, delirium, liquid stools containing worms. Day 11, death. 207.

Epidemics, Book III, 1st Series (11 cases)

Case 2. Hermocrates.

Fever, tension of hypochondrium, *urine thick red, no sediment.* Day 5, urine thin. Day 6, jaundice. Day 11, urine thicker, reddish. Day 27, death. Deafness persisted throughout, urine thick and red without deposit, or thin, colourless with clouds (enaiorema) floating in it. 219.

Case 8. *Youth who lay sick by the Liars' Market.*

With fever. Day 1, copious stools, urine *thin and blackish*, no sleep. Day 3, nausea, delirium, tension of the hypochondria. Day 7, death. 233.

[*Case* 11. *Wife of Hicetas.*

♀. Miscarriage, fever. Day 5, general exacerbation, delirium, urine scanty *thin and blackish.* Day 7, death. 235.]

EPIDEMICS, BOOK III, 2nd SERIES (18 cases)

[*Case* 2. *The woman who lay sick by the cold water.*

♀. Childbirth. Day 3, fever. Day 8, delirium, rapid recovery of reason. Day 11, urine copious *thin and black.* Day 80, death. The urine was throughout *black*, thin and watery. 261.]

Case 3. *Pythion.*

Violent rigor, acute fever, urine *blackish* with a cloud (enaiorema). Day 3, nausea. Day 4, all symptons exacerbated, *urine black* with a 'cloud' in it. Day 7, urine oily, delirium. Day 9, comatose, nausea when he awoke. Day 10, death. 263.

Case 9. *Heropythus.*

Acute ardent fever, vomited copious bilious matter, thirst, urine *thin and black.* Day 14, deafness, urine the same. Day 40, copious epistaxis. Day 60 (about), epistaxis stopped, violent pain in right hip, fever increased. Day 80, all symptoms relieved, urine of good colour. Day 120, complete crisis. 271.

Case 10. *Nicodemus.*

Fever, nausea, urine thin and black. Day 2, fever increased, bilious yellow vomits, urine the same. Day 4, rigor, much fever, urine thin with clouds (enaiorema). Day 20, urine white, thick, no sediment. Day 24, urine white, much deposit, crisis. 275.

[*Case* 11. *In Thasos a woman of gloomy temperament.*

Day 1, feverishness, convulsions, delirium. Day 3, coma, then wakefulness. Day 3 about, *urine black* and thin, with particles, mostly round, floating in it. 277.]

Case 13. *Appollonius.*

Swollen abdomen, pain in region of liver, jaundiced, flatulent, exacerbations of fever, urine thin and scanty, painful swelling of the right hypochondrium. Day 14, rigor, delirium, copious bilious stools, *urine black, scanty* and thin, evacuations either black, scanty and verdigris coloured or else greasy . . . or at times like milk. Day 34, death. This patient suffered from disordered bowels; urine thin and black . . . delirious throughout. 279.

[*Case* 14. *A woman in Cyzicus.*

Parturition. Day 1, acute fever. Urine thin, colourless. Day 11, urine black, thin, then oily. Day 17, death. 281.]

APPENDIX 3

BLACK URINES

Galen [1]

Urina ei nonnunquam quod epotum est colore similis apparet. . . .

Quin igitur lotium rei potae colorem retinuerit, si aquae aut alicujus albi tenuisque vini potio fuerit, aqueum albumque conspicitur; si vinum crassum nigrumque fuerit, nigrior urina et crassior apparebit, quemadmodum et flavior, si vetustum fulvumque sit. Kuhn (1829), **17,** II, 275.

Demonstratum autem est nigras urinas ob serum bilis atrae una cum excrementis aquosis emissum procreari. Kuhn (1829), **16,** 512.

Color vero viridis sit in transitu ad nigrum, et est quoddam veluti prooemium nigri; nam si morbus malignus fuerit et vomitionibus et alvi dejectionibus et urinis viridibus postmodum nigrae superveniunt. Kuhn (1825), **9,** 605.

Aretaeus [2]

On ' Causus ' or Ardent fever. [Περὶ Καύσων] ' Heat indeed everywhere, both acrid and subtil but especially in the internal parts; respiration hot, as if from fire; inhalation of air large; desire of cold; dryness of tongue; parchedness of lips and skin; extremities cold; urine intensely tinged with bile; insomnolency; pulse frequent, small, and feeble; eyes clear, glancing, reddish; healthy colour of the countenance.' Adams (1856), Ch. IV, 272.

On Icterus

' In cases, therefore, of black icterus, the patients are of a dark green colour, are subject to rigors, become faintish,

[1] Galen 131–201 A.D.
[2] Aretaeus of Cappadocia, second half of second century.

inactive, spiritless; emit a fetid smell, have a bitter taste, breathe with difficulty, are pinched in the bowels; alvine evacuations like leeks, darkish dry, passed with difficulty; urine deeply tinged with black [*οὖρα κατακορέα ἐπὶ τὸ μελαντερον*].' Adams (1856), 83, 326.

Theophilus Protospatharius [1]

Quid significat Crassa Nigra? Haec etiam complexio datur, et humoris melancholici evacuationem declarat, ut in quartanae febris declinatione, et melancholiae (morbi) solutione. Guidotius (1703), 97. Ideler (1841).

Prosper Alpinus [2]

Thick black urine always derives its Colour from a more than ordinary copious Excretion of a gross atrabilious Humour or black Bile, or adult Blood; whence in Quartans and disorders proceeding from the Spleen and Melancholy, a thick and black Kind of *Urine* is evacuated. James (1746), **2**, 282.

Hart (1625)

In a critical and most entertaining work treats in Chap. V 'Of blacke urines . . . as also of blew, ash-coloured or leaden and greene coloured urines, together with their severall significations and uncertainties.' 75.

Our old father Hippocrates . . . doth peremptorily affirme that as well in men as in women, blacke urines are always dangerous. And . . . his trustie interpreter Galen, confidently avouching that he never knew anyone recover whose urine was altogether blacke; howbeit the danger was the lesser if the residence (i.e. residue or sediment) only were blacke; lesse again if the middle part or swimme, and least of all if the cloud onely were of this colour. 77.

Blew urines, called commonly *veneta* et *caerulea*, being as it were a more remisse blacke, and not dyed with so great a quantity of that humour. . . . 82. Hart (1625).

[1] Greek anatomist, early seventeenth century. [2] 1553–1617.

Willis * (1684).

For it is an errour commonly committed when the Urine being yellow and tinging the linen by the taking of Rhubarb, Saffron, Sanders, and the like, undoubtedly to believe it a sign of the Jaundice; also the urine being imbued with blackness by the taking of Cassia, to attribute it to the melancholick Tumor or black Bile. Pordage (1684), Treatise 3, 17.

Summary

' Black ' urines may be due : (1) to the drink being ' black,' (2) to bile, (3) to drugs.

The urines of at least categories 1 and 3 are what we should now-a-days term ' dark,' or ' highly-coloured ' urines. It is noteworthy that the urines of the case-histories of Hippocrates are not termed ' bloody.'

* 1621–1675. ' The anastomosis at the base of the brain . . . is to this day known as the circle of Willis.'

APPENDIX 4

MALARIA PARASITES IN B.W.F.

Day 1a.*		Day 1.		Day 2.		Authority.
Cases.	Pos.	Cases.	Pos.	Cases.	Pos.	
0	0	2	2	1	1	Arkwright and Lepper (1918a), 130, 132.
2	1	5	0	7	0	Barratt and Yorke (1909a).
		3	3			Barreto (1913).
		1	1			Brault (1903).
1	1	1	0	1	0	Brem (1906).
		16	2	14	3	Broden (1906).
1	1	9	3	12	4	Campenhout and Dryepondt (1901).
		1	1	1	0	Capogrossi (1910).
		15	0	4	2	Cardamatis (1911).
		1	1	1	1	Carducci (1907).
		10	6			Christophers and Bentley (1908a).
2	2	12	10	19	10	da Costa (1906).
3	3	3	1	2	0	Daniels (1901).
		4	1	2	0	Deaderick (1907).
28	14	36	12	42	7	Deeks and James (1911), 45.
		4	2	4	1	Esquier (1922).
		2	0	2	1	Fairley and Bromfield (1934).
		1	1	1	0	Frere (1910).
4	4	1	1	1	1	Fletcher (1914), 33, 50.
		1	1			Gastou and Dufougeré (1911).
1	1	2	2	2	1	German East (1909–1910).
		1	0	2	1	Grattan (1907).
		1	0	1	0	Jungels (1911).
2	2	2	1	1	0	Kleine (1901).
7	5	10	6	8	1	Koch (1899).
				1	0	Krauss (1904).
				1	0	Külz (1908).
				1	1	Külz (1910).
3	2	6	2	7	1	Manson-Bahr and Sayers (1927), 273.
				1	0	Marshall (1910).
				1	1	Masterman (1906).
2	1	1	0			da Matta (1912).
1	1	42	24	34	6	Nigeria (1916, 1919, 1920, 1921, 1922).
		19	4	16	2	Nigeria (1928).

* 1a = day before the b.w.f.

Day 1a.*		Day 1.		Day 2.		Authority.
Cases.	Pos.	Cases.	Pos.	Cases.	Pos.	
1	1	1	0	1	0	O'Donoghue (1912).
				1	1	Orme (1908).
1	1	1	0	1	0	Otto (1902).
13	11	25	17	23	6	Panse (1902).
		1	1			Patrick (1918).
5	5	11	8	11	4	Plehn, A. (1896).
		20	17	10	3	Plehn, F. (1898).
2	2					Powell (1898).
				1	0	Römer (1911).
		16	5			Ross (1932), 74.
1	0	1	0	1	0	Ross, Thompson and Simpson (1910).
1	1	1	1	1	0	Ruge (1902).
2	2	3	1	3	1	Seyfarth (1918a), 268.
2	1	10	5	17	5	Stephens and Christophers (1901).
				2	1	Whipple (1909).
		3	3	1	1	Wiener (1917).
5	0	5	0	5	0	Yorke, Murgatroyd and Owen, 1930.
90	61	310	145	278	67	

* 1a = day before the b.w.f.

APPENDIX 5

INTERVALS BETWEEN QUININE AND HGBURIA *

	Quinine.	Hgburia.	Interval.	Authority.
1	6 p.	11 a.	17	'Africa' (1912), 12.
2	7 p.	10 a.	15	Ibid., 14.
3	6 p.	10 p.	4	Ibid. (1914), 63.
4	5 a.	11 a.	6	Ibid., 61, Case 49.
5	7 p.	12 m.	5	Ibid., 61, Case 51.
6	3.30 p.	8 a.	16½	Ibid., 24.
7	6.30 a.	10.50 a.	4⅓	Ibid., 4, Case 1.
8	7 p.	2 a.	7	Ibid., 20, Case 20.
9	11 a.	11.30 a.	½	Ibid., 37, Case 33.
10	6 a.	7 a.	1	Ibid. (1915), 38.
11	7 a.	10 a.	3	Ibid., 80.
12	7 a.	9 a.	2	Ibid., 69.
13	6 p.	6 a.	12	Ibid., 71.
14	9 p.	1 a.	4	Arkwright and Lepper (1918[a]), 152.
15	10 a.	12 n.	2	Barratt and Yorke (1909), 177.
16	12 n.	3.30 p.	3½	Ibid., 182.
17	12 n.	5 p.	5	Ibid., 207.
18	9 a.	10.15 a.	1¼	Ibid., 217.
19	12 n.	4.45 p.	4¾	Ibid., 222.
20	7 p.	10 p.	3	Ibid., 226.
21	7 a.	4 p.	9	Ibid., 231.
22	10 a.	11 a.	1	Brahmachari and Sen (1925–26), 337.
23	11.30 a.	12.15 p.	¾	Ibid.
24	9.50 a.	1 p.	3⅙	Ibid.
25	8.50 a.	11 a.	2⅙	Ibid.
26	10.40 a.	12.45 p.	2 1½	Ibid.
27	11 a.	2 p.	3	Brahmachari (1929), 2.
28	11 a.	1 p.	2	Brahmachari, Brahmachari and Bannerjea (1932), 121.
29	7 p.	9.30 a.	14½	Ibid.
30	9 a.	5 p.	8	Du Bose (1899), 539.
31	10 a.	5 p.	7	Burkitt (1915), 1138.
32	9 a.	6.20 p.	9⅓	Brem (1906), 1904.
33	11 a.	1 p.	2	Brem (1911), 156.
34	8.30 a.	10.30 a.	2	Ibid., 157.
35	9 p.	11.15 p.	2¼	Ibid., 159.
36	9 p.	5.30 a.	8½	Ibid., 154.
37	6 a.	11 a.	5	Broden (1906), Case 5.
38	3 p.	6 p.	3	Ibid., Case 6.
39	4 p.	6 p.	2	Ibid., Case 7^1.
40	6 a.	12 n.	6	Ibid., Case 7^2.

* The data refer to those cases where the time of the last dose of Q. and the time of the onset of Hgburia are both given.

	Quinine.	Hgburia.	Interval.	Authority.
41	3 p.	5 p.	2	Broden (1906), Case 8.
42	4 p.	10 p.	6	Ibid., Case 9.
43	10 a.	5 p.	7	Ibid., Case 10.
44	10 a.	4 p.	6	Ibid., Case 12.
45	6 a.	9½ a.	3½	Ibid., Case 13.
46	12 n.	1 p.	1	Ibid., Case 14.
47	10 p.	9 a.	11	Ibid., Case 15.
48	8 p.	2 a.	6	Ibid., Case 16.
49	7 a.	2 p.	7	Ibid., Case 18.
50	8½ a.	11½ a.	3	Ibid., Case 19.
51	8 a.	1 p.	5	Ibid., Case 20.
52	5 p.	12 m.	7	Ibid., Case 21.
53	8 a.	11 a.	3	v. Campenhout and Dryepondt (1901), Case 2.
54	6 a.	12 n.	6	Ibid., Case 4.
55	2 a.	3 a.	1	Ibid., Case 7.
56	7 p.	5 a.	10	Ibid., Case 12.
57	5 p.	7 p.	2	Chevreau (1908), 139.
58	5 p.	9 a.	16	Ibid., 95.
59	7 a.	2 p.	7	de Chanal (1908).
60	7 a.	8 a.	1	Ibid.
61	7 p.	12 m.	5	Ibid.
62	6 a.	12 n.	6	Ibid.
63	2 p.	4 p.	2	Ibid.
64	8 a.	5 p.	9	Ibid.
65	4 p.	5 p.	1	Ibid.
66	3 p.	6 p.	3	Ibid.
67	7 a.	11 a.	4	Ibid.
68	7 a.	12 n.	5	Ibid.
69	12 n.	12 n.	0	Christophers and Bentley (1908[a]), Case 6.
70	9.30 a.	2 p.	4½	Ibid., Case 4.
71	7 a.	11 a.	4	Ibid., Case 8.
72	10 a.	2 p.	4	Ibid., Case 9.
73	7 a.	11 a.	4	Ibid., Case 10.
74	8 a.	2.30 p.	6½	Ibid., Case 20.
75	2.30 p.	5.15 p.	2¾	Ibid., Case 21.
76	12 n.	4 p.	4	Ibid., Case 26.
77	10 a.	2 p.	4	Ibid., Case 27.
78	7 a.	2 p.	7	Ibid., Case 28[1].
79	7 p.	3 a.	8	Ibid., Case 29[1].
80	9 p.	4 a.	7	Ibid., Case 29[2].
81	7 p.	2 a.	7	Connal (1922[a]), Case 5.
82	7 a.	3.45 p.	8¾	Ibid., Case 27.
83	1.30 p.	4 p.	2½	Connal (1922[b]), Case 1.
84	1.30 p.	3 p.	1½	Ibid., Case 1.
85	6.30 a.	8.30 a.	2	da Costa, Case 1.
86	11 a.	11½ a.	½	Ibid., Case 3.
87	10 p.	11.30 p.	1½	Ibid., Case 7.
88	3 p.	5 p.	2	Ibid., Case 8.
89	5 p.	10 p.	5	Ibid., Case 12.
90	9 a.	11 a.	2	Ibid., Case 14.
91	8.50 a.	9 a.	⅙	Ibid., Case 15.
92	6 a.	9 a.	3	Deaderick (1907).
93	2.30 p.	4.30 p.	2	Ibid.

	Quinine.	Hgburia.	Interval.	Authority.
94	11 a.	1 p.	2	Deeks and James (1911), 63.
95	4.30 p.	7 p.	2½	Ibid., 109.
96	7 p.	11 p.	4	Dempwolff (1898), Case 19[3].
97	3 a.	8 a.	5	Ibid., Case 20[2].
98	7 a.	12 n.	5	Ibid., Case 21[1].
99	9 p.	2 a.	5	Ibid., Case 21[3].
100	9.30 a.	12 n.	2½	Ibid., Case 23.
101	11 a.	12.30 p.	1½	Doering (1898), Case 1.
102	9 a.	1 p.	4	Ibid., Case 6.
103	8 a.	10 a.	2	Ibid.
104	8 p.	12 n.	4	Ensor (1906), 390.
105	9 a.	3.40 p.	6¾	Easmon (1885).
106	2.30 p.	6 p.	3½	Fairley and Bromfield (1934–35), Case 1.
107	4 p.	6 p.	2	Ibid., Case 7.
108	2 a.	4 a.	2	Ibid., Case 8.
109	5 p.	8.30 a.	15½	Ibid., Case 9.
110	4 p.	5.30 p.	1½	Fink (1912), Case 15.
111	7.30 a.	10 a.	2½	Ibid., Case 15.
112	8 a.	11 a.	3	Fletcher (1914), 45.
113	6 p.	12 m.	6	Gaskell (1920), Case 1.
114	6 p.	12 m.	6	Ibid., Case 2.
115	6 p.	8 p.	2	Ibid., Case 3.
116	2 p.	4 p.	2	Ibid., Case 4.
117	6 p.	12 m.	6	Ibid., Case 4.
118	8 a.	4 p.	8	Ibid., Case 6.
119	9 a.	9 a.	0	Gouzien (1900[a]), 15 (r.).
120	4.30 a.	11.30 a.	7	Karamitsas (1879), Case 1.
121	3 a.	4 a.	1	Ibid., Case 3.
122	8 a.	10 a.	2	Ketchen (1906), 1258, Case 1[5].
123	6 p.	10 p.	4	Ibid., Case 1[7].
124	8 a.	10 a.	2	Ibid., Case 1[8].
125	10.30 p.	8 a.	9½	Kleine (1901[c]), 666, Case 2.
126	9 a.	3 p.	6	Ibid., Case 2[2].
127	9 p.	1 a.	4	Ibid., Case 5.
128	8 a.	11 a.	3	Ibid., Case 15[3].
129	6 a.	8.30 a.	2½	Koch (1899), Case 17[1].
130	11 a.	2.45 p.	3¾	Ibid., Case 17[2].
131	11 a.	3 p.	4	Link (1906), 1833.
132	9 a.	9 a.	0	Lemoal (1907).
133	5 p.	9 p.	4	Ibid., 265.
134	12 n.	8 p.	8	Mann (1902), 528.
135	12 n.	4 p.	4	Ibid.
136	12 n.	4 p.	4	Ibid.
137	12 n.	8 p.	8	Ibid.
138	2 p.	8 p.	6	Ibid.
139	12 n.	8 p.	8	Ibid.
140	7 a.	10 a.	3	Ibid.
141	7.45 p.	5 a.	9¼	Manson Bahr (1926–27).
142	3 p. (20th)	11 a. (21st)	20	Marcandier (1916), 658.
143	8 p.	10 p.	2	Mollow (1910), 1338.
144	9 a.	12 n.	3	Moreschi (1920).
145	11 a.	6 p.	8	Nocht (1905).
146	7 a.	1 p.	6	Ibid., 218.

	Quinine.	Hgburia.	Interval.	Authority.
147	5 p.	7 p.	2	Newell (1909), Case 1.
148	10.30 a.	2.15 p.	3¾	Ibid., Case 2.
149	9 a.	12 n.	3	Ibid., Case 5.
150	8 a.	4 p.	8	Ott (1916).
151	11 a.	12 n.	1	Pampoukis and Chomatianos (1888), Case 1[2].
152	6 a.	8 a.	2	Ibid., Case 2[2].
153	9.30 a.	3 p.	5½	Parrot (1918), 846, Case 1.
154	10 a.	2 p.	4	Ibid., Case 1.
155	9 a.	2 p.	5	Ibid., Case 2.
156	8 p.	4.30 a.	8½	Parrot (1921).
157	10 a.	5 p.	7	Patrick (1919).
158	8 a.	11 a.	3	Panse (1902), Case 14.
159	8 p.	10½ p.	2½	Ibid., Case 15.
160	6 a.	12 n.	6	Ibid., Case 19.
161	6 a.	10 a.	4	Ibid., Case 21.
162	8.30 a.	10 a.	1½	Ibid., Case 26.
163	8 a.	12 n.	4	Ibid., Case 27.
164	8 a.	5 p.	9	Ibid., Case 28.
165	8 a.	5 p.	9	Ibid., Case 32.
166	9 a.	12 n.	3	Ibid., Case 33.
167	8½ a.	2 p.	5½	Ibid., Case 34.
168	9 a.	4 p.	7	Ibid., Case 35[1].
169	8 a.	11 a.	3	Ibid., Case 35[2].
170	9.30 a.	12 n.	2½	Ibid., Case 35[3].
171	10 a.	2 p.	4	Plehn, A. (1896), Case 2.
172	11 a.	8.45 p.	9¾	Ibid., Case 4.
173	11 a.	5 p.	6	Ibid., Case 9.
174	6 p.	8 p.	2	Ibid., Case 10[1].
175	5½ p.	1 a.	7½	Ibid., Case 16.
176	3 a.	8 a.	5	Ibid., Case 17[3].
177	11 a.	2 p.	3	Ibid., Case 17[4].
178	8 a.	12 n.	4	Ibid., Case 23[1].
179	8 a.	11½ a.	3½	Ibid., Case 23[2].
180	7 a.	10 a.	3	Ibid., Case 24[1].
181	7 a.	3 p.	8	Ibid., Case 24[2].
182	8 a.	5 p.	9	Ibid., Case 27[2].
183	12 n.	3 p.	3	Ibid., Case 30.
184	9½ p.	12 m.	2½	Ibid., Case 31[1].
185	3½ p.	3.35 p.	$\frac{1}{12}$	Ibid., Case 31[2].
186	9 a.	2 p.	5	Ibid., Case 35.
187	11 a.	1.20 p.	2⅓	Plehn, F. (1898), Case 16[1].
188	9 p.	12 n.	15	Ibid., Case 16[2].
189	10.30 a.	12 n.	1½	Ibid., Case 17[1].
190	7 a.	10½ a.	3½	Ibid., Case 18.
191	6 a.	12 n.	6	Ibid., Case 22.
192	11 a.	12½ p.	1½	Ibid., Case 24.
193	9 a.	11 a.	2	Ibid., Case 25.
194	7 a.	10 a.	3	Ibid., Case 27.
195	7 a.	8½ a.	1½	Ibid., Case 28.
196	10 a.	1 p.	3	Ibid., Case 33.
197	10 p.	5 a.	7	Ibid., Case 37.
198	7 a.	11 a.	4	Ibid., Case 39.
199	6 a.	8 a.	2	Ibid., Case 40.

	Quinine.	Hgburia.	Interval.	Authority.
200	5 p.	8 p.	3	Plehn, F. (1898), Case 19.
201	2 p.	5.45 p.	3¾	Ramsden, Lipkin and Whitney (1918), 247.
202	6 p.	10 p.	4	Rivers (1904), 159.
203	8 p.	10.30 p.	2½	Ross (1927).
204	8 p.	2 a.	6	Ibid.
205	9 a.	10.30 a.	1½	Ibid., 80.
206	7 p.	12 m.	5	Ross and Low (1903).
207	11 a.	8.30 p.	9½	Ruge (1902), 504.
208	4 p.	8.30 p.	4½	Ibid., 505.
209	8 a.	10 a.	2	Schäfer (1911), 793.
210	9 a.	12 n.	3	Schumacher (1911), 672.
211	10 a.	4 p.	6	Seyfarth (1918[a]), 268.
212	7 p.	9 p.	2	Stephens and Christophers (1900), Case 1.
213	10 p.	8 a.	10	Ibid., Case 4.
214	12 n.	5 p.	5	Ibid., Case 5[1].
215	8 a.	3.30 p.	7½	Ibid., Case 5[2].
216	12.30 p.	4.30 p.	4	Ibid., Case 8.
217	6 a.	12.30 p.	6½	Stephens and Christophers (1901), Case 9.
218	6 p.	10 p.	4	Ibid., Case 13.
219	6 a.	6 a.	24	Ibid., Case 16.
220	10 a.	5 p.	7	Ibid., Case 19.
221	3 p.	3 a.	12	Stephens and Christophers (1902), Case 20.
222	6 p.	9 p.	3	Thomson (1924), Chart X.
223	12.30 p.	4.45 p.	4¼	Ibid.
224	10 p.	12 m.	2	Tomaselli (1897), 14.
225	6 a.	8 a.	2	Ibid., 15.
226	8 p.	11 p.	3	Ibid., 17.
227	4 a.	6 a.	2	Ibid., 20.
228	5 a.	8 a.	3	Ibid., 36.
229	5 a.	7 a.	2	Ibid., 86.
230	5 a.	9 a.	4	Ibid., 96.
231	6 a.	7 a.	1	Ibid., 97.
232	9 p.	5 a.	8	Ibid., 118.
233	9.40 a.	11.35 a.	2	Ibid., 120.
234	12 n.	2 p.	2	Williamson (1909).
235	7 a.	11 a.	5	Ibid.
236	2 p.	6 p.	4	Yorke, Murgatroyd and Owen (1930), Case 1.
237	2 p.	6 p.	4	Ibid., Case 2.
238	6 p.	8 a.	14	Ibid., Case 3.
239	6 p.	10.30 a.	16½	Ibid., Case 4.
240	2 p.	4 p.	2	Ibid., Case 4.

Note.

Two errors occur in the summary, p. 127.

No. 92. The interval was taken erroneously as 2 instead of 3.

No. 181. The figures were taken erroneously as 7 a., 12 n., 5, instead of 7 a., 3 p., 8.

DAY OF DEATH

Day.	Deaths.															Total.	Total.
1									1							1	
2	1		1			1		1		3				1	1	9	
3	1	1	1				1	1		2	8			1	3	19	
4	1				2		2	1		1	7	1	4	5	1	25	
5	2			1	1	1	1			1	3	1	5	3	1	21	
6							1			1	2		1			5	
7					1		2			1	1		2			7	87
8		1	1		1	1				1	3		1	3	1	13	
9						1			1		2					4	
10			1	2					2							5	
11	2				1							1				4	
12													1			4	
13											2				1	3	
14						1	1				2				1	5	38
15																	
16					2											2	
17				1												1	
18														1		1	
19											1					1	
20																0	
21																0	5
21+	2						1									3	3
	Bérenger Féraud (1874).	Crosse (1892).	Fisch (1896).	Plehn, A. (1896).	Plehn, F. (1898).	Koch (1899).	Panse (1902).	Christophers and Bentley (1908[a]).	Barratt and Yorke (1909[a]).	Deaderick (1910).	Deeks and James (1911).	'Africa' (1912).	'Africa' (1914).	'Africa' (1915).	Gaskell (1920).	Connal (1922[a]).	133	133

APPENDIX 7

CINCHONA (PERUVIAN BARK)

Discovery [1]

Caput I.

De Loco natali Corticis, seu Arboris Cortiferae. Quod hic referam habeo ab Epistola M.S. Italica M. Antonii Bolli Mercatoris Genuensis, cui ideò praestanda fides est, tùm quia id meretur ipse, et quia mercimonia exercuit cum hominibus Indianis. Referit itaque natales Arboris istius ad Americam; nascique ait in Regno *Quitensi*, sed non ubique eam frondescere; nam peculiari quodam loco nascitur, qui dicitur patrio Indorum sermone *Loxa*, seù *Loia*; distatque 60 *Leucas* a Civitate, quae *Quito* dicitur. 16.

Redeo ad Historicam Bolli narrationem, narrantis in cit. Epistola, jam olim *Indis* hominibus innotuisse Corticem sibique in morbis illum adhibuisse; at conatos semper fuisse omni spe, ne Hispanis hominibus innotesceret Remedium quibus potissimùm et Europaeis insensi sunt. 21. Bado (1663).

He (Mr. William Arrot [2]) assured me that the current opinion at Loxa is, that its Qualities and Use were known by the Indians before any Spaniard came among them, and that it was applied by them in the Cure of intermitting Fevers, which are frequent over all that wet unhealthy Country. Gray (1737–38), 86.

The use of Quinquina was known to the Americans before it was known to the Spaniards, and according to the manuscript letter of Antoine Bollas, a Genoese merchant who had done business in that country (quoted by Sebastian Bado,

[1] Peru was discovered in 1513, and submitted to the Spanish yoke about the middle of the century.

[2] Had travelled in Peru.

Lib. 1, Cap. 1), the natives of the country had for a long time concealed this specific from the Spaniards, which is very likely, seeing the antipathy which they still have to-day for their conquerors. Condamine (1740).

The Antifebrile Virtue of the Peruvian bark was discovered by Chance. Some trees which bear it being blown into a Canal or Pool of Water, lay there till the Water acquired so bitter a taste that no Person could drink it; one of the neighbouring Inhabitants, however, being seized with a violent hot Fit of an Ague, and finding nothing else to quench his Thirst ventured upon a large Draught of this bitter Water, which cured him of his Fever and Thirst at the same time. . . . Upon a diligent Search after the Cause of this Bitterness, they at length traced it up to the Bark of these Trees. Geoffroy (1736), Pt. I, Ch. V, 41; Pt. III, Sect. II (6), 303.

According to an ancient tradition, the truth of which I do not vouch for, the Americans owe this discovery to the lions, which some naturalists allege are subject to a kind of intermittent fever. It is said that the natives having noticed that these beasts gnawed the bark of the *Quinquina* made use of it in attacks of fever, common enough in that country, and recognized its salutary virtue. I should note by the way that the Lions of America are very much smaller and quite different from those of Africa, as for Tigers I have seen some very large ones in America appearing to differ in no way from African tigers. Condamine (1740).

Nihilominus labente tempore aliquid subolfieri coeptum ab Hispanis et Remedium quod tàm sedulò ab Indis custodiebatur nosci coepit. . . .

Aegrotebat forte in *Civitate Limensi* quae est *Metropolis* Regni Peruviae, Uxor Proregis, qui tùm temporis erat *Com. del Cinchon* (falluntur qui *Marchionem* de *Mancera* * fuisse dicunt) eratque morbus ejus *Tertiana* febris. . . . Rumor hujus aegritudinis (ut sit de Magnatibus) per Urbem statim vulgatus, ad finitima quaeque loca pervasit, *Loxamque* usque-

* Viceroy of Peru, 1640–1650.

tenuit. Fluxuerint, puto ab eo tempore, ad id temporis, triginta, vel quadraginta anni.

Praefecturam tùm agebat eo loci *Hispanus* homo, qui de Comitissae aegritudine certior factus, deliberavit per *Litteras* maritum Proregem admonere, quod posteà fecit, in arcanis scribens, sibi esse *Remedium* quoddam quo si uti voluisset Prorex, sponsor indubius ei erat, convalituram ejus Uxorem febrique omni liberandam. Admonuit de hoc nuncio Uxorem maritus, quae statim annuit . . . Quibus auditis, deliberatum est de sumendo *Remedio*; quod sumpsit et mirum dictu, dicto citius convaluit, stupentibus omnibus. 22.

Nec tàm deferri jussit magnum Remedium, scilicet Corticem quàm voluit illud suis manibus *dispensare* frequentibus aegrotantibus. . . . Et hinc factum, ut is Cortex *pulvis Comitissae* vocatus deinceps sit quod Hispani dicunt *los polvos de la Condeça.* 23. Badus (1663).

1630

19 April, 1629, the new Viceroy, Don Luis Jeronimo de Cabrera y Bobadilla,[1] proceeded to Lima with his wife, Doña Francisca Henriquez Ribera, who hardly a year after her arrival fell ill of intermittent fever. Treated without success by the Court physician, Juan de Vega, her condition became very serious; it was then that the Jesuit, P. Diego de Torres Vasquez (1574–1649), vice-provincial of Peru, persuaded the Count, whose confessor he was, to allow the bark to be given to the patient, who in a short time got well, to the astonishment of all. Canezza (1933), 90.

1638

The virtues of Quinquina bark, though known to the Spaniards of Loxa and recognised and put to the test in all that canton, as is established from various witnesses,[2] were

[1] Count of Chinchon, Viceroy of Peru, 1628–1639.

[2] Among others, *D. Joseph Fausto de la Cueva*, a native of Loxa, where, employed in various occupations, he died in 1718, aet: 76. He told *D. Andrés*

for a long time ignored by everybody else, and the efficacy of this remedy only acquired a certain celebrity when the Countess of Chinchon, suffering from an obstinate tertian fever, did not recover after some months. Sebastian Bado tells the tale, but gives no date, contenting himself with saying that it was 30 or 40 years before the time he wrote. I have discovered the date, as I will now relate; it was in 1638, i.e. a year before the end of the Viceroyalty of the Count of Chinchon, who ended his governorship on 17 Dec., 1639, that this remedy almost unique, and which with reason one can call specific, rose from its obscurity; the historical fact is, moreover, well known; I will recall, however, some new details.

The *Corregidor* of *Loxa*,* a dependent of the Count of Chinchon, informed of the obstinacy of the Vice-reine's fever, which no remedy could control, sent to the Viceroy, his patron, some *Quinquina* bark, assuring him by letter that he would answer for the cure of the Countess, if the febrifuge were given her; the *Corregidor* was at once summoned to *Lima* for himself to prescribe the dose and its preparation, and after some trials successfuly made on other patients the Countess took the remedy and was cured.

I owe the greater part of the preceding historical elucidation to a Spanish manuscript almost entirely forgotten, and strayed into the Apothecaries' shop of the College of *Jesuits* in *S. Paul de Lima*, shown to me by R.P. *Bertrand Herbert*, a French *Jesuit* in the same town. This manuscript, of which the title and preface only are in Latin, is entitled *De Cortice Quinae Quinae et de Loxa etsi diversorum arborum uniformis virtutis.* It appears from a citation in the text that the author wrote in 1696, and at the end it is dated 1699. The author was Dr. *Dom Diego de Herrera*, who died in 1712 or 13, aged about 100. de la Condamine (1740), 239.

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de Munibo, an official of the archbishop of *Lima*, from whom I learned it, that when his father came from Europe, and before *Quinquina* was known *at Lima*, that this remedy was commonly used at *Loxa*.

* Don Juan Lopez de Canizares.

1640

The secret (of the Bark) was inviolably kept till the year 1640, when a Spanish soldier quartered in an Indian's house . . . was seized with a severe Ague. The Indian . . . brought him the Bark, which, having taken, he was soon perfectly cured. . . . The Soldier who was Master of the Secret, told his Commanding Officer that if he would allow him to go to *Lima*, he would cure the Vice-Queen . . . having succeeded in a very little time, he was amply rewarded. . . . The Spaniards made use of the Secret from that Time forward with so great Success, that the Physicians were astonished and half starved. Geoffroy (1736), Pt. III, Sect. II, 304.

P. Muzio Vitelleschi (1563–1645), General of the Company of Jesus, in a letter records the event. It is directed to P. Nicola Mastrilli (1570–1653), an Italian living in Nola, then a province of Peru. (Date not given.*)

'Grande soddisfazione ha recato la notizia della quarigione ottenuta dalla Ecc. ma Contessa de Cinchón per mezzo dei nostri confratelli. Cosi ha destinato N. S. a premiare la generosità degli Ecc. mi conjugi verso la nostra Compagnia e Specialmente verso il loro confessore, al cui suggerimento risale il bene conseguito. Abbiamo ricevuto dal P. Procuratore una certa quantita del medicamento che non si mancherà di sperimentare.' Canezza (1933), 90.

De Nomenclatura Arboris, et ejus Corticis.

Multifariam vocatur *Arbor* ista, sivè ab incolis, sivè ab aliis qui vocabulis Peruanae Regionis utuntur. Sunt qui *Gannanaperide* vocant, sunt qui *Chinanepide*, sunt qui *Guananepide*. Alii dicunt *Guananegide*. Sunt qui aliter vocari narrant. Hispanis dicitur *Palos de Calenturas* quod est dici *lignum febrium*. . . . De *Corticis* nomine dicendum, in quo est vis precipua, imò tota. Vulgato satis nomine dicitur *China China*, nescio cur geminent. Aliis dicitur *China febris*. Aliis *Gentiana Indica* appelatur, et ità *Hoeferus*

* From internal evidence this would appear to be the third quarter of 1632.

appellat lib 6. Herc. Med. C. 3. Alicubi *pulvis Jesuitarum. Romae* et in Thuscia *pulvis Cardinalis de Lugo*, Italicè *la polvere del Cardinal di Lugo :* nec immeritò sanè; nam ei in primis debetur, quòd Cortex in Europam translatus sit. Badus (1663), 25.

1694

Peru Bark comes from a tree about the bigness of a Plumb tree, with Leaves like Ivy, but not quite so big and are always green. The Indians call it Querango. . . . This account I received from an Ingenious Apothecary in Spain, A.D. 1694, who had lived in Peru and seen it growing, and gathered it several times. Oliver (1704–05), 1596.

He (Mr. William Arrot) could not tell me by what Artifice or Stratagem the *Jesuits* have got this Bark to be called after them, if not that they carried it first into *Europe*, and gave themselves out as the first Discoverers of its virtues. Gray (1737–38), 86.

Joseph de Jussieu especially, who visited Loxa in 1739, definitely fixes the cradle of the science of this precious remedy among the Indians of the village of Malacatos, some leagues south of Loxa. It forms part of his unedited memoire on quinquina.* ' It is certain that the first to have knowledge of the virtue and efficacy of this tree were the Indians of the village of Malacatos. . . . Forte fortuna, tum unus ex societate Jesu iter habuerat per vicum Malacotas, is laborans febri intermittente. Misericordia commotus Indorum dux, *Cacique* vocant cognito R.P. morbo; Sine paululum, inquit, et ad sanitatem perfectam te restituam. Hoc dicto, exilit ad montem Indus, corticem dictum attulit et decoctum ipsius patri propinavit. Sanatus et ad perfectam sanitatem restitutus Jesuita, perquisivit quod genus medicamenti applicaverat Indus. Cognito cortice, hujus non exiguam quantitatem collexit Jesuita, et, ad patriam redux, eadem ac in Peruviana regione pollere expertus est,

* Published 1936. *Vide* References, Jussieu.

inde notus primo fuit cortex *Pulveris jesuitici* nomine. . . . Weddell (1849), 15.

1643 (prior to)

'On the recovery of the Countess she distributed a large quantity of the Bark to the Jesuits, in whose hands it acquired still greater reputation, and by them it was first introduced into Europe, and hence called Cortex, or Pulvis jesuiticus, Pulvis Patrum; and also Cardinal de Lugo's Powder, because that charitable prelate bought a large quantity of it at great expense for the use of the religious poor of Rome.' Lambert (1797), 40.

APPENDIX 8

CINCHONA

Introduction of the Bark

1583

Though this Jesuits' Powder is not a Medicine newly found (the vertues for stopping of *quartan* Agues, having been experienced above a hundred years [1] since) but revived by a debauch'd Apothecaries Apprentice [2] of *Cambridge*, in the application to all intermittent Feavors. Harvey (1683), 165.

1632. *Introduction into Europe*

S. Barba, Professor of Medicine at Valladolid and body physician to Philip IV, quoted J. Villerobel, a Spanish physician, to the effect that it reached Spain in 1632, though it was not used until 1639 in Madrid. Barba (1642). Rolleston (1931), 263.

Extracts from the letter of D. Jos Villerobel are also given by Bado (1663), 202.

1632

For the earliest transportation of the bark we must thank the Jesuit Barnabé de Cobo (1582–1657). . . . In his capacity of Procurator of the Peruvian province of his order he brought the bark from Lima to Spain, and afterwards to Rome and other parts of Italy in 1632.[3] Rompel (1907), 372.

[1] Harvey was ascribing to *Cinchona* a historical fact which rightly belonged to the febrifuge bark of the Peruvian Balsam tree (*Myroxylon*). He, like many others, did not know that the new 'Quina' (Cinchona) was an entirely different tree from the old 'Quina,' Peruvian Balsam.

[2] Sir Robert Talbor.

[3] It is open to question whether Cobo came to Europe at this time.

1632

Transported from Peru, its place of origin, the remedy appeared in Rome in 1632. The Jesuit P. Alonso Messias Venegas (1557–1649), sent from this distant country as procurator to inform the general of the Order as to the progress of the mission established there, had jealously guarded during his voyage of about 2 years the foreign product, desiring to present at Rome these coveted first-fruits. Canezza (1933), 90.

1640

Straightway she (the Countess) had sent from *Loxa* a quantity of the same bark. (*Badus* states that it was at the request of the town of *Lima*, which made a deputation to it for that purpose.) However that may be, she herself distributed the remedy to all who had need of it, and it began then to be known as the *Countess's Powder*. Some months later she ceased from the work, giving what remained to the RR.PP. *Jesuits*, who continued to give it away gratis, and it then took the name of the *Jesuits' Powder*, which it has long borne in America and Europe. Shortly afterwards the *Jesuits* of *Lima* sent—when the Procurator-General of the province of Peru was returning to Rome—a quantity to *Cardinal de Lugo* [1] of the same Society, at whose Palace it was at first distributed and afterwards at the Apothecaries' shop of the Roman College, with the same success as at Lima, and under the same name or under that of the *Cardinal's powder*, gratis to the poor, and at its weight in silver to others, in order to pay for the expense of transport, which continued to the end of another century; it is stated also that this same Procurator, in his voyage through France to Rome, cured of fever with *Quinquina* the late King *Louis XIV*,[2] then Dauphin.

In 1640 the Count and the Countess [3] of *Chinchon* having

[1] Juan de Lugo. Born in Madrid 25 Nov., 1583. Made a Cardinal by Urbano VIII, 14 Dec., 1643. Died 20 Aug., 1660.

[2] Louis XIV, 1643–1715.

[3] The Countess died and was buried in 1641 at Carthagena, in Columbia, then a Province of Peru. 'Souvenir' (1930), 10.

returned to Spain, their physician *Juan de Vega*, who followed them, and who had brought a supply of *Quinquina*, sold it at *Séville* for a hundred reals the pound; it retained the same price and the same reputation until the *Quinquina* trees, not already barked, becoming rare, some of the inhabitants of Loxa, for motives of cupidity and having not the wherewithal to supply the quantity that Europe asked for, mixed different barks in the shipments they made to the fairs of Panama in the time of the Gallions, and this being recognised, *Loxa Quinquina* fell into such discredit that people were willing to give only half a piastre [1] per pound for which formerly they had paid 6 piastres at Panama and 12 at Séville. Condamine (1740).

1645

When P. Bartolomé Tafur (1589–1655), thirty years later in 1645, he also being a procurator of the Peruvian province, brought to Rome new supplies of the drug then carefully selected, many stated that it had already been imported and was known by the name of *gannaperide*. Canezza (1933), 90.

1646 (?)

Roma deinde in Belgiam attulere Societatis Jesu Patres qui ad electionem Praepositi Generalis in Urbem confluxerant. Sed et etiam Michael Belga *à Veteri molendino* cognominatus, Bruxellam attulit exipso Peruvio; ubi in regia civitate Lima per annos aliquot egerat in familia Marchionis de Macera Peruvii Proregis.[2] 51. Chifletius (1653).

1649

Nec tàm deferri jussit magnum Remedium, scilicet Corticem quàm voluit illud suis manibus *dispensare* frequentibus aegrotantibus. . . .

[1] A piastre is worth 8 reals, which corresponds to 5 pounds and some sous of our money to-day.

[2] 1640–1650.

Et hinc factum, ut is Cortex *pulvis Comitissae* vocatus deinceps sit, quod Hispani dicunt *los polvos de la Condeça*. . . . 23.

Quarè indè (Hispania) oportuit ad exteras quoque Regiones deferri adeoque ad *Italiam* nostram quemadmodum factum fuit Anno Dom. 1649, conante id in primis et curante *Ioan Cardinali de Lugo* Soc. Iesu. 24.

Sed neque debitis laudibus fraudandi *RR. Admod. et Religiosiss. PP. Soc. Iesu* qui Romae è Romani Collegii *ditissima Pharmacopaea* Corticem perindè largiuntur pauperis hominibus et Religiosis Viris mendicantibus *gratis* et *amore Dei*; exigentis duntaxat premiùm à ditioribus. 26. Bado (1663).

1649

In 1649 Father de Lugo, a Jesuite, then Procurator General of his Order, and afterwards a Cardinal, brought some of this bark to Rome.* . . . They sold it for more than the weight in gold; and to disguise it the better never parted with it but in Powder. From that time it was called *the Jesuites Powder*, because these Fathers were the sole Masters of it. . . . Two drachms were at that time thought sufficient for the Cure of any intermitting Fever. Geoffroy (1736), Pt. III, Sect. II, 305.

1653 (*before*)
Cardinal de Lugo

Chiflet in his work confines himself to the statement that the bark was brought to Cardinal de Lugo and so required fame. P. Honoratus Faber made known the generosity of his 'brother,' whom he knew in Rome for his gratuitous distribution of the drug acquired at his expense. Bado sung the praises repeatedly of the Cardinal, whom he met at Rome, for the same charitable work. Canezza (1933), 92.

Schelenz, H., concludes that the Cardinal carried on in reality a trade in drugs to the profit of the Order. Schelenz (1904).

* There appears to be no evidence for this statement.

APPENDIX 9

CINCHONA

Use of the Bark in England

Controversy

1655

Cortex Peruvianus cujus *Pulvis Patrum* vulgò nomine insignitur, annis ab hinc quinque et viginti (si benè memini) apud Londinenses nostras in exterminandis Febribus Intermittentibus, maxime Quartanis primum Coepit inclarescere. Sydenham, Epistolae, Ed. I (1680); Ed. II (1685), 15.

1656

There is a record of a pregnant woman at Brampton, near Huntingdon, who was cured by small doses of the Jesuits' powder by John Metford, M.D. Metford (1656). Rolleston (1931), 264.

1658

The bark advertised in "*Mercutius Politicus, comprising the sum of foreign intelligence, with the affairs now on foot in the three nations, for the information of the people.*

From Thursday, December 9, *to Thursday, December* 16, 1658."

The fever bark, commonly called the Jesuite's powder, which is so famous for the cure of all manner of agues, brought over by James Thompson, merchant of Antwerp . . . with directions for the use. Which bark, or powder, is attested to be perfectly true by Dr. Prujean * and other eminent doctors and physitians, who have made experience of it. Baker (1785), 190.

* President of the College of Physicians, 1650.

1659

Letter from Brady * to Sydenham

In sectione prima, Cap quinto, libri tui paucis egisti de usu Corticis Indici et ejusdem exhibendi methodo. Equidem scio quosdam haud infimi subsellii Medicos, qui in magna quantitate et dosi saepius repetitâ eum exhibent, alios item qui ex eodem extracta, infusiones, et ex infusionibus julapia et emulsiones conficiunt, quibus modis se non tantum Intermittentes, sed et continuas quasdam certò curare affirmant: Magnum procul omni dubio in Curandis Intermittentibus est remedium. Ego quidem per 20 plus minus annos dictum Corticem variâ forma et multiplici praeparatione maxima cum successu exhibendum curavi. . . . Vale, Vir integerrime qui hisce peragendis totam Medicorum turbam meritò divincies, inter reliquos verò,

Tibi jure meritoque amicissimum

Cantabrigiae R. Brady.

Decemb. 30. 1679.

Sydenham, 'Epistolae' (1680).

1660

De Cortice isto Peruviano, quia nuper quotidiam usus esse cepit, erunt haec nonnulla quae observationi communi prostant dicenda. Willis (1660), 164. (1676), 102. (1682), 70.

1663

Ità tandem. . . . Pharmacum hoc divinum, et in plurimis aliis morbis ac in Febre intermittente proficuum Anno 1663 . . . adaptatum est. Morton (1693), 143.

1663

The term 'Peruvian bark,' according to the 'New English Dictionary on historical principles,' is first used by Boyle (1663): 'That Peruvian bark that now begins to be somewhat taken notice of under the name of the Jesuits' Powder.'

* 1627–1700, Regius Professor of Physic, Cambridge.

1668

Me quod attiret Ego fidenter dico, idque postquam jam ad 25 annos quotidiano usu, ejus vires explorando expertus sum, me nusquam novisse aliquid mali abusu Corticis cuiquam evenisse, praeter *Surditatem* aliqualem tempore usûs molestam. Morton (1693), 139.

1668

In 1668 Sydenham (1624–1689), then in the height of his reputation, had still strong prejudices against the use of it . . . had hardly carried the principle (of its right use) into practice even in 1680. Baker (1785).

Its credit in Britain continued in a fluctuating state until the latter days of Sydenham. Relph (1794), 9.

1672

Talbor, Talbot Sir Robert, 1642(3)–1681

Assistant to an Apothecary (Dent.) He drew the attention of Prof. Nott in Cambridge to a better method of preparing Cinchona. Retired to the sea coast of Essex to experiment with this new preparation. This succeeded so well that he was often called to London to cure cases, and finally settled there in 1671. In 1672 he published his 'Pyretologia,' which brought down on his head the violent hostility of the Physicians, especially Morton and Lister,* so that the government had to protect him by a letter against the College of Physicians. He cured Charles II, and he was made King's Physician in Ordinary, and was knighted 27 July, 1678. *Dict. Nat. Biography*, **55**, 288.

Comitiis censoriis Maii 3, 1678.

Missae sunt literae Praesidi a Magno Camerario Dño Arlington.

Sir,

His Majesty having received great satisfaction in the abilities and success of Dr. Talbor for the cure of agues has caused him to be admitted and sworn one of his physitians

* Lister, M., F.R.S., 1638(?)–1712, second Physician-in-Ordinary to Queen Anne.

. . . has commanded me to signify his pleasure unto you that you should not give him any molestation or disturbance in his practice. . . .

I remain your humble servant, Arlington. May 2, 1678. Baker (1785), 208.

Ob suspiciones nescio quas in crimen adduci caepit, et paullatim in desuetudinem abire: donec nuperis annis Dominus Robertus Talbor dosi ejus valdè auctâ, non minus felici successu quam incepto audaci, febribus omnibus profligatis usum resuscitavit. Hic enim non intra scrupulos subsistebat, sed ad drachmas et uncias adscendebat indéque voti compos factus magnam et sibi et pulveri famam conciliabat.

J. Raii, Hist. Plant, tom. II, p. 1797. Baker (1785), 209.

1676

CHAP. II. of BARKS

Colledge). Of Hazel, Oranges, Barberry Tree . . . of Peru . . .

SALMON's Comment

24. *Peruanus:* If the Colledge mean the *Peruvian* Bark, of which the Jesuits Pouder is made, it is an excellent thing against all sorts of Agues: of which the Learned *Boyl* has given ample Testimony; my own Experience confirms it, for the Cure of the Rickets: Some suppose it the bark of the Sassafras-tree. Salmon (1676), 22.

1677

The bark made its appearance in the London Pharmacopeia * under the name *Cortex peruanus.* Flückiger and Hanbury (1874).

1678

The term 'Jesuits bark' is first used by Gideon Harvey in 'the Family-Physician and the House Apothecary'

* Of 1667. Henry (1924), 125.

(1678). It occurs among a list of Cortices or barks, ' Jesuits bark, the ounce 4s.,' but it does not occur in the same list in the 1676 edition of his work, but in a later work Harvey (1683) has a good deal to say about it. Harvey (1678). Harvey (1683).

1680

At verò non ita multo tempore elapso, duabus de causis, non quidem levibus, damnatus in desuetudinem prorsus abiit. Primo quia paucis horis ante adventum Paroxysmi, pro-recepto id temporis more, exhibitus aegrum nonnunquam è medio tolleret; quod et civi cuidam Londinensi Eidemque Senatori Urbano, *Underwood* * nomine et Capitaneo nomine *Potter* in vico vulgiò dicto *Black Fryars* Pharmacopolæ memini accidisse, Funestior hic pulveris exitus, quamvis oppidò rarus. . . . Ego verò jam ab aliquot retro annis haud vulgarem Corticis vim serio perpendens, animoque re-volvens, non alio magis quam hoc Herculeo medicamento Febres Intermittentes debellatas iri confidebam, si qua par erat cura accederet et diligentia. Sydenham, Epistolae, 1st Ed. (1680); 2nd Ed. (1685), 15.

1683

After all, I could wish these Fathers had kept their *Indian Bark* to themselves, and sure I am hundreds would be on this side the Grave, whose Bones are now turned into their first element. 154.

If you shall meet with a Physician, that can safely and not over speedily Cure you without giving the Jesuits Powder, never meddle with the Jesuit, with whom the less a man has to do either sick or well, it's the better. 162.

In fine, the effects appear so miraculous to many of 'em, that they imagine the Jesuits by Imprecations, Exorcisms, and Charms on their *Bark*, have made use of their Cloven-footed Master. 169. Harvey (1683).

* Died in 1658. Baker (1785).

1692

Quamplurimae etiam futiles et inanes controversiae, nugae sanè et tricae, ex doctrina Humoristarum ortae, inter doctissimos viros cum eruditione, specie tenùs et zelo agitatae sunt per decennium et quod excurrit sc. à primo Corticis in Europam adventu usque ad annum salutis 1663. quas enumerare vix operae pretium duxi. Morton (1692), 123.

1733

Nobody who has had but a tolerable share of Practice amongst the Sick can be ignorant that this, and the last year's fevers were of a changeable and uncertain Nature, and that the Peruvian Bark hath quite lost that Force and Certainty of Curing which formerly it was so famous for, and that from a too free (especially a too early) Use of it a Thousand ill Symptoms and those of the worst sort, have plentifully flowed. Warren (1733), 4.

1751

The prejudices against this Medicine which I had early imbibed from some of the most approved Authors made me for a long time use it with too much Diffidence. Cleghorn (1751), 197 ; (1779), 215.

1765–1767

The advantage of administering the bark as early as possible in the disease fully appeared in the year 1765 and the two following years during an uncommon prevalence of remitting and intermitting fevers, which spread themselves over the greatest part of England and furnished me with a number of patients. 294.

In the year 1765 and the two following years I annually prescribed upwards of an hundred and forty pounds weight of bark. 305.

During the late epidemical rage of intermitting fevers (in England) in the years 1765, 6, and 7, I seldom visited

less than thirty or forty patients every day. 323. Lind* (1788).

1789–1793

Pounds of bark imported and exported into Britain.

Year.	Imported.	Exported.
1789	168,038	19,832
1790	115,620	27,121
1791	63,760	29,618
1792	175,788	22,845
1793	111,577	24,361

Relph (1794), 2.

* Lind, James (1716–1794), author of the 'Treatise on Scurvy' (1753), and physician to the Royal Hospital at Haslar, near Portsmouth.

APPENDIX 10

CINCHONA

Use of the Bark in France

Controversy

1664

Cinchona appears to have been first used in France by Charles Barbeyrac,* the famous physician of Montpellier in 1664. Rolleston (1931), 266.

Chapter XII of his *Medicamentorum constitutio seu Formulae* (1751) is entitled ' De usu Kinaekinae (et Cascarillae).'

1675

It is the most certain remedy that ever yet was known, to hinder the fits of Agues. The manner of using it for a great while past has been to give the patient the powder from half a drachm to two drachms, with a little white wine, at the coming of the fit. But this method has been quite changed in our days, for at present we do infuse an ounce of the powder in two quarts of the wine . . . and the patient is made to drink every day three or four glasses of it, at some distance from the Paroxysm. The use of this remedy is continued a fortnight at least. . . . You must observe to purge your patient well before you give him the *Bark*, because this remedy shuts up the humors for some time, and when they come to ferment a-new, they do sometimes cause more dangerous maladies than he had before. Lemery (1675). Harris (1686), 393.

* 1629–1699.

1679

In 1679 he (Sir Robert Talbor) went to Paris, where he made many cures and treated the Dauphin with such success that the King bought his remedy for 2000 Louis d'or and a pension for life of 2000 francs and the publication of his remedy after his death. In 1679 he went to Spain to attend the Queen Louisa Maria. In 1682 after his death was published ' The English remedy.' *Dict. Nat. Biography*, 55, 288.

1679

Cùm etiam insuper media Medici caeteroquin docti et probi animadvertissent Pulverem febrifugum paroxyismum tantùm unum aut alterum, aut fortasse plures avertere, nec febrem penitus expugnare, verùm aegrotum plerumque recidivam pati . . . paulatim in desuetudinem abivit, donec anno 1679 Robertus Tabor * vel Talbot Eques Anglus . . . Kinae Kinae usum sub *Anglici remedii* nomine, vulgo le remede Anglois, in Galliâ resuscitavit.

Hic enim non intra scrupulos aut drachmas subsistebat, sed at uncias et libras ascendebat; sicque magnam sibi et remedio famam conciliavit. Geoffroy (1741), 2, 183.

1682

The English Remedy or *Talbor's wonderful Secret*

It is an Error in Physick to make a hodge-podge of a great many ingredients . . . and therefore as Quinquina or the Bark of Peru . . . is without contradiction the surest of all simple Febrifuges so it is the only basis of the English Remedy. 29.

The First infusion of Quinquina, or the Jesuits Powder making a part of the English Remedy. 31.

The Dose of it . . . is five or six ounces, that is about half an *English* pint. 33.

The Second infusion of Quinquina, making part of the English remedy. 35.

* Talbor, Talbot Sir Robert, 1642(3)–1681

The same Dose as of the first but only once a day in the morning when the Patient awakes. 36.

The third infusion of Quinquina, making part of the English remedy. 36.

And so to continue until the Patient hath taken of all the three Infusions about eight quarts. 38.

The Essence or Tincture of Quinquina, making part of the English Remedy. 38.

The virtue of each Dose of that (the first) infusion is to be encreased and fortified by the addition of five, six or even seven or eight drops of this Tincture, as often as the contumacy of the Ague hath resisted its operation after several doses. 39.

An Opiat prepared with Quinquina, making part of the English Remedy. 40.

There are some Patients upon whom the first infusion, though fortified by the addition of the Essence or Tincture has not sufficient virtue to stop the Ague fits; to these the specifick is to be given in substance and the best and most commodious way of doing it is the Opiat . . . four to six Drachms once or twice a day. 41.

A Purging Wine making part of the English Remedy. 42.

When by reason of the Patient's repletion or supervement constipation the belly must be opened, we must add to each quart of the infusion of *Quinquina* three or four spoonfuls of the above described Purging-Wine. 43.

When there is no considerable repletion and that the costiveness is but moderate, simple glysters made of Milk and the yoalks of Eggs are to be preferred before all kinds of purgatives, too great a looseness of the belly being always contrary to the operation of the specifick. 44.

Other observations of the King's chief Physician,* concerning the Virtues of the English Remedy.

Never did Remedy better deserve the name of a specifick Febrifuge. 49.

And we must confess that we are in some manner obliged

* Monsieur D'Aquin.

to Sir Robert Talbor for having given us a Preparation much to be preferred before all others . . . and it may be said that his boldness . . . hath not a little contributed to the knowledge which we have at present of its use and manner of application. 50. Talbor. 'The English Remedy' (1682). De Blegny (1682).

1682

Le quinquina devint populaire en France vers 1682. Coindet (1851).

1692

La Fontaine, at the solicitation of the Duchess of Bouillon, who had been cured of a dangerous fever by taking Peruvian bark, composed a poem (Poème du Quinquina) in two cantos to celebrate its virtues. Markham (1862), 8.

1827

Madame de Genlis wrote her novel, 'Zuma, o el desciolrimiento de la Quina novelda Peruana' (Spanish Edition).

APPENDIX 11

CINCHONA

Madame de Sévigné on Talbot

667

De madame de Sévigné *au comte* de Bussy

A Paris, ce 25 août 1679.

. . . Notre bon abbé de Coulanges a pensé mourir. Le remède du medecin anglois l'a ressuscité. Dieu n'a pas voulu que M. le cardinal de Retz s'en servit, quoiqu'il le de mandât sans cesse.[a]

674

A Livry, vendredi 29 septembre 1679.

. . . L'Anglois (*le chevalier Talbot*) est venu voir le bon abbé sur ce rhume qui nous faisait peur; il a mis dans son vin et dans son quinquina une certaine chose douce qui est si admirable que le bon abbé sent son rhume tout cuit, et nous ne craignons plus rien. C'est ce qu'il donna à Hautefeuille, qui le guérit en un moment de la fluxion sur la poitrine dont il mouroit, et de la fièvre continue : en vérité, ce remède est miraculeux.

675

A Livry, mercredi 4 octobre 1679.

. . . Le bon abbé se porte très bien ici; Son Anglois lui guérit encore son rhume, en mettant je ne sais quoi dans son quinquina.

[a] Madame de Sévigné donne plus de détails sur la dernière maladie du cardinal de Retz dans une lettre qu'elle écrivit le même jour au comte de Guitaud ' Il tombe malade, il demande ce remède (*du chevalier Talbot*); il a la fièvre, il est accablé d'humeurs qui lui causent des foiblesses; il a un hoquet qui marque la bile dans l'estomac. . . . Quand ce pauvre cardinal fut à l'agonie, ils (les médecins) consentirent qu'on envoyât quérir l'Anglois. Il vint, et dit qu'il ne savoit pas ressusciter les morts ' (*Voyez les Lettres* a M. de Guitaud, page 31).

683

De madame DE SÉVIGNÉ *à madame* DE GRIGNAN

A Livry, mercredi jour de la Toussaint 1679.

. . . Ce n'est pas que la saison ne soit contraire aux médecins. Ce remède de l'Anglois, qui sera bientôt public,[a] les rend fort méprisables, avec leurs saignées et leur médecines.

685

A Paris, mercredi 8 novembre 1679.

. . . Je crois que le maréchal de Bellefonds ne relèvera point de la maladie dont il est accablé.[b]

688

A Paris, vendredi 24 novembre 1679.

. . . Je vous assure qu'ils sont fort décriés et fort méprisés ici; hormis les trois ou quatre que vous connoissez, et qui conseillent le remède de l'Anglois, les autres sont en horreur. Cet Anglois vient encore de tirer de la mort le maréchal de Bellefonds. Je ne crois point que le premier médecin ait le vrai secret.

719

A Paris, vendredi 15 mars 1680.

. . . Ce fils ressortit pour crever; et après plusieurs agitations, plusieurs cabales, Gourville contre l'Anglois, Langlade pour l'Anglois, chacun suivi de plusieurs de la famille, et les deux chefs conservant toute l'aigreur qu'ils ont l'un pour l'autre, M. de Morsillac décida pour l'Anglois; et hier à cinq heures du soir M. de la Rochefoucauld prit le remède de l'Anglois, et à huit encore. Comme on n'entre plus du tout dans cette maison, on a peine à savoir la vérité; cependant on m'assure qu'après avoir été cette nuit à un moment près de mourir, par le combat du remède et de l'humeur de la goutte, il a fait une si considérable évacuation,

[a] Le roi acheta le secret du chevalier Talbot et le rendit public c'est a cet Anglois que l'on doit l'introduction de l'usage du quinquina en France.

[b] Il fut guéri par le chevalier Talbot (*Voyez* la lettre du 24 novembre suivant). Il ne mourut que le 5 décembre 1694.

que, quoique la fièvre ne soit pas encore diminuée, il y a sujet de tout espérer: pour moi je suis persuadée qu'il en réchappera.

784

De madame DE SÉVIGNÉ *à madame* DE GRIGNAN

Aus Rochers, dimanche 29 septembre 1680.

. . . La fièvre du chevalier n'a-t-elle pas été le plus desobligeante du monde? J'ai senti le chagrin que vous en auriez. Il m'écrit qu'il sera bientôt en état de partir et qu'il a été guéri et M. d'Evreux aussi, par notre Anglois: son remède a fait des merveilles cette année; M. de Lesdiguières en a été guéri comme par miracle, et mille autres.

795

A la même

A Paris, vendredi 8 novembre, 1680.

. . . L'Anglois (*le chevalier Talbot*) a promis au roi sur sa tête, et si positivement, de guérir MONSEIGNEUR dans quatre jours, et de la fièvre, et du dévoiement, que, s'il n'y réussit, je crois qu'on le jettera par les fenêtres: mais si ses prophéties sont aussi véritables qu'elles ont été pour tous les malades qu'il a traités, je dirai qu'il lui faut un temple à Esculape. C'est dommage que Molière soit mort; il feroit une scène merveilleuse de Daquin,[1] qui est enragé de n'avoir pas le bon remède, et de tous les autres médecins qui sont accablés par les expériences, par le succès et par les prophéties comme divines de ce petit homme. Le roi lui a fait composer son remède devant lui, et lui confie la santé de MONSEIGNEUR. Pour madame la dauphine, elle est déja mieux; et le comte de Gramont disoit hier au nez de Daquin:

Talbot est vainqueur du trépas [2]
Daquin ne lui résiste pas;
La dauphine est convalescente,
Que chacun chante, etc.

On ne parle à la cour que de cela. de Sévigné (1820).

[1] Premier médecin du roi.

[2] Parodie du choeur de la scène 1re du Ve acte *d'Alceste*.

APPENDIX 12

CINCHONA

Use of the Bark in Europe

Controversy

1639. Spain

Ex litteris doctissimi viri D. Joseph Villerobel Hispaniarum Regis Legati in Urbe, modò Mediol. pro Rege Gubernatoris, Medici meritissimi.

Pro narratione Historica Corticis, notandum est quod ait primum ejus experimentum in Hispania *Compluti* patratum fuisse in *D. Michael de Barreda, qui hoderne die*, ait, in *schola Complutensi vespertinam Theologiae Cathedram moderatur.* Et hoc accidit An. 1639. Bado (1663), Lib. II, 202.

1642. Seville

P. Barba wrote his treatise on the method of curing a Tertian. As the title implies, it was to defend the bark against the attacks of the Spanish physicians Barba (1642).

1649

Circum annum salutis 1649 famam suam indies magìs, magìsque provexit, non tantùm per *Hispaniam* verùm etiam *Italiam*, *Romamque* usque, conatibus imprimis *Johannis Cardinalis de Lugo Soc. Jesu*, et caeterorum *Collegii Jesuitarum Romae* patrum qui eum gratis religiosis et pauperis largiebantur. Unde infausto omine, atque in vulgi Reformati terrorem, ac Scandalum, *Pulvis Patrum* vulgò audit (Anglicè The Jesuit's Powder). Morton (1693), Cap. VII, 125.

1651. Rome

Adfertur cortex iste ex Peruviae Regno, vocaturque China febris. Exhibetur contrà febrem tertianam, et quartanam, quae cum frigore aegros praehendunt. Prae-

paratur autem in hunc modum. Corticis drachmae duae tunduntur subtiliter, ac per setaceum trajiciuntur. Tribus horis antè paroxismum pulvis maceratur in vini albi potentis cyatho, dumque frigus febrile incipit, vel sentitur aliquod accessionis principium, sumitur tota dosis praeparata aegerque se componit in lecto. 'Schedula Romana' (1651), in Italian. Chifletius (1663), 52, Latin version.

1653. Louvain

Chifletius wrote against it. The following are the titles of his three last chapters.

Caput IV. Miracula pulveris febrifugi non sunt perpetua quot quot hic Bruxellae eo sumpto à quartana liberati omnes sunt relapsi.

Caput V. Expenduntur commoda et incommoda Peruviani pulveris; ostenditurque usum ejus Europaeis necessarium non esse.

Caput VI et ult. Non etiam tutus videtur usus pulveris Peruviani ob graviora mala quae ab illo sequi possunt. Chifletius (1653).

1653. Madrid

LITTERAE D. IOANNIS GUTIERRII A. GODOY, MEDICI CUBICULARII REGIS CATHOLIC. I.

Legi atque iterùm perligi tractatum tuum* de Pulvere Peruviano. . . . Testis est amicus meus et socius, Medicus Regius, qui importunè à Marchione de Mancera, Peruvii Prorege, hujus pulveris advectore rogatus, ut ejus famulo et ancillae, simplici quartanâ laborantibus, illum exhiberet; utrique duplex febris reddita fuit; et famulo quidem cum majoribus accessionibus per longum temporis intervallum; ancilla verò praeter duplicatam quartanam continuâ febre tandem extenuata periit. Plura exempla, ne sim taedio, praetereo, cùm ista duo in pulverum advectoris aedibus visa sufficiant. Benè vale. Madriti Kalend. Iun. M.DC.LIII. Plempius (1655), 7.

* I.e. Chiflet's tract.

1655

Controversy continued to rage as to the merits of the bark, and we have a defence from Rome by Conygius [1] and a reply to the defence from Louvain by Plempius, who uses the anagram Melippus.

He says on the third page of his short 12-page tract:

Renatus Moraeus, Professor Lutetiae primarius IX. Jul. M.DC.LV ad amicum quemdam suum Bruxellae agentem sic scripsit: La reputation de la poudre du Peru est tellement morte en ceste ville, qu'on n'en parle plus, et que nous n'en ordonnons plus. Plempius (1655), 3.

1656. Rome

Cum ergo circa Annum 1649, translatum fuerit e Regione *Quitensi* in Hesperiam Remedium, nemo neget, quin inter primos, qui illud admiserint, vere sit connumerandus *Frassonus*. . . .

Reluctabantur interim, et, quoad vixit idem *Frassonus*, semper obstrepuere omnes fere Civitatis Medici, adeo ut evitandum severum eorumdem tribunal, profugus, et exul Cortex non ausus fuerit in Pharmacopœas introire, sed quasi clam intra Claustra quarumdam Monialium fuerit coactus sese recipere, unde postea illum petebat Vir solertissimus, ut Aegris sibi commissis subministraret Torti (1755); Edited by Ascoli (1925), 5.

1656. Rome

Et sane recensendus ille inter primos Corticis receptores, cujus rei testimonium exhibit idem Cl. *Badus* in citato, Libro, cui titulus—*Anastasis Corticis Peruviae*, ubi Epistol [2] *Frassoni* ipsius inserit sibi inscriptam sub anno 1656, in qua idem *Frassonus* refert, se ante annos aliquot de Cortice felix periculum fecisse in pluribus. Torti (1755). Ascoli (1925), 5.

[1] The pseudonym of P. Honoratus Faber (1607–1688), rector of the College of Penitentiaries of S. Peter's, Rome.

[2] Bado (1662), Lib. III, 245.

1661. Rome

Posso testimoniare per mia esperienza che la polvere viene adoperata con grande larghezza nell' Arcispedale di Santo Spirito; assai spezzo, in una sola volta lo speziale ne ha fatto acquisto per la somma di venti scudi. . . . Anteriormente all' uso della polvere i quartanari ed i terzanari venivano esclusi dall' accettazione, essendo la loro malattia, benchè più longa, non letale, e d'altra parte refrattaria ai mezzi terapeutici. Oggi no solo i perniciosi, como sempre, vengono accolti, ma anche i febbricitanti più leggeri, che prontamente guarascino con poche dosi del rimedio. Brunacci (1661).

1663. Seville

Bado replied to the opponents of the bark with a preliminary note in 1656 (Canezza (1933), 91), and published his ' Anastasis Corticis Peruviae seu Chinae Chinae defensio, Sebastiani Badi Genuensis etc contra Ventilationis Joannis Jacobi Chifletii gemitusque Vopisci Fortunati Plempii ' in 1663.

1663

Itaq; subit *mirari*, quod obiter dico, cur corticem repudient *Londinenses Medici*, sivè in tertianis sivè in quartanis . . . cum tot alii Medici in omni *Europa*, sivè in Gallia, sivè Hispania, Germania, Flandria, Italia ne dum usurpent, sed mitis laudibus extollant. Bado (1663), Lib. I, Cap. XX, 105.

1681. Antwerp

Roland Sturm wrote his ' Corticis China Chinae ejusque virtutum et virium descriptio.'

1696

Baglivi [1] and Lancisi [2] were contemporaries at Rome; the former wrote against, the latter in favour of the bark.

Romae scribo, et in aëre Romano; Et ideo garriant quicquid velint chinae-chinae fautores: aliis forsan in region-

[1] Baglivi, 1668–1707. [2] Lancisi, 1654–1720.

ibus, et urbibus egregium est remedium, hîc noxium experior, et unquam eo utor, aut rarò. 53.

Nonnulli in hisce casibus solent more solito chinam chinae praescribere, quo autem cum successu, pluribus in locis hujus operis animadverti. Nam hoc remedium impuro corpore dare, saepe in aegroti perniciem vertitur, potissimùm in maximo apparatu humorum in messenterio. 58. Baglivi (1696). Baglivi (1704), 58.

1702

Ramazzini. Oratio Quarta Habita Die VI. Novembris MDCCII.

Tam exacto rei obstrusissimae scrutamini non parùm velificati visa est Fortuna advecto in Europam inter peregrinas merces Peruviano Cortice, antipyreticorum omnium quotquot excogitavit Antiquitas, et Chymicorum solertia conflavit, facilè Principe: E singulari hujus remedii praestantia, quod in periodicas Febres vim suam potissimùm exerat. . . .

Ramazzini compares the revolution brought about in medicine by the introduction of the bark with that effected in warfare by the introduction of gunpowder.

Profectò postquam hujus remedii usus innotuit, et praemissis justis purgationibus, non semel tantum, ut olim, sed plures ad dies exhibeti caeptus, donec febrile miasma fuerit penitùs exantlatum, talem circa Febrium doctrinam, ac illam curandi methodum factam fuisse fateri oportet, qualem in re militari post inventum pulverem pyrium omnes norunt. Ramazzini (1716), 53.

1714

Ramazzini. De Abusu Chinae Chinae Dissertatio. Epistolaris.

'Adverto quaeso mi Nepos, ad diligenter observa, febres intermittentes post epotam *Chinam Chinam* nunquam ad veram, & perfectam apyrexiam pertingere, qualis contingit quando natura spontè per sudorem aut alias vias accessionem discutit.' 226.

Idem hoc de cortice Peruviano Gannaperide vel ut alias vocatur China China, censeo, ut pote qui prae caeteris amaris aut Febrifugis revera nihil peculiare, aut tanta laude dignum praestet. Certe sive genuinum, sive adulteratum sit, quod venditur, ab ejus usu interdum quidem febrem aliquando delituisse, seu plerumque subsecutam pejorem recidivam, in aliis et frustraneam, et nocivam extitisse. 227. Ramazzini [1] (1716), ' De Abusu.'

1712

Torti in 1712 wrote his famous ' Therapeutice Specialis.' It is one long eulogy of the bark, the concluding words of the preface to which are: 'Amice Lector. . . . In hoc Studio tibi primus impendendus labor; tum vero rectam et rationalem, non mere empiricam, Peruviani Corticis administrationem ex hujus Operis lectione percipies; sin minus de tuo profectu actum est. Vale.' Torti (1712). Ascoli (1925), XXV.

Torti [2] replied to Ramazzini's attack in his ' Responsiones iatro—apologeticae ad criticam dissertationem Ramazzinii ' (1715).

1718

Lancisi [3] writes in favour of it :

Dosis chinae singulis vicibus non excedebat scrup. 2, vel drach 1. . . .

Incredibile dictu est, quâ felicitate chinatis hisce bolis, quasi totidem herculeis sagittis ferox haec Leoninae paludis hydra fuit interfecta. Lancisi (1718), Lib. II, Epidem. I, Cap. VIII, Sectio II. 169.

1800. Rome

The French physician L. Valentin, who visited Rome in 1800, records from the data of the Custom-house that 10,200 lbs. of the bark reckoning 12 ounces to the pound were used annually in the city and its environs. Canezza (1933), 96

[1] 1633–1714. [2] 1658–1741. [3] 1654–1720.

APPENDIX 13

CINCHONA

Use of the Bark in India and China

1650. India

About the middle of the 17th century, bark was used by Jesuitical Missionaries in India, but it appears to have fallen into disrepute for a season, until revived under the name of 'Talbor's Powder' or the 'English Remedy.' Moore (1870), 161.

1757

I have been favoured with the following ingenious observations by Dr. Bogue of Titchfield. 'The diseases most fatal at Calcutta, while I was there in 1757 . . . were obstinate putrid intermitting fevers. . . . Bark and other antiseptics were administered in large quantities, after first giving an emetic and emptying the bowels.' Lind [1] (1788), 94.

1762

'Qui tamen facili negotio arceri potuit, si cortex Peruvianus paucos dies ante expectatum accessionis tempus exhibitus ac usque quo illud sit elapsum continuatus fuerit.' Lind [2] (1768).

1692. China

The Jesuits in China had supplies of the bark by this time and the emperor K'ang Hsi, acting against the advice of his regular medical attendants, took the bark and was cured. Lockman (1762), **2**, 112–118. Lettres (1832), **14**, 131–138. Rolleston (1931), 266.

[1] Lind, James (1716–1794), Physician to the Royal Hospital at Haslar. The author of a 'Treatise on Scurvy' (1753). Had not been in India.

[2] Lind, James (1736–1812), F.R.S., Physician to the royal household at Windsor. In Bengal in 1762.

APPENDIX 14

CINCHONA

Note on the Barks of Commerce

1640–1776

Pale Cinchona bark, Crown bark or Loxa barks. From 1646–1776 the only bark of commerce came from the forests in the neighbourhood of Loxa. Markham (1862), 10.

1779

The red or *C. succirubra* (Pav.) or Chimborazo bark. First reached England in 1779 through the capture of a Spanish ship bound from Lima to Lisbon by the 'Hussar' frigate. Markham (1862), 26.

1775–1800

The yellow or *C. calisaya* (Wedd.) or Bolivia bark. Introduced at this time from Bolivia and Southern Peru. Pereira (1853), 1641.

Towards the end of the eighteenth century the Calisaya and Red Peruvian barks were replacing the old Loxa barks. The essence of the change was that the more efficacious quinine barks were replacing the less efficacious cinchonidine barks. In the early nineteenth century the still more fundamental change was the replacement of barks, which had been in use for about 200 years, by quinine.

APPENDIX 15

QUININE

Discovery and Use

1820

Quel est le principe actif des quinquinas; quelle est, dans ces écorces, la substance qui agit dans le traitement des fièvres, et qui combat si énergiquement l'intermittence? . . . nous sommes convaincus que ce principe est la base salifiable, la cinchonine dans le quinquina gris,[1] la quinine dans le quinquina jaune [2] et ces deux substances dans le quinquina rouge.[3] 361.

Du reste, espérons que quelque practicien habile joignant la prudence à la sagacité, fera des recherches thérapeutiques sur les alcalis du quinquina et donnera ainsi à notre travail une utilité médicale. 365. Pelletier [4] and Caventou [5] (1820).

1821

At first more especially occupying themselves with the pale bark, they soon observed that the crystallizing principle discovered by Dr. Garnil (Gomes?) of Lisbon, and which he had called *Cinchonine* . . . was a substance of this kind (a salifiable base, as the morphine in opium, the strychnine in the nux vomica . . . etc.).

Passing on to the analysis of the yellow bark, Messrs. Pelletier and Caventon (*sic*), in place of detecting the cinchonine, obtained a substance not crystallizable and differing

1 *Kina loxa, Cinchona condaminea.* 291.
2 Cinchona cordifolia. 345.
3 Cinchona oblongifolia. 357.
4 Pelletier, Pierre Joseph, 1788–1842. Joint Director, School of Pharmacy, Paris, 1832.
5 Caventou, Joseph Bienaimé, 1795–1877. Professor at School of Pharmacy, Paris.

from the former in its physical and chemical properties. . . . Its salts . . . are more bitter—in this respect having a nearer identity to that of the yellow bark.

After establishing the difference which exists between the salisfiable base of the pale and of the yellow bark, (they) have thought proper to call that of the latter *kinine* . . . which seems to be to the yellow bark what the cinchonine is to the pale bark.

The red bark has in its analysis presented a very extraordinary fact: it is the simultaneous presence of the *cinchonine* and of the *kinine*, and each in greater quantity than is afforded by the pale and yellow bark. The red bark then is very justly regarded the best. Pelletier and Caventon (*sic*) (1821).

1820. *France*

In September and October 1820 M. Double tried the sulphate of Quinina in six cases of intermittent fever. 547.

It cannot be afforded at a lower price than three guineas an ounce. 561. Elliotson (1823).

In France, Chomel at Paris appears to have been one of the first to use the sulphate successfully. Busch *et al.* (1831), 509.

1821

Morson, Thomas, N.R. He was . . . the first to make sulphate of Quinine and Morphine on a commercial scale in England, and this was in the Old Pharmacy, 65 Fleet Market. 'Souvenir' (1930), 105.

1823

Manufactured at Amsterdam. Rolleston (1931), 268.

Sulphate of quinine should be tried in continuous fevers. Corosin (1823).

1828

Manufactured in Germany. Rolleston (1931), 268.

1828

The use of Q. sulphate appears to have been unknown to Macculloch. Macculloch (1828).

1831. *Gold Coast*

The best effects of this useful medicine are found to result from the daily administration of from fifteen to twenty grains of it. 184.

A super-sulphate of Quinine . . . has sometimes appeared to deserve the preference. 196.

Mr. Tidlie writing in 1822 says 'In my own person I found bark of no use.' 199. Boyle (1831).

1835. *Corsica*

Quinine was first used in Corsica about 1835. Pitti Ferandi (1901).

1837. *India*

No subject can be more important than the manufacture of quinine. We extract the following from Pereira's lecture in the (London) Medical Gazette. (Various data with regard to Q. preparations.) Dumas says about 120,000 ounces are annually made in Paris. Editor (1837), 240.

1839. *Senegal*

Quinine was given him, 0·6 g. by the mouth and 1·25 g. as an enema for several days. Bérenger Féraud (1874), 12.

1843. *W. Africa*

In a disease like the Niger fever . . . no medicine was found so efficacious as quinine in diminishing the severity of the paroxysms. McWilliam (1843), 198.

1844. *Canada*

Quinine was used in a number of cases of intermittent fever at Port Maitland Canada. Stratton (1844).

1844. *North America*

Quinine at the South—Quinine instead of *Calomel* is now considered in the South the *Sampson* of the Materia Medica.

. . . The doses of this medicine (Q.) have been increased from two grains up to ten, twenty and upwards and its beneficial effects are often truly wonderful. . . . The quantity of this article used in the South (of N. America) this season is prodigious. It has been impossible to supply the demand. . . . It was ascertained just at night . . . that *an ounce* could be procured about 30 miles distant. It was determined to start a runner for it, before day, the following morning . . . but . . . he found himself *far too late.* New Orleans Medical Journal. Anon (1844), 348.

1847. *W. Africa*

Of all the remedies employed in fever or in its sequelae upon the west coast of Africa, there is not any so unequivocally valuable as the disulphate of quinine; cinchona bark . . . is seldom used when the former can be obtained. So general has the use of quinine now become, that there is hardly any part of Western Africa, where there are resident Europeans, in whose houses it is not to be found. Bryson (1847).

1853. *Nossi-Bé*

Du mode d'administration du sulfate de quinine. . . Je n'avais guère dépassé, pendant le premier hivernage . . . la dose de 1 gramme. Le Roy de Méricourt (1853), 54.

1854. *Gaboon*

Day 4. B.w.f. Blisters applied to the calves in order to give Q. by the endermic method . . . 2 grammes of sulphate of Q. placed on the surface of the blisters, death during the night of day 5.

20 May, 1854. Signed: E. Monéstier. Bérenger Féraud (1874), 38.

1899. *U.S.A.*

Consumption of Quinin in the U.S. Imported last year into the United States 1,539,056,750 grains of quinin. Something like twenty grains for every man, woman and child in the country. ' Anon ' (1899).

APPENDIX 16

QUININE

Hypodermic Injections

1862

Dr. Chasseaud,* physician to the Hôpital de St. Antonio of Smyrna, had treated 150 cases of malaria by subcutaneous injection of quinine sulphate. McCraith (1862).

1862

Chasseaud in 1862 (or earlier?) was treating a case of sciatica complicated with intermittent fever with injections of atropin, when it occurred to him to attack the intermittent factor by the same method, i.e. by injections of quinine. Goudas (1862).

1863

Moore of the Bombay medical service treated 30 cases of intermittent fever and several cases of remittent by subcutaneous injection of Q. That Chasseaud had already used the method was unknown to him at the time. Moore (1863).

1863

Gaullia treated 49 cases at Brescia and only once observed abscess. Proust (1866).

1864

Desvignes treated several hundred cases in Tuscany. He thinks the subcutaneous method (for quinine?) was 'first used by the French Army Surgeons in Lombardy during the last Italian war.' Desvignes (1864–67).

* The secretary of Lady Hester Stanhope was a M. Chasseaud, member of a well-known family settled in Beirut and Smyrna. Kinglake's 'Eothen' (1906), Henry Frowde, London, p. 286.

1864

Rosenthal in Austria (Germany ?) stated that he had used hypodermic injections in 1863 following McCraith's recommendation. He used 1 scupl (*sic*) Bisulf. Chinin to 2 Dr. distilled water without the addition of acid. Rosenthal (1864).

1864

Zuelzer subsequent to Rosenthal's communication stated that he with his colleagues had been using the method for some time. Zuelzer (1864).

1864–65

Maury during the winter of 1864–5 treated some 25 cases of intermittent fever in the General Hospital, Greenville, Ala. 'In the severer cases eight grains (of sulphate of quinia) was the (total) quantity used.' In 1858 . . . the use of morphia hypodermically was introduced by Dr. Geo. T. Elliot, Bellevue Hospital, New York. Maury (1866).

1864–67. *Smyrna*

McCraith, senior surgeon to the Smyrna and Aidin railroad, was using hypodermic injections of Q. for the cure of malarious diseases among the men employed on the works of the railway. The epidermic acid treatment was accidentally suggested to the author a few years since by Mr. Wordsworth. McCraith (1864–1867).

1865. *France*

Pihan-Dufeillay used them in France for the first time. Pihan-Dufeillay (1865).

1866. *U.S.A.*

Q. was being administered hypodermically in U.S.A. in 1866. Anon. (1899).

1867. *Algeria*

Arnould was using hypodermic injections in Constantine, Algeria. Arnould (1867).

1867. *India*

I selected all the most severe cases of intermittent fever and injected about five grains subcutaneously . . . we may add that in the malarious fevers of Bengal hypodermic injection of Q. has been tried largely at several stations for several years past . . . at Debroogurh . . . 1868, . . . at Kishnagur 1867. Tuson (1870), 3.

1869. *Senegal*

'Des injections hypodermiques de sulfate de quinine.' The title of a paper by Borius (1869).

1874. *Senegal*

Bérenger Féraud states that he was unable to give hypodermic injections himself for lack of a Pravaz syringe, but that Borius in Senegal had obtained good results by their use. Bérenger Féraud (1874), 326.

1880. *Réunion*

Mac-Auliffe in Réunion used bromhydrate of quinine dissolved in sulphuric ether and rectified alcohol. De Beurmann and Villejean (1888).

1888

William Chasseaud does not appear to have himself described his injections of 1862, but he writes pointing out that his name had been mis-spelt 'Schachaud' by Goudas of Athens (1862), who had visited him at Smyrna. Chasseaud (1888).

Bihydrochloride of Q. was first prepared by Vitali and used by Galignani (1872) and later by Schivardi (1880).

APPENDIX 17

QUININE

Toxicity

Amaurosis

History of Q. on various recent occasions. Then Q. mixture for 4 days. While taking this his sight began to fail. He was completely blind and could not see shadows. There was no perception of light in either eye. The left eye showed pallor of the disc with ill-defined edges; . . . there were no retinal changes. Twelve days later he could see his way about. Stones (1924–25), 182.

Aphonia

Calicut, India, girl, aet: 16.

12.10.29. T. 103·8°, P. 126, 2 p.m. Q. sulphate grains 4; 6 p.m. patient began to lose her power of speech; 10 p.m. she could not articulate at all.

13. Morning, patient all right. Q. again given; in 4 hours time again aphonia, which lasted until the evening. Iyer (1930), 17.

Aural

A patient on our advice took 3 g. Q. sulphate to cure an asthma which recurred daily at the same hour. Four hours later he experienced buzzing in the ear, stupor, vertigo and terrible vomiting. We saw him seven hours after he took the Q.; he was blind and deaf, delirious, could not walk, so great was the giddiness; he vomited constantly—in short, he was poisoned. Trousseau and Pidoux (1869), 487.

Man, aet: 37. After Q. HCl 1·2 g. violent tinnitus aurium, pain in left ear, stupor, attacks of vertigo, and marked deafness. Schwabach (1884).

Erythema

Patient aet: 53, given a pill containing arsenous acid grain $\frac{1}{80}$ and quinine grains 2. 12 hours later, erythematous rash all over body, with intense itching and puffiness of the face. In five days, free desquamation, and 6 weeks later still desquamation of palms and soles. Patient gave a history of similar attacks whenever he took quinine, on one occasion following a small quantity of elixir of calisaya (yellow bark) in a cocktail. Hare (1901), 294.

General

Mélier enumerates the following accidents as due to sulphate of Quinine: (1) Death, (2) delirium and coma, (3) pulmonary symptoms, (4) haematuria, (5) blindness, (6) deafness, (7) stubborn gastralgia, (8) diarrhoea, (9) epileptiform attacks, (10) paralyses. Mélier (1843).

1. Very soon . . . after the medicine was taken the face became suffused with an erythematous eruption, and a tingling itching sensation, very severe and distressing in its nature, followed and extended over the body and extremities.

2. In case second there was produced considerable oedema with wheals, ending with desquamation.

3. The cutaneous eruption and irritation were not so severe as with the others, but the pulmonary oppression and constriction of the throat were the more prominent symptoms. Slocum (1887), 334.

The eruptions which follow the ingestion of Q. are multiform in character. The prevailing type of the Q. exanthem is erythematous, but every form of elementary lesion—macules, papules, wheals, vesicles, bullae, pustules, purpura, etc.—have been observed. Morrow (1893), 465.

K., aet: 22. Much fever. At first Q. 1·0 g. × 2 weekly. For 10 days Q. 1–2 g. daily.

19 June. Complains of 'Nerves,' loss of appetite, weakness, tinnitus and swimming vision. T. 39·5°, P. 87, very soft, tremor of hands, systolic anaemic murmur, abdomen somewhat tender,

spleen +. Red cells 2·65 m., white 6700, parasites neg.

20–23 June. Q. 2–2·5 daily. T. 38·7°, 39·6°, 38·8°, 39·5°.

24 June. Red cells 2·246 m., white 6500, T. 38·5°, Q. as before.

25 June. T. 38·5°. Q. as before.

26 June. T. 39·3°. Complains of a blackness and of constant swimming of objects before his eyes.

27 June. Q. stopped.

29 June. T.N.

8 July. Distinctly better. Plehn, F. (1898), 199.

S.M.S. 'Veneta.' Crew 514. West African Coast. 10 Dec., 1904, to 7 March, 1905. None had had malaria and none had Q. before. Anti-malaria prophylaxis, Q. 1·0 g. every 4th day, in tablet form. 21, i.e. about 4%, developed more or less severe symptoms during this prophylactic treatment.

1. *Petechial eruption:* 2 cases, on day 25 and day 28 respectively. The eruption in both cases developed in about 12 hours after the last prophylactic doses.
2. *Urticaria:* 1 case. The wheals appeared 24–30 hours after taking Q. and persisted for 8–10 hours. Subsequently no eruption although Q. continued.
3. *Herpes:* 1 case. 3 days after the 3rd prophylactic dose.
4. *Itching:* 1 case. Patient complained on the Q. days of intolerable itching of the skin, 1 hour after taking the dose. There was nothing visible.
5. *Fever:* 16 cases.

10–14 Dec. (first and second prophylactic doses). Only a few complained of ill effects.

18 Dec. (3rd dose). 16 of the crew affected with headache, nausea, vomiting, pain in the body, feeling of heat, tinnitus, fever and rigors. In 4 cases T. was over 39°. Blood neg., albuminuria neg.

22 Dec. 4 of the cases were given by mistake Q. 1·0 g. The same train of symptoms ensued.

26 Dec. 1 of the cases that had been most severely affected given Q. 0·5 g. The same train of symptoms ensued. All these patients were quite well when Q. was not given. Gudden (1905), 500.

59 subjects. German East Africa.

Period of prophylaxis varied from 1 month to 2 years 6 months.

The dose varied from 0·5 to 1·0 g.

The interval between the doses from 4–8 days.

	Cases of malaria.	Cases of b.w.f.	Authority.
Before prophylaxis . .	44	3	Meixner and Kudicke (1905), 479.
During prophylaxis .	20	1	

Some 40 of those undergoing prophylaxis suffered from more or less unpleasant symptoms, such as tinnitus, deafness, tremors, headache, restlessness, lassitude, itching, nausea, vomiting, cramp in the stomach, stupor, etc. *Ibid.*

F. C., treated some 9 months ago for lupus erythematosus, receiving altogether 60 powders of 0·3 g. On account of a relapse, the treatment repeated. After the first powder patient complained of indisposition, nausea and tinnitus. Accordingly advised to take only a half dose, 0·15 g.

The patient became extremely ill. The whole face swollen, oedematous, thick blood clots reach from the angle of the eye to the angle of the mouth, corresponding to the edges of the lupus. The lupus itself covered by innumerable petechiae.

Also there was purpura haemorrhagica of both legs and a Hge in the right conjunctiva.

Besides acute dyspnoea, there was Hgic vomit, diarrhoea, haematuria, and mucosal Hges of the mouth and nose.

By styptics and analeptics a cure was effected in a few days. Salomon (1908), 1787.

Patient aet: 4½. *P. vivax.* Various quinine prepara-

tions produced abdominal pain, tenesmus, bloody stools, vomiting, general urticaria.

18 May. 3 p.m. Q. formate 0·5 g. subcutaneously.
5 p.m. Swelling of the lips and eyelids, cyanosis of mucosae, vomiting, colic, itching, redness of skin. The condition lasted until next day.
6 Aug. For preceding 3 days $CaCl_2$ 1·0 g. given daily. Then Q. formate (? dose) subcutaneously. Symptoms of intolerance practically nil. Gros (1909).

Symptoms of Q. intoxication: gastritis, nausea, headache, trembling, vertigo, dimness of vision, cardiac 'trouble.' Gouzien (1911), 62 (r.).

Patient aet: 30. History of anaphylactic symptoms for the last five years whenever a small dose of Q. is administered. Blood. *P. vivax*. Q. dose and time (?). He complains of creeping sensations in finger and toes, which gradually extend to the palm and the sole and finally the whole part becomes slightly oedematous. At the same time he complains of acute pain in the abdomen and restlessness with profuse sweating. Banerji (1928), 533.

1. Chronic malaria. Ill-developed urticaria and gastro-intestinal trouble.

2. Chronic malaria. Severe urticaria, pseudo-asthma, distress, fainting and prolonged loss of consciousness.

3. Chronic malaria. Urticaria and transient coma.

4. Recent simple tertian. Oedema of legs non-symmetrical, pruritus.

7. Chronic malaria. Oculo-nasal catarrh with obstinate sneezing.

These patients cured of their malaria by giving Q. before the dose already absorbed—and which caused the various symptoms given above—was eliminated. Manoussakis (1931).

Haematuria

Grégoire (1861) quotes Monneret to the effect that quinine determines after a little, cystitis, sometimes even haematuria. Monneret. Grégoire (1861), 16.

One knows that the experiments made by Briquet with a view to determining the physiological action of quinine have shown that in big doses it can produce haematuria. Briquet. Pellarin (1876), 196.

Haemoptysis

4 cases (3 of intermittent fever, 1 of rheumatism) where doses of Q. caused haemoptysis. The only cases of this kind seen among about 3000 cases of malaria fever treated.

1. Day 5. After a total of Q. 2·5 g., blood spitting. Lungs, etc., normal. Q. stopped.
   Day 15. Q. treatment resumed.
   Day 18. Blood spitting, which ceased in some hours. Q. stopped.
2. Tertian fever, spleen enlarged. Q. 0·6 g. daily.
   Day 6. Blood spitting. Q. stopped.
   Day 7. Blood spitting stopped.
   Day 15. Q. 0·5 g. daily.
   Day 18. Blood spitting. Q. continued.
   Day 19. Blood spitting, which stopped some hours after Q. stopped.
3. 4 times in eighteen months, after taking Q. sulphate 0·3 g. or 0·4 g. for several days, blood spitting.
4. Subacute rheumatism. Q. in pills 1·6 g. daily.
   Day 4. Blood spitting: almost pure blood. Q. stopped. Blood spitting stopped.
   Day 6. Q. 1·6 g. in powder. 36 hours later blood-spitting.

In all these cases, mouth, throat, lungs, heart, normal so far as any relation to the blood spitting concerned. Simon (1861).

Haemorrhage

C. P., aet: 17. Greece.

22 Aug., 1887. Q. sulphate 1·2 g. in three doses at half-hourly intervals. Hardly an hour after the

third dose, vomiting at first bilious, then bloody or rather true haematemesis. He had over 20 haemato-diarrhoeic stools in 2 hours.

28 June, 1888. After 6 days of intermittent fever, without having taken the least dose of quinine, he again had haematemesis and bloody diarrhoea. Quinine tannate 1·5 g. prescribed in a mixture.

29. Feeling well. The mixture continued. In the evening his mother, thinking her son had fever, used Q. frictions on the abdomen, thigh and armpits. Insomnia during the night, anxiety, agitation.

30. a.m. Vomiting bilious, then bloody, and 10 bloody stools. Urine: blood, negative. Pispiris (1891), 121.

Negro, Barbadian, aet: 22.

June and Dec., 1908. In hospital, Q. treatment for 'fever,' no ill effect.

15 Aug., 1910. Complains of headache, fever, chills and nausea. Blood: *P. falciparum*. Q. grains 20, calomel and salts.

16. Bleeding from the mouth. A patch of capillary oozing on the cheek and one on the soft palate, each the size of a ten-cent piece and a series of smaller spots on the gums.

16–20. Q. grains 30 daily.

17. Haematuria, which persisted until 21, when Q. discontinued.

18. Clotting index of blood normal.

20. Petechial Hges all over his body, which disappeared by 23.

24. Q. 10 × 3 grains. Reappearance of all the Hgic symptoms.

25. Q. discontinued. Disappearance of Hges.

29.–3 Sept. Q. treatment. More or less constant oozing from the gums.

10–12. Q. grains 15 daily. No Hges. Deeks and James (1911), 67.

A Creole workman who had contracted malaria in Rivière Noire (Mauritius). Quinine 1·0 g. given. On the following day, urine high-coloured, no Hgburia, conjunctival icterus, extensive ecchymotic and haemorrhagic swelling of the gums, extensive sub-lingual haematoma, large ecchymotic patches over the body. This condition occurred three times in three months, on each occasion following a large dose of Q. Chevreau (1908).

Chinaman, Sumatra.

12.11.07. T. 38·5°. Blood *P. vivax*; 3 p.m. Q. 0·5 g.

13.11.07. T.N. Parasites neg.; a.m. Q. 0·5 g., which was at once vomited; 3 p.m. Q. 0·5 g.; 3·30 p.m. patient goes to the bath-room (?). Suddenly profuse sweating sets in and patient collapses without a word. Taken immediately into the ward. From the nose there is a profuse flow of fresh bright red blood, which was checked by plugging. Pupils dilated, do not react, P. 56, tense. Recovers fairly soon from his deep swoon, but cannot reply to questions in a definite manner, as his powers of apprehension are considerably delayed. After about 3 hours there is a sudden discharge of about ½ a litre of blood per rectum. P. 100. Intravenous saline with adrenalin 1 in 1000, 7 drops. As this was being given extravasations the size of a penny or a child's hand appear under the skin and spread out flat-wise, also under the conjunctiva and in the mucosa of the cheeks. He brings up quarter of a litre of fresh blood and coughs up bloody foam. P. 140. From the anus flows almost in a jet ½ litre of fresh blood. P. imperceptible. Death. Post-mortem widespread Hges in the organs. Baermann (1909), 2319.

1. Sailor, aet: 23. Infected with malaria in Congo. Q. prophylactically 0·8 g. every 4 days. No ill effect. Q.

used after a malaria attack led to profuse haemorrhage from mouth, nose, throat and stomach. Two weeks later a Q. injection again led to haemorrhages, but not so severe. In hospital. No signs of cutaneous or mucosal haemorrhages.

T. only slightly raised, parasites present, Q. 0·1 g. well borne. Q. 0·2 g. 2½ hours later, cutaneous and mucosal haemorrhages, but not very severe. Then plasmochin given without ill effect.

2. Patient admitted during a severe "tertian" attack. Numerous petechiae over the whole body, a few in the mouth. Quinine urethane, 0·1 g. intramuscularly, 1 hour later, profuse cutaneous and mucosal haemorrhages. Mühlens and Fischer (1927), 32.

Female aet: 43. Patient was admitted with malignant tertian malaria. Previous quinine treatment was said to have produced severe haemorrhage from mucous surfaces. On the third day an intramuscular injection of 5 grains of quinine bihydrochloride brought on profuse uterine haemorrhage. Ross (1927[a]), 258.

Patient with malaria (tertian) and distinct Q. idiosyncracy. Q. urethane 0·1 g. intramuscularly. 1 hour later pronounced cutaneous and mucosal haemorrhages. Some days later Q. urethane 0·25 g. intramuscularly. There followed not only cutaneous and mucosal haemorrhages as before, but also a typical attack of b.w.f.

During the haemorrhagic symptoms and b.w.f. clotting time prolonged, and bleeding time lengthened by 1 hr. (pointing to an idiosyncracy and not to a property of the b.w.f. attack). Kikuth (1927).

Hysteria

Sometimes Q. produces all the stages and degrees of hysteria apart from fever and any sign of hysteria. In a woman aet: 32, 0·3 centigramme produced attacks. Pispiris (1891), 122.

Mania

We have seen at the 'hospital de Tours' a young nun made maniacal for a day, after a dose of 1·25 g. Q. sulphate. Trousseau and Pidoux (1869), 487.

Large doses

12 g. Giacomini records the case of a person who took Q. 12·0 g. by mistake at one time and whose life was saved by the use of stimulants.

41 g. Guersent records the case of a woman who took 41 g. in a few days, with resulting loss of sight, hearing and speech, but recovered.

120 g. Briquet records the case of an insane doctor who took for 10–12 days extraordinarily large doses. After 120 g. he became prostrate and died. Briquet, 585. Plehn, F. (1898), 191.

25 g. Stille records a non-fatal case after 25 g.

30 g. Clapton records a case with delirium and stupor only, after 30 g. Roux (1885), 346. Plehn, F. (1898), 191.

Q. 8·1 g. Unconsciousness; fall of T.; lividity; slow superficial respiration, pulse 45, small; pupils dilated, superficial, deep reflexes abolished, coffee-ground vomit, deafness (a week), blindness (5 months). Roberts (1894). Mannaberg (1905), 471.

Two soldiers, Q. sulphate 12·0 g. by mistake. Soon after intense tinnitus, total deafness, cramps in stomach, pallor of skin, pupils dilated, respiration shallow, pulse small irregular. One died in 4 hours, the other recovered. Baills (1883).

11 Feb. Rigor, Hgburia. As soon as the patient discovered that his urine was blackish red, he took 20 tablets of Q. HCl, 0·5 g. each (i.e. 10 g.). The result was excruciating pain in the head, trembling in all the limbs, and almost complete deafness. The Hgburia persisted. Death. Plehn, F. (1898), 123.

Pte. McK. In hospital, Chatham. A comrade stated that McK. appeared somewhat 'queer' in his manner. Swallowed in the afternoon the contents of the bottle. At the lowest calculation 240 grains must have been swallowed. The man at once complained of sickness, retching quickly followed, and was favoured by an emetic. There ensued flushing of the face, violent trembling, rapidly increasing helplessness and unconsciousness within 5 minutes. Face ghastly pale, with clammy perspiration, pupils widely dilated, insensible to light and touch. Respiration very slow and in spasmodic gasps. Pulse barely perceptible. Under stimulation pulse improved, but became imperceptible again. Artificial respiration also used. Death at 7·30 p.m. with convulsions principally of the lower extremities. Quill (1903), 306.

Ocular

Following continuous use of Q. amblyopia with clouding of the vitreous. Geschwind (1892), 43.

Q. up to 8·0 g. per diem in treatment of b.w.f. In one of 4 cases amaurosis lasting 14 days. Küchel (1895).

Pruritus

About an hour after (taking 3 grains of Q.) he declared he must die, for he could not stand the itching all over his body and the strange sensation in his head, which, with all the features of his face, felt as if swollen to twice their natural size. . . . In half an hour, the severity of the symptoms had subsided. (Two other cases mentioned.) Farquhar (1866), 29.

Purging

Another effect I have observed in a good many instances is that of *severe* purging from doses of ten grains and upwards. Farquhar (1866), 29.

Purpura

1. Woman, aet: 50, was taking sulphate of Q. 10 centigrammes every 6 hours for neuralgia. The following day

dose increased to 15 cg. and a blister placed in the axilla. The following day the blister area was black and a blood serum oozed from it; the whole body also was covered with purpuric spots. Q. left off; in nine days the body normal. Q. prescribed again for toothache and purpura reappeared.

2. Woman, took Q. for a tertian fever; the second day epistaxis; the body covered with purpuric spots; the gums bleeding; the stools dark and bloody. Q. left off: the spots disappeared in 8 days.

3. Boy, aet: 12 Took Q. for general debility. After some days purpura developed. Q. continued. Purpura increased, gums bleeding. Q. left off. In ten days the skin was clear.

4. A man taking Q. for a ' larval ' fever. After 15 days no trace of purpura; 3 days later, 20 spots on the shoulders. Vépan (1867).

Tarrytown, N.Y. ♀ aet: 42. Suffering from malarial fever.

1. She had taken fifteen grains of Q., and shortly after Hgic symptoms appeared, purpura haemorrhagica covering the greater surface of the body, together with severe hemorrhage from the buccal and vaginal mucous membranes.

2. Five months later . . . in a similar condition . . . the Hge had not appeared until after quinine had been taken.

3. Suffering from malaria. Wishing to test the case, I prescribed Q., and the Hge appeared. Fleming (1896), 426.

Quinine disease

The slighter sequelae of quinine as tinnitus, impaired hearing, swimming of objects, nausea, follow, as is well known, after large doses.

More severe sequelae are also recorded, such as urticaria, scartaliniform rash, petechiae, mucosal Hges, fever, gastritis, enteritis, amblyopia, deafness after single doses or prolonged use.

The quinine disease occurred among those taking pro-

phylactic Q. 0·3 g. daily, and 0·9 g. instead of 0·3 g. once a week. When this latter dose was omitted the cases ceased. They occurred a few days after the beginning of prophylaxis or after some months. The symptoms are: (1) Rash, (2) fever, (3) oedema.

The Rash: urticaria-like swellings over the whole body, or a scarlatina eruption, or rubeolar, or a diffuse reddening like sun-burn or erysipelas. Itching in about half the cases.

The Fever: followed the rash usually. T. on an average 39°, but sometimes over 40°. Sometimes fell in 2–3 days, but usually lasted 3–6. A secondary rise after this time implied sepsis.

The Oedema: not so regular a symptom as the rash, but only absent in a few cases. The face, and especially the auricles and eyelids, chiefly affected, but also the hands and feet. Besides the oedema occasionally a deep cyanotic colour of the hands and feet occurred.

Urine: albumen neg., blood neg. Regendanz (1917), 306.

Scarlitiniform rash

A case in a woman aet. 40, in good health, of oedema of face and limbs, and an unusual erythematous rash following the taking of about 1 grain of quinine sulphate. In about 4 days, when the condition had improved, a quinine mixture was given as a tonic. Two hours after the first dose of 2 grains . . . all the former symptoms recurred. Garraway (1869).

A 'scarlatinal' rash following 2 doses of Q. 1 grain. The patient said, 'I know this to be quinine, as it occurred twice before . . . some years ago.' Hemming (1869).

Patient at her second visit told her medical man that he had been giving her Q., as she had developed a rash over the body. This she said had happened to her on 4–5 previous occasions following the taking of Q. Thorowgood (1869).

Patient stated that for nearly a year he had taken quinine by the mouth, but recently even a small dose had produced dermatitis.

After six successive febrile attacks, he consented to try the effect of a small intravenous injection of quinine. One grain of the bihydrochloride was given intravenously at 10.30 a.m. A scarlatiniform rash began to come out in the evening, and next day was well developed and very itchy. . . . The rash lasted for three days. A similar acute dermatitis of the face occurred on other occasions, once after a short exposure to sunlight, and once after he had washed with Carbolic soap.

Another patient had never been able to take quinine; two grains, he said, made him ill and produced a scarlatiniform rash which was followed by desquamation. At the age of 14 he had gone to work with a manufacturing chemist . . . work he got to do, with quinine powder, produced dermatitis and apparently also malaise. Patrick (1919), 427.

Suicide (attempted)

In the last 4 years in the whole of Bulgaria quinine self-poisoning amounts to $\frac{1}{3}$ of all other forms. The largest dose taken was in two cases 16 g., the majority had taken 4–6 g. and some only 2 g. Among 86 cases in 10 years there were 0 deaths. Nephritis was not uncommon, with transient albuminuria and red cells in the sediment. In some cases amblyopia or transient blindness persisted longest. Dobreff (1934), 290.

Syncope

He gave him a six-grain dose, and on his next visit was asked to give him no more, as he had fainted as usual, after taking it, and lain a considerable time insensible in his bath-room. Farquhar (1866), 30.

He took a wine-glass full (240 grains of Q.) and immediately fell down in the state of syncope, in which he was found (quite insensible and pulse imperceptible). (Recovery under

stimulant treatment of repeated doses of brandy and ammonia.) O'Connor (1867), 181.

Urinary

Diuresis and polyuria followed in several healthy people after Q. 0·5 to 1·0 g. for neuralgia of Vth nerve. Schulz (1887).

Urticaria

Dyspnoea, which apparently had threatened to become fatal. Patches about the size of half-a-crown (of urticaria) all over his body. The cause was a 'dose of neuralgic drops' containing about 2½ grains of Q. Floyer (1886), 739.

Woman. Q 0·1 g. Face became turgid, profuse lachrymation, orthopnoea, profuse sweating, urticaria. The symptoms always followed Q. Rizu (1887).

APPENDIX 18

QUININE FEVER AND HAEMOLYSIS

E.M. aet: 30. Nürnberg, Germany. Spleen enlarged, tender.

Date.	Q. hydro-chloride, g.	Hours interval.	T.	Remarks.
3 Nov.	0·2	1		Giddiness, great weakness, violent
		2	40·3°	rigor.
4			37·4°	
5	0·3	2	39·9°	In the evening patient well. T. 37·4°.
7	0·3	2	39·0°	Rigor.
10 a.m.	0·3		39·5°	
12 noon	0·2		39·8°	No further rigor. Evening, T. fell.
8			T.N.	
13	0·2		40·2°	Rigor. T. fell in the evening.
26	0·1	2	40·2°	Rigor. Evening, T.N., quite well.

Merkel (1885), 356.

13.11. Q. ·5 g. × 2 partly vomited; 12 noon, rigor, high T., vomiting; 4.30 p.m. rigor, T. 39·0°, vomiting, Hgburia.

22. 9 a.m. vomiting, headache, T. 38·2°. Blood: parasites pos. Evening, Q. 1·0 g. I.M. Some hours later rigor, fever. Urine normal. Plehn, A. (1896), 44.

5 April. Cameroons. The urine was somewhat clearer. Blood negative. The patient now took daily a small dose of Q., beginning with 0·19 by the mouth. Blood neg. Icterus diminished.

14. Q. 1·0 g., 6 hours later had a chill T. 39·9°. The urine passed in the night looked brownish, Hgb negative, marked icterus. Kleine (1901[c]), 665.

Missionary woman. Took Q. irregularly. Two attacks of b.w.f. in Sept. of previous year.

Date.	Parasites.	Quinine.	Shivers (Frost).	Hgburia.	Remarks.
27 Oct.	+	Q. tartrate 1·0 g.*	+	—	After 4 hours.
7 Nov.	+	Q. tartrate 1·0 g.	+	—	
16		Q. tartrate 1·0 g.		+	After 10 hours.
19		Q. 0·4 g.	—	—	
21–31		Q. 0·6 g.		—	Q. every third day.
3 Dec.		Q. 0·8 g.		+	After 8 hours.
10	+	Q. 1·0 g.			Scarcely any reaction.
11–15	—				
16	+	Q. 1·0 g.	+		
17–20	—				
21	+	Q. 1·0 g.	+		After 4 hours.
22–25	—				
26	+	Q. 1·0 g.		+	After 6 hours.
27			+	+	Relapse.
31	+	Q. 1·0 g.		+	After 6 hours.
			+	+	12 hours after the initial Hgb (relapse).

* A milk enema (milk 150, water 750 c.c.) at 40° was given with each dose of quinine in order to lessen as far as possible the chief danger in b.w.f.–kidney obstruction.

In these attacks the duration of the Hgburias was transient (a few hours), but no data are given. Fisch (1902), 10.

J. L. aet: 23. Sempstress. For the last 4 years resident at Magdeburg, since in Berlin, 13 June. Admission, spleen palpable.

Date.	Q., g.	T. before Q.	T. after Q.	Remarks.
21 June 8 p.m.	0·5	T.N.		
22			39°, 39·7° 38·8°	Nausea, retching, slight tinnitus.
30 8 p.m.	0·75	T.N.	40°	Rigor, vomiting.
1 July			40°, 38°	
2 8 a.m.	0·5	38·2°	39·3°	At night.
7 7.30 a.m.	1·0	T.N.	40·6°	7 and 13 July. Acute attacks with swelling of the joints, and such extreme prostration that the impression was got that further Q. doses would lead to a very dangerous condition of collapse.
13 8.30 a.m.	1·0	T.N.	39·4°	
24 11 a.m.	0·5	T.N.	40·5°	
29 4 p.m.	0·4	T.N.	40·6°	
4 Aug. 6 a.m.	0·2	T.N.	38·3°	
14 midnight	0·1	T.N.	37·5°	

Herrlich (1885).

'Paradoxical Quinine Fever' of F. Plehn; 'Rudimentary Blackwater' or 'Haemolysis *sine haemoglobinuria*.'

Date.	Time.	Q., g.	Time.	T.	Parasites.	Hgburia.
15	11 a.m.	1·00	12 noon	40·6°	+	6.30 p.m.
20	7 a.m.	0·75	10 a.m.	40·6°	P.B.*	1 p.m.
25	8 a.m.	0·20	12 n.	39·8°	P.B.	
27	12 n.	0·20	2 p.m.	37·6°		
29	8 a.m.	0·30	12 n.	39·6°		
31	8 a.m.	0·30	2 p.m.	37·2°		
2	6 a.m.	0·40	10 a.m.	38·6°	P.B.	
4	8 a.m.	0·50	12 n.	38·4°	P.	
6	8 a.m.	0·60	12 n.	39·0°	—	
8	8 a.m.	0·60	4 p.m.	37·6°		
10	8 a.m.	0·70	12 n.	39·6°		
12	8 a.m.	0·70	12 n.	38·0°		
14	10 p.m.	0·70		Normal		
16	12 n.	0·80	2 p.m.	37·4°		
18	12 n.	0·90	3 p.m.	37·4°		
20	2 p.m.	1·00	4 p.m.	37·4°		
22	2 p.m.	1·00	4 p.m.	37·2°	P.	
23–29		1·00	Daily	T. remained normal		

* P = Polychromasia, B = Basophilia.

The records show that on five of eight occasions an increase in the dose of Q. was followed by a rise of T., while if the dose was not increased no rise followed.

The T. on the days between the Q. doses was normal or subnormal. Nocht (1905), 218.

Quinine fever during uninterrupted Q. treatment is, I believe, to be explained in the same way as bilirubinuria *pro.* Hgburia, viz. by the excessive blood destruction. Seyfarth (1918[a]), 273.

Quinine haemolysis

Patient recovered from an attack of b.w. A quinine habiteration cure commenced. After small doses there regularly followed a fall in the red cell count and in the Hgb%. No details given. Kikuth (1927), 513.

APPENDIX 19

QUININE IN THE ORGANS AND EXCRETA

Blood

The ratio $\frac{\text{Serum Q.}}{\text{Corpuscles Q.}}$ exceeds $\frac{3}{1}$ in a guinea-pig. 239.

The amount of Q. in the blood of malaria patients ranged from 1 to 16·6 mg. per litre. 242. Ramsden, Lipkin and Whitley (1918).

The amount of Q. in blood ranges from a minimum of 1 mg. per litre to 10 mg. per litre. Foy and Kondi (1935), 510.

Faeces

Traces only of Q. are excreted in the faeces. Giemsa and Schaumann (1907).

Only those rendered diarrhoeic (by Q. sulphate grains 90 on each of two consecutive days) produced faeces in which Q. could be detected in more than traces. In case 1, those of the second day contained at least 100 mgms. Q. Ramsden, Lipkin and Whitley (1918), 248.

The amount of Q. excreted in the faeces passed during the 48 hours of the experiment is, like that for urine, subject to very wide variations, ranging from a minimum of 12 mg. to as much, in some cases, as 300 mg. in the whole stool, after a dose of 400 mg. of the sulphate. Foy and Kondi (1935), 509.

Milk

Quinine hydrochloride 0·5 g. was given to 10 women. Quinine was found in the milk subsequently for 1 hour. The maximum quantity excreted was 5 milligrams in 100 c.c.

of milk. 5 cg., for each year of age is taken as the necessary prophylactic dose for a child. Boulay, Lhuerre and Mitard (1928).

Organs

2.1. 9 capsules each of 0·2 g. Q. = 1·8 g. taken at a single dose.
3. Admitted b.w.f., urine scanty, contained quinine.
4. Urine clear.
6. Death. 200 c.c. of urine examined, negative for quinine.

Examination of the organs for quinine gave the following result.

Test.	Liver.	Kidney.	Spleen.	Suprarenals.	Pancreas.	Brain.	Blood.
Fluorescence .	+	+	+	+	+	+	o
$KI.HgI_2$ . .	+	++	+	+	+	+	o
Thalleiochin .	+	++	o	o	o	o	o

The amount of quinine present in the various organs is so slight that quantitative estimations were not possible, but it should be noted that quinine was last taken on 2 Jan. It is noteworthy that the kidney gave the highest results (qualitatively). Giemsa (1908), 79 (179).

	Guinea-pig 1.	Guinea-pig 2.	Rabbit.	Authority.
Dose of Q., mgms. per 100 g. body-weight .	125	12	11·1	Ramsden, Lipkin and Whitley (1918), 239.
Minutes after dose .	45	75	75	
	Q., mgms. in 100 g.	Q., mgms. in 100 g.	Q., mgms. in 100 g.	
Blood . . .	3·285	1·6	1·45	
Suprarenal . .	2200	162	5·5	
Kidney . . .	104	24	7·0	

Urine

Q. hydrochloride, g.	How given.	% excreted in 24 hrs.	Authority.
2·0	*Per os*	25	Kleine (1901[a]).
2·0	,,	20	
1·0	,,	27	
1·0	,,	27	
2·0	,,	10 *	
2·0	Per enema	18	
2·0	,,	17	
1·7	,,	18	
0·5 †	Hypodermically	11	
0·5 †	,,	10	
0·5 ‡	,,	15	

* On a full stomach. † Bihydrochloride. ‡ Hydrochloride.

Empty stomach.	Full stomach.	
(1) Q. can be detected in the urine in 20–3 minutes.	2 hours.	48.
(2) Tinnitus, nausea and tremors most pronounced in 3–6 hours.	6–9 hours.	26.
(3) Q. not found in urine on day 3.	Not found on day 5.	42.

(4) Of a given dose (at meal time) the excretion was as follows :

Day 1.	Urine	1500 c.c.	23% (approx.)
Day 2.	,,	2200 c.c.	12% ,,
Day 3.	,,	1600 c.c.	5% ,,
In 3 days	,,	5300 c.c.	40%

Hence 60% of the Quinine is ' lost ' or ' disappears ' in the body. 49.

(5) When Q. is given in fractional doses instead of in a single dose (equivalent to the sum of the fractions), more Q. is excreted in the urine; about 24% (for a single day's excretion) in the case of a single dose, and about 28% for fractional doses. It is concluded that in the latter case quinine is being better utilised in the body, not so much ' disappearing.' 81.

(6) In cases of b.w.f. receiving daily, quinine hydrochloride 1·0 g. *per os*, the average daily excretion is greater than normal, viz. 34% (approx.). This was independent of whether the urine contained Hgb or not (contrary to Marchoux, who found that while the urine contained Hgb Q. could not be detected in the urine). 71.

(7) It is concluded that in b.w.f. patients the body is not capable of 'destroying' as much Q. as is normally the case. 83.

(8) Quinine occurs in the urine, as quinine, but in what combination is unknown. Giemsa and Schaumann (1907).

It makes no difference to the amount of Q. excreted whether it is given *per os* in a single dose or in fractional doses during the day, or whether it is intramuscular. In fact, the greatest percentage excreted, 37·5%, was from an intramuscular injection. The greatest percentage excreted occurred in non-malaria controls who had never before taken Q. It varied from 19% to 30%. The percentage excretion in those (malaria patients) who had taken Q. in large doses for a long time was less, 11% to 19%. In four cases a considerable decrease in the excretion took place after the 3rd intramuscular injection (excretory insufficiency ?). The percentages fell from 16, 11, 16 and 24 per cent. to 5, 7, 8 and 13 per cent. respectively. Plehn, A. (1918), 385.

Malaria patients. Of 238 mgms. orally 23%, of 480 mgms. intravenously 37%, and of 2150 mgms. orally 24% was excreted in the urine. In the case of those taking large doses—90 grains a day on each of two successive days—6·8%, 6·7% and 10·6% were excreted respectively in each of 3 cases. 251.

Healthy men. Q. taken on an empty stomach appeared in the urine at intervals varying from 8 to 18 minutes. (Catheter not used.)

The secretion period after single doses may extend to 3 days, and after multiple doses to 7½ days. 249. Ramsden, Lipkin and Whitley (1918).

Dose of Q. sulphate 400 mg. 3 experiments on the same individual.					
	Total urine, c.c.	Hours.	Q., mg. recovered.	Max. excretion at 10th h., mg. per litre.	Authority.
1	1644	42	35·0	72	Foy and Kondi (1935), 501.
2	1402	35	26·78	38	
3	1579	51	33·5	113	

The maximum excretion occurred after 9–10 hours. In experiments 1 and 2, traces only were found at 42 and 35 hrs. and in experiment 3, negative at 51 hours.

Q. excretion and sp. gr. of urine

0·7 g. Q. hydrochloride in a gelatine capsule given to a patient who had taken much Q. for malaria over 3 years. The urine collected for 24 hrs.

Urine collected, c.c.	Sp. gr.	Urine Q., g.	Q. in 100 c.c.
190	22	(Before Q.)	
210	14	·0096	·0048
170	12	·0092	·0054
110	23	·0092	·0084
80	28	·0140	·0175
150	27	·0135	·0900
100	23	·0051	·0051
350	14	·0176	·0051
		·0782*	11·4

* The total given in the original is ·0756.

The last 2 figures only of the sp. gr. are given. The sp. gr. first falls, then rises as the excretion of Q. rises, falls again as the excretion of Q. falls. This signifies that the renal vessels dilate with a certain Q. concentration; they contract with increasing concentration in the blood; they contract and dilate again as the concentration falls. The quantity excreted is as great as that in a person who had never taken Q. Warasi (1934).

Quinine and urobilin

The persistently high Q.-content of the blood (16·6 mgm. per litre for 2 days) in case 8 (malaria) was associated with marked urobilinuria. . . . Since urobilinuria is a common precursor of b.w.f., its appearance in this case is suggestive of some increased haemolysis due directly or indirectly to Q. Ramsden, Lipkin and Whitley (1918), 243.

APPENDIX 20

CINCHONA FEVER

Patient excessively anaemic from long mercury treatment. Hard sore on glans penis.

Decoct. Chin. reg. (30–200) ordered. A short time after the 21st spoonful of the medicine, there occurred, rigor, high T., itching and burning, especially on the hands and arms, slightly on the face and feet, which were red and swollen. Patient was agitated and complained of thirst and oppression. The fever fell for 3 days and ceased in a further 14 days with slight desquamation.

Later Q. sulphate was given 1 to 150. On the same day the same symptom complex set in, rigor, fever, anxiety, etc., but with far greater intensity than after the decoction. The fever lasted some days longer and the hands swelled to shapeless masses from which the epidermis scaled off *in toto* like a glove. Pflüger (1877), 547.

E. P., aet: 65–70. Whenever she takes a grain of Q. it produces T. 104–105° an hour after the dose, P+, R+, rigors, slight delirium, nervous disturbance, thirst, dry parched tongue and hot dry skin. These symptoms pass off in 12–24 hrs. Similar symptoms have occurred 3 or 4 times in the same patient at intervals of some months, and in each instance within an hour or so. Peters (1889), 727.*

Zimmer observed that workmen engaged in powdering quinquina were attacked with a special fever, which he called *febbre di China China*, but his observations have been considered inconclusive. Zimmer. Tomaselli (1897), 56.

* Quinine not Cinchona fever.

APPENDIX 21

CINCHONINE

Discovery

1804

Although Sequin certainly discovered the extraordinary fact that cinchona contains a soluble principle, which is precipitated by tannin, it by no means follows that that principle must be gelatin. . . .

These experiments (of Duncan) only prove that gelatin and cinchonin are essentially different in chemical properties, but by no means that cinchonin is the febrifuge principle. Duncan (1804), 253.

Vide, Annals of Medicine (1804), 3; *Lustrum* 2, 240; *Bulletin des Sciences*, No. 77; *Journal* (Nicholson's) *of Natural Philosophy* (1803), 6.

1811

It would appear that Dr. Duncan, though he made the remarkable discovery of Cinchonin, never obtained it completely separated from the other principles of Peruvian bark. 420.

Hence it is only the cinchonin which can now be recognised as the principle that renders cinchona eminently febrifuge. 431. Gomes * (1811).

1816

Cinchonine was isolated in 1816 by Dr. Gomes, a Portuguese. Howard (1906), 97.

Enfin M. le Dr. Gomès, qui, le premier, a obtenu la cinchonine, quoiqu'il n'ait pas connu sa nature alcaline et ses

* Gomes, Bernardino Antonio G. 1769–1824. Practised in Lisbon as a physician. In 1797 visited Brazil as a ship's doctor. In 1805 (?) published his paper 'Ensaio sobre a cinchonino e sobre sua influencia na virtute da quina.'

principales proprietés chimiques, n'hésite pas à regarder la cinchonine comme le principe actif du quinquina. Pelletier and Caventou (1820), 363.

Cinchonine

1821

Isolated in 1821 from grey quinquina by Pelletier and Caventou, who first recognised its alkaline properties, it had already been obtained, but not in a pure state, by Gomes of Lisbon, who had not recognized its alkaline properties. de Savignac (1875), 300.

APPENDIX 22

HAEMOLYSIS

Quinine

The amount of Q. required to haemolyse 1 c.c. of an emulsion of washed red cells at 37° was determined.

Healthy control. ·001–·00082 g. Malarial patient. ·0008–·00062 and ·0005 g. once during Hgburia after Q.; the drug having diminished his resistance to Q. *in vitro*. Vincent and Dopter (1906), 350.

Vide, p. 629.

Acid salts of Q., e.g. bihydrochloride (Q. 2HCl) and bisulphate (Q. H_2SO_4), and double salts of Q., e.g. Q.-urea chloride (Q. $HCl.CON_2H_4.HCl$), are powerful haemolytic agents. *Neutral* salts of Q. are only slightly haemolytic, except arsenite and phosphate, which have no deleterious action on the blood, and arsenate, which, like *Q. alkaloid* itself, seems to protect the red blood corpuscles and delays autolysis. MacGilchrist (1913–14), 163.

1. 5 c.c. of ·85% saline.

2. 1 drop, 2 drops, etc., of Q. HCl (neutral) solution (5 g. in 5 c.c. H_2O).

3. 3 drops of an emulsion (E) of red cells freed from plasma and washed in ·85% saline.

The tubes were kept for 2 hours at 37°.

					Authority.
Saline, c.c. . .	5	5	5	5	Bijon (1914), 64.
Drops of Q. . .	1	2	3	3 (H_2O)	
Drops of 'E' .	3	3	3	3	
Haemolysis . .	CH	CH	CH	Nil	

CH = Complete haemolysis. Haemolysis is due to quinine.

Q. and adsorption

0·5 mg. Q. were added to saline containing various quantities of a sheep red-cell suspension. The distribution

of the Q. between the fluid and the red cells was as follows:

Red cells, c.c.	Q. in red cells.	Q. in fluid.
1·0	·483	·017
·7	·434	·066
·5	·407	·093
·2	·327	·173

If arsenic is added to the suspensions the adsorptive property of the red cells is decreased, and the red cells retain their normal colour, whereas when Q. alone is present the colour changes from bright red to dark red (Met-Hgb). Warasi (1934).

Q. and amboceptor

Q. inhibits the haemolysis of haemolytic amboceptors *in vitro*. Nocht (1929).

Date.	Hgb.	Hgbaemia.	Hgburia.
Dog 6·0 kg., 1 c.c. haemolytic amboceptor intravenously.			
9.4	100%	+ Slight	—
10	80%	+	—
11	80%	—	—
Dog. 10.0 kg., 1·7 c.c., Q. 0·1 g. + 1·7 c.c. haemolytic amboceptor.			
9.4	100%	++	++ Blackish brown
10	60%	+++	+
11	35%	+	+
Dog 12·0 kg., 3 c.c. haemolytic amboceptor intravenously.			
12.12	90%	+	—
13	80%	+	+ Brown
14	70%	+—	+ Slight, dark yellow
15	65%	—	—
The same dog, Q. 0·2 g. + 3 c.c. haemolytic amboceptor.			
7.1	55%	+++	
8	35%	+++	++ Pitch black
9	28%	+++	+ Dark blackish brown
10	20%	+	

Experiments on 18 dogs, 4 cats, 8 rabbits gave the same result. In the animals which received amboceptor + Q. the haemolysis was earlier and much more extensive than in the control animals which received amboceptor only. This activating action of Q. was not got with cinchonin, antipyrin or plasmochin. Nocht and Kikuth (1929).

A dog was made anaemic, Hgb 30%, by repeated injections of amboceptor. 14 days later Q. was given intravenously.

Day 15. Urine much albumen. Q. again injected.

Day 16. Death. Urine in bladder, dark brown, Hgb +

In other cases the results of giving quinine to anaemic animals was negative. Nocht and Kikuth (1929).

Q. and antiamboceptor

Dog 1. H.A. (haemolytic amboceptor) = Hgburia +.

Dog 2. H.A. + Anti-H.A. = Hgburia —.

Dog 3. H.A. + Anti-H.A. + Q. = Hgburia +.

Dogs treated for some time with small doses of haemolytic amboceptor develop anti-haemolysins, so that they now withstand larger doses of amboceptor without haemolysis than they do normally.

The data show that quinine does away with this protective action. Nocht and Kikuth (1929), 361.

Quinine and bile

Q. constant, bile variable.								
Q., mgm. . .	0·5	0·5	0·5	0·5	0·5	0·5	0·5	0·0
Bile (1–10), c.c. .	0·1	0·2	0·3	0·4	0·5	0·6	0·0	0·3
Haemolysis .	—	+	+	+	+	+	—	—
		in ½ h.	Immediate					
Bile constant, Q. variable.								
Q., mgm. . .	0·4	0·2	0·1				0·05	0·0
Bile (1–25), c.c. .	1·0	1·0	1·0				1·0	1·0
Haemolysis .	+	+	+				+	+
	In 5′		In 10′				CH in 1 h.	Slight in 1 h.

Mixtures made of diluted ox bile and quinine solutions, total volume 1 c.c. 0·1 c.c. of defibrinated blood added to each. Tubes, 1 hour in the incubator.

Concentrations of Q. and bile which separately are non-haemolytic, are haemolytic in combination. Kligler (1923), 207.

Q. and cholesterin

By increasing the cholesterin content of the blood of animals by feeding on or by injections of cholesterin, the haemolytic effect of a given dose of amboceptor can be lessened or completely obviated.

Quinine in small doses can destroy this protective action. Thus:

	Hgbaemia in 4 hrs.	Hgburia (next day).
Cholesterin rabbit, 2200 g., 3 c.c. HA* (intravenously)	—	—
Cholesterin rabbit, 2300 g., 3 c.c. HA + Q. 0·01 g. .	++	+++

* HA = haemolytic amboceptor.

But intravenous injections of colloidal cholesterin solutions have no effect on the haemolysis of an amboceptor, whether injected before, during or after the haemolyses.

Quinine has an activating effect on several haemolytic processes going on in the body.

Di-sodium phosphate (as used by Matko in b.w.f.) has no action on these haemolytic bodies—amboceptors and lecithin. Nocht and Kikuth (1929), 373, 374.

Quinine and lecithin

Lecithin in high dilution activates a non-haemolytic mixture of quinine and red cells thus:

Lecithin.	Control.	Lecithin + Q.	Q. control.	Authority.
1 in 5,000	N.H.	C.H.		Kritschewsky and Muratoffa (1923–24).
1 in 10,000	N.H.	C.H.	1 in 100	
1 in 20,000	N.H.	C.H.	N.H.	
1 in 40,000	N.H.	C.H.		

Each tube contains 1 c.c. of lecithin solution, 1 c.c. of 5% red-cell emulsion and 1 c.c. of Q. solution.

Lecithin is dissolved in methyl alcohol and the dilutions made with salt solution.

The red cells of different individuals behave differently in their capability of being thus made susceptible to haemolysis by quinine-lecithin mixtures.

Cholesterin has practically no inhibiting action on this Q.-lecithin haemolysis, the Q. haemolysis differing thus very markedly from haemolysis, e.g. by snake venom, which is inhibited by cholesterin.

Lecithin has an activating action on the haemolytic property of a chemical substance like quinine, like it has on a complex albuminoid substance like snake venom.

Haemolysis *in vivo* may thus depend on the presence or absence of certain properties in the red cells or serum of certain individuals, i.e. *in vivo* as *in vitro*. There may be an individual factor, e.g. the variation in the lipoid content of the corpuscles or serum. In persons liable to Q. haemolysis an increase in lipoid content is probable.

The toxic effect of all poisons is accompanied by a change of the state of dispersion of the colloids.

The haemolytic action of Quinine *per se* is slight; it is only displayed in the presence of quinine-activating lipoids. Kritschewsky and Muratoffa (1923–24), 41, 55, 56.

Q. haemolysis without lecithin.			Q. haemolysis with lecithin.		Authority.
Q. drops.	2 h.	16 h.	2 h.	16 h.	
1	—	—	+	+	Kessler (1925).
3	—	+	+	+	
5	—	+	+	+	
7	—	+	+	+	
9	+	+	+	+	

Q. hydrochloride 2·5 g., salt solution 300 c.c. Lecithin solution 1 in 10,000 (non-haemolytic).

Washed red cells of a healthy person, 1 drop in each tube, made up to the same volume with salt solution.

Lecithin activates the haemolysis of Q. solutions.

Experiments with lipoid rich sera of diabetic coma did not give an activating result. Kessler (1925).

A Q. solution in salt solution of insufficient strength to haemolyse red cells becomes haemolytic on the addition of a solution of lecithin (in salt solution), in itself also non-haemolytic.

This haemolytic action of lecithin-quinine can be checked by the addition of small quantities of serum, whether from cases of b.w.f. or other diseases.

In no case was the addition of sera found to have an increased effect on lecithin-quinine haemolysis—in fact they have anti-haemolytic properties.

Q. increases the haemolytic action of lecithin, but small quantities of homologous serum prevent it, so that it is necessary to use washed corpuscles.

Cholesterin has strong preventive properties in regard to ' all ' haemolytic processes *in vitro* (except taurocholate H.).

Normal cholesterin values are 120–160 mgms. per 100 c.c. Kikuth (1927).

The individual factor

Red cells: The activating action of non-haemolytic lecithin solutions on non-haemolytic Q. solutions varies with different human red cells, e.g. Red cells ' 4 ' + lecithin 1 in 100,000 + Q. 1 in 100, haemolysis = trace, but with red cells ' 5 ' H = complete. 302.

Similarly lecithin + non-haemolytic cobra toxin 1 in 1500 gave, with red cells ' 3,' H = trace, but with red cells ' 2 ' H = complete. 305.

Sera: Some have an activating, others an inhibiting action on Q. haemolysis. Thus Q. 1 in 50 + red cells, H = trace, and on addition of serum ' 15,' H = complete, but with serum ' 9,' H = 0, whereas in the control, H = almost complete. 307.

The activating effect of serum is not destroyed by heating to 56° for 30′. The activating effect of lecithin on Q. haemolysis is analogous to that of lecithin on cobra toxin,

and the activating effect of serum may be due to similar lecithin-like bodies. Ebert (1927).

Q. activates the haemolysis of lecithin *in vitro*. Lecithin in the body is generally non-haemolytic with or without Q. Nocht (1929).

Q. and lysocithin

Lysocithin is prepared by the action of cobra venom on yelk of egg. Cobra venom contains a ferment which splits off from lecithin a monopalmethyllecithide (lysocithin), which has strong haemolytic properties.

	Hgbaemia, 4 h.	Hgburia, 20 h.
1. Rabbit, 1950 g., 14 c.c., 1% lysocithin	+ Slight	—
2. Rabbit 1800 g., 12 c.c., 1% lysocithin + Q. 15 mg. . . .	++	+++ Dark brown

Quinine also increases the haemolytic effect of (dilute) cobra-toxin solutions. Nocht and Kikuth (1929), 368.

Quinine and organ extracts

Quinine Bihydrochloride 2·5 g. Salt solution 300 c.c. 1 c.c. = ·00833 Q. 1 c.c. = 28 drops. 1 drop = ·0003 Q. Washed red cells. Organ extracts made by rubbing with sterile sand and subsequent filtering.

Each tube contains serum, extract, red cells, Q. solution except where stated.

Q. Drops.	No extract.	Extract of b.w.f. organs.		
		Liver.	Kidney.	Spleen.
1	—	—	—	+
3	+	+	+	+
5	+	+	+	+
7	+	+	+	+
9	+	+	+	+
11	+	+	+	—
13	+	+	+	—
Control. No Q.	—	—	—	+

+ = haemolysis, — = no haemolysis.

Whereas b.w.f. spleen extract is in itself haemolytic, unlike b.w.f. liver and kidney extracts, yet with increasing strength of Q. (11 and 13 drops) it inhibits the haemolysis.

Q. Drops.	No extract.	Extract of normal organs.		
		Liver.	Kidney.	Spleen.
1	−	−	−	−
3	+	+	+	+
5	+	+	+	+
7	+	+	+	+
9	+	+	+	+
11	+	+	+	+
13	+	+	+	+
Control. No Q.	−	−	−	−

Each tube contains 1 c.c. of serum, 1 in 4.

Tubes containing normal serum only, without Q, show no haemolysis. The haemolytic action of Q. solutions 3 drops upwards is positive in all tubes.

Normal spleen extract behaves in the same way as normal liver or kidney extract.

Summary: The extracts of normal organs are non-haemolytic, the extracts of b.w.f. liver and kidney are non-haemolytic. The extract of b.w.f. spleen is haemolytic, but it inhibits the haemolytic action of Q. as the concentration of the latter is increased. Nocht and Kessler (1924).

Q. and serum

(Haemosozic value.) *

No lowering of the haemosozic value occurred after administration of Q. HCl; in the majority of cases the value was increased.

In order to bridge the gap between ·630 (the lowest value observed after administration of Q. sulphate) and ·47, at which haemolysin *in vitro* takes place, it is suggested that a haemolysin reduces the resistance of the red cells to such an

* The term haemosozic value indicates those constituents (e.g. salt) present in the serum which preserve the red cells from solution. Laking normally takes place at about ·47%.

extent that the administration of Q. sulphate would now become a determining factor in the onset of b.w.f. McCay (1908).

Normal individuals.			Authority.
Case.	NaCl, % before Q.	NaCl, %, after Q. sulphate.	
2	·850	·808–·630	McCay (1908).
3	·888	·742–·707	
4	·965	·762–·736	
Malaria. *P. falciparum.* Normal red cells as indicator of haemosozic value.			
2	1·004	·970	*Ibid.*
3	1·027	·976–·812	
4	·928	·849	
5	·928	·742	

We have not therefore been able to find the reduction in the haemosozic values * noted by McCay after the administration of Q. sulphate. 139.

In b.w.f. even quite early in the attack there is no marked if any lowering of the haemosozic value below the normal, and certainly no such lowering as could conceivably result in haemolysis by osmotic tension. That there is not some raising of the haemosozic value during the attack is less certain. 137. Christophers and Bentley (1908[a]).

Human serum contains substances which activate, i.e. produce haemolysis of human red cells in a Q. solution non-haemolytic *per se*, and also substances which check the haemolysis (antitoxic) of a haemolytic Q. solution.

These activating bodies are not destroyed by temperatures of 56°–62°. They are (probably) lipoids, and among them lecithin, which is haemolytic *in vitro* in minimal doses.

Differences exist in regard to the facility with which the red cells of different individuals are haemolysed.

* The haemosozic value or osmotic tension of a serum can be determined by a comparison of the resistance of red cells in various dilutions of serum with that of red cells in saline dilutions.

Cholesterin, which checks the haemolysis of animal toxins + lecithin, has no appreciable effect on Q. + lecithin mixtures.

Haemolysis in malaria will depend on the individual properties of the red cells and on the lipoid content of the red cells or serum. The toxic action of Q., in itself slight, comes into play with an increase of lipoids (of the red cells).

The individual factor

Red cells : With a certain strength of Q. solution some g. pig red cells are haemolysed, those of other g. pigs are not.

Serum : Some sera will activate non-haemolytic Q. solutions, while other sera will inhibit, haemolytic Q. solutions.

Lecithin in minimal non-haemolytic doses, activates non-haemolytic Q. solutions, so that they are now haemolytic.

We are justified in believing that Q. in therapeutic doses causes such slight injury to the physico-chemical properties of the red cell that no toxic symptoms arise, but that when the lipoids (of the lecithin type) are increased to such an extent as to activate Q., that then they occur.

Solutions of quinine of a certain percentage strength may be non-haemolytic for red cells of certain individuals, but haemolytic for those of others.

The addition of human blood serum to such a non-haemolytic mixture *induces* haemolysis thus :

	Q. solution 1 in 100, 5% emulsion of red cells.							Authority.
C.c. of serum	0·1	0·3	0·5	0·7	0·9	Control quinine	Control serum	Kritschewsky and Muratoffa (1923–24).
Haemolysis	A.C.H.	C.H.	C.H.	C.H.	C.H.	No H	No H	

Each tube contains 2·5 c.c., Q. 1 c.c., red cell emulsion 0·5 c.c. + salt solution.

On the other hand, if the Q. solution alone haemolyses

the red cells of an individual, the addition of serum may *diminish* the effect thus :

	Q. solution 1 in 150, 5% emulsion of red cells.							Authority.
C.c. of serum	0·1	0·3	0·5	0·7	0·9	Control quinine	Control serum	Kritschewsky and Muratoffa (1923–24).
Haemolysis	No H	trace	trace	trace	trace	A.C.H.	N.H.	

A.C.H. = Almost complete haemolysis. N.H. = No haemolysis.

Serum would thus appear to contain bodies which activate and paralyse (antitoxic) Q. haemolysis. They are not destroyed by heating to 56° or 62°. Kritschewsky and Muratoffa (1923–24), 40.

5% emulsion of washed normal red cells + Q. hydrochloride, with and without serum. Haemolysis after 12 hrs. at 39°.

	Q. concentration, %.									
	0·1	0·2	0·3	0·4	0·5	0·6	0·7	0·8	0·9	1·0
Q. alone.						(+)	+	+	+	+
Q. + normal serum .					+	+	+	+	+	++
Q. + b.w.f. serum .			+	++	++	+++	+++	+++	+++	+++

The table shows that serum increases the haemolytic power of Q. *in vitro*. In the case of the normal serum experiment, normal red cells were used, and in the case of the b.w.f. serum experiment, red cells from a case of malaria. Ghiron (1927), 117.

Solutions of quinine, quinidine, and cinchonine respectively in strengths from 0·1 to 1·0%. To these are added 2 drops of a 5% emulsion of red cells of a malaria patient + 2 drops

of fresh serum from a Q. Hgburia case (5 cases), or in 2 cases, instead of using serum of a Q. Hgburia case, that of a Quinidine Hgburia and a Cinchonine Hgburia respectively were used. The Haemolysis under these conditions then compared. Q. hydrochloride produces H with all the Hgburic sera. Qd. hydrochloride produces H with the Hgburic sera of Qd. and Q. C. hydrochloride is the only salt that gives a negative reaction with non-cinchonine Hgburic sera. Cinchonine is the safest base to use in the cure of Q. Hgburic cases. Lega (1928).

Quinine and serum and *Plasmochin and serum*

Ghiron's technique employed. The tubes contained: 1. Plasmochin from ·1 to 1%. 2. 2 drops of suspension of washed malaria red cells. 3. Heated to 37° for 5 minutes. 4. 2 drops of blackwater serum. 5. Heated to 37° and readings of the haemolysis made every 10 minutes.

Control tubes of quinine hydrochloride ·1 to 1% also made. The haemolysis of plasmochin is in all cases less prompt, less complete and requires a much higher concentration than is the case with quinine. Torrioli (1929).

Quinine and haemolytic sera

Solutions of Q. bihydrochloride or hydrochloride in strengths not having any direct haemolytic action on red cells inhibit haemolysis in a haemolytic system. Brahmachari, Banerjea and Brahmachari (1932), 309.

The blood sera of malaria patients mainly during the attack or directly after it (Parasites +) have *in vitro* a distinct inhibitory action on the Q. haemolysis of human red cells.

The blood serum of a severe case of b.w.f. (when taken ?) also inhibited the Q. haemolysis of the patient's or other red cells.

If we assume that in malaria there is frequently a + lipoid value for the serum and corpuscles, this + lipoid value in view of the *in vitro* results can have nothing to do with the H. in blackwater. Asbelew (1926), 94.

Quinine and urine

1. 10 c.c. of a 0·4% quinine bisulphate solution in urine of the person examined is prepared and his red corpuscles added thereto.

2. 3 samples of urine were examined daily for 10 days from 10 healthy and 15 malaria patients, i.e. 750 urines. 225 of 750 samples of urine had an antihaemolytic action, 525 of 750 samples of urine had a haemolytic action.

3. The antihaemolytic action of urine is only exhibited at times; thus of 30 urines from one case 9 were antihaemolytic, 21 haemolytic.

4. The antihaemolytic effect is so strong in certain cases that there is no change in blood cells kept for an hour at 37°.

The 25 (10 healthy and 15 malaria) cases were now treated with quinine (Nocht's * course) and the urine tested as before (but without any addition of quinine) for 10 days, 3 times daily.

20 (8 healthy and 12 malaria) cases now passed urine which at times was more or less strongly haemolytic. The haemolytic property bore no relation to the quinine excretion.

In 14 cases the haemolytic action present only on the first 2 days, and in only 2 of the 6 urines in each case.

In 10 cases the haemolytic action developed in 4 hours after the beginning of the quinine course.

In 1 case in 2 hours.

In 5 cases haemolytic urines were passed for the whole 10 days.

In 1 case haemolytic urine only passed once. Matko (1918[a]).

Samples of urine to which 1% Q. hydrochloride has been added are much less actively haemolytic on a 5% or 2% suspension of red cells than saline containing the same quantity of Q. (one exception). Dudgeon (1920), 232.

* Nocht's course: 0·25 gramme 4 times daily for 8 days, then 2 days free, etc., etc.

Serum and lecithin

Lecithin 1% in methyl alcohol. Serum, diluted 1 in 3. The volume of fluid in each tube made the same with salt solution (or serum), 1 drop of a red cell emulsion added to each tube.

Lecithin. Drops.	H. in 16 h.	Lecithin + serum, 1 c.c.	Remarks.
1	+	−	
2	+	−	
3	+	−	
4	+	−	Serum inhibits lecithin haemolysis.
5	+	−	
6	+	−	
7	+	+	Kessler (1925).
8	+	+	
8	+	+	
10	+	+	

The diminishing effect of sera on amboceptor, lecithin or lysocithin haemolysis *in vitro* is probably due to their cholesterin content. The neutralising effect was approximately the same for all the sera (18 cases) tried. Three exceptions were noted.

(1) A case of blackwater.

(2) A case of general paralysis. Par. +.

(3) " " " "

In these three cases the anti-haemolytic effect was less than in the rest, and the cholesterin content of their blood was low, 80–90 mg. (120–160 mg. normally), but a similar effect was not observed in other cases with a low cholesterin content. Nocht and Kikuth (1929), 369.

APPENDIX 23

ANTI-HAEMOLYSIN AND HAEMOLYSIN

Anti-haemolysin

A fatal case of anuria. Day of examination ?.

1. Resistance of red cells to salt solution.

   (*a*) *Washed red cells :*

   Haemolysis occurred between 0·34 and 0·28% saline, i.e. their resistance is greater than normal.

   (*b*) *Unwashed red cells :*

   About the same results. It is concluded that there is no antihaemolysin present (sufficient to prevent haemolysis by hypotonic saline).

2. Resistance to haemolytic serum (rabbit anti-human).

   (*a*) Patients' red cells are haemolysed by $\frac{1}{8}$ of the quantity of H.S. required to haemolyse normal red cells (3 controls), i.e. patients' red cells are less resistant than normally.

   (*b*) If, however, the haemolytic experiment is carried out with the addition of patients' serum (heated to destroy its own complement), then 5 times as much haemolysin is required to haemolyse patients' red cells as is required in the absence of the serum. (Control experiments do not give this result.) It is concluded that the patients' serum contains an antihaemolysin revealed only by biological tests. Ameuille, Sourdel and Marcorelle (1918), 559.

'Cold' Haemolysin

Soldier aet: 24. Always good health before joining army. Arrived Madagascar April 1895. Invalided home Dec. 1895.

2 Feb. 1896. Rigor. Hgburia.
10. Second attack. Hgburia.
15. Third attack. Hgburia.
18. Fourth attack. Hgburia.
19. Red cells 620,000.
2 Mar. Red cells 3·25 millions.
8. The right middle finger was ligatured at the base and placed in ice water for 10 minutes. Blood then withdrawn from this finger, and an equal amount from the adjoining ring finger. The samples of blood placed in tubes in a cool place.
10. *Middle finger blood :* clot less retracted, serum turbid, slightly tinged with Hgb.
Ring finger blood : clot more retracted, serum limpid, amber-coloured.

The blood of the patient, in spite of its apparent improvement, was still more vulnerable, as it could be modified by the action of cold. Ferrier (1896), 462.

16 cases (thirty observations) examined for the cold haemolysin *in vitro* (Donath-Landsteiner reaction).

Oxalated plasma used, and a red cell emulsion of 1 part red cells to 100 plasma. A positive result, i.e. haemolysis, obtained in two cases * (possibly one only). Barratt and Yorke (1909[a]), 65.

Day 4. Red cells of patient + serum of patient; 0° ½ hour; 37° = No H.
Red cells of control + serum of patient; 0° ½ hour; 37° = No H. Achard and Saint-Girons (1912), 753.

Haemolysin (general)

The serum in 7 of 100 cases of malaria was auto-haemolytic and iso-haemolytic. In 5 cases the action was definite, but in 2 extremely slight.

* In both bacteria were present.

12.30 a.m. Blackwater.

1.30 a.m. Serum gave very slight haemolysis with normal corpuscles.

3 a.m., 5 a.m., 11 a.m. Serum was non-haemolytic. Simpson (1912).

Day 3. Blood by dry cupping. Serum deep green. Red cells + serum in test tube. No haemolysis. This emulsion poured on to a grey filter paper; sudden haemolysis, the filtrate the colour of Bordeaux. Lahille (1915), 909.

Haemolysis of organ extracts (*b.w.f.*)

Pieces of liver, spleen, kidney, supra-renal taken 2 hours after death and pounded fresh or after drying at 56°. Made up to 1 in 10 with water.

5 c.c. of deplasmatized red cells, washed, and suspended in 5 c.c. of normal saline. Various quantities of extract added. No haemolysis except with supra-renal extract.

Conclusion. No haemolytic bodies present, the supra-renal action being due to adrenalin. Porak (1918).

APPENDIX 24

RESISTANCE OF RED CELLS (ISOTONIC POINT)

Resistance of red cells

	Salt solutions differing by ·01 g. %.				
	1.	2.	3.	4.	5.
Case 1.					
Day 3 . . .	—	—	—	—	—
Control 1 . .	—	—	h.	h.	H.
Control 2 . .	h.	h.	H.	H.	H.
Case 2.					
Convalescent (10 days)	—	—	H.	H.	H.
Control . . .	—	H.	H.	C.H.	CH.

— = No haemolysis, h. = slight, H. = haemolysis, C.H. = complete haemolysis.

In these two cases of b.w.f. the tonicity was lowered (i.e. the resistance is raised)—in the fatal case markedly so, in the convalescent less markedly. Stephens and Christophers (1900). 64, 74.

Sometimes (but not always) I have been able to establish this lowered resistance to anisotonic salt solutions. Plehn, A. (1903[b]), 517.

Time.	Hgburia.	NaCl, %.	Authority.
Before attack . .		·44	Vincent and Dopter (1906), 350.
1 h. after Q. . .	Beginning	·46	
4 h. later . . .	Ended	·41–·42	
9 days later . .		Normal	

Marked changes in the isotonic point have never been found by us in blackwater fever. Christophers and Bentley (1908[a]), 130.

Case 1. 3 days after cessation of Hgburia.

Haemolysis at $\frac{n}{250}$ NaCl. Normally $\frac{n}{40}$ to $\frac{n}{50}$ NaCl.

Case 2. Relapse on day 4. (1) Attack 'wearing off.'

H. at $\frac{n}{60}$ to $\frac{n}{70}$.

(2) 2 h. after 2 pints of 1·2% saline + ·03% $CaCl_2$.

H at $\frac{n}{90}$ to $\frac{n}{100}$.

(3) 48 h. after H at $\frac{n}{100}$ to $\frac{n}{180}$.

The corpuscles become resistant as recovery takes place. McCay in Gupta (1916), 420.

The globular resistance is much diminished in the first hours of the attack. The red cells haemolyse in 0·7% salt solution. The resistance rapidly reaches the normal figure 0·42%. Armand-Delille, Paisseau, Lemaire (1917).

Hgburia apparently induced by X-rays. *Vide* Appendix 25.

Red cell resistance (20 hours after the beginning of the attack) against salt solutions.

Patient.	Min. ·46%.	Max. ·34%.
Control.	,, ·48–·45%.	,, ·32–·36%.

Deutsch (1917).

30 May. 1.40 p.m. Q. 1·0 g.
31. Hgburia.
14 June. Q. 1·0 g.
15. Hgburia.
23. Parasites +. Resistance of red cells. Min. ·48%. Max. ·38%.
3 July. Q. 2·0 g.
4. Hgburia.
18. Parasites +. H. begins at ·50%.
19. H. begins between ·50% and ·58%.

Concluded that b.w.f. is due to constitutional fragility

of red cells following malaria, and set going by Quinine. Garin, Girard and Sarrouy (1917–18), 485.

Day 1. Washed red cells of patient. Resistance diminished as haemolysis began at 0·68%, was intense at 0·52% and complete at ·40%. Amblard and Eschbach (1917). 814.

Day ? Washed red cells of patient.
Haemolysis took place between ·34% and ·28% saline, i.e. resistance increased. Ameuille, Sourdel and Marcorelle (1918), 559.

Numerous experiments were made on the fragility of the red cells of patients in the acute and convalescent periods of b.w.f. . . . The fragility remained within the limits of normal blood in every instance. Dudgeon (1920), 212.

Case.	NaCl, %, minimum.	NaCl, %, maximum.	Cases.	Remarks.
1	0·76	0·60	B.w.f. 3	The malaria and b.w.f. cases show diminished resistance, lowest in the first b.w.f. case where H. occurred between 0·76% and 0·60%.
2	0·68	0·54	,, 2	
3	0·64	0·50	,, 1	
4	0·50	0·40	Malaria	
5	0·58	0·50	,,	
6	0·72	0·50	,,	
7	0·68	0·50	,,	
8	0·63	0·50	,,	
9	0·60	0·50	,,	Barrenscheen and Glaessner (1923), 417.
10	0·68	0·45	,,	

One drop of defibrinated blood added to 1 c.c. of salt solutions of various strengths.

The b.w.f. was tested ' shortly after the attack.'

The results were compared with those of normal blood.

In both cases there was practically no haemolysis with salt solutions of 0·36%.

0·2% solution of quinine hydrochloride caused laking of normal and of b.w.f. blood.

There is no difference in the resistance of the red cells of normal persons and those of b.w.f. patients. Kligler (1923), 203.

Normal men (25).				
% of red cells remaining in	Simmel's fluid. 70%.	60%.	50%.	40%.
Maximum . .	96	92	55	4·7
Minimum . .	74	31	4	0·3
Average . .	84·8	73	25	1·6
Normal females (15).				
Maximum . .	99	90	77	20
Minimum . .	73	63	5	0·4
Average . .	85·4	75·6	33·2	2·8

Simmel's fluid is isotonic with whole blood, is buffered to approximately the same extent, has the same *p*H, and the salts are approximately in the same proportion as in whole blood. Leake and Pratt (1925), 899.

A solution devised by Simmel (1923), with slight modification, was used. This solution has the following composition: NaCl 8·2 g.; KCl 0·2 g.; $MgCl_2$ 0·2 g.; $CaCl_2$ 0·2 g.; NaH_2PO_4 0·2 g.; $NaHCO_3$ 0·05 g.; H_2O 1000 c.c.

This standard solution is then diluted with water so that the first dilution contains 30, the second 40, the third 50 and the fourth 60 per cent. of water.

Blood is then taken (from the finger or ear) and diluted in 5 ordinary blood-counting pipettes; in the first case with the standard undiluted solution, in each of the 4 other pipettes with one of the 4 dilutions. A blood count is made in the ordinary way, diluting with Hayem's fluid or with Simmel's undiluted fluid as above, in order to determine the 'normal' value of the blood to be examined. All the pipettes are then kept at room temperature for 1 hour. Counts are then made of the red cells remaining in each tube, and these are expressed as percentages of the 'normal' value. Thus if the 50% diluting fluid has been used and 3 m. red cells per mm.^{3} remain in the tube at the end of the hour, $\frac{3}{5}$ of the red cells or 60% are resistant (assuming that the count when the standard fluid was used was 5×10^6 per mm.^{3}).

In this way a series of graphs is constructed.

% of red cells remaining in	Simmel's fluid. 70%.	60%.	50%.	40%.
Normal cases (20).				
Maximum . .	99	93	60	2·6
Minimum . .	80	65	8	0·3
Average . .	92	85	30	1·6
Blackwater cases (6).				
Maximum . .	97	90	55	2·4
Minimum . .	86	70	13	0·5
Average . .	90	81	32	1·5

In 5 cases the observations were made within 24 hrs. of the commencement of Hgburia. In 1 case, 4 days after the beginning of Hgburia.

The figures show no appreciable difference between normal and b.w.f. bloods taken at the times stated. Ross (1928).

Case.	B.w.f. H_1.	H_2.	H_3.	Remarks.
1	·62	·58	·50	The resistance to salt solutions is lowered at the time of the Hgburic attack. Ott (1932[a]), 737.
2	·51	·46	·38	
3	·48	·44	·40	
4	·44	·38	·32	
5	·60	·40	·30	
6	·49	·40	·30	
7	·70	·46	·30	
Mean	·55	·44	·35	
	Normal annamite.			
Mean	·44	·38	·32	

H_1 = Commencing haemolysis, rosy tint above the red cell sediment.
H_2 = Definitely red, indicating 'central haemolysis.'
H_3 = Complete haemolysis.

The values for the normal Annamite are the mean of 4 cases. It is not clear when the observations on the b.w.f. case were made.

Resistance and cholesterin

Cases.	Cholesterin, g. per litre.		Remarks.
	Serum.	Red cells.	
Normal annamites.	1·39	1·23	It is not clear how many cases of b.w.f. were examined, nor when. Ott (1932[a]), 505.
B.w.f. . . .	0·98	1·11	

B.w.f. Cases.	Induced hypercholesterinaemia.			Remarks.
	Before injection.	24 h. later.	48 h. later.	
Serum (1) . .	0·82	1·20	0·82	Cholesterin in olive oil injected subcutaneously or I.M. in doses varying from 0·5 to 1·0 g. in b.w.f. cases.
(2) . .	0·64	0·69		
(3) . .	1·27	1·21	0·72	
Mean .	0·91	1·03	0·77	
Red cells (1) .	1·27		1·42	
(2) .	1·15	3·03		
(3) .	1·38	2·13	3·75	
Mean .	1·27	2·58	2·58	Ott (1932[a]), 507.

The increased values especially in the case of the red cells are considered to be due not to simple absorption by the cells, but to the excitation of cholesterigenic centres.

Before injection.			After injection.		
H_1.	H_2.	H_3.	H_1.	H_2.	H_3.
60	52	38	42	36	28
38	38	22	38	30	20
48	42	36	44	38	20
44	38	30	37	32	26
38	32	26	36	30	26
45	40	36	45	40	36
42	34	30	36	30	24
52	44	38	48	42	36
46	38	34	42	38	32
51	46	38	50	42	30
44	38	32	42	36	?
49	40	30	45	36	26

The figures indicate percentages of salt, thus 60 = ·60% salt.
H_1 = Commencing haemolysis above the sedimented red cells.
H_2 = Haemolysis in centre of tube.
H_3 = Complete haemolysis.

The first 9 cases are cases of malaria, the last 3 of b.w.f. The result of the cholesterin injection has been to lead uniformly to an increase of resistance, to salt solutions. 510.

Resistance and defibrination.

Resistance to salt solutions, of red cells got by mechanical defibrination and from oxalated plasma respectively.

	Defibrinated red cells.			Oxalated red cells.		
	H_1.	H_2.	H_3.	H_1.	H_2.	H_3.
(1)	41	36	30	49	42	36
(2)	44	35	30	50	42	38

After the partial haemolysis on defibrination, the red cells were washed 3 times and then tested for their resistance.

It requires less salt (more water) to haemolyse defibrinated red cells than it does oxalated red cells, i.e. the red cells left after the partial haemolysis are more resistant than the total oxalated cells ; or, expressed differently, as some of the Hgb has already disappeared by laking, the appearance of Hgb in the tubes will be less for each tube, and so the curve of haemolysis will begin at a greater concentration of salt than normally, i.e. the resistance of the cells remaining after defibrination will be greater. 739.

Defibrinated red cells. Cholesterin 1·32 g. per litre.
Oxalated red cells. ,, 1·245 g. ,, ,,

The total red cells have less cholesterin and are less resistant than the red cells got by defibrination, i.e. the cells which remain after partial laking have more cholesterin.

Concluded that in b.w.f. red cells poor in cholesterin are attacked, those that remain afterwards will have a higher value than normal. 740. Ott (1932[a]).

Resistance to Q. formate solutions before and after cholesterin injections. B.w.f. red cells 30′ at 37°.				Remarks.
	H_1, g.	H_2, g.	H_3, g.	The resistance is *increased*. Before injection ·0025 g. produces complete H, after injection ·0105 g.
Before .	·0015	·0020	·0025	
After .	·0085	·0095	·0105	
				Ott (1932[a]), 510.
Resistance to haemolytic serum before and after cholesterin.				
	H_1.	H_2.	H_3.	The figures refer to dilutions of H.S. In 3 cases the resistance was *decreased* as shown. In 3 cases there was no change.
Before * .	1/2000	1/5000	1/4000	
After † .	1/3400	1/2800	1/2800	

* Before injection red cell cholesterin = ·87 g. per litre.
† After injection red cell cholesterin = 1·53 g. per litre.

Summary :—

1. Red cells of b.w.f. are less resistant than others to salt solution and to formate of quinine. *Vide infra.*

2. The cholesterin content of red cells can be increased by injections of cholesterin. Such cells are now *more resistant* to salt solutions and formate of Q. than they were before, but they are *less resistant* to a haemolytic immune serum.

3. The Cholesterin content of b.w.f. cells is less than those of others. Ott (1932[a]).

Resistance and quinine

	Q., x g.	Q., $\frac{1}{2}$x g.	Q., $\frac{1}{4}$x g.	Q., $\frac{1}{8}$x g.	Q., $\frac{1}{16}$x g.
	Saline, 1 c.c.	Saline, 1 c.c.	Saline, 1 c.c.	Saline, 1 c.c.	Saline, 1 c.c.
Patient's red cells	+	+	Agg.	Agg.	Agg.
Normal control .	+	+	—	—	—

\+ = Haemolysis. — = No haemolysis. Agg. = Agglutination.

Stephens and Christophers (1900), 25.

Haemolysis of normal and b.w.f. red cells by Q. formate solutions.

Case.	During b.w.f. 737.			Remarks.
	H_1, g.	H_2, g.	H_3, g.	Whereas normal red cells are only completely haemolysed by a strength of Q. formate solution of ·0065–·0080 g., the cells of b.w.f. are completely haemolysed by Q. ·0015–·0025, i.e. in b.w.f. the red cells are less resistant. Ott (1932[a]).
1			·0025	
2			·0025	
3		·0010	·0015	
4	·0015	·0020	·0025	
5			·0025	
Case.	Normal annamite. 499.			
	H_1, g.	H_2, g.	H_3, g.	
1	·0025	·0050	·0065	
2	·0055	·0065	·0080	
3	·0050	·0060	·0070	
4	·0040	·0060	·0070	
5	·0042	·0058	·0071	

Tubes 2 h. at 37°, then centrifuged and readings taken.

1. Rabbit = 2620 g.

Date.	Q. hypodermic.	H. begins.	H. complete.	Remarks.
		·48% (control)	·42%	The resistance of red cells is diminished by Q. injections. The resistance gradually dimishes in the first few days, then suddenly. Bijon (1914).
10 June	1 c.c. of a solution of ·17 g. per c.c.			
11	1 c.c. Q. solution	·50%	·46%	
13		·56%	·46%	
14	1 c.c. Q. solution			
16		·60%	·52%	
25		·50%	·48%	

Tubes 2 h. at 37°. Readings after 24 h.

2. Rabbit 2220 g.

Date.	Q. hypodermic.	H. begins.	H. complete.
		·48% (control)	·42%
16 June	1 c.c. of Q. solution, ·10 g. per c.c.		
18	1 c.c. of Q. solution	·50%	·42%
20		·54%	·48%
21		·60%	·50%
3 July		·54%	·52%

Kayes. Senegal

Blood from a vein. 3 drops in each tube of salt. Kept over-night at room temperature (about 30° C.).

1.		H. begins.	H. complete.	Remarks.
20 June	*P. praecox*	·50%	·42%	The increase in resistance from ·50 to ·44 attributed to the Q., destroying the parasites (and thereby their lysins) though in itself it diminishes the resistance.
21	,,	·50%	·42%	
26	Q. 1·0 g.			
27	Q. 1·0 g.	·46%	·42% (incomplete)	
2 July		·44%	·42% (incomplete)	
2.		H. begins.	H. complete.	
20 June	Parasites	·52%		Ditto.
21		·52%		
26	Q. 1·0 g.			
27	Q. 1·0 g.	·50%	·42% (incomplete)	
3.		Haemolysis.		
27 July	B.w.f.			
28	Parasites neg.	·60% intense		
29		·80% beginning		
31	Death			

Bijon (1915), 599.

Red cells treated with Q. HCl 0·1–0·25% and then washed have their resistance to salt solution decreased. They now haemolyse at ·64% instead of at ·42% (normal).

They are also less resistant to lecithin haemolysis. The effect is attributed to the injurious action of the Q., and not to an 'activating' effect of lecithin on Q. haemolysis, as considered by Kritschewsky and Muratoffa (1923–24). Asbelew (1926), 95.

Resistance of red cells to Q. formate solutions.

	H_1, g.	H_2, g.	H_3, g.	Remarks.
Normal . .	·0042	·0058	·0071	
Malaria . .	·0055	·0063	·0073	
B.w.f. . .	·0010	·0015	·0020	

H_1 = Commencing haemolysis, a rosy tint above the sediment.
H_2 = Definitely red, indicating central haemolysis.
H_3 = Complete haemolysis.

The resistance of b.w.f. red cells to formate of Q. is less than that of normal or malaria red cells.

In the case of hydrochloride and bihydrochloride of Q. no difference is appreciable. Ott (1932[a]).

Resistance and serum

Red cells of	Serum of	Saline, per ecnt.		Agglutination.
		Haemolysis before.	Haemolysis after.	
Malaria 1	B.w.f. 3	·50–·40	·63–·50	1 in 10
Malaria 2	,,	·58–·50	·82–·50	1 in 80
B.w.f. 2	,,	·68–·54	·81–·59	1 in 40
Malaria 3[a]	B.w.f. 2	·68–·50	·68–·50	1 in 40
Normal 1	,,	·46–·32	·46–·32	0
Malaria 3[b]	Normal 1	·68–·50	·68–·50	0
Normal 3	Normal 2	·43–·30	·42–·30	0

The washed cells of malaria patients, of one b.w.f. case and of two normal patients were treated for 1 hour at 37° with the serum of two b.w.f. cases and two normal persons as shown in the table. After washing again, their resistance to saline was tested. The serum of b.w.f. Case 3 produced a lowering of the resistance of the treated red cells. The serum of b.w.f. Case 2 produced no change, neither did normal serum in the treated red cells.

Further b.w.f. Case 3 serum agglutinated the treated red cells, while that also occurred in the case of b.w.f. Case 2 serum, though it had not altered the resistance of the cells.

The results could be explained by changes in the plasma (e.g. increase of CO_2 and decrease of alkali), but we believe that they are due to substances which have become anchored to the red cells. Barrenscheen and Glaessner (1923), 417.

APPENDIX 25

NOTE ON HAEMOGLOBINURIAS

Antipyrin

9.7.1903. Patient had a rigor in the morning and a second one about 2 p.m. He does not know if he had fever, but states that he passed black urine in the evening. The patient is certain that he has taken no Q. during the day, but only a tabloid of Antipyrin 0·5 g. Broden (1906), 19.

Beans (Phaseolus)

In different parts of Greece, especially in Spring, it is often found that Hgburia results from eating fresh beans in the pod, and more rarely from the flowers (seeds ?) only. A case has been seen of a child aet. 6 found dead in a field of beans in full flower, following an attack of uraemic Hgburia. As the inhabitants of certain villages in Greece and in the isle of Rhodes are aware that eating beans in the field where they grow will produce vertigo, somnolence and gastroenteritis, they forbid their children to do so. Cardamatis (1910), 104.

Glycerin

Date.	Q.	T.	Hgburia.	Remarks.
8.10.1910	0·2 g. × 4	39·7°	+	Rigor, icterus.
10			+	Cholestearin 3·0 g. in olive oil per rectum. Fever continues.
12		39·6°	+	
13			—	T. subnormal. Urine normal.
16 a.m.			—	Enema glycerin, 10 c.c.
p.m.		39·5°	+	Rigor, icterus.
17 a.m.		T.N.	+—	
p.m.		39·5°	+—	
18 a.m.		T.N.	+—	Enema glycerin, 10 c.c.
p.m.		39·5°	+	Rigor more violent than on 17th.
25			—	

On 16.10 there began a remitting T. of 15 days' and Hgburia of 9 days' duration. Hgb appeared in the urine only during the few hours of the daily elevation of T. (about 39°). The onset of the Hgburia on 16 and 18 was attributed to the glycerin enema. Werner (1913), 10.

Miscellaneous

Drs. St. Ar. and St. Ag. Varvouzos have seen Hgburia following the smelling of resin.

Koukouliotis mentions a case in a child aet. 8 following the eating of a lot of figs.

Talliadouros has also seen Hgburia follow a dose of *Quassia amara*, and also from a decoction of absinthe. Cardamatis (1910), 105.

Naphthalene

5 days before admission had ground up and swallowed two ' camphor balls ' (naphthalene). There followed giddiness, diarrhoea, pain in urethra and bladder, dark urine and faeces. Admitted for ' Icterus and anaemia.' Severe anaemia, some jaundice. Liver neg., spleen neg. Oxy- and Met-Hgburia. Taylor (1932), 48.

Phenacetin

Patient, aet: 17. Printer's apprentice. During the last $3\frac{1}{2}$ weeks has taken 4 Phenacetin powders of 1 g. for occipital headache.

19 Oct. 9.30 p.m. Phenacetin 1·0 g. At night vomiting.

20. 7.30 a.m. Great weakness, blue-grey face and lips, T. 39°; patient complains of headache, vomiting and diarrhoea, urine chocolate colour, increasing icterus.

21. p.m. Skin dirty grey colour, cyanosis of lips, ears, hand and feet, discharge from right auditory meatus. Sepsis suspected. No lead-line on gums.

22. Patient moribund. Urine (by catheter) dark reddish

brown. No intact red cells, but reddish coarsely granular masses. Diagnosis: Phenacetin poisoning with probably sepsis. Krönig (1895), 999.

Dec. 3. Berlin. T. 38·5°.

4. T. S.N.

5. T. 39·6°. Violent rigor, very ill, loss of strength, a cramp-like cough. Complains of acute frontal pain and headache. Urine somewhat dark. Phenacetin 0·75 g.

6. a.m. T. 37·8°.

7. T. 40·5°. Herpes on nose, lips and inner angle of eye.

8. a.m. T. 36·2°. 8 p.m. Phenacetin 0·75 g. 10 p.m. T. 40·4°, rigor, stupor, slight delirium, Hgburia, icterus, vomiting, apathy, unconsciousness.

9. 3 p.m. Q. 0·5 g. × 4.

10. *P. falciparum.* Continuous hiccough. (Recovery.)

The urticaria-like eruption which the patient had had in Africa reappeared with intense itching and much troubled the patient. Schlayer (1902), 506.

Phenocol

On the Möwe in E. Africa in 1891, after 4 grammes of phenocol in the day, Hgburia and collapse.

(Sanitätsbericht über die Kaiserl. Deutsche Marine für den Zeitraum vom 1 April 1891–31 Marz 1893. p. 53.) Plehn, F. (1898), 212.

Phenyl cinchonine acid

A death from this compound reported in *Morning Post*, 4 Sept., 1934. No details given.

Plasmoquine

3 cases.

1. Gametes of *P. vivax* and *P. falciparum* rapidly disappeared.

2. Rapid shrinkage of the spleen. A 9-inch spleen was not palpable after a week.

3. Urobilinogen increased during and after treatment.
4. Toxic phenomena: (*a*) total dosage 0·24 g.:—
   1. Ash-grey cyanosis of skin, nails and lips.
   2. Forcible contraction of spleen.
   3. Urobilin increased.
   4. Blood chocolate brown. No evidence of red cell destruction.

   (*b*) *P. falciparum* and *P. vivax* present, total dosage 0·4 g.
   1. Sudden cyanosis of whole body, especially of lips, nails, palate.
   2. Great and painful contraction of spleen.
   3. Met-Hgbaemia (and apparently Met-Hgb in the red cells) and Met-Hgburia.
   4. Urinary excretion 8 oz. and 14 oz. on consecutive days.
   5. Icterus of 4 days duration. 1·5 m. red cells destroyed. Manson Bahr (1926–27), 413.

Salipyrin

History of b.w.f. in German East Africa. Invalided to Europe. Malaria attacks treated with Q., which usually had no unpleasant result. Only once did the urine become dark again and the skin yellowish. When next unwell, patient took, on the advice of his doctor, Salipyrin 2·0 g. Next day the urine was the colour of blood and in the next 24 hours almost black. Spleen +, icterus. Blood: *P. vivax*. Kleine (1901[b]), 479. (1901[c]), 666.

Thymol

Thymol Hgburia occurred in a certain number of Formosans during a course of treatment for ankylostomiasis; two of the cases ended fatally. Hatori (1914–15), 653.

Hgburia and X-rays

23 Dec. The last time Q. was taken.

3 Jan. Blood, parasites scanty. Spleen, parasites scanty. Spleen enlarged, very tender. Liver to 5th rib, not

palpable. Urine alb. neg. Daily attacks of fever, which ceased from 9–16 Jan. during X-ray treatment from 7–16 Jan. A dose of 54X to each quadrant of the spleen during 9 days' treatment, total 216X.

17. p.m. Patient noticed that his urine was black without any special feeling of illness.

18. Icterus. Complained of faintness and weakness and slight dyspnoea, due apparently to the high position of the right diaphragm, the posterior pillar of which reached the 7th rib. This was due to the extreme engorgement of the liver, which was tender, but not palpable. Blood count reduced from 4·28 m. (on admission) to 2·4 m. Hgb from 53% to 34%.

About 2 months later, febrile attacks again. X-ray radiation of 220X in 14 days. No influence on the attacks, no b.w.f. Deutsch (1917), 907.

APPENDIX 26

ADDENDA

CHAPTER 1

Chagres fever

When I first came here (Panama) in 1906, I remember very well that the American physicians in the old Colon Hospital used the term Chagres fever as a synonym for blackwater fever and for malignant malaria.

Dr. W. M. James (Correspondence).

Mélanurique

Duchassaing gives as the title of his paper 'Maladie paludéene ictérique,' and as synonyms fièvre jaune; typhus ictérode; fièvre rémittente bilieuse; fièvre rémittente pernicieuse mélanurique.

Duchassaing (1850), 743.

Although Bérenger Féraud (1874), 434 gives the title of his (1872) paper, Bull. de l'acad. de méd. 1.2ème série. 1154, as 'Note sur la composition de l'urine dans la fièvre bilieuse mélanurique,' the actual last words are 'fièvre dite hématurique.' The paper is given in title only.

CHAPTER 2

India

In India some cases occur on the east coast near Gadshamberge among German missionaries. Fisch (1896[a]), 271.

BALUCHISTAN: Six cases, 1932–33.

NORTH-WEST FRONTIER PROVINCE: Five cases, 1932–34. Amy (1934), 179. Amy (1935), 110.

CEYLON: Records of 13 cases, 1913–35. Six occurred in the malaria epidemic of 1934–35. Col. C. A. Gill (Personal communication).

Burma and the Far East

UNFEDERATED MALAY STATES: Seven cases, 1933. Tropical (1935).

BORNEO: Haemoglobinuric malaria occurs in Borneo, although but rarely. Stewart (1896).

PHILIPPINE ISLANDS: Either very rare, or else was not being reported. Wright (1901).

'Blackwater fever (hemoglobinuric fever) with a report of two fatal cases occurring in the U.S.A. military hospitals at Manila, P.I.' (Title). Curry (1902).

'A case of blackwater fever from the Philippines' (Title). Hartsock (1902).

DUTCH NEW GUINEA: Upper Digul River. Internment Camp. 1928–29. Population 1928. B.w.f. cases 72. H. de Rook (Correspondence).

N. America

PHILADELPHIA: I have observed several instances of malarial haematuria in the Kensington district of Philadelphia, where the milder forms of malaria prevail. Anders (1915), 355.

S. America

ARGENTINE: Metán Salta. Three cases. Mazza, Caro and Serna (1936), 860. Rosario de la Frontera. Two cases. Mazza and Cores (1936), 865. Jujuy. A second case, in a girl aet. nine. Mazza and Zurveta (1936), 858.

DUTCH GUIANA: A case of Q. sensitiveness in a b.w.f. convalescent. Flu (1910), 211.

West Indies

WINDWARD ISLANDS: One case, 1933. Tropical (1935).

CHAPTER 4

Age

Age.	Individuals.	Cases.	Authority.
0–10	14	20	
11–20	36	44	Yofé (1929), 108.
21–30	47	54	
31–40	15	22	Palestine.
41–50	13	17	
51–60	9	11	
61–70	2	4	
	136	172	

Altitude

Rural townships. Southern Rhodesia.				Authority.
Feet . . .	— 3000.	3000–4000.	4000 +.	
Pop. (1926) . .	455	3230	1921	Ross (1932), 46.
Cases (1924–28) . .	8	26	3	
Mean daily $\frac{\text{Max. T.} + \text{Min. T.}}{2}$		4°–6° F. above T. at next level		
Min. annual T. . .		35°–37° F. (— 4000)	32° F.	

1. Rainfall: can be excluded.
2. Temperature: data as above.
3. Humidity: greater in low-lying districts.

Humidity

Southern Rhodesia. The humidity is generally lowest in October, but rises sharply during the early months of the rainy season, to reach its maximum in January. The figure remains fairly stationary until about March, when it commences the decline to the minimum.

The epidemic phase of b.w.f., *i.e.* the January to August

period of increased incidence, with the maximum in May, begins at a time when the percentage humidity has reached its highest figure . . . and ends when the humidity has just about reached its lowest limit.

Locality.	Max. Humidity.	Min. Humidity.	Authority.
Salisbury . . .	75	50	Ross (1932), 44.
Bulawayo . . .	78	47	
Shamva . . .	86	62	
Gatooma . . .	73	53	

Disposition

Certain features point to the fact that this does not arise suddenly, but gradually. I have been repeatedly assured by patients, that for a long time before the occurrence of b.w.f., following every taking of Q., they had noticed a strikingly dark colour of the urine and slight icterus. The urine is described as not having the reddish tint of Hgb, but a pure brown colour up to that of coffee. Doering considers these cases to be a sub-division of b.w.f.

Koch (1899), 321.

Residence

Months of residence .	1–6.	7–12.	13–24.	Authority.
Monthly pop. Average .	69·5	61·1	24	Plehn, A. (1901).
B.w.f. cases . . .	3	22	12	
%· · · · ·	4·3	36	50	

The figures refer to a number of persons kept under observation for 2 years. Initially there were 75, but this number had dwindled to 42 in the 13th and to 5 in the 24th month. Of the 12 cases in the second year, 9 occurred in the first half and 3 in the second half of the year.

Years of residence.							Total cases.
6 mos.	1	2	3	4	5	5+	
12	42	41	(14 later)				97 [1]
0	8	40	12	5	1		66 [2]
25	46	71	33	9	4	5	168 [3]
13	25	8	5	3	1		42 [4]
38	71	79	38	12	5	5	210 [5]

[1] Camerun colonists. Plehn, A. (1903[b]), 515.
[2] Europeans. Duars, India. Christophers and Bentley (1908[a]), 42.
[3] Americans and Europeans. Ancon Hospital, Panama.
[4] Negroes. Ancon Hospital, Panama.
[5] = 3 + 4. Deeks and James (1911), 33.

Cases.	Under 1 year.	1–5.	5–10.	10–15.	15–20.	20+.	Authority.
10 E.		5	5				
44 A.	3	22	7	8	1	3	(1922), 56.
13 E.	1	5	5	2			(1923), 50.
64 A.	3	33	16	7	5		
9 E.		3	1	1	2	2	(1925), 57.
8 E.		2	3	1	2		(1926), 68.
19	1	6	2	5	2	3	(1927), 63.
52	1	11	10		14	16	(1928), 76.
219	9	87	49	24	26	24	Uganda Official Medical Reports.
E. = European, A. = Asiatic.							

Season (erratum)

The figures (those of the original) in columns 2, 6, and 8 do not add up to 1200. In columns 2 and 3, for 140 + 40, read 165 + 65. In column 2, the errors in the other figures extend only to units. In columns 6 and 8 it is not possible to say what the correct figures are. *Vide* p. 79.

Month.	Cases.	Departure from Av. 16·8.	Month.	Cases.	Departure from Av. 16·8.	Authority.
Jan.	7	− 9·8	July	8	− 8·8	
Feb.	12	− 4·8	Aug.	14	− 2·8	Yofé (1929),
March	11	− 5·8	Sept.	46	+29·2	107.
Ap.	9	− 7·8	Oct.	43	+26·2	
May	2	−14·8	Nov.	29	+12·2	Palestine
June	2	−14·8	Dec.	19	+ 2·2	

Syphilis (and gonorrhoea)

Venereal disease does not appear to influence either the tendency to b.w.f. or its severity when present.

Barratt and Yorke (1909[a]), 169.

Temperature

Southern Rhodesia. The epidemic incidence of b.w.f. commences in the hot season when the diurnal variation is least, continues through the autumn, and terminates in the cold season just after the weather is coldest, and the diurnal variation is at its maximum.

Ross (1932), 44.

CHAPTER 5

Malaria and b.w.f.

Stephens and Christophers were the first to establish the malarial nature of b.w.f., a fact which later work has completely confirmed.

Yorke (1934), vii.

Correlation between malaria and b.w.f.

Greece, 1923–35. Hospital (3) Admissions.					
Month.	Malaria.	Departures from Average 1780.	B.w.f.	Departures from Average 59.	Authority.
Jan.	1,162	— 618	58	— 1	H. E. Foy (Correspondence).
Feb.	873	— 907	36	—23	
March	853	— 927	42	—17	
Apr.	750	—1,030	34	—25	
May	920	— 860	32	—27	
June	963	— 817	30	—29	
July	2,121	+ 341	27	—32	
Aug.	3,039	+1,259	44	—15	
Sept.	3,392	+1,612	85	+26	
Oct.	3,097	+1,317	106	+47	
Nov.	2,444	+ 664	114	+55	
Dec.	1,736	— 44	96	+37	
	21,350		704		

Inoculations

The inoculation of malaria-positive and negative blood, taken, after varying periods of time, from the first passage of black urine, from 58 cases of b.w.f. into 106 mental patients failed in every case to produce Hgburia.

Anophelines of the species *elutus*, *superpictus* and *maculipennis* fed on 35 different cases of b.w.f. . . . 'back fed' on 68 cases of general paralysis, never produced a case of b.w.f.

All the cases were kept under observation for from 9 to 18 months after their blood inoculation or mosquito feed.

Foy and Kondi (1936), 433.

Inoculated malaria

One of our *P. falciparum* cases after the Q. injection suffered from Hges at the site of injection, and from epistaxis. At the site of camphor injections there developed subcutaneous haematomas. The gums and buccal mucosa showed crust-like deposits. The mucosae of the penis and rectum bled. On the whole skin there were sugillations. The urine was very bloody. Death.

Pleurae, lungs, serosa of the gut and surface of the spleen showed many Hges. The pelves of the kidneys and the bladder were filled with fresh blood. We learnt later that the patient in a malaria attack in the tropics could not tolerate Q.

Weygandt (1926), 444.

27.8. 10 c.c. malarial blood I.M. 8 attacks.
17.9. Q. 0·3 g. and myosalvarsan 0·15 g. in the evening.
18. Q. 0·2 g. Patient became extraordinarily pale. Cell count 1·0 m. Hgb 40%, urine not dark.
19–20. Death.

Westphal (1927), 2474.

CHAPTER 6

Quinine

Date.	Max. T.	Q.	Hgburia.	Date.	Max. T.	Q.	Hgburia.	Remarks.
4	103·8°	+*	—	8	98·0°	+	—	* *P. falciparum* +.
5	102·5°	—	—	9	105°	+,—	+	Brem (1911), 159.
6	98·0°	—	—	10	102·4°	—	+	
7	97·5°	+	—	11	101·0°	—	+ D.	

15.2. *P. falciparum.* Plasmochin Co. (Q. = 0·3 g.). 3 hrs. later rigor, T. 41·4°, bilious vomiting, Hgburia (1).

24. P. Co. (Q. = 0·06 g.). Shortly after, rigor, T. 40·5°, bilious vomiting, acute pain in liver and stomach region, Hgburia (2).

11.3. Q. urethane, 3 × 0·01 g., well tolerated.

12 Q. urethane, 3 × 0·02 g.

13. Q. urethane, 1 × 0·05 g. Rigor, T. 39·5°, Hgburia (3).

17. P. Co. (Q = 0·03 g.). Parasitic febrile attack lasting until 23.3.

3.4. Q. urethane, 0·03 g. Evening, T. 38·3°.

4. 3.30 p.m. Q. urethane 0·05 g., 8 p.m. T. 40·0°, nausea, Hgburia (4).

5. 3.30 p.m. Q. urethane 0·07 g., 10 p.m. T. 39·0°, Hgburia (5).

6. Q. urethane 0·10 g., evening T. 39·6°, 7 p.m. Hgburia (6).

10. Q. urethane 0·1 g. Evening, T. 40°, no rigor, acute splenic pain.

12. Q. urethane 0·1 g. T. 40°, acute splenic pain.

13. 11 a.m. Q. urethane 0·1 g., 4 p.m. T. 38·8°, 4.45 p.m. Hgburia (7).

15. Beitusan * (Q. HCl 0·075 g.) Evening T. 40·1°, no rigor, acute splenic pain.

* Beitusan = Double salt of Q. hydrochloride and lactate.

16. Beitusan (Q. HCl = 0·1125 g.), vomiting, T. 40·5°, Hgburia (8).
19–27.6. Beitusan.
28. Beitusan. 4 × 0·01 g. Rigor, liver and spleen enlargement, T. 39·4°.
29–2.7. Beitusan.
3. Beitusan. Total dose 0·55 g. Rigor, vomiting, T. 40·6°. Hgburia (9).

Mühlens and Knabe (1931), 73.

Quinine per rectum

Day 1. 10 a.m. Q. 2·0 g. as enema; 1 hour later tinnitus; 3 hours later, rigor, Hgburia.

Plehn, A. (1896), 148.

Q. increased dose

Day.	Q. g.	Hgburia.	Day.	Q. g.	Hgburia.	Authority.
1	1·0	+	4	0·5	—	Case 29.
2		+—	5	0·5	—	Panse (1902),
3	0·25	—	6	1·0. 8 a.m.	+ p.m.	22.

Q. minimal doses

The dose of Q. necessary to the production of Hgburia may be less than the ordinary therapeutic dose—0·50, 0·20, and even 0·10 and 0·05 g. (grains 7½ to as low as grain ¾) having been known to cause the symptoms referred to.

Marchiafava and Bignami (1900), 472.

Q. habituation

I naturally thought that this accident could be avoided by using Bezredka's disanaphylactic vaccination. That is to say, before giving a normal dose of Q. inject a small quantity 0·05 g. diluted with some c.c.s of water. For the last year I have treated in this way all old malarials who have had one or more attacks of b.w.f., in a word all patients in whom I had all reason to fear this accident.

David (1914), 511.

No quinine

If the rigor be regarded as the first indication that lysis of the red blood cells is taking place . . . then it is probable that in Cases (6) . . . Q. was administered after and not before the damage was done. This would mean that including Case 33 where no Q. was taken there were 7 (of 34) cases in which Q. was neither an exciting nor a predisposing cause.

In 6 cases the intervals between Q. and the appearance of the rigor or Hgburia were 28 hr., 4 d., 16 h., 36 h., 14 h., 21 h.

Nigeria (1928), App. A, 27.

Q. to Hgburia (Short intervals)

Day 1. 7 a.m. Q. 2·0 g. Directly afterwards T. rises to 39·2°; 12 noon, collapse.

Plehn, A. (1896), 128.

As the malaria (*P. falciparum*) appeared to be assuming a pernicious form, 5 grams of Q. dihydrochloride were injected intravenously, and the same dose repeated four hours later. A severe attack of Hgburia resulted almost immediately after the second injection and he passed urine which was black in colour.

Paterson (1932), 366.

Euquinine

13 June. *P. falciparum*, T. 39·7°, spleen 2 c.m. beyond costal margin.
19. Eu-Q. 1·0 g., T. 36·8°, 38·6°.
20. Eu-Q. 1·0 g., T. 36·7°, 39·4°.
21. Eu-Q. 1·5 g., T. 36·2°. Morning, rigor, T. 40·3°. Noon, Hgburia, collapse. Evening, urine clear.

Arbeiten (1904), 49.

CHAPTER 8

Anuria

Date.	Urine c.c.	
23	200	Rigor, delirium, dark red urine, bilious vomiting. 3 p.m. T. 41·2°, P. 120, icterus slight, no vomiting. Hot bath 30° C. for 10 minutes, enema; evening hot pack, T. fell to 39·8°.
24	110	Sleepless night, vomiting off and on. Two wet packs each of 2 hours' duration; hot bath 30° C. for 10 minutes, then sweating and slow fall of T.
25	0	T.N. skin moist, icterus increasing, uncontrollable vomiting, slight hiccough, commencing apathy. Bath, enema, soda water, etc. 700 c.c. 0·6% saline, subcutaneous.
26	7	T.N. Urine (36 hrs.) turbid, greenish yellow, blood +, alb. ++. 4 hours' sleep, constant vomiting, increasing hiccough. Baths, cold effusions, enemata, irrigation of bladder with hot 0·9% saline, drinks, stimulants.
27	0	Liq. pot. acetat. vomited. Diuretin 0·5 g. subcutaneous, ammoniacal urinous sweat.
28	3–5 × 3	Black motion.
29	3–5 × 2	Evening, clonic cramps, 5 minutes' duration, no loss of consciousness, later amnesia.
30	10 × 2	Urine passed in bath. 3 motions of pure bile. Vomited twice. Hiccough persists, stimulants and diuretin 1·2 g. subcutaneous.
31	10	T. 35·4°. Condition as before. Diuretin 5·0 g. *per enema*.
1		Sleepless night owing to hiccough. T. 36°—. Intellect clear, yet without appreciation of the condition. 7.45 p.m. after a bath, an uraemic attack, nystagmus, Cheyne-Stokes R. ether 2·0 g., 5 minutes' stupor, then cramp. Before 8 p.m. in spite of ether death.

Dempwolff (1898), 161.

Multiple attacks, intervals

Days,* after Attack 1 on which Attacks 2 and 3 occurred.						Remarks.
2.	3.	Case.	2.	3.	Case.	Plehn, A. (1896).
17	32†	6	9		23	† Attack 6 on day 166.
70	D	8	15		24	
17		10	13		27	
92		15	19		29	
	14	17	8	33	31	
19	76	21	84	243‡	19	Dempwolff (1898).
34		24	99		20	‡ Attack 4 on day 442.
40		22				
8		24	18	39	16	Plehn, F. (1898).
18	38	21	48	86		
35		1, 166	188		101, 206	Deeks and James (1911). The case numbers are the serial numbers (not given in the original).
59		13	213		15, 188	
61	238	64, 102	222		214	
74		17, 113	346		14, 99, 129	
102		140	453	802	165, 119, 39	
112		19, 22				
19		25	18		30	Africa (1914).
12						Patrick (1922), 452.
7		4				Yorke, Murgatroyd and Owen (1929–30).

* Reckoned from and including day 1 of initial Hgburia.

Intervals between Attack 1 and Attack 2.						Authority.
Years.	Cases.		Years.	Cases.		
1–6 m.	7	0	5–6		1	a. Christophers and Bentley (1908[a]). The Duars, India.
6–12 m.	9	1	6–7		3	
1–2	10	6	7–8		3	
2–3	1	5	8–9		1	b. Ross (1932), 89. S. Rhodesia.
3–4		6	9–10		1	
4–5		0	10 +		10	
	a.	b.		a.	b.	
	No. of Case.			No. of Case.		
1 m.	11		2 m. +	30		c. Koch (1899).
6 m.	2		3 m. +	35		d. Panse (1902).
9 m.	8		4 m. +	27		
2 years	3		5 m. +	20		
			1 year	3		
			2 years	5		
	c.			d.		

Multiple attacks, frequency *

Total Cases.	Number of cases that have had attacks.						Authority.
	2.	3.	4.	5.	6.	6 +.	
30	3	2					Bérenger Féraud (1874).
35	9	6	1			1	Plehn, A. (1896).
46	3	6	3	1		1	Plehn, F. (1898).
7	1	3	2				Dempwolff (1898).
15	3	1					Daniels (1901).
35	5 or 6	1 or 2	3	1		1	Panse (1902).
128	24	4					Christophers and Bentley (1908[a]), 215.
32	1	1					Ibid., 229.
17	5	2	1	2			Barratt and Yorke (1909[a]).
34	7	3		1	1	2	Deaderick (1910), 195.
233	11	2					Deeks and James (1911).
23	1	1					Africa (1914), 60.
78	6						Phear (1920).
7	1	2					Gaskell (1920).
536	85	32	11	8	2	5	Uganda. (1922), 57. (1923), 52. (1924), 58. (1925), App. 1, 58. (1926), App. 1, 68. (1927), App. 1, 63.

* A sharp line cannot always be drawn between an 'intermittent Hgburia' and a second attack.

Complications, pyuria

Death in this case was not due to uraemia, but to a purulent focus in the kidney, always a fatal complication.

Van Campenhout and Dryepondt (1901), 83.

Complications, various

Day ? Pyorrhoea and abscess of the breast. Case 6.

Gaskell (1920), 21.

Death, sudden

Day 1. He had passed a small quantity of porter-coloured urine (about a pint) in the morning and since then *nil.*

Day 2. . . . Towards evening he passed a small quantity of apparently clear water into the bed, and expressed himself as feeling better, and slept. He suddenly woke up in the night, sat up in bed, and fell back dead.

Seal (1899), 180.

Diarrhoea

Day 1. He suffered from a very offensive green diarrhoea —six or seven stools.

Seal (1899), 180.

Itching

Day 13. Urine 1·75 c.c. The skin is covered with a red pustular eruption and tiny petechiae 1 mm. in diameter. Patient complains of intolerable itching.

Day 15. Urine 1000 c.c. +. Intolerable itching. Patient constantly scratches himself to the point of bleeding. 71.

Day 6. Urine, a few c.c. (catheter), alkaline, spectroscope bands of haematin, odour of acetone.

Day 7. Urine 120 c.c. (catheter), Hgb neg., no motion, intense itching of the skin. 78.

Van Campenhout and Dryepondt (1901).

In severe cases there is sometimes itching which much distresses the patient.

Broden (1906), 6.

Hgburia, intermittent

Case.	No. of intermissions.	Day.	Case.	No. of intermissions.	Day.	Authority.
1	4	3	4	1	2	Daniels (1901), 50.
2	1	1	5	1	1	
3	2	3		2	2	

Day.	Hgburia.	Day.	Hgburia.	Remarks.
1	+	8	− + −	Case 23. Panse (1902), 14.
2	− +	9	− + −	
3	+ −	10	− + −	The Hgburia from day 6 to day 13 lasted for a few hours only daily, and was accompanied by rises of T. to 39° and over.
4	—	11	− + −	
5	− + −	12	− + −	
6	− + −	13	− + −	
7	− + −			

No. of relapse.	Duration in hours of Hgburia + or −.		No. of relapse.	Duration in hours of Hgburia + or −.		Authority.
	+	94†		−	22½	
	−	5	6	+	2½	Barratt and Yorke (1909[a]), 210
1	+	5½		−	23	
	−	9	7	+	3½	
2	+	2½		−	39½	† Initial Hgburia.
	−	8	8	+	4	
3	+	9		−	1⅓	
	−	3½	9	+	2⅙	
4	+	5		−	18	
	−	7½	10	+	11	
5	+	6				

Hgburia, intermittent and Quinine.

Day.	Q.	Hgburia.	Day.	Q.	Hgburia.	Authority.
1	+	+	14		−	
2		−	15		+	Morin (1920), 143.
3		−	16		+ −	
4		−	17		− + −	Madagascar.
5		−	18		− + −	
6	+	+	19	+	− +	
7		−	20		− + −	
8		−	21		− + −	
9		−	22		—	
10		−	23		− + −	
11		−	24		− + −	
12		−	25		− + −	
13		−	26		− + −	

Hgburia, intermittent, and Temperature.

Date.	Hour.	T.	Hgburia.	Authority.
25.6.1900	5 a.m.		black	Obs. XII. Van Campenhout and Dryepondt (1901), 80.
	a.m.	39·4°		
	noon	39·7°		
	p.m.	39·3°		
26.	a.m.	39·3°		
	noon	39·9°		
	1 p.m.		clearing	
	p.m.	38·7°		
27.	a.m.	38·6°	clear	
	noon	39·2°		
	2.30 p.m.		rosy	
	p.m.	40·6°	black	

Date.	Max. T.	Hgburia.	Date.	Max. T.	Hgburia.	Authority.
27		Retention	3	98·1°	—	
28	98·5°	—	4	100·8°	+	Case 13.
29	98·8°	—	5	98·4°	—	Brem (1906), 1903.
30	98·0°	—	6	100·1°	+	
1	99·6°	+	7	98·5°	—	
2	98·5°	—				

Cases 18. In case 13 there appeared to be a correlation between the height of the fever and the darkness in the colour of the urine.

Arkwright and Lepper (1918[a]), 138.

Heart, pulse rate in anuria

The pulse which was rapid at first slowed down. Day 4, it was 80 and was slower later in the disease. Day 13 (?) death. Ross (1932), 218.

Icterus

Day 1. Icterus —.

Day 2. Icterus +.

Days 3–5. Icterus deepened, but then gradually disappeared.

Day 12. Death. Before death icterus no longer observed, and an ashen-grey colour replaced the bronze. A case of oliguria. 217.

Day 4. Intense icterus . . . as the disease progressed . . . it became more and more intense.

Day 13 (?). Death. A case of oliguria. 218.

Ross (1932).

Icterus, frequency

Of 30 fatal cases, in 13 there was well-marked jaundice and in 17 the generalized icteric staining of the skin was intense.

Phear (1920), 5.

Icterus (intermittent) and T.

Day.	Hour.	T. max.	Hgburia.	Icterus.	Authority.
2	a.m.	98°	—	—	
	p.m.	99·0°	+	+	Gunther (1936),
3	a.m.	98°	—	—	543.
	p.m.	99·2°	+	++	New Guinea.
4	a.m.	98°	—	—	* Icterus obscured
	p.m.	100°	+±+	+	by atebrin.
5	a.m.	99·1°	+	*	
	p.m.	100·3°	+−+	*	

Nervous system, delirium

Day 1. 9.30 a.m. Q. 1·2 g. Mid-day following apparently the vomiting of a quinine capsule, a 1-hour rigor, delirium, dark red urine, vomiting.

3 p.m. Intellect clear.

Dempwolff (1898), 161.

Nervous system, general

Day 6. Urine 26 c.c. Extremely weak, subicterus, intermittent squint in the right eye, fibrillary contractions of the muscles of the face, of the lips which are violet.

Day 10. Urine 50 c.c. Subsultus tendinum, delirium, hallucinations.

Day 12. Urine 25 c.c., condition bad, subsultus tendinum, frequent vomiting.

Van Campenhout and Dryepondt (1901), 70.

Ocular, pupil

Day 2. Noon. Anuria persists. Some miosis.
Day 3. Anuria, intense dyspnoea. Mydriasis. Death.
Alain (1930), 92.

Pain, shoulder

Day 3. Besides the same condition of great weakness, pain in the liver and right shoulder.
Dempwolff (1898), 157.

Rigors, time of onset

Time.	Rigors.	Deviation from Av. 4.	Authority.
12–3	4	0	Ross (1932), 83.
3–6	1	− 3	
6–9	3	− 1	
9–12 n.	8	+ 4	
12–3	3	− 1	
3–6	4	0	
6–9	4	0	
9–12 m.	5	+ 1	
	32		

Sweating

Day 1. 7 a.m. Q. 1·0 g.; mid-day T. 38·2°, Hgburia, icterus, vomiting, great weakness. In the afternoon with profuse sweating T. falls without drugs.
Day 2. Urine clear. 158.

Day 1. Painful micturition, uncontrollable vomiting, sleeplessness, profound exhaustion, sweating. With every breath of air, a shiver and often a rigor. T. now 36°, now 40° +. 160.
Day 5. No urine. Ammoniacal urinous sweat. 161.
Dempwolff (1898).

Day 2. Hgburia negative. T.N. Patient sweats extraordinarily profusely.
Mühlens and Knabe (1931), 76.

Temperature (post-Hgburic)

Day.	Q.	Max. T.	Day.	Q.	Max. T.	Authority.
1			13		38·6°	
2	+	40·6°*	14	+	39·4*	Nr. 14.
3		38·8	15		39·1	Koch (1899), 315.
4		38·9	16		39·5	
5		39·0	17		40·1	
6	+	41·0*	18		39·8	Parasites absent throughout.
7		38·0	19		39·5	
8		38·3	20		39·0	
9		38·5	21		39·3	* = Hgburia.
10		38·0	22		40·0	
11		38·4	23		39·9	
12		38·5	24	+	41·6*	

T., which had gradually fallen to normal on day 3, showed daily rises to 38° from day 4 to day 10. Parasites absent since day 2. Case 33. Panse (1902), 25.

Temperature, post-Hgbic and albuminuria

Date.	Q.	T.	Hgb-uria.	Alb-umin-uria.	Date.	Q.	Hgb-uria.	Alb-umin-uria.	Remarks.
3 Feb.	+		−	−	14	+	−	+	Case 7.
4	+		−	−	15	+	−	+	Brem (1906),
5	+		−	−	16	+	−	+	1899.
6	+	+	+	+	17	+	−	+	* An intermit-
7	+	+	+	+	18	+	−	+	tent T. con-
8	+	*	+	+	19	+	−	+	tinued for 15
9	+		−	−	20	+	−	+	days.
10	+		−	+	21	+	−	+	
11	+		−	+	22	+		+	
12	+		−	+	23			−	
13	+		−	+					

CHAPTER 9

Biocholine (Chlorhydrate of choline)

Laos and Tonkin.

2 ampoules 0·02 centigramme injected daily until Hgburia negative. 1 ampoule during convalescence. 1 ampoule

every 2 days with or without Q. to 'consolidate' the treatment.

Cases 35. Deaths 3.

Nguyên-Sanh-Chaû (1933).

Neo-arsphenamine

Treatment more or less empiric: Cases 41, deaths 8, relapses 37.

Neo-arsphenamine treatment: Cases 26, deaths 0, relapses 2.

Cort (1929), 401.

Urotropin

Classical treatment. Cases 10. Deaths 3. Mortality 30%.

Urotropin alone or mixed treatment. Cases 8. Deaths 0.

Urotropin 1·0 g. I.V. morning and evening.

Vu-Dinh-Tuan (1934), 940.

CHAPTER 10

Acidosis

Wakeman (1929), 170. For a more elaborate discussion of this and 2 other cases *vide* Wakeman, Morrell, Eisenman, Sprunt and Peters (1932).

Leucocytes

Inoculated malaria. Day 10. Q. 0·5 g. × 2, Hgburia. Day 11, Hgburia neg.

Day.	Total leucocytes.	Basophil.	Eosinophil.	Neutrophil.			Lymphocytes.		Monocytes.
				Young.	Rod.	Segmented.	Large.	Small.	
11	14,600		1	1·5	9·5	53	21·5	3·5	10
16	10,700	1·5	1·5	1	7	62·5	16·5		10
24	11,800		4		8	66	11	5	6

Schilling and Jossmann (1924), 1498.

General

Group.	Case.	Hgburia had lasted.	Mgms. per 100 c.c. blood.					
			Sugar.	N.P.N.	Urea N.	Uric acid.	Chlorides.	Phosphates.
I	1	16 h.	105	22·7	15·7	2·4	510	
	2	30 h.		60·0	42·3	3·2	495	
	3	48 h.	97	36·7	15·6	2·3	445	
	4	48 h.	82	40·0	26·3	2·8	462	3·22
II	5	20 h.	95	84·2	49·0		445	
	6	14 h.	85	75·6	42·3	4·7	478	
	7	18 h.	250	60·4	29·6	3·7	495	5·2
III	8	4 h.	94	85·6			594	3·6
		3 d.	87	157·8	84·3		511	7·2
	9	5 d.	64		24·9		472	
	10	6 d.	88		25·5		437	
IV	11	24 h.	90	57·1	37·0	3·6	504	2·6
	12	18 h.	95	39·9	20·4	3·0	478	3·4
		7 d.	81	36·3	16·1	2·72	528	
		10 d.	94	42·0	18·6	2·72	541	3·2

I. Mild to severe uncomplicated Hgburia.
II. Severe Hgburia with early toxic symptoms.
III. Severe Hgburia with suppression.
IV. Long-continued and relapsing Hgburia.

Ross (1932), 115.

Hgbaemia and Hgburia

Case.	Hgburia.	Colour of serum (S) or plasma (P.)		Bands.	Authority.
15	+	Red	S + P	Oxy-Hgb †	Fletcher (1914), 33.
12	+	Orange	S	Met-Hgb	
13	+	Greenish yellow	P ‡		
14	−		S + P	−	
16	−		S + P	−	

† = 0·25% blood. ‡ + $(NH_4)_2S$ + KHO = haemochromogen.

Pseudo-Met-Hgb (*vide* p. 409)

Cases.	Blood.			Urine.			
14.	Oxy-Hgb.	Pseudo-Met-Hgb.	Met-Hgb.	Oxy-Hgb.	Pseudo-Met-Hgb.	Met-Hgb.	Urobilin.
2	+	−	−	+	−	−	
2*	−	+	−	−	−	−	++
10	+	+	−	+	−	+	

* Day 3 and day 6, respectively.

Pseudo-Met-Hgb does not occur in the urine. Met-Hgb in the urine is derived from Oxy-Hgb after the latter has left the blood. Met-Hgb does not occur in the blood. In polyuric cases with post-Hgbic fever and progressive anæmia, Pseudo-Met-Hgb occurs in the blood, while the urine contains urobilin only. Repeated transfusions are required for the anæmia, which otherwise may be fatal.

N. H. Fairley (1937), Personal Communication.

Urobilinaemia

Day 3. *P. falciparum* +; urine increased urobilinogen; blood cholesterin 55 mgm. %; bilirubin in serum 2·5 mgm. %; urobilin in traces.

Mühlens and Knabe (1931), 75.

CHAPTER II

Anuria

Day.	C.c.	Reaction.	Sp. gr.	Urea, g. per mille.	Alb., g. per mille.	Day.	C.c.	Reaction.	Sp. gr.	Urea, g. per mille.	Alb., g. per mille.
4	0					15	1000+	a	8	8	t.
5	50					16	1200	A	10		t.
6	26	a	30	1·83	4	18	Invol.	A		8·1	t.
7	10					19	1226	a	8	4	t.
8	40					21	++				
9	50	a	6	2·06	3	22	1200	A	7	4	
10	50					23	1150	a	8	5	t.
11	30					27	Invol.	a	7	5	
12	25					29	Invol.	a		4	0·25
13	1·75	a	6	10	0·5	31				5	0·25
	2·65	A	10	8	t.	33		Pus		3	
14	++	n	8	8	0·25	35	Death				

a = alkaline, A = acid, n = neutral, t. = trace. The last 1 or 2 figures only of the sp. gr. are given.

Obs. VIII, Van Campenhout and Dryepondt (1901), 68.

Bilirubinuria (post-Hgburic)

Case 21.				Case 24.			Case 35.		
Day.	Hgb.	Alb.	Bil.	Hgb.	Alb.	Bil.	Hgb.	Alb.	Bil.
1	+	+		+			+		
2				+			+	$\frac{2}{3}$	
3	−	+		+			+		−
4				+				$\frac{1}{3}$	−
5				−				$\frac{1}{6}$	
6		−	++	−					++
7			+	−				+	++
8				+				+	
9								t.	t.
10				−	−	+			−
	Panse (1902).						Plehn, A. (1896).		

Water elimination

The increased blood urea cannot be explained by a simple retention as in cases of anuria from other causes; such a high value does not arise in so short a time. 3 days from

the beginning of Hgburia and 2½ days from the occurrence of anuria it was 5·85‰. The high blood urea was maintained for longer than a week, although there was only a slight amount of N. in the food, and there was a considerable increased value during the diuresis which began some hours after admission on the 19th (day 4). The question arises whether increased production without any kidney lesion can lead to such a marked increase of blood urea. Still less than in Weils' disease do my investigations of b.w.f. lead to such an assumption. I have found injury of the kidney secretion in all my cases of b.w.f. with azotaemia. As a rule this shows itself through markedly diminished secretion up to anuria. In many cases there is no marked fall in the volume of urine, but that the water excretion is injured is shown by the bad result of the water experiment, and occasionally for some time after the cessation of Hgburia. Not only the water excretion, but the power to excrete N. products is in all cases injured. In no case was the urine urea highly concentrated in spite of the azotaemia, as would occur with an azotaemia of + production without injury to the excretory power of the kidney. A sign of the diminished concentrating power of the kidney is afforded also by the polyuria as the condition improves, which must be regarded from its amount and long duration as an indication of diminished concentrating power—a forced polyuria—and not simply an overflow of retained water. *Vide* p. 460.

Georgopoulos (1933).

Sediment, needles

Day 2. Urine 400 c.c. very turbid; the sediment in suspension, besides some détritus and red cells, consists almost entirely of short bright yellow needle-like bodies.

Dempwolff (1898), 156.

Sediment, red cells

Attack 1. Day 1. 300 c.c. clearer, sherry colour. With acetic acid, etc., Teichmann's crystals. Quite scanty red cells. 155.

Attack 2. Day 2. 11 a.m. urine dark red without deposit except on filtering . . . haemolysed red cells. 5 p.m. Besides détritus many red cells. 156.

Dempwolff (1898).

Faeces, bile

Day 8. Increasing weakness and apathy, intellect clear. Urine 10 c.c. twice in hip-bath. Three spontaneous motions; pure bile.

Dempwolff (1898),161.

APPENDIX 13

1672–81, *India*

Here is a *Brachmin* doctor who has raised a good fortune . . . comes every day, and feels every man's pulse in the Factory, and is often made use of for a powder for Agues, which works as infallibly as the Peruvian Bark;* it is a preparation of Natural *Cinnaber*.

Fryer (1672–1681), Crooke (1909), 288.

APPENDIX 15

1820, *general*

Quelques mois après sa découverte, il était en mesure d'envoyer à Barcelona, où régnait une épidémie de fièvre, une importante quantité de quinine. Pelletier et Caventou n'avaient d'ailleurs pas voulu conserver pour eux le privilège de leur découverte; aussi d'autres fabriques s'édifièrent rapidement en France, en Angleterre, aux Pays-Bas et aux Etats-Unis d'Amérique. En France une fabrique fut fondée en 1827 par Levaillant et une autre en 1828 par Delondre. Ces deux fabriques, ainsi que celle de Pelletier, fusionnèrent le 7 avril 1836 sous la raison sociale 'PELLETIER, DELONDRE ET LEVAILLANT' qui acquit bientôt une réputation mondiale sous le nom de 'MARQUE DES 3 CACHETS.'

Société (1936), introduction.

1835. *Corsica*

Q. has only been used since about 1835, still it is used with extreme caution as the peasants, still to-day, very

* Quinquina was sent from Pondicherry to China in 1693. 'Lettres édifiantes et curieuses.' Edition 1781, **17**, 305–309.

unwillingly take a gramme of Q. at a time, and will not take high doses from the danger of pernicious accidents. And moreover a multitude of contra-indications have been raised which have no basis in reality, but have given rise to many critics and such repugnance to the status of the drug.

Pitti-Ferrandi (1901), 39.

1872

Le sulfate de quinine est actuellement payé par le consommateur de 1500 fr. à 2000 fr. le kilogramme. . . . On fabrique actuellement en France pour une valeur de quarante millions de sulfate de quinine.

Briquet (1872), 939.

APPENDIX 17

Q. in pregnancy

Most authors to-day admit that a pregnant woman the subject of malaria is more liable to abort without quinine than with.

Laveran (1907), 486.

1. Aet. 35. 8 weeks pregnant in course of abortion, Q. 0·4 g. × 2 in 2 hours. 4 hours later great unrest, deafness, defective vision, slight mental disturbance, nausea, retching, cyanosis. Urine, haematoporphyrin. 14 hours after the Q. death.
2. A second similar case. Kutz and Traugott, quoted by Halban and Seitz (1927), 819.

1. Aet. 35. 2 months pregnant. Admitted with signs of threatening abortion. To promote expulsion, hypophysin and Q. 0·5 g. × 3, in 2 hours resulting in expulsion of the ovum. 5 hours after the Q. urine (catheter) burgundy red, almost black, Oxy + Met-Hgb. Icterus. Day 3, leucin and tyrosin in the urine. Death day 12.
2. Healthy patient 2 months pregnant. Vomiting. Soap irrigation of the vagina to induce abortion. Q. 1·5 g. 2 hours later Hgbaemia and Hgburia, icterus, leucin and tyrosin in the urine. Death day 12.

3. Aet. 45. 3 months pregnant. Very unwell. Slight icterus. Patient getting worse. Metreurysis proceeded with and on account of feeble pains, hypophysin and Q. 0·5 g. × 3 given. 24 hrs. later as the foetus was not expelled and the patient was worse and icterus extraordinarily increased, the foetus removed under ether. Urine (catheter), Hgb, leucin, and tyrosin. Death in a few hours.

As in all 3 cases, doses of Q. from 0·8 g.–1·5 g. were given in an interval of 2 hours, once also veronal 0·175 g., the suspicion arises that the haemolysis was due to Q.

Halban and Seitz (1927), 817.

Aet. 41. Pregnancy of about 3 months' duration interrupted by a lay abortionist. 20 5-grain tablets of Q. in addition to other tablets and pills. Dose taken unknown. (Q. 0·2 g. recovered from liver at autopsy.) Date of onset of symptoms unknown. Oliguria present. During final days of life urine became loaded with red blood cells. P.m. Hgb casts and masses in the convoluted and collecting tubes.

Terplan and Javert (1936), 529.

APPENDIX 18

Quinine fever

Date.	Q. mgms.	T.	Remarks.
22		40·6°	Hgburia.
24		T.N.	
25	2 × 100	,,	
26	4 × 100	,,	
27	8 × 100	,,	
28	5 × 200	40·8°	About 2 hours after the last dose. Parasites —.
29		40·4°	
30		39·4°	
31	8 × 100	Sub-N.	Parasites +.
1	8 × 100	39·8°	2 hours after the last dose. Parasites —.
2	8 × 100	39°	
3	9 × 100	39·5°	
4	3 × 100	40·2°	Flu (1910), 211.

APPENDIX 19

Q. in blood

Time after dose.	Q. 0·5 g. I.V.	Q. 0·5 g. *per os*.	Q. 0·5 g. I.M.	Authority.
	Percentages of original dose calculated for total blood.			Hartmann and Zila (1918), 228.
30′	9·7	2·4	1·2 [1]	
	12	2·9	0·5 [2]	[1] 38 minutes.
1 h.	8·5	2·4	0·5	[2] 37 minutes.
	4·9	2·4		Two figures refer to different patients.
2 h.	3·1	1·2	1·2	
8 h.	1·2		0	
10 h.	0	2·4		

Q. sulphate *per os*, grains 10, 9 a.m.; grains 10, 1 p.m. (22 patients).			Authority.
Time.	Q. mgms. per litre.		
	Max.	Min.	
9.30 a.	4·83	0·86	Vedder and Masen (1931), 225.
10·30 a.	6·19	1·72	
11.30 a.	5·23	2·24	
1.30 p.	6·29	1·81	
2.30 p.	6·38	2·15	
3.30 p.	4·13	1·90	

Q. sulphate 1·95 g.			Q. sulphate 0·325 g. Every 4 hours.			Authority.
Case.	Max. mgms. per litre.	In — hrs.	Case.	Max. mgms. per litre.	In — hrs.	
S	6·20	1	H	2·86	24	St. John (1932), 101.
O	6·08	1½	S	8·21	25¾	
S	7·50	8	A	5·00	23¾	
J	4·30	8	M	7·82	25½	
Q. sulphate 0·650 g. every 4 hours.*						
B	11·8	47¾	I	13·3	71¼	
P	13·2	47½	G	19·0	— 44	
J	9·3	95½	S	11·7	47¾	
L	10·7	49¼				

* A comparatively high concentration of Q. in the blood may be maintained by this method for at least 4 or 5 days.

Dose. Q. 0·5 g.	Case.	Mgms. per 100 c.c. blood at various times.			Authority.
		15′.	2 h.	24 h.	
Intravenous	1		0·25, 0·65	0	Chopra, Roy and Das Gupta (1934), 563.
	2	1·20	0·55	0	
	3	0·62	0·40	0	
	4	0·80	0·30	0	
Intramuscular	1		0·95	0·20	
	2	0·60	0·50	0	
	3		0·80	0	
	4	0·40	0·50	0·10	
Oral	1		0·65	0	
	2	0·15	0·55	0	
	3		0·26	0·15	
	4	0·10	0·30	0	

Q. in red cells

1 c.c. of plasma contained 0·0000083 g. Q. base.
1 c.c. of corpuscles contained 0·000005 g. Q. base.

Hartmann and Zila (1918), 232.

Q. can be detected in the red cells 48 hours after intravenous injection, in a dog, while at this time the plasma is negative.

Binet and Fabre (1929), 1068.

Dog injected intravenously with 0·80 g. Q. hydrochloride in form of Q. urethane. Blood taken by puncture of the heart at various times.

Time.	Red cells, c.c.	Q., concentration.	Q., mgms.	Plasma, c.c.	Q., concentration.	Q., mgms.	Authority.
1 h.	24	1 in 10,000	1/10	24	1 in 25,000	1/25	Binet and Fabre (1929), 1068.
48 h.	22	1 in 40,000	1/40	24	1 in 500,000	1/500	
96 h.	20	1 in 500,000	1/500	25	1 in 500,000 (less than)	?	

Q. in spleen

In the dog (anaesthetized) the splenic blood contains twice as much Q. (of a given dose) as arterial blood because splenic blood contains twice as many red cells, on which Q. is fixed.

Binet and Fabre (1931), 1116.

Q. in tissues

Vide p. 453.

Q. in urine

11.3. Q. urethane 0·01 g. × 3.
12. Q. urethane 0·02 g. × 3.
13. Q. urethane 0·05 g., rigor, T. 39·5°, Hgburia. Q. in urine negative.
14–15. Hgburia negative.
17. Plasmochin Co. (Q. 0·03 g.), Hgburia negative; Q. in urine slight.
18. Q. in urine slight.

Mühlens and Knabe (1931).

APPENDIX 22

Haemolysis

1. The tubes contained (*a*) plasmochin (P.) 0·1 to 1·0%, (*b*) 2 drops of a suspension of washed malaria red cells.
2. Heated to 37° for 5 minutes.
3. 2 drops of b.w.f. serum. If preserved serum was used, 1 drop of fresh human or guinea-pig serum added.
4. A control series with Q. HCl (Q.)
5. Tubes incubated at 37° and readings made every 10 minutes. The results after 30 minutes were as follows:

	0·1.	0·2.	0·3.	0·4.	0·5.	0·6.	0·7.	0·8.	0·9.	1·0.
Serum of a fatal case of Q. Hgburia.										
P.								+	++	++
Q.	−	−	−	−	−	+	+++	+++	+++	+++
Serum of a slight Quinidine Hgburia.										
P.	−	−	−	−	−	−	−	++	+++	+++
Q.	−	−	−	−	−	+	++	++	+++	+++
Serum of a fatal case of Hgburia.										
P.							+	++	+++	+++
Q.						++	+++	+++	+++	+++
Serum of a grave case of Cinchonine Hgburia.										
P.							+	++	+++	+++
Q.						+	++	+++	+++	+++
Dilutions of plasmochin alone.										
P.							+	++	+++	+++

* + and ++ = partial, +++ complete haemolysis.

Vide p. 623. Torrioli (1929), 1313.

APPENDIX 25

Methylene Blue

10.8. *P. falciparum.*
10–14. Methylene blue 0·8 g. daily.
15. Antipyrin 2%, a tablespoonful.
15, 16. Methylene blue 2 × 0·5 g.
17. 8 a.m. Methylene blue 2·0 g. Afternoon, rigor.
18. Obstinate vomiting, icterus, urine 20 c.c., Hgb +.
22. Hgburia —.

Case 30. Panse (1902), 22.

29 Oct. B.w.f. after Q.
29 Nov. *P. falciparum.* Almost daily, T. 40° +. Q. treatment avoided owing to previous attack after Q.
4 Dec. Methylene blue 0·2 g. × 3 with musk. Noon T. 40·6°. Evening T. 38·1°. The drug was at first vomited, then tolerated, slight bladder discomfort.
5. Methylene blue 0·2 g. × 4. Midday T. 39·6°, moderate bladder discomfort. Great exhaustion and psychical depression.

6. Methylene blue 0·2 g. × 4. 11 a.m., marked icterus, Hgburia, rapid loss of strength.

11. Death. 50.

2 attacks of b.w.f. following Q. in the previous half-year.

16 Jan. Mid-day M.B. 0·15 g. 2-hourly.

17. 7 a.m. T. 35·8°, P. 78. 9 a.m. T. 39·9°, P. 136. Antipyrin 1·0 g. 11.30 a.m. violent rigor, T. 40·6°, P. 152. 12 n. T. 41·2°, moist packs. Subcutaneous ether with good effect for feeling of oppression and irregularity of the heart. 1.15 p.m. T. 40·5°, P. 154. Soon after 200 c.c. urine, Hgburia. 50.

Arbeiten (1904).

In only 3 of 46 cases of b.w.f. could Q. be not in the slightest degree incriminated. Moreover in 2 of these 3 cases a substance having certainly a special action on malaria parasites—methylene blue—had been given before the attack.

Case 1. An Arab child, at death's door, had certainly not had Q.

Case 2. Methylene blue 0·15 g. three hours before the attack.

Case 3. Methylene blue enema 0·15 g. 1 hour before the attack.

In a considerable number of my cases methylene blue (as well as Q.) had been given before the attack. Palestine.

Yofé (1912).

Plasmoquine.

1. *P. vivax.* Never had Q.

Days 1–3. 'Atebrin plasmochine,' 0.01 g., t.d.s.

Day 4. Collapse, jaundice, bilious vomiting, T., brownish black urine, 'mainly Met-Hgburia and Met-Hgbaemia.' Hgb fell from 65% to 17%.

2. *P. vivax.* T.N.

Day 1. Plasmochine, 2 tablets, t.d.s.

Day 2. 'Had nothing.'

Day 3. Collapse, jaundice, T., bilious vomiting, black urine. Met-Hgburia and Met-Hgbaemia. Egypt.

Khalil (1936), 94.

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