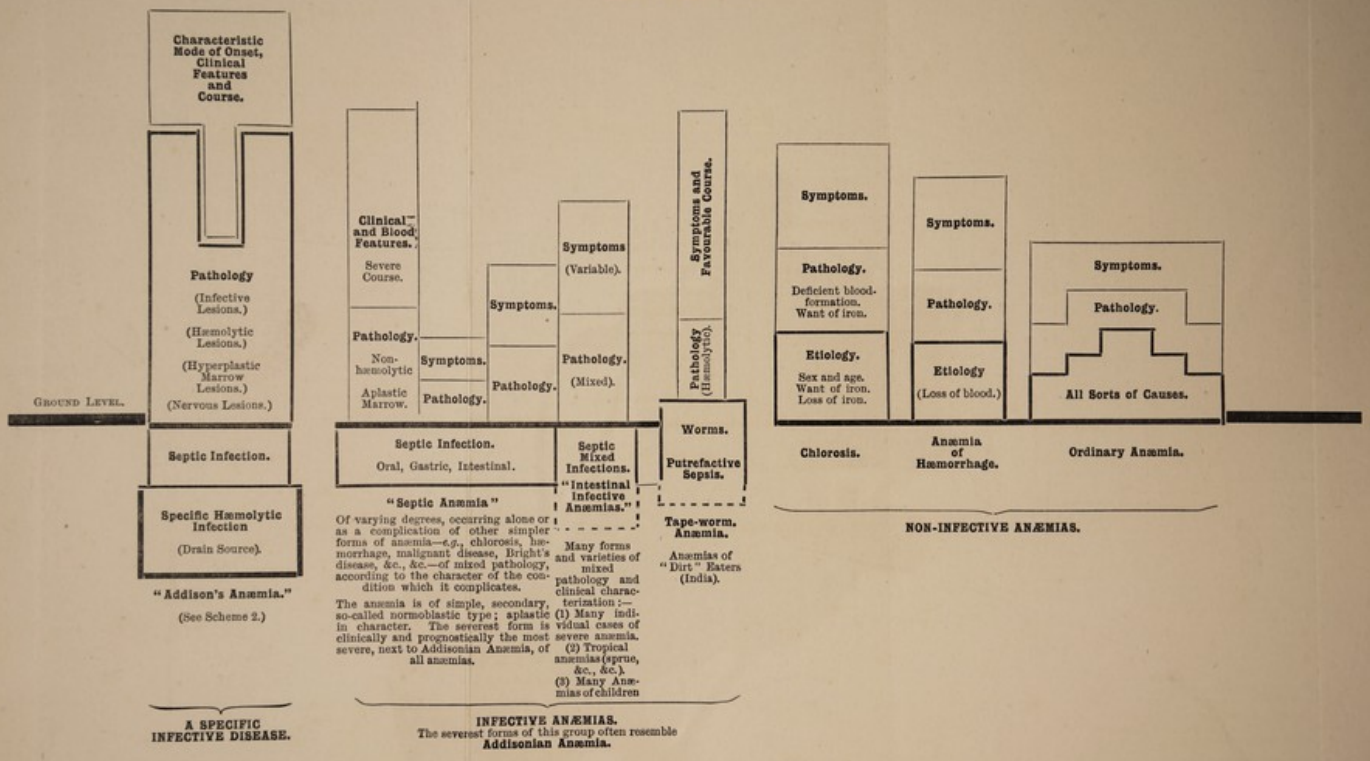
Severest anaemias, their infective nature, diagnosis and treatment / by William Hunter.

SEVEREST ANÆMIAS

ETIOLOGICAL RELATIONS OF SEVEREST ANÆMIAS TO EACH OTHER AND TO OTHER FORMS OF ANÆMIA (HUNTER).

(See pp. 63 and 186.)



Front.]

SEVEREST ANÆMIAS

THEIR INFECTIVE NATURE

DIAGNOSIS AND

TREATMENT

BY

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VOLUME I

WITH HISTORICAL SCHEMES, CHARTS AND PLATES

MACMILLAN AND CO., LIMITED
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1909

TO THE MEMORY

OF

My Brother

John Bowman Hunter

I DEDICATE THIS WORK

AUTHOR'S PREFACE

THE title and sub-titles of this work indicate its scope and the general character of the anæmias with which it deals. For reasons which will appear in every chapter and almost on every page, I have definitely abandoned the use of the term "pernicious" for any form of anæmia, and have done so out of regard for the patient and in the interests of Clinical Medicine. For, as will be made clear in a section of this work (Part IV) to which I specially invite attention, this term connotes nothing but confusion—historical, clinical, etiological, pathological, diagnostic, prognostic and hæmatological—without its equal in the history of any disease or group of diseases. I have given the severe disease known to English observers as Addison's anæmia the position amongst Infective Diseases to which it is in my observation entitled, and the title "Addisonian," which connotes it and nothing else. The title "Septic" has been selected as the most appropriate one for purposes of etiological characterization and treatment, to denote those anæmic conditions which most resemble the Addisonian anæmic disease and are most commonly mistaken for it. For the etiological factor common to them all, which gives them their resemblances to each other and to Addisonian anæmia, is septic infection. Their relationships to each other and to Addisonian anæmia are represented schematically in the Frontispiece.

The conditions here dealt with are very entangled in their history and obscure in their characters. I have endeavoured at every stage by every possible means to make them clear to my readers. Wherever possible I have grouped the facts—historical, clinical, etiological, pathological or otherwise—in tabulated summaries, or represented them graphically by schemes, maps, charts, and plates. The history of their observation and interpretation is dealt with in full detail, and a full bibliography, extending to some 400 Papers, is appended, up to the year 1903, when this work was commenced.

The standpoint from which the whole subject of these severest anæmias is approached is etiological, clinical, and pathological. The results are indicated in the accompanying Frontispiece. The nature of these anæmias has been a life-long study to me; and it is my experience to be daily concerned with the problems in treatment which they present. The more I have seen of them the more satisfied I am that their infective and clinical characterizations go far deeper into their real nature, and carry further in their diagnosis and treatment, than those which have regard solely to the more purely hæmatological criteria, which observers have continuously striven to connect with these anæmias.

I have endeavoured to bring out this fact in every chapter of this work, for I am satisfied that its proper appreciation is of essential importance in the early diagnosis and effective treatment of these anæmias. If I succeed in making this clear to those concerned with their treatment, I shall feel that one of the chief objects of this work has been attained. For the results here recorded break down once and for all the misleading etiological and diagnostic traditions—summarized graphically in Schemes I and III—associated with, and largely created by, the ill-chosen title "pernicious." They substitute for these traditions the new facts with old facts in new relations—summarized in Frontispiece and in Scheme II—which, according to the writer's observations and interpretation during the past twenty years, afford a fuller and clearer conception of the nature of these anæmias, and furnish surer guides for their early recognition and effective treatment.

The anæmias here dealt with are very common. If recognized in their early stages—as they definitely can be by their infective characterizations here described, *but not by their blood characters*—they can be arrested. This applies even to Addisonian anæmia. The author's sustained interest in this anæmia is due to the fact that in endeavouring to lay bare the etiological foundations of this, the most mysterious and severe of all blood diseases, he has found himself digging deep among the foundations of all severe anæmias. The result has revealed that the etiological factors which give them their severity are

of infective nature, and that the seat of this infection in by far the largest proportion of cases is the alimentary tract. This outcome is of no mere pathological interest. On the contrary, it is of the utmost practical importance. Both classes of facts afford indications in the treatment of these diseases which are daily yielding, in my experience, better and better results, and are destined as they become more fully recognized to remove from most of these anæmias the characters which have hitherto given them their severity.

In inviting the attention of readers to the curious—and at parts dramatic—story of the observation and interpretation of these anæmias, as it is here gradually unfolded, I would only add one further prefatory remark.

So far as Addisonian anæmia is concerned, it is a story of steadily increasing recognition of its individuality, in spite of the persistent efforts on the part of observers to fuse it with other anæmias or ignore it altogether. So far as allied forms of anæmias are concerned, it is a story of "pernicious" confusion, with many figures on the stage, much movement, crowded action, numerous scenic changes, many excursions and alarums, and not a few dramatic situations behind the scenes unobserved by the onlookers. The author, who may claim to have been both before and behind the scenes for the past twenty-one years, has endeavoured to make some of these latter known for the first time. The attention of the profession is invited more especially to the singular history of the original and erroneous identification of Addisonian anæmia with Biermer's "progressive pernicious anæmia"—described in chapter x; to the character of the cases termed "pernicious" on which Professor Ehrlich made his first blood observations —described on p. 168; and to the singularly misleading etiological and hæmatological traditions, which in consequence of these observations have for the past thirty to forty years gathered around the unhappy and unfortunate name of "pernicious" anæmia.

103 *Harley Street*
November 1908.

BOOK I

ADDISONIAN ANÆMIA

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BOOK I

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ADDISONIAN ANÆMIA

PART I

THE PROBLEMS OF THE DISEASE

CHAPTER I

Introductory.

Few diseases, from the very outset of their history, have been wrapped in such mystery as this severe disease. Its chief feature —its very essence—as first observed by Combe (1822), and originally described by Addison (1855) under the title of "Idiopathic Anæmia," was the mystery of its origin—its occurrence "without recognizable cause whatever—without any lesions which could properly or reasonably be regarded as the causes of such serious consequences." Twenty, thirty, and forty years later, in spite of extensive observations, representative observers have held that this mystery applies even to its clinical and pathological features.

Writing in 1878 and 1891, Professor Eichhorst, a representative German observer, thus characterized it :—

> "The clinical picture presented by the disease shows no special features ; these are only results of the anæmia, and can therefore be met with in other forms of anæmia. One is therefore not justified in diagnosing it from the clinical features alone (1878). . . . The clinical picture is dependent only upon the degree of anæmia ; specific symptoms independent of the want of blood scarcely occur. All the clinical changes depend upon the poverty of the blood, including the fever and the nervous symptoms, the former caused by irritation or perhaps paralysis of the heat centres, the latter on similar causes, more rarely on hæmorrhages (1891) . . . None of the anatomical changes are peculiar to the disease ; they are merely the results of the anæmia. One cannot diagnose the disease from the anatomical changes alone." (1878.)

According to Dr. Pye-Smith (1883), a representative English observer, and himself a pupil of Addison, not only did its origin remain mysterious, but it was

> "without any symptoms during life and without any lesions after death, which cannot be explained as directly due to the anæmia . . . We are not able to point to any definite anatomical change as decisive in our diagnosis."

And as recently as 1900, Professor Ehrlich and Dr. Lazarus, after excluding all other anæmias, and even all other forms of what they consider to be "progressive pernicious anæmia," consider that one form still remains as to which

> "not a single point can be got out of the history to throw any light on the origin of the disease; clinical observation and necropsy alike fail to reveal any changes in the organs to which the severe disease can be referred—'primary,' 'essential,' 'cryptogenetic anæmia.' . . . Even among these it is not to be doubted that there are many forms differing entirely from one another in their origin and pathogenesis."

At the same period (1900-3), as the outcome of his investigations conducted from 1885 onwards, Addison's Anæmia is defined by the present writer as

> "not merely a special form of anæmia but a very remarkable disease—a well-characterized hæmolytic *infective disease* localized to the alimentary tract — not producible by ordinary causes of anæmia, however severe they may be; with a characteristic group of clinical features, and a characteristic clinical course; with certain infective and hæmolytic lesions invariably associated with it; and with a very definite number of points in its history throwing light on its mode of origin and on the sources of its specific (hæmolytic) infection.

Such is the form of anæmia—surely "remarkable" enough alike in its history and in its mystery—which is here dealt with. The *problems* which it has from the first presented have been those of *nosology*, *etiology* and *pathology*. Is it, as its original observers, Combe and Addison, thought, a special form of anæmia demanding separate recognition? Are its clinical, pathological, and more especially etiological features sufficiently marked off from those of other apparently similar conditions to justify us in classing it apart from them, and in regarding it as a form of anæmia *sui generis*? Or is it, on the other hand, as so many observers, following Biermer (1871), Quincke (1868), and Eichhorst (1878), have concluded, merely an extreme condition? May any anæmia,

however caused, take on its features provided only that it grows steadily worse, proves unamenable to treatment, and terminates fatally ?

Nosology and Etiology.

The problem which the disease has continued to present throughout its whole history was never more clearly stated than in the words of its first observer, Dr. Combe (1822), viz. :—

> "A very peculiar disease. . . . Unfortunately, however, such is the allowable diversity of opinion on most medical subjects, that it is very possible that the following case (disease) may be viewed in different lights, and receive different appellations ; and while some may be disposed to regard this anæmia as constituting a morbid state *sui generis*, others may consider the defect in the red circulatory mass (so extreme that every organ in the body, with the single exception of the spleen, was deprived of its red blood), as an accidental and occasional circumstance denoting some peculiar change in the assimilative powers, the primary stages of which we have been unable to detect. Doubtful myself which of the two opinions may be the most correct, I shall do little more than state correctly the phenomena of the case, and minutely the appearances presented on dissection. One remark only I may at present offer, that if any train of symptoms may be allowed to constitute *anæmia a generic disease*, the following may be considered an example of it *in its most idiopathic form*."

No less definite was the attitude assumed by Addison. In his earliest communications (1849), as in his later (1855), there is from first to last no obscurity as to the precise limits of his knowledge, the relation of his observations to those of others, or the exact view which he took of this anæmia. The chief feature in this disease which arrested his attention was its occurrence

> "without any discoverable cause whatever . . . apart from the usual causes of the anæmic state, and without any organic lesion that could properly or reasonably be assigned as the cause of such serious consequences."

The main character of the original English conception was, thus, the necessity of *separating* this particular anæmia from the common forms of anæmia producible by various causes. It was an altogether special form—"Anæmia in its most idiopathic form" (Combe) ; a "remarkable form of anæmia—a very remarkable disease" (Addison).

I have defined the nature of the original English conception. The point at issue between this conception and that involved in

the teaching of Biermer and the many German and English and American observers who have followed him is clearly brought out in the appraisement of Biermer's work by Professor Eichhorst (1878), the author of the most important monograph on the condition Biermer termed "progressive pernicious anæmia." (The italics are mine.)

> "The chief merit of Biermer's work—the great and invaluable service he has rendered — is that it *brought together* into one common group, under one title, *a number of different forms of anæmia* which have certain characteristic features in common. From the etiological standpoint there are as many forms of progressive pernicious anæmia as there are causes to be found. One cannot emphasize too much Biermer's statement, 'a spontaneous origin without clear etiology is one of the rarities.' . . . It is absolutely necessary that we hold fast to this statement if we desire to be clear as to the degree and character of the services Biermer has rendered to the subject. . . ."

Here, then, the fundamental difference between the conceptions of Addison and Biermer is clearly defined—on the one side, "separation of a very remarkable form of anæmia" as the chief feature of the English work ; on the other side, the very reverse process, viz., the "grouping together of many different forms" under one title, as the chief merit of German work. The issue thus defined is the one which has so deeply engrossed the interest of all observers who have studied this disease, as the further consideration now to be given to the history will gradually reveal. Some fifty years have elapsed since Addison's first description of the disease ; and it is a unique tribute at once to its remarkable character, to the mystery of its origin, and to the difficult character of the problems which it presents, that controversy should still prevail as to its existence as a disease at all, or as to its relation to other forms of anæmia.

The historical development of this disease in relation to other anæmias has been the following remarkable one :—

(1) The recognition of a particular form of grave anæmia (Addison, 1855), admitted by all subsequent observers to exist, whose chief feature, next to its gravity and fatal tendencies, is the absence of any obvious cause (*Addisonian Anæmia*).

(2) The grouping together of this anæmia (Biermer, 1871) with other forms of anæmia due to many causes, in virtue of certain clinical and anatomical features in common (*Progressive Pernicious Anæmia*), and the transference of this name to

Addisonian anæmia—even although, as is admitted, it did not correspond etiologically with Addison's anæmia.

(3) The further grouping together (Ehrlich, 1892) of this larger group of anæmias—progressive pernicious anæmia—with other forms of anæmia, in virtue of certain megaloblastic blood changes common to them all (*Megaloblastic Anæmias*), and the summary identification of this group of anæmias with progressive pernicious anæmia, "even if this does not correspond clinically with Biermer's pernicious anæmia." [*Sic.*]

(4) Lastly, the assertion (Ehrlich and Lazarus, 1899, and Schauman, 1900) that the most typical form of all these anæmias, termed *progressive* and *pernicious* is bothriocephalus anæmia—which has nothing progressive and pernicious about it, but is one of the most easily curable of all anæmias. [*Sic.*]

Despite these interesting groupings and identifications with other and simpler forms of anæmia, irrespective of cause, and of the course they pursue, Addisonian anæmia still retains its striking individuality—for the patient, one of the most severe of all diseases ; for the observer, the remarkable disease with the mysterious origin, obscure characters, and deadly tendencies, which first led to its recognition and identification.

The problem is the one which divided English and French physicans sixty years ago in connection with the identity or non-identity of typhoid and typhus fevers, then grouped together under the title of "Continued Fever." The latter asserted that "typhoid and typhus fever are one and the same disease . . . present not only analogy but the most perfect resemblance. . . . The deepest darkness prevails regarding the cause of typhoid fever. . . . . The causes of typhoid fever are wrapped in the greatest obscurity" (1840). In 1850 Sir William Jenner finally decided the matter once and for all by showing that "typhoid and typhus fevers are equally distinct diseases—by difference in symptoms, course, duration, lesions, and *cause*"; and Murchison supplemented (1858) these observations by bringing typhoid fever into relation with drain poisoning.

So with regard to this remarkable blood disease—"Addison's anæmia"—the surmise of its first English observers, that it was a *separate disease sui generis*, has in my observation and judgment proved to be the correct one. But each attempt to keep it apart has been met by a series of observations of German workers having for their object, as they expressly state, to *group together* (*see* Schemes I and III) this disease with other forms of anæmia

under the title of "progressive pernicious anæmia." The writer's investigations of 1888 regarding the distinctive hæmolytic nature, the toxic cause and gastro-intestinal site of the disease, "profoundly influenced" the work and conception of English and American observers in an opposite direction. They were generally recognized as the "strongest argument in favour of the independence of the disease that had yet been advanced," as *separating* more and more Addison's anæmia from other forms of anæmia, even from "progressive pernicious anæmia." But in 1892 the line of cleavage between English and German work was once again made even more marked by Ehrlich's work, emphasizing "megaloblastic degeneration" as a feature of certain forms of anæmia—"megaloblastic anæmia"—and forthwith identifying this group with progressive pernicious anæmia, "*even if this does not correspond clinically with Biermer's pernicious anæmia.*" [*Sic.*]

The extraordinary confusion thus created by the persistent attempt of the past fifteen years to connect particular forms of anæmia with particular morphological changes in the blood could not receive better illustration. In the writer's experience the essential changes of Addison's anæmia are no more megaloblastic than is fever or diarrhœa the essential change in typhoid fever; or any particular manifestation of scarlet fever—for example, angina, rash, or desquamation—the essential change in that disease. To so regard them is to miss the whole striking clinical, pathological, and infective characterizations presented by this disease.

Pathology.

With regard to the *pathology* of this obscure affection, the real "pathos" of so severe a disease can only be correctly gauged by having regard to all the features—etiological, clinical, diagnostic, prognostic, as well as the narrower ones of Morbid Anatomy and Hæmatology, usually associated with the title of Pathology. For in truth there is much "pathos" connected with every aspect of this remarkable disease; with the confusion and controversy connected with its earlier identification and observation by English and German observers respectively—without its equal in the history of any disease; still more pathos connected with the nature of the disease itself—its pathology, its clinical features, and severe course.

To be struck down, sometimes quite suddenly, in the midst of perfect health by a fell disease, mysterious in origin; to have

strength sapped day by day by symptoms possessing, it is stated, no distinctive features, but merely the result of the anæmia; to be suddenly restored to health, in many cases in the most marvellous manner—so much so that the patient often states he has never felt so well in his life; and then, after a period of three, six, or nine months, to be again suddenly reduced in a period of a few weeks to a condition of the most extreme bloodlessness and weakness such as no other disease displays—such represent some of the pathos which must be taken into account in determining the true character of this most remarkable disease, and its relations to other allied conditions of anæmia which, however closely resembling it in one or other of its features, differ from it profoundly in their total clinical characterization, especially in respect of their fatality.

In dealing with a disease such as is here outlined, it does not avail to assert that, desperate as is the anæmia, mysterious as is its source, it nevertheless does not essentially differ pathologically from other simpler forms of anæmia, such as "tapeworm anæmia," which can be cured in a few weeks; that it is simply due to the malignant direction taken by the blood formation, and to a reversion of the blood to an embryonic type; that its chief feature is a megaloblastic degeneration of the red cells, although "the discovery of such cells in the blood often requires great patience—careful searching over several slides of blood with the aid of an oil immersion."

Such an explanation is, indeed, a pathological one, inasmuch as it adds immeasurably to the "pathos" of the disease. Even if true, the problem still remains to explain why, in his particular case, the blood-forming powers of a man formerly healthy should so suddenly and completely have gone to pieces in the first instance; why they should so marvellously recover themselves in a few months; and why they should again, without cause, revert to their alleged embryonic type.

I desire, then, to emphasize here, at the outset, more than has hitherto been done in connection with the pathology of this disease, the importance of prognostic considerations in gauging the real pathos—the true pathology—of this remarkable anæmia. Due regard to all the features of this disease is the more important; for the issue involved is, in the writer's judgment, the existence of a well-defined specific infective disease.

Nomenclature.

The problem of the nature and etiology of the disease has been infinitely complicated and confused by another problem of an entirely subordinate nature connected with *Nomenclature*—namely, whether the anæmia termed "idiopathic" by Addison (1855) is or is not the same as that later described by Biermer (1871) as "progressive pernicious anæmia" or more simply "pernicious anæmia."

The first knowledge which English observers obtained (1874) of Biermer's "Progressive Pernicious Anæmia" was derived (*see* p. 88), at second hand from Professor Immermann's account of it. He described it as "of unknown cause" (1874). Dr. Pye-Smith immediately pointed out (1875) that, as thus defined, this anæmia was the same as Addison's "Idiopathic Anæmia," and observers were thus led very generally to adopt the new name for the anæmia known to them as "idiopathic anæmia." This new title rapidly made its home in English literature. The term "idiopathic" lost its original meaning and was given a generic significance which included both chlorosis and pernicious anæmia, or was reserved as the title for only one form of "progressive pernicious anæmia," termed by German observers the "primary" form.

Since 1875 it is under the name of "progressive pernicious anæmia" or the shorter title of "pernicious anæmia," that the disease has been known. The title "Addison's Anæmia" is only rarely applied to it in English literature, although English observers (especially the present writer) have Addison's account in their minds when they speak or write of "pernicious anæmia." On the other hand, the title "Biermer's anæmia" is one of the commonest names given to it in German literature—the latest modification of this, suggested as a tribute to Professor Ehrlich's work upon it, being that of "Biermer-Ehrlich Anæmia" (1900).

The general assumption has been that Addison's and Biermer's accounts refer to one and the same condition. In German literature the account given by Addison is regarded as being of quite subordinate interest. It is said to relate merely to one form (so-called "primary") of what they consider should be included under the designation of "progressive pernicious anæmia." This position has been maintained throughout in German literature as being one quite unassailable, and in many cases in English literature as well.

Now, the particular name by which a disease is known may be a matter of relatively little importance, provided that all are agreed as to the identity of the disease itself. But the matter is otherwise if any question exists from the very outset as to whether we are really dealing with one and the same disease—whether Addison's "idiopathic anæmia" and Biermer's "progressive pernicious anæmia" really connote the same diseases. It becomes of real importance if it turns out, as I find, that the two conditions are not the selfsame, and that the conceptions of their original describers were fundamentally different.

The investigations here detailed show that Addison's conception of "idiopathic anæmia" and Biermer's conception of "progressive pernicious anæmia," although touching each other in certain points, were fundamentally different from the standpoint of etiology; these differences were at once accentuated by the interpretation put upon Biermer's work by Swiss and German observers—Immermann (1879), Quincke (1876-80), Eichhorst (1878); since then they have been even further accentuated by the hæmatological observations of Ehrlich (1888, 1892), and by the studies of Schauman regarding bothriocephalus anæmia (1894-8), and by the interpretation put upon these observations by their authors and most German observers. In short, the identification of "idiopathic anæmia" with "progressive pernicious anæmia" too hastily made by English observers when Biermer's work was first brought to their notice was, as will presently be shown, a huge mistake—having a curious origin, which I have found almost as difficult to trace as the origin of the disease itself—which has unquestionably proved the cause of more confusion in nomenclature than has probably ever obtained in the case of any other disease.

As I shall show in a later chapter, all three observers originally concerned in creating this confusion—Biermer, Immermann, and Eichhorst—completely contradicted themselves and each other at different times as to what they considered Biermer's anæmia to be. The one point made clear is, that historically, from first to last, progressive pernicious anæmia never was identical with Addison's anæmia. To mark this distinction, the time has, I consider, come to separate off, once and for all, by its own name, "*Addisonian anæmia*" from progressive pernicious or pernicious anæmia.

Apart from its historical necessity, there is a necessity out of regard to the sufferer, for giving it some other name than that

of "pernicious." To him that name is an additional cruelty which he resents, since it deprives him of the comfort of hope, even during the remarkable vicissitudes of his disease. It even interferes with its proper treatment ; for so constant and remarkable are the recoveries which mark the course of this disease in its earlier stages (when, in my experience, it is amenable to successful treatment, and even to arrest), that he discredits the accuracy of the title of pernicious as applicable to his disease. He is induced thereby to leave off treatment, or to wander about from doctor to doctor in the hope of obtaining a diagnosis with a less fearful title than the one—erroneously, as he thinks—given to his disease.

In view of the endless and pernicious controversy associated with it and the continually changing connotation attaching to it from the first up to the present time, the title "pernicious" can only be regarded as a singularly confusing one, and in the interests of clinical medicine it had better be dropped altogether. The anæmias simulating Addisonian anæmia in some or other of their features would best be given the title which I now suggest and which etiologically best describes them, namely, "Septic Anæmias."

It will be the purpose of the following work to make clear the grounds on which these conclusions regarding the striking individuality of this malady are based.

Book I—Addisonian Anæmia.

(*a*) The historical development of our knowledge regarding this disease and its relations to other forms of anæmia ; and (*b*) the etiological, clinical, pathological, diagnostic and prognostic observations which have satisfied the writer of the claim of this mysterious anæmia to be in reality not merely a form of anæmia but also a specific infective disease.

Book II—"Septic Anæmias."

PART II

HISTORICAL PREFACE

CHAPTER II

Period I (1822-70).

"*Idiopathic Anæmia*" (*Addison*, 1855).

The first recorded case of this remarkable form of disease is that described by Dr. J. S. Combe, M.D., of Edinburgh, under the title of "A History of a Case of Anæmia," in the *Transactions of the Medico-Chirurgical Society of Edinburgh* for May, 1822. The account ran as follows :—

Combe's Account.

The case now recorded appears to me entitled to still further attention as exhibiting a well-marked instance of a very peculiar disease, which has excited little attention among medical men, and which has been altogether overlooked by any English author with whose writings I am acquainted. Unfortunately, however, such is the allowable diversity of opinion on most medical subjects that it is very possible the following case may be viewed in different lights, and receive different appellations ; and while some may be disposed to regard the peculiar characteristic from which it derives its denomination of anæmia as constituting a morbid state *sui generis*, others may consider the defect of the red circulating mass as an accidental and occasional circumstance, denoting some peculiar change in the assimilative powers, the primary stages of which we have been unable to detect. Doubtful myself which of these opinions may be the most correct, I shall do little more than state correctly the phenomena of the case and minutely the appearances presented on dissection. One remark only I may at present offer, that if any train of symptoms may be allowed to constitute anæmia a generic disease the following may be considered an example of it in its most idiopathic form. . . .

The case was a man, aged 47, who had been born and had spent the greater part of his life in the country, where his duties were neither laborious nor unhealthy ; who had led a regular

and temperate life, and had enjoyed perfect health since childhood, and had never lost any blood.

I was much struck by his peculiar appearance. He exactly resembled a person just recovering from an attack of syncope ; his face, lips and the whole surface were of a deadly pale colour ; the whites of the eyes bluish ; his motions and speech languid ; he complained much of weakness ; his respiration, free when at rest, became hurried on the slightest exertion ; pulse 80 and feeble ; inner part of the lips and fauces nearly as colourless as the surface ; bowels very irregular, generally lax, his stools very dark and fœtid ; urine reported to be copious and very pale ; appetite unimpaired, of late his stomach has rejected almost every kind of food ; constant thirst ; he has no pain referable to any part, and a minute examination could not detect any structural derangement of any organ.

It was only about two months ago since he began to complain, but not until his friends had observed his altered complexion ; he then lost strength and said his head troubled him. Of this last symptom he has no distinct recollection. His feet became œdematous and his appetite failed him. . . .

My attention was drawn to the skin, which was of waxen colour, soft and delicate, the cellular tissue about the eyes and breast slightly distended with watery effusion. The pulse was feeble and easily excited by any emotion. . . . A very minute examination of the case, and a careful consideration of its history, scarcely solved the nature of the affection ; and its long continuance and inveteracy rendered our prognosis much more doubtful.

He died six months after being first seen, from aggravation of all his symptoms, extension of the œdema to face and upper extremities, and evident marks of effusion into the chest. He died with all the symptoms usually attendant on hydrothorax. At first the treatment seemed to check the progress of the disease, but latterly the stomach and bowels became so irritable as scarcely to admit of any medicine and only of the mildest diet.

Post mortem.—The subcutaneous fat was scanty, of a pale yellow colour and semi-fluid. Not a drop of blood escaped on dividing the scalp. . . . The heart when cut into was of a pale colour, and did not tinge linen when rubbed upon it ; it appeared like flesh macerated many days in water. The right ventricle contained a pale coagulum. The left side was wholly empty. There was a considerable moisture bedewing the viscera of the abdomen. The liver was of its proper size and structure, but of a light brown colour. The spleen was the only viscus of its usual colour ; it was very soft, and its contents, on pressure being applied, turned out like a sac. The kidneys were nearly bloodless ; pancreas of a pale reddish hue. The stomach and intestines were perfectly sound, thin, showing no vessels, and transparent. The muscular substance throughout the body was, like that of the heart, very pale, and exuded no blood, but only

a pale serum, when cut into. The arteries were empty, and so were the jugular, femoral, and humoral veins. . . .

The only morbid appearances detected may be considered the effusion into the thorax and abdomen, the ossification of the dura mater, and the nearly bloodless state of every viscus and structure in the body, with the exception of the spleen. . . . A state, like that of our patient's, in which every organ was nearly deprived of its red blood, is one, I believe, of very rare occurrence, and of which we have very few cases on record.

He then referred to the only two cases he could find—one by Reiselius (1684); the other observations of Lieutaud (1761), who was "the first to give a precise account of anæmia (chlorosis)," and concluded :—

"It is probably owing to some disorder of the digestive and assimilative organs, that its characteristic symptoms have their origin."

Although thus preceded, the observer whose name is associated with the early observation and description of this anæmia is Dr. Thomas Addison, M.D.Edin., Physician to Guy's Hospital, London. His first communication appeared in 1849 under the double title of "Anæmia : Disease of the Suprarenal Capsule." The first words of that communication at once struck the keynote of his subsequent conclusions, for he described the disease as :—

"A remarkable form of anæmia which, although incidentally noticed by various writers, had not, he thought, attracted by any means the attention it really deserved. It was a state of general anæmia incidental to male adults, and had been with him for several years a subject of earnest enquiry and very deep interest."

Then followed an admirable description of its general features as he afterwards more fully described them in 1855. The precise limits of his knowledge at this date were, that he had not then differentiated this anæmia from the disease of the suprarenal capsules he was engaged in working out. Unknown to himself he was really dealing with and seeking to differentiate not one but two extraordinarily obscure conditions; and this was the unique task he accomplished in his next communication, in which he established the existence of the well-known suprarenal disease since known by the name of "Addison's Disease."

His keen interest in the rare form of anæmia cannot be better described than in his own words : "It was while seeking to throw some additional light upon this form of anæmia that he stumbled upon the curious facts" relating to the suprarenal disease.

These facts were made known in his well-known work, "On the Constitutional and Local Effects of Disease of the Suprarenal

Capsules" (1855); in the introduction to that work the first description of "Idiopathic Anæmia" as a generic disease was given in the following terms :—

Addison's Account.

As a preface to my subject, it may not be altogether without interest or unprofitable to give a brief narrative of the circumstances and observations by which I have been led to my present convictions.

For a long period I had from time to time met with a very remarkable form of general anæmia occurring without any discoverable cause whatever—cases in which there had been no previous loss of blood, no exhausting diarrhœa, no chlorosis, no purpura, no renal, splenic, miasmatic, glandular, strumous, or malignant disease. Accordingly, in speaking of this form in clinical lectures, I, perhaps with little propriety, applied to it the term "idiopathic," to distinguish it from cases in which there existed more or less evidence of some of the usual causes, or concomitants of, the anæmic state.

The disease presented, in every instance, the same general character, pursued a similar course, and, with scarcely a single exception, was followed, after a variable period, by the same result.

It occurs in both sexes, generally, but not exclusively, beyond the middle period of life; and so far as I at present know, chiefly in persons of a somewhat large and bulky frame, and with a strongly marked tendency to the formation of fat.

It makes its approach in so slow and insidious manner that the patient can hardly fix a date to his earliest feeling of that langour which is shortly to become so extreme.

The countenance gets pale, the whites of the eyes become pearly, the general frame flabby rather than wasted; the pulse perhaps large, but remarkably soft and compressible, and occasionally with a slight jerk, especially under the slightest excitement. There is an increasing indisposition to exertion, with an uncomfortable feeling of faintness or breathlessness on attempting it; the heart is readily made to palpitate; the whole surface of the body presents a blanched, smooth, and waxy appearance; the lips, gums, and tongue seem bloodless; the flabbiness of the solids increases; the appetite fails; extreme languor and faintness supervene, breathlessness and palpitation being produced by the most trifling exertion or emotion; some slight œdema is probably perceived about the ankles. The debility becomes extreme; the patient can no longer rise from his bed; the mind occasionally wanders; he falls into a prostrate and half-torpid state, and at length expires. Nevertheless, to the very last, and after a sickness of perhaps several months duration, the bulkiness of the general frame and the obesity often present a most striking contrast to the failure and exhaustion observable in every other respect.

With perhaps a single exception, the disease in my own experience, resisted all remedial efforts, and sooner or later terminated fatally.

On examining the bodies of such patients after death I have failed to discover any organic lesion that could properly or reasonably be assigned as an adequate cause of such serious consequences; nevertheless, from the disease having uniformly occurred in fat people, I was naturally led to entertain a suspicion that some form of fatty degeneration might have a share at least in its production: and I may observe that, in the case last examined, the heart had undergone such a change, and that a portion of the semilunar ganglion and solar plexus, on being subjected to microscopic examination, was pronounced by Mr. Quekett to have passed into a corresponding condition.

Whether any or all of these morbid changes are essentially concerned—as I believe they are—in giving rise to this very remarkable disease, future observation will probably decide.

The cases having occurred prior to the publication of Dr. Bennett's interesting essay on *Leucocythæmia*, it was not determined by microscopic examination whether there did or did not exist an excess of white corpuscles in the blood of such patients.

It was while seeking to throw some additional light upon this form of anæmia that I stumbled upon the curious facts which it is my more immediate object to make known to the profession.

Dr. Addison then proceeded to describe the disease of the suprarenal capsules, since known by his name, "Addison's Disease."

Under Addison's title of "Idiopathic Anæmia" the condition from that time forward became known to English physicians. Even before Addison's formal description in 1885 a typical case of the disease was recorded by *Dr. Barclay*, under the title of "Death from Anæmia" (1851). Other cases were subsequently described by *Drs. Wilks* (1857), *Bristowe* (1858), *Barlow* (1861), *Habershon* (1862), *Barclay and Dickinson* (1863), *King* (1871); and the disease was the subject of teaching and comment by *Sutton*, *Bright*, *Barclay*, *Bence Jones*, and other London teachers.

"Thanks to the teaching of Dr. Sutton and the writings of Dr. Wilks calling attention to Addison's description I have been familiar with the disease since a student," wrote *Dr. Stephen Mackenzie* in 1878.

"The dim and distant beginnings of my knowledge of the subject extend back to the time (1849) when I wrote for the *Edinburgh Monthly Journal of Medical Sciences* an abstract of Addison's paper on 'Suprarenal Disease,' which brings in the idiopathic anæmia idea," so wrote *Sir William Gairdner*, of Glasgow, to the author,

in a private letter dated February, 1903. In his "Clinical Medicine" (1862), under the title of a "A Fatal Case of Anæmia," he recorded a typical case of what he terms "this most mysterious form of disease . . . . a remarkable case of pure anæmia, fatal, without any explanatory organic complication . . . . the blood presented an extreme deficiency of red, and certainly no increase of white, corpuscles. After death, which occurred from pure exhaustion, every organ was carefully examined, and the only morbid appearances presented were in the heart, liver and kidneys, which were all more or less occupied by fatty granular deposit. I have only to say in regard to this most mysterious form of disease, that it has no real relation with the chlorosis of young women. In fact, the only two cases which I have seen exactly resembling this one occurred in men and at middle age. The general appearance is much more that of malignant disease than of any other condition with which I am familiar."

Moreover, Addison's teaching was not confined to his own country—it was also known abroad. According to Professor Osler, his old teacher of medicine—*Professor Howard*, of Montreal—taught to his classes in 1869 the existence and symptoms of idiopathic anæmia. *Sir T. Clifford Allbutt*, of Cambridge, testifies (1901) to the interest taken in the disease by *Professor Trousseau*, in Paris, in 1860, as well as by his teachers in St. George's Hospital. The eighteen cases collected by *Dr. Frederick Taylor* (1876), actually recorded in English literature up to the time when the first notice of the condition entitled "Progressive Pernicious Anæmia" appeared in an English journal (1874), represents the degree of interest taken in the subject by English physicians, and the early history was fully dealt with by *Dr. Pye-Smith* in 1883.

Such is the history of the early observations of this disease in English literature. Under whatever name the condition was described—"idiopathic anæmia," "fatal anæmia," "idiopathic fatty degeneration"—the chief character always commented on was that emphasized by Combe (1822) and Addison (1855), namely, the "very peculiar" (Combe), "very remarkable" (Addison), "most mysterious" (Gairdner) form of disease; its occurrence without any recognizable cause and without any *post-mortem* lesions sufficient to explain it; and its fatal course, "with, perhaps, one single exception" (Addison).

In French medical literature, according to *Lépine* (1877), the first observer, after Addison, to establish the existence of a parti-

cular group of symptoms depending on anæmia and accompanied by fatty degeneration of the viscera, was *Perroud* (1869). He considered the fatty change in the liver to be the principal cause of the anæmia, the order of events being fatty degeneration of the liver, impoverishment of the blood, cachexia, anasarca. Prior to that, however (1860), *Cazenave*, recorded three cases under the title "Essential Anæmia."

In Germany the first observer, according to Eichhorst (1878), was *Lebert* (1858), who described it under the name of "Essential Anæmia." Professor Lebert's account, as given later by himself (1871), is as follows :—

"In a series of cases I have observed the whole picture of anæmia without any organic cause, and without finding anything *post mortem* to explain it; and I have, therefore, termed these cases 'Essential Anæmia.' This idiopathic anæmia seldom ends fatally [*sic*]; when it does, one finds no organ essentially diseased (1868). . . . . In rare cases idiopathic anæmia, without being complicated by any loss of blood or any organic disease, may end fatally. . . . . We must, therefore, not forget that anæmia can, of itself, lead to death, although this is seldom the case."

In America the earliest observer, according to Professor Musser (1885), appears to have been *Dr. Channing* (1842), in a paper entitled "Notes on Anæmia."

Summary.

The results of the observations of this earlier period (1855-70) may be summarized as follows :—

Nomenclature.—"Anæmia in its most idiopathic form" (Combe, 1822); "Idiopathic Anæmia" (Addison, 1855, and later observers); "Fatal Anæmia" (Barclay, 1851, Bristowe, 1858, Gairdner, 1862, King, 1871); "Essential Anæmia" (Lebert, 1858, Cazenave, 1860).

Conception.—"A very peculiar disease" (Combe, 1822); "A very remarkable form of anæmia. . . . this very remarkable disease. . . . this form of anæmia" (Addison, 1855); "This very mysterious form of disease" (Gairdner, 1862).

Etiology.—"Occurring in a man, aged 47, who had led a regular, temperate life, had enjoyed perfect health since childhood, and had never lost any blood" (Combe, 1822); "occurring without any discoverable cause whatever—no previous loss of blood, no exhausting diarrhœa, no chlorosis, no purpura, no renal, splenic, miasmatic, glandular, strumous, or malignant disease" (Addison, 1855); "no real relation with the chlorosis of young women" (Gairdner, 1862).

Antecedent Conditions present in the individual cases.—Epistaxis, recent parturition, frequent parturition, pregnancy, hæmorrhage, diarrhœa, bilious attacks with vomiting, privation, suckling, starvation, dyspepsia, frequent vomiting — all of them subsequently regarded as causes but, be it noted, not during this period assigned as causes.

Clinical Features.—In general, the features were those admirably described by Combe (1822) and Addison (1855), viz., the gradual onset of anæmia, with pallor, dyspnœa, palpitation, vertigo, cardiac murmurs ; in some cases œdema, anasarca, vomiting, or diarrhœa, or both ; occasionally pyrexia, usually without emaciation ; in certain cases slight jaundice and delirium.

Pathological Changes.—Mostly negative ; chiefly anæmia *plus* fatty degeneration of the heart, liver and other organs.

" Without any organic lesion that could reasonably or properly be assigned as an adequate cause of such serious consequences." (Addison, 1855.) The conditions usually found were extreme anæmia, pallor of skin, no wasting, fat firm and yellow, often œdema, sometimes with hydrothorax, ecchymoses of dura mater and of pleura ; the commonest change noted was fatty degeneration of the heart, liver and kidneys.

Blood.—Very pale and scanty (Combe, 1822) ; very deficient in red cells (Gairdner, 1862) ; no increase of white cells (Wilks, 1857, Bristowe, 1858, Gairdner, 1862, Barclay and Dickinson, 1863) ; red corpuscles very variable in size (Leared, 1858).

Lymph Glands.—No enlargement. (Addison, 1855.)

Spleen.—Very variable in size ; " the only viscus of its usual colour." (Combe, 1822.)

Liver.—Fatty ; in one case contained leucin and tyrosin (Lebert, 1858) ; *of a light brown colour* (Combe, 1822).

Conclusion.

After fullest credit has been given to the observations of others, this period in the history of the disease appears fully to justify the conclusion expressed impartially by Professor Eichhorst (1878) : " We come to the result that this (what he terms ' the primary ' form of the) disease was first described in England, both in the form of single cases and as a definite clinical disease."

So far as individual cases are concerned, this recognition is specially deserved by the first recorded case—that of Dr. Combe. In the light of the conclusions reached by the present writer regarding the nature and features of this disease, the account given by Dr. Combe appears to him to deserve altogether special notice

for clearness of conception and accuracy of observation. The problem of the disease, its obscure etiology, mode of onset, clinical features (including those connected with the gastro-intestinal tract described, but erroneously regarded as causes, by Biermer), and clinical course (including the temporary recovery followed by relapse, one of the most striking features of the disease) are admirably described. Even more striking, if possible, is his pathological account. This includes mention of four of the most constant features of the disease, viz. : (1) the almost entire bloodlessness of the body ; (2) " the heart of pale colour, like flesh macerated many days in water " (an admirable description of the fatty heart) ; (3) " the liver of a light brown colour " (the characteristic appearance of the pigment liver) ; and lastly (4) " the spleen, the only viscus of its usual colour "—perhaps the most strikingly accurate of all his observations. As it happens, this curious feature was independently observed and commented on by the present writer (1888), in the first case which he examined *post mortem ;* and since then it has been always looked for and found by him as a striking feature of the disease.

The second case recorded in the literature—that by Dr. Barclay in 1851—contains, oddly enough, the first observation of an equally notable character regarding the glossitis to which the present writer has been led to attach the greatest clinical, pathological, and diagnostic importance. The illness began after confinement, and the account proceeds :—

> Soon after her confinement she had a sore mouth, for which she applied for advice. To this she attributed her debility, as she had continued to suckle her child, and had never been able to get up her strength properly.

By an equally curious coincidence, although he had never previously heard of the condition, a similar history of sore mouth marking the onset of the disease and the striking appearances presented by the tongue arrested the particular attention, and was made the subject of comment and interpretation by the author in the first case (1888) which he clinically studied. As he subsequently found on perusal of the literature (1900), only two or three observers had deemed it worthy of mention in their cases, although it must have been present in many cases, viz. : Müller (1877), in five out of his sixty-two cases, and Laache in four out of his ten cases. The former dismissed it as a curious effect of the disease, the latter made no comment upon it. On the other hand, the whole of the author's subsequent work (1890-1900) regarding the *specific infective* characterization of the disease, and the great part played

by *sepsis* (oral, gastric, or intestinal), *not as its cause* but as the chief predisposing factor favouring its contraction, was the outcome of the interest then raised by, and of the attempt to explain, the curious sore tongue presented by that case. The importance of it in connection with his subsequent interpretation of the disease may be gauged by the following opinion of the late Sir William Gairdner, of Glasgow, who was acquainted with Addison's anæmia from 1849 to 1903 :—

I wish I could say I had taken note of the glossitic phenomena you describe, but I am afraid I am of the number of those who have passed over things much within view, and I shall now (1903) have no opportunities of repairing my omissions. If you can make that point (*i.e.*, the glossitis) clear, as being of the frequency you describe, you will have won your case (interpretation) against all gainsayers. (*See postea*, p. 114.)

The clinical features so well described by Dr. Combe, with the history of sore mouth as one of the earliest symptoms noted by Dr. Barclay's patient, comprise, in the author's experience, the surest clinical criteria of the existence of this remarkable disease. The *post-mortem* findings described by Combe represent in their turn in his experience the surest pathological criteria—far more important than the various blood criteria, singly or collectively, which subsequent observers have in turn laboriously striven to connect with the disease. Taken together, they supply the three groups of pathological changes which, in his experience, as described from 1890 to 1900, invariably characterize the disease, namely : (1) the *infective lesions* in the tongue (or lower down), accompanied by sore mouth (or gastric and intestinal symptoms); (2) the resulting *hæmolysis* with profoundest anæmia, marked by the pigment liver and the intense anæmia of all organs with the single exception of the spleen ; and (3) the *fatty changes* in the heart (and other parts) as the result of the toxic influences at work. If to these were added (4), the *hyperplastic marrow changes*, denoting, as he interpreted them (1888), the efforts of the marrow to compensate by excessive activity the intermittent hæmolysis of the disease, the great pathological picture presented by this disease would be complete in all its essential details.

These remarks touch upon some of the most contentious points connected with the interpretation of the disease. They are here introduced, not with the object of prejudging their importance, but to show the historical accuracy of the conclusion—that the credit of having first correctly recognized and described this disease belongs to English observers.

CHAPTER III

Period II (1870-87).

"*Idiopathic Pernicious Anæmia*" (*Pye-Smith*, 1875).

"Not a disease *sui generis*, but a mere group of symptoms" (Most Observers).

This period opens with the account given by Professor Biermer, of Zürich, of "a form of *Progressive pernicious anæmia, generally associated with fatty degeneration in the circulatory apparatus, and in consequence with capillary hæmorrhages.*" It is concerned with: (1) The stimulus given to the study of the subject by these observations; (2) the marked influence they had on the conceptions of Continental, English, and American workers; (3) the general conclusion reached that "pernicious" and "idiopathic" might be regarded as interchangeable titles equally applicable to the remarkable form of anæmia already known to English observers as "idiopathic anæmia."

"Anæmia idiopathica perniciosa" was the title of the paper in *Virchow's Archiv*, 1875, in which Dr. Pye-Smith drew the attention of German observers to the existence of Addison's anæmia. "Idiopathic Anæmia of Addison, since called Essential, Pernicious or Progressive Anæmia, with a Commentary and Tables of Selected Cases" (103 in number) was the title of his later admirable paper, published in the *Guy's Hospital Reports* in 1883, in which he established, beyond all question of dispute, the great historical and clinical identity of this grave disease, and strove, almost alone among the observers of this period, to keep Addison's anæmia from being absorbed into the large and ill-defined group of anæmic conditions of multiple origin described by Biermer under the name of "progressive pernicious anæmia."

His efforts were effective to this extent—that the historical identity and priority of observation of Addison's anæmia were fully admitted by Professor Eichhorst in his treatise on "Progressive Pernicious Anæmia," published in 1878. For the first time in the history of Biermer's group of anæmias a definite place was assigned to the anæmia without known cause. It was termed the primary form of that group, and this recognition was definitely

noted by Immermann as one of the chief merits of Eichhorst's work. In other words, it was recognized as a great service, even by Biermer's chief exponents, that Addison's anæmia should have been identified and separated from the other conditions with which it had been grouped by Biermer (!). (Map 2, p. 66.)

Addison's anæmia was, however, still relegated to a subordinate position in that group. It was termed the primary form without recognizable cause. It was held, moreover, to be impossible to distinguish it, either during life or after death, from the other anæmias with which it had been grouped ("septic" anæmias, as they will here be designated by the writer, both for clearness and brevity's sake).

Towards the close of the period certain pigment changes, first noted by Quincke (1876), but regarded by him as inconstant and non-pathognomonic, and by all other observers of this period as without any pathogenetic significance, were shown by the author (1885-8) to belong to Addison's anæmia, enabling that anæmia to be recognized and sharply differentiated from the allied forms with which it had been grouped. These observations, with the experimental studies throwing light on the nature and seats of blood-destruction in health and disease, and localizing this process to the portal tract, were at once recognized as "an important stride"; "we now know the seat of the disease"; "a great diagnostic advance"; "dispelling illusions and emphasizing the individuality of the disease"; "the strongest argument in favour of this that has yet been advanced." Being further extended in clinical and pathological directions from 1888 to 1890, they mark the end of this confused ("pernicious") period in the history of the disease, and the commencement of a third period, constituting what may be termed its "Toxic Hæmolytic Period." (*See* Map 1, p. 65.)

Apart from the foregoing brief summary of the outcome of this period in relation to Addison's anæmia, this period is most definitely marked by a truly *pernicious* confusion introduced into the subject by Biermer's work and teaching, and by the ill-judged and all-too-hasty adoption of the name "pernicious" for Addison's anæmia. The account of Biermer in 1871 is here given in full; his earlier account will be found in Chapter X. It will be seen that from first to last they added nothing clinical or pathological to what Addison and other English observers had already described, with the single exception of drawing attention to the

existence of retinal hæmorrhages. And they differed fundamentally from Addison's account in overlooking the essential feature which arrested Combe's and Addison's attention, namely, the absence of sufficient cause for so grave a malady.

In view of Biermer's accounts, and of the interpretation put upon them by the first and chief exponents of his work (Quincke 1876, Müller 1877, and Eichhorst 1878), it has appeared to the author, in the light of the conclusions he has reached regarding the striking individuality of Addison's anæmia, to be almost inexplicable why Biermer's name of "pernicious" should have been so quickly accepted by English observers for the anæmia of Addison. He has therefore closely and repeatedly examined the literature between 1871 and 1880 to ascertain if any cause other than the presumed identity or similarity of Addison's anæmia with Biermer's progressive pernicious anæmia could be found to explain the hasty adoption of the latter name for the former disease. The result of this examination is a curious record of confused conception and self-contradictory statements on the part of Biermer and of Biermer's exponents as to what constituted his anæmia—surely unique in the history of the observation of any disease or group of diseases. (*See* Chapter X.) It is a record of pernicious confusion, which satisfies the author that alike in the interests of historical accuracy, of nosology, etiology, pathology, clinical characterization and diagnosis, the name pernicious should once and for all be dropped in connection with this grave malady, and that it should henceforth, in the interests of Clinical Medicine, bear the title given to it in this work of *Addisonian Anæmia*.

Biermer's Account.

Professor Biermer gave an address on a form of *progressive pernicious anæmia*, often observed by him, *which seemed to be generally associated with fatty degeneration in the circulatory apparatus*, and, in consequence, with capillary hæmorrhages in the skin, retina, brain, meninges, and other serous membranes. He had observed the peculiarities of this form for the last five years, and had already (1868) made a preliminary communication upon it. Since then the number of his cases had increased to fifteen, so that it could be said that the disease, in the Canton of Zürich at least, was not uncommon. It was found amongst *poor* people ; especially in women about thirty years of age, among whom, in addition to poverty, puerperal conditions appeared to be favouring causes. It occurred, however, also among old and young of either sex. The youngest patient was 15, the oldest 52. Insufficient and unsuitable feeding, unhealthy surroundings,

discharges—especially persistent diarrhœa—sometimes also hæmorrhages, usually preceded the disease and caused it. The most common cause, according to his observations, was chronic diarrhœa with and without gastric disturbances. Chlorosis appeared to be but rarely a cause ; it was but rarely also that the disease originated spontaneously—without a cause. Neither with splenic disease nor with malaria had the disease any connection. The *only organic lesions* which so far had been found in some cases, and which might be blamed for the disease, were follicular ulcers of the colon.

The *Symptoms* were the following : (1) *Appearances of Anæmia and Hydræmia.*—Great pallor, poor nutrition, but no disappearance of subcutaneous fat as in cancer or phthisis ; often a yellowish-white complexion without jaundice. In advanced cases, slight general œdema of face, feet, hands ; also some ascites.

(2) The usual *Nervous Symptoms* of anæmia.—Weakness, giddiness, palpitation, &c.

(3) *Digestive Disturbances* consequent on the anæmia.—Anorexia, weak digestion, sometimes gastric discomfort, very often periodic diarrhœa.

(4) *Circulatory Disturbances.*—Bruits in the heart and great vessels, the former so marked as often to raise the question whether valvular disease was present. The bruits were systolic ; usually harsher over the base than over the ventricle, where they were of a more blowing character. The murmurs were not always to be heard at first, but they always appeared later and became stronger. In the arteries of the neck bruits were also to be heard, occasionally also over the jugular vein. If the heart's action were excited, the heart impulse diffused, and the cardiac dulness increased (as was often the case), the picture presented was very like that of a case of cardiac disease, and might, especially as fever was often present, be mistaken for endocarditis. *Post mortem*, however, nothing of the kind was discoverable, but simply partial fatty degeneration of the heart muscle. The heart's action was usually quickened, the impulse diffuse and undulating, never strong.

(5) *Fever* was unessential, but was met with from time to time in nearly all cases ; sometimes very slight, at other times more marked ; without special type, and only for short periods. In one case it was for a time like that of a case of typhoid, and it was for that condition the patient was sent into hospital. Usually it was slight and apparently causeless ; hence in the clinic it was often, for the sake of brevity, termed "anæmic fever." He thought the fever was of a "humoral" character, but considered it also possible that the small hæmorrhages in the body, as also the gastric disturbances, might be causes of it. Definite local causes for the fever were not to be found.

(6) Of interest also were the *retinal hæmorrhages*, which were generally present—even in cases in which there were no subjective symptoms of visual disturbance. If absent in the first instance

they usually appeared later. In one case they were so severe as to cause sudden loss of sight in the left eye. They were to be found *post mortem*, and formed very striking pictures.

(7) *Subcutaneous Hæmorrhages* and *Petechiæ* were not so common. Hæmaturia and epistaxis were only once observed, albuminuria quite exceptionally.

(8) *Capillary Hæmorrhages* in the brain, the subdural arachnoid, and in the pia mater, were, on the contrary, common, sometimes without any characteristic symptoms during life. One patient died of a large capillary hæmorrhage in the brain. Another was seized suddenly with pain in the right arm and leg, impaired speech, right hemiplegia (including facial paralysis), the whole symptoms passing off in half an hour. Delirium was often present in the later stages.

The *course* of the disease was in all cases one of gradual increase of anæmia and hydræmia, appearance and increase of heart symptoms, accidental capillary hæmorrhages, serous effusions, occasional fever, consequent anorexia, and often diarrhœa. Pneumonia and erysipelas were rarer complications. Death occurred in all cases with the exception of one, which left the hospital improved.

Post mortem.—In addition to the anæmia, there was generally found fatty degeneration of the *musculi papillares* of the heart, and of the small vessels—the former explaining the heart murmurs, the latter the capillary hæmorrhages. The papillary muscles appeared yellowish and mottled, the muscle of ventricular wall and septum was often similarly affected. It was exceptional, however, for the fatty degeneration of the heart muscle to be excessive. In the large arteries there was nothing abnormal, or, at most, slight fatty degeneration of the intima ; this latter was more common in the smaller arteries, *e.g.*, of the kidneys ; still more common in the capillaries, especially of the brain. In three cases small flat extravasations were found in the subdural arachnoid, without, however, any sign of pachymeningitis ; they were, therefore, probably purely hæmorrhagic in origin and connected with the fatty changes in the capillaries. The capillary hæmorrhages in the brain, retina, epicardium and pericardium were to be referred to nutritive disturbances in the capillary walls. Both these and the fatty change in the heart-muscle were caused by the altered condition of the blood, and were analogous to the fatty changes caused in tissues by cutting off their blood supply. Liver, spleen, kidneys showed nothing special.

This communication of Biermer aroused great interest among Continental observers. Although never claimed as such by Biermer himself, the condition he described was regarded by Swiss and German observers as a new disease ; and it was under that title of "A New Disease" that the first account of Biermer's observations derived from Professor Immermann (1874) appeared even in English literature in an Editorial comment (1874). Up to

the present time (1903) the title often given to the condition in German literature is that of "Biermer's Anæmia." The condition described under the names of *progressive pernicious anæmia*, *essential anæmia*, *severe primary anæmia*, is stated to have been "both clinically and anatomically first described by Biermer and thereby introduced into pathology: the fame of having firmly grasped and defined with greatest clearness the whole essential symptom-complex of these diseases [*sic*] and having made it known to the medical world belongs to Biermer" (Professor Grawitz, 1896); "The famous address of Biermer forms the starting point of our description of the disease. All subsequent works dealing with progressive pernicious anæmia, as also those which deny to this particular condition the right to be dealt with in a special chapter of pathology, are based, directly or indirectly, consciously or unconsciously, on Biermer's publication" (Professor Ehrlich and Lazarus, 1900).

The best commentary on these reiterated claims regarding the clearness of Biermer's conception and the grasp which he had of the features of this anæmia is that described in later chapters. (*See* VI and X.)

These claims cannot be admitted as in any degree accurate or just. The condition described as "Progressive Pernicious Anæmia," so far as clinical and anatomical features were concerned, was obviously the same condition as that known to English observers as the *Idiopathic Anæmia* of Addison. Addison's account was evidently not known to Biermer or to the earlier observers of *progressive pernicious anæmia*, until attention was drawn to it by Dr. Pye-Smith (1875), one of Addison's own pupils. Biermer's conception was, as will be afterwards made clear, a singularly confused one, even to himself, and the cause of an infinite confusion which has persisted up to the present time. The only merit that can be claimed for it is that while previous contributions to our knowledge had been comparatively few, Biermer's account excited general attention. The great point of difference between Addison's and Biermer's conceptions was in respect of etiology. The notable feature of his "Idiopathic Anæmia," according to Addison, was the absence of any recognizable cause. Biermer, on the other hand, stated of his "progressive pernicious anæmia" that absence of a clear etiology was the exception, and especially emphasized its prevalence among the *poor* classes among whom the ordinary causes of anæmia are most prevalent and most severe. The influence of

this teaching of Biermer was most marked, and has continued to be felt, especially in all German work, up to the present date.

As has just been stated, the immediate effect of Biermer's communication was to arouse great interest. During the next fifteen years a large number of important contributions were made to the subject by Swiss, German, English, French, and American observers. The most notable were : among *Swiss* observers those of Professor Immermann, of Basle (1874 and 1879), and the first monograph on the disease by Dr. Hermann Müller, of Zurich (1877) ; among *German* observers, or in German literature, the extended observations of Professor Quincke, of Kiel (1876, 1877, 1880, 1882, 1883), and the valuable monograph of Professor Eichhorst, of Jena (1878) ; and observations on individual points by Cohnheim (1876) on bone-marrow changes ; Eisenlohr (1877), Scheby-Buch (1876), Rosenstein (1877), Nothnagel (1879), Ehrlich (1880), on blood changes ; among *English* observers, those of Drs. Byrom Bramwell (1877), on the value of arsenic ; Stephen Mackenzie (1878), Samuel Fenwick (1877) on gastric atrophy ; Broadbent (1875 and 1880), Pye-Smith (1875), Habershon (1876), Grainger-Stewart (1876), Frederick Taylor (1876), Coupland (1881), Pye-Smith (1883, with literature), Bristowe (1888) ; among *American* observers, those of Professor Pepper (1875), of Professor Osler (1877 and 1886) on bone-marrow changes and gastritis ; and Kinnicutt (1887) ; among *French* observers, those of Lépine (1877), and Ferrand (1876) ; and among *Norwegian* observers, the valuable monograph of Professor Laache, of Christiania (1883), on the blood changes.

Summary of Observations of this Period (1870-88).

The subordinate position assigned to Addison's "Anæmia" in the heterogeneous group of anæmias termed Progressive Pernicious Anæmia is represented in the accompanying Scheme I, and Map 2, p. 66.

Nomenclature.

"Progressive Pernicious Anæmia." (Biermer, 1871.)

"Idiopathic Pernicious Anæmia." (Pye-Smith, 1875, Mackern and Davy, 1877.)

"Essential Anæmia." (Scheby-Buch, 1876, Lépine, 1876, Ferrand, 1876, Lebert, 1876.)

"Pernicious Anæmia." (Quincke, 1876, Cohnheim, 1876, Stricker, 1877, Rosenstein, 1877, Nykamp, 1877, Quincke, 1877, Eisenlohr, 1877, Fenwick,

1877, Bramwell, 1877, Boucaud, 1878, Nothnagel, 1878, Weigert, 1880, Hampeln, 1880.)

"Essential or Pernicious Anæmia." (Broadbent, 1875, Mackenzie, 1878.)

"Essential Pernicious Anæmia." (Immermann, 1874, 1879.)

"Idiopathic, Essential, or Progressive Pernicious Anæmia." (Mackenzie, 1878.)

"Progressive Anæmia." (Lépine, 1877.)

Conception.—"No ground whatever for separating pernicious anæmia from other forms of anæmia,"—Quincke (1876); "nothing more than a well-characterized group of symptoms which can have very different causes,"—Eichhorst (1878); "nothing more than the highest form of anæmia however produced,"—Immermann (1879), and almost all observers, Bramwell (1877), Mackenzie (1878), Fenwick (1877), Coupland (1881), Eisenlohr (1877), Lépine (1877), Lichtheim (1886), Litten (1887), Rosenstein (1877), Reyher (1887), Runeberg (1886), Nothnagel (1878).

Almost alone among writers of this period, Dr. Pye-Smith (1883) strove to limit the disease to the condition contemplated by its original observers, Combe and Addison. "It is idiopathic, primary, or essential, without any symptoms during life and without any lesions after death which cannot be explained as directly due to the anæmia—not depending on known loss of the constituents of the blood, nor on diminished income, nor on increased destruction of formed elements. Even cases showing bone-marrow changes must be excluded."

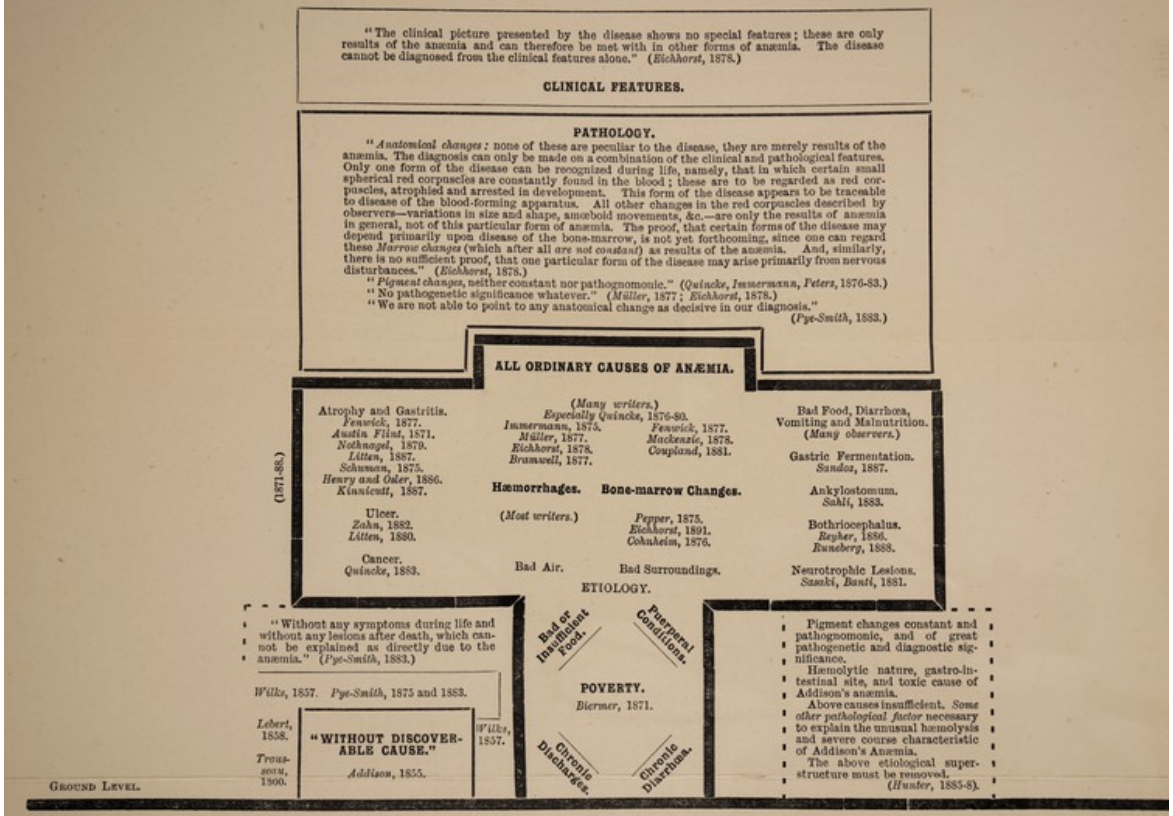
Confusion.—The degree of confusion of this period regarding the features entitling a case to be called "progressive pernicious anæmia" may be illustrated by the following. The chief criterion was held to be "the absence of any symptoms and any lesions other than those due to the anæmia," as Dr. Pye-Smith (1883) pointed out, and all observers, especially Eichhorst (1878), agreed. But within the limits of this agreement they all felt justified in criticizing and, if necessary, arbitrarily excluding each other's cases, in accordance with standards of purity which each observer created for himself. The best illustration of this was, perhaps, that afforded by Eichhorst, who was one of the chief founders and upholders of the view that in addition to the "primary" forms—the Addisonian form occurring without recognizable cause—(17 cases), there were "secondary," "symptomatic," "deuteropathic" forms, due to known causes—(67 cases).

He excluded from this group of secondary forms and classed as "doubtful cases": (1) no fewer than 32 of the cases recorded

SCHEME I.

PERIOD II. (1871-88).

THE EARLIER OBSERVATION AND INTERPRETATION OF "PROGRESSIVE PERNICIOUS ANÆMIA (BIERMER, 1871.)



"PROGRESSIVE PERNICIOUS ANÆMIA." (BIERMER, 1871.)

"A spontaneous origin without clear etiology is the exception." (*Biermer.*)

"The result of the present further observations (on 11 cases) serves to confirm the view expressed in my former—that pernicious anæmia, like anæmia generally, is the product of very various morbid processes and represents the highest form of anæmia. Etiologically there appears to me to be no ground whatever for separating pernicious anæmia from other forms of anæmia (1877, p. 17).

"Pernicious anæmia is essentially a clinical picture." (*Quincke.*)

"The chief merit of Biermer's work—the great and invaluable service he has rendered—is that it *brought together* into one common group and under one title a number of different forms of anæmia possessing certain characteristic features in common (1878, p. 31). One cannot emphasize too much Biermer's statement, '*A perfectly spontaneous origin without clear etiology is one of the rarities.*'"

"From the etiological standpoint there are as many forms of progressive pernicious anæmia to be distinguished as there are causes to be found. It is absolutely necessary that we should hold fast to this statement if we desire to be clear as to the degree and character of the services Biermer has rendered to the subject" (1878, p. 31). (*Eichhorst.*)

"It is a fact that progressive pernicious anæmia attacks especially poor, overworked people. I have not found a case in the literature where the disease has attacked a person living in good circumstances of life (1878, p. 30). . . . One has to distinguish between primary, essential, idiopathic forms (the smaller group) and secondary deuteropathic and symptomatic forms (the larger group)." (*Eichhorst*, 1878.)

"In the latter a feature is the *gross disproportion* between the causes and the effects . . . in short, a *kind of predisposition* is essential to the development of the disease (1891). . . . Secondary progressive pernicious anæmia can be produced by *mental overstrain* and *excessive psychical efforts* alone. In many cases *bad home surroundings*, *bad air* (in factories), *deficient food* (potatoes, coffee) are the cause. Sometimes the disease develops during *pregnancy*, or after *parturition*, without any special complication having occurred. Sometimes *diarrhœa*, *vomiting*, repeated *nose-bleeding*, or *discharges* of any kind—*e.g.*, chronic ulcers of the leg—are causes. Also exceptionally it can develop after *enteric fever* and *syphilis*; Atrophy of Stomach (*Fenwick*, 1877). Gastritis (*Nothnagel*, *Oker*). Cancer of Stomach (*Quincke*, *Eisenlohr*, 1877)." (*Eichhorst*, 1878.)

To face p. 28.

by other observers, including the important cases recorded by Cohnheim (1876), Osler and Gardner (1877), and Pepper (1875) describing the bone-marrow changes now so generally recognized as a typical feature of the purest forms of this condition—Dr. Pye-Smith also stated "that the bone-marrow cases should be excluded"; and (2) no fewer than 19 out of Biermer's 67 cases recorded by Müller (1877).

He excluded even from this last group of "doubtful cases" and classed as "cases with anatomical changes in internal organs and therefore not progressive pernicious anæmia," no fewer than 23 cases described by various observers. Among these cases were one of the two cases recorded by Dr. Pye-Smith (1875), and one recorded by Dr. (Sir) Samuel Wilks (1857)—both of them pupils of Addison himself, four of Quincke's original ten cases, and five more of Müller's cases.

Müller, the author of the first monograph on the disease based on 67 cases from Biermer's clinic, thus fared very badly at Eichhorst's hands; no fewer than 19 of his cases were classed by Eichhorst among the doubtful group, and five were characterized as "non-progressive pernicious anæmia." Quincke's original ten cases (1876) fared no less badly. The only one of them which Eichhorst admitted to his "primary" (*i.e.*, Addisonian) group was Case 8; and this as it happens was the one in which the liver gave no reaction of iron—one, therefore, which in the present writer's judgment was not Addison's anæmia! Case 10, in which the liver gave the reaction of iron, and which was probably a true case, was grouped by Eichhorst among the secondary forms; and the remainder of Quincke's cases were excluded as of doubtful nature, or as not being progressive pernicious anæmia at all.

After a careful perusal of all the cases thus treated by Eichhorst as doubtful, or excluded altogether, the present writer considers that, taken on their merits (and apart from the pigment changes which are not mentioned and which he regards as distinctive), all the cases so classed had as much right to be considered genuine cases of this anæmia as any accepted by Eichhorst.

Etiology.—As the result of Biermer's (1871), and still more of Quincke's teaching (1876-7), a wide departure was made from the original teaching of English observers regarding "idiopathic anæmia." The great majority of observers held that all the ordinary causes of anæmia could produce the condition, and that there was nothing distinctive about it except its severity.

"Etiologically there is no ground whatever for separating it from other forms of anæmia." (Quincke, 1877.) "It can have very different causes." (Eichhorst, 1878.) Among such causes were organic diseases, such as cancer of the stomach (Eisenlohr, 1877); gastric atrophy and gastritis (Fenwick, 1877); follicular ulcers of colon (Biermer, 1871); and bone-marrow changes (Pepper, 1876, Cohnheim, 1877); also all sorts of exhausting processes such as gravidity, poverty, overwork, frequent puerperia, over-lactation, chronic alcoholism, epistaxis, convalescence from typhoid fever; chronic gastric and intestinal catarrh. "These causes were sufficient for most cases. It is not necessary to believe that absence of sufficient cause is characteristic of this disease." (Quincke, 1876.) Poverty of circumstances was in particular a notable cause (Biermer, 1871; Quincke, 1876); in the opinion of Eichhorst the condition was never met in the well-to-do classes. Another important cause was intestinal parasites—*Bothriocephalus latus* and *Ankylostomum duodenale*. (Reyher, 1886; Runeberg, 1887; Lichtheim, 1887; Sahli, 1883.)

In short, the title idiopathic or pernicious anæmia was a sort of provisional shelter for a multitude of cases, possibly of various origins. (Immermann, 1879.)

Yet despite these conclusions, it was noted even by Quincke that all cases were not thus to be explained; that the disease could develop under favourable circumstances of life, and apparently without recognizable cause. These were put into a small group and termed "primary"; while the larger number of cases due to the above recognizable causes were put into a group termed "secondary." (Eichhorst, 1878.)

Symptoms.—These were also held to be in no way distinctive; they were only those of simple anæmia aggravated and intensified. They were not even distinctive as a whole; the disease could not be diagnosed from its clinical features alone (Eichhorst); even those who, with Quincke, held a contrary view that the disease constituted a clinical entity admitted that a picture of the disease in every way complete could be presented by cases of cancer of the stomach, cirrhosis of the stomach, or atrophy of the stomach (Fenwick) or loss of blood.

Morbid Anatomy.—There was likewise nothing distinctive about the disease; it was not due to any one morbid state, or any one anatomical condition; it might be found without any lesions that could not be ascribed to the anæmia itself, *e.g.*, fatty degeneration; it might, on the other hand, be the product of very various

morbid processes, *e.g.*, malignant disease (Eisenlohr, Quincke), bone-marrow changes (Pepper, Cohnheim), atrophy of the stomach (Fenwick, Osler and Henry, Kinnicutt). In short, the disease could not be diagnosed from the anatomical changes alone. (Eichhorst.) "We are unable to point to any definite anatomical lesion as decisive in our diagnosis." (Pye-Smith, 1883.) "Addison's anæmia is idiopathic, primary, essential, without any symptoms during life, and without any lesions after death, which cannot be explained as directly due to the anæmia. . . . With regard to the pathology, such cases show with equal constancy fatty degeneration of the heart, numerous but small internal hæmorrhages and slight passive exudations, but no lesion which cannot be ascribed to the primary anæmia." Acting consistently on this view he even excluded cases showing changes in the red marrow (Pepper and Cohnheim)—"these cases must be separated from those of idiopathic anæmia."

The general view was, that there were two types of the disease; one *primary*, corresponding to Addison's original description, occurring without any lesion which could not be ascribed to the degree of anæmia present (a comparatively small group); and the other, *secondary*, associated with already existing disease (the larger group). One observer only, Dr. Pye-Smith, strove to limit the disease in the sense contemplated by Addison, *i.e.*, to the group called primary. According to him, the disease showed "no lesion which could not be ascribed to the primary anæmia."

The chief pathological observations of this period were those relating to the *blood*, viz., the great degree of oligocythæmia (Quincke, Laache, 1881, and others); the existence of poikilocytosis (Quincke, 1876); the proportionally high hæmoglobin ratio (Ferrand, 1876, Hayem, 1876, Laache, 1881); the presence of abnormal microcytes—"Eichhorst's corpuscles" (Eichhorst, 1878); the presence of nucleated red cells—small and large—"normoblasts" and "megaloblasts" (Ehrlich, 1880-8).

Nature of the Anæmia.—The chief and by far the most important foundation was supposed, by most observers, to be *defective blood-formation*, as evidenced by the poor blood, the misshapen corpuscles, the changes in the bone-marrow described by Pepper and Cohnheim (1877), and the presence of nucleated red corpuscles in the blood, to which special importance was attached by Ehrlich (1880). Quincke's observation (1876) of the presence of pigment in certain organs (liver, pancreas, kidney), *in some cases not in all*, appeared to touch upon another possible foundation, namely, some

"hæmophthisis"—as a feature of "some cases." But the very existence of this particular change was doubted by the few observers who referred to Quincke's observations—still more its importance. "It has no pathogenetic significance whatever, and depends probably on the free administration of iron as a medicine." (Müller, 1877.) "In all of these there is the suspicion that the increase is an artificial one due to the overloading of the liver with iron preparations." (Eichhorst, 1878.) "The condition of the liver noted by Quincke is probably connected with the administration of the drug medicinally" (Mackenzie, 1878, and Coupland, 1881); "perhaps due to local extravasations" (Mackenzie); *neither constant nor pathognomonic* (Immermann, 1878, and Quincke, 1880). "A very common occurrence in different diseased conditions." (Quincke and Peters, 1883.) (*See postea*, p. 104.)

In short, these pigment changes were *without any diagnostic significance* (all observers with one exception). The cases showing them were of "second order"; those of "first order" were due to defective blood-formation. (Quincke.) The anæmia had nothing distinctive about it either pathologically or etiologically. (Quincke.)

> The essential anæmias differed from each other in degree only and not in nature; they were all due to fibrin-ferment intoxication, causing first circulatory disturbances, and then, as a result of these, defective blood-formation. The two chief questions regarding blood-diseases were (1) the place and nature of blood-formation, (2) the importance of hæmoglobin for the whole bodily metabolism, more especially in respect of its power of causing fibrin-ferment intoxication, such as Schmidt had described. In pernicious anæmia we had to do with a blood exceptionally rich in fibrin-ferment, and this explained all its characteristic symptoms. It was through the disturbance in blood-formation alone that the anæmia was to be explained. This explanation applied to other forms of anæmia as well—to certain forms of chlorosis, and primary (simple) anæmia. (Silbermann, 1886.)

Only one observer at this period took a different view of the pathological and diagnostic significance of these pigment changes. In the course of an independent series of experimental investigations regarding the Nature and Seats of Blood-destruction, after extravasation and transfusion (commenced in 1885 without any reference to pernicious anæmia, and, fortunately, without any knowledge of its vexed controversial history), the author stumbled upon a case of pernicious anæmia in the *post-mortem* room. The information which he already possessed *as the results of his experiments* led him

to recognize that the pigment changes which he found in the liver and spleen in that case were something quite unusual. The results of his transfusion experiments showed that these pigment changes were not of an ordinary character such as could be reproduced by transfusion. Their excess and their distribution between the liver and spleen were fundamentally different, and were unlike anything he had previously observed in other diseases. His interest in the disease dated from that day, and has been continuously sustained by the many problems which it has successively presented to him up to the present time.

It was this observation that first aroused his interest in the disease pernicious anæmia, and he incorporated his earlier conclusions in a Thesis (University of Edinburgh, April, 1886). The conclusion he there expressed was, that mere weakness of corpuscles, due to marasmus, such as Quincke suggested, could not explain the excess or the peculiar distribution between the liver and the spleen present in the case. For after his transfusion experiments the spleen constantly contained the great bulk of the pigment, while little or none was to be found in the liver. It seemed to him that some *acute process of destruction of blood* was at work (in the liver), probably as the result of some *chemical agent* possessing, like phosphate of soda, the power, as he found, of causing an unusual deposit of iron in that organ.

> In pernicious anæmia we have to do with an organism whose blood-corpuscles are being destroyed with unusual rapidity. The conclusion seems unavoidable that excessive destruction of corpuscles (in which the liver takes part) is a far more important factor in the production of forms of anæmia characterized by their perniciousness than has hitherto been considered probable or even possible. Confirmation of this view of the pathology of pernicious anæmia can only be obtained by examination of the various organs in a great number of cases, both of pernicious anæmia and other diseases.

The enquiry here outlined was pursued without interruption during the following three years (1886-9), and the results were recorded in his "Investigation into the Pathology" (1888); "Observations on the Urinary Changes" (1889); and "Observations on the Toxic Clinical Features and Nature and Treatment" (1890). The experiments were fully recorded later in his monograph on Pernicious Anæmia in 1900.

Their result was to draw attention to—(1) the constancy and diagnostic importance of the pigment changes; (2) their hæmolytic

nature, with bone-marrow changes secondary to the disease; (3) the nature and seats of blood-destruction in health and in this anæmia; (4) the gastro-intestinal site and toxic cause of this increased hæmolysis; (5) the toxic character of many of the chief clinical features—hæmolytic, gastro-intestinal, febrile and nervous; (6) the probable infective nature of the agencies at work in the gastro-intestinal tract responsible for the poisons formed, and of the lesions (*e.g.*, gastritis) which from time to time had been found in this tract more often than in any other situation. (7) Prominent among the lesions in the case he described (1889) was a peculiar *glossitis* which specially arrested his attention—dating in its origin from a definite exposure to a *drain infection.* To both of these conditions he was led (as the result of his pathological studies and for the first time in the history of the disease) to attach a definite pathogenetic significance, the exact nature of which it became the object of his later studies (1890-1900) to throw light upon.

(*See* Map 1, p. 65.)

CHAPTER IV

Period III (1888-1900).

"*Toxic Hæmolytic Anæmia*" (Hunter, 1888).

"*A Specific Anæmia, of Hæmolytic Nature, Gastro-intestinal Site, Toxic Cause, and Infective Origin.*" (Hunter.)

A Form of Myelogenous (Megaloblastic) Anæmia of Non-specific Nature. (Ehrlich.)

I.

This period (1888-1900) is marked by a steadily increasing interest in the disease, and by numerous and extensive observations relating to its morbid anatomy, experimental pathogeny, chemical changes, clinical features, diagnosis, prognosis, and treatment, influencing materially the conception regarding the nature of this condition and its relation to other forms of anæmia.

This period has to do with: (1) The influence of the pathological and experimental studies of the author (described at the end of the last period and extended in clinical and chemical directions in 1888-90) regarding the essentially hæmolytic nature of Addisonian anæmia, the secondary and compensatory character of its bone-marrow changes, and its independence from the other forms with which it had been grouped (*e.g.*, anæmia of cancer, loss of blood, &c.).

(2) The confirmation and acceptance of this view of the disease at the hands of many English and American observers (especially by Mott in 1890 and Muir in 1894, in respect of the bone-marrow changes), with the result that the individuality of Addisonian anæmia received far more recognition than it had ever previously done, although still under the title of pernicious anæmia given to it in the previous period. This was the case at least so far as English and American observers were concerned, and up to the year 1894-5. (*See postea*, Chapter VI.) (Map 1, p. 65.)

(3) From that period onwards the influences which in the previous period, under the teaching of Biermer, had grouped it with other ("pernicious") forms came once more strongly into force.

In 1892, Ehrlich laid down an entirely new set of criteria for simple and severe anæmias connected with the blood changes which he emphasized as the essential changes, and with the presence or absence of one particular abnormal blood-cell—a large nucleated red cell—the so-called megaloblast. The presence of this he regarded as proof positive of the existence, not only of Addisonian, but of all "pernicious anæmias" (megaloblastic anæmias, as they were termed). The presence of the normal nucleated red cell (normoblast) was regarded as denoting a simpler and more favourable type of anæmia (normoblastic anæmias, as they were called). On this purely hæmatological and morphological basis Ehrlich built up a whole series of new generalizations—clinical, pathological, diagnostic and prognostic—in connection with the so-called megaloblastic anæmias with which Addisonian anæmia was now grouped—and these have received wide acceptance from hæmatologists. (*See* Part VII and Map 1, p. 65.)

(4) The effect on Addisonian anæmia has been to relegate it, according to German interpretation, to a position even more subordinate than it had ever previously occupied. (*See* Map 2, p. 66). The effect on Biermer's historical "pernicious anæmia" has been hardly less disastrous, for Ehrlich promptly identified his whole group of megaloblastic anæmias with Biermer's group of anæmias—"even although this does not correspond clinically with Biermer's anæmia." [*Sic.*] And this identification, strange to say, has been endorsed by German exponents of Biermer's anæmia. (*See* p. 176.)

(5) The author saw the extraordinary and even more *pernicious* confusion which was thereby introduced into the subject. He dissented (on morphological, pathological, clinical, diagnostic, and prognostic grounds, which will afterwards be described) from the interpretation put upon this abnormal red cell as the criterion of Addisonian anæmia, or, indeed, of any other form of anæmia, and from the whole series of generalizations which Ehrlich had based upon its presence or absence. To mark this dissent, his work on "Pernicious Anæmia," published in 1900, recording his studies from 1885 onward, contained no mention of megaloblastic change at all, since it had played no part in his interpretation of the disease; and over 150 pages of his work were devoted to the subject of hæmolysis. In the work of Ehrlich and Lazarus, on the other hand, published in 1899, the subject of hæmolysis in relation to Addisonian and pernicious anæmias alike was dismissed in three paragraphs. The pigment changes were summarily characterized as being probably connected with the tendency to the occurrence of hæmorrhages. (Stockman, 1895.)

(6) The close of the period was marked by the publication (1900) of a fresh set of observations by the author in direct continuation of his former series in 1888-90, emphasizing still further, on etiological grounds, and fresh clinical and pathological grounds, the marked individuality of this disease. These will be described under Period IV. (*See* Map 1, p. 65.)

II.

As regards *conception*, *nature* and *cause* of the disease, this period shows the influence of four sets of studies, more particularly :—

(1) Those of the Author (1888-90)—histological, experimental, chemical and clinical—regarding the hæmolytic nature, gastro-intestinal site, toxic cause, probable infective origin, and specific nature of this anæmia. (Map 1, p. 65.)

(2) Those of Ehrlich (1888-92)—solely hæmatological—emphasizing "megaloblastic degeneration" of the blood and bone-marrow as "the essential changes," and "the cause" of this, as well as other forms of "progressive pernicious anæmia."

(3) The extensive observations of Dr. Schauman (1894, also 1898) regarding the nature of "Bothriocephalus anæmia," and the identity of its blood changes and clinical features with those of Biermer's "pernicious anæmia." (Maps 1 and 2.)

(4) A series of intermediate observations and conclusions, based largely on those of the Author (1888) and Schauman (1894) above mentioned, denoting what is variously termed the "toxic origin," the "enterogenous origin," the "auto-intoxication origin," the "gastro-intestinal origin" of the conditions termed "progressive pernicious anæmia" (various writers, especially Professor Grawitz, 1896-1900) ; or its "hæmorrhagic origin" (Stockman, 1895).

These observations are so numerous that only the briefest historical summary can here be given. The literature alone extends to close on two hundred papers.

The following is a brief summary of the chief of these observations in the order of their publication :—

(1) *Histological Studies*, regarding the constancy and pathognomonic importance of the pigment changes, by the Author (1888), William Russell (1889), Mott (1889-90), Crozier Griffith and Burr (1891), Osler (1892), Gowland Hopkins (1894), Warthin (1901), and many other English and American observers ; by Stühlen (1895), a pupil of Quincke, as almost the sole German observer, reaffirming the conclusion always held by Quincke (1876), that these pigment changes were "neither constant nor pathognomonic."

(2) *Experimental Studies*, by the Author (1888), regarding the nature and seats of blood-destruction in health and in pernicious anæmia, the hæmolytic nature, toxic cause, and gastro-intestinal (portal) site of this anæmia ; Schauman and Tallqvist (1898), regarding the toxic and hæmolytic action of substances extracted from the bodies of the intestinal parasite *Bothriocephalus latus;* Muir (1901) and Bunting (1905), regarding the bone-marrow changes.

(3) *Chemical Studies*, by the Author (1889), regarding the excretion of aromatic sulphates, diamines, urobilin and iron in the urine, and the presence of iron in the liver, kidney and spleen ; by Mott (1889-90), regarding the excretion of urea, uric acid, urobilin in the urine, percentage of iron in the organs ; by Hopkins (1894), regarding the excretion of aromatic sulphates and of iron in the urine, and percentages of iron in the organs in five cases ; by Stockman (1895), recording a very extensive series (twenty-one) of analyses of iron in the organs in various diseases, including two cases of pernicious anæmia ; by von Noorden (1890), Grawitz (1896), Ewald (1896), Martius (1897), and others, regarding deficiency of HCl in the gastric juice—*achylia gastrica*—as a feature of the disease ; also Stewart (1895) ; Einhorn (1892).

Hæmatological Studies of a most extended kind regarding every feature of the blood changes : poikilocytosis, leucopenia, variety of the leucocytes, the degenerative changes (polychromatophilia) presented by the red corpuscles (many observers) ; and more especially the variety of nucleated red cells—normoblasts and megaloblasts—and their special significance as denoting a myelogenous origin and a "megaloblastic degeneration" as the chief pathological and pathognomonic manifestation of it—(Ehrlich, 1888-92 ; Müller, 1893 ; Askanazy, 1895 ; Schauman, 1894 ; Engel, 1898 ; Lazarus, 1900) ; Gulland, 1905 ; Cabot, 1901. Among other studies of the blood must specially be noted a series of original observations by Haldane and Lorrain Smith (1898-1900) regarding the volume and oxygen capacity of the blood in this anæmia, showing that the volume of blood varies enormously.

Bone-marrow changes, by Rindfleisch (1890), by Mott (1890), Ehrlich (1892), but especially by Muir (1894), the most extensive studies relating to the character of the bone-marrow changes. Also Müller (1893), Askanazy (1895), Engel (1898), and Pappenheim (1896), and most recently Bunting (1905).

Clinical and Critical Studies regarding the clinical features and pathology of the disease, by the Author (1889), Hale-White (1890),

MacPhedran (1891 and 1892), Stephen Mackenzie (1891), Bristowe (1890), Ewald (1896), Grawitz (1896), Grainger Stewart (1894), Gibson (1894), Cabot (1896), and especially Coupland (1898), and Stockman (1895), Birch-Hirschfeld (1892), Ehrlich (1892), Lazarus (1900), Colman (1900), Gulland (1905), Adami (1900).

The association of anæmias with *nervous lesions* and *symptoms*, by Minnich (1892), James Taylor (1895), Nonne (1893), Bowman (1894), Burr (1895), Putnam (1891), Dana (1891), Colquhoun (1896), Russell (1898), Bastianelli (1896), Lloyd (1896), J. M. Clarke (1897), A. W. Campbell (1898), Matthes (1898), Burr (1898), Jacob and Moxter (1898), Juliusburger (1898), Goebel (1898), Mott (1900), Nonne (1899), Putnam and Taylor (1901), J. M. Clarke (1904), Taylor (1904), Russell, Batten and Collier (1890).

The *Nature of Bothriocephalus Anæmia* and its relation to "progressive pernicious anæmia": important studies by Schauman (1894), and Schauman and Tallqvist (1898), Dehio (1892), Wiltschur (1893), Eckert (1893).

Etiological Studies regarding the infective nature of the glossitic, gastric and intestinal lesions associated with Addisonian Anæmia (Author, 1900-3); and *Historical Studies* regarding the relation of Addisonian Anæmia to Progressive Pernicious Anæmia (Author, 1903-7).

The Unity or Plurality of Addison's Anæmia.

The results of this period as regards the *conception and pathogeny* were the following :—

The Unity of the Disease. (Map 1, p. 65.)

"A specific form of anæmia, of hæmolytic nature, gastro-intestinal site, toxic cause, infective origin, and characteristic clinical features and course." (Hunter, 1888-90.)

"A specific form of anæmia consisting in hæmolysis, probably induced by toxic agents absorbed from the gastro-intestinal tract." (Coupland, 1898, and most English and American observers, 1889-1900.)

The Plurality of the Condition. (Map 2, p. 66.)

"Not a disease *sui generis*, but a mere group of symptomatic conditions, of mixed nature—hæmogenic or hæmolytic; due to many causes; of myelogenous origin (Ehrlich, 1892, and others); of enterogenous—auto-intoxication—origin (Ewald, 1895; Grawitz, 1896-1901, and many others); of parasitic origin (Schauman and many others); of hæmorrhagic origin (Stockman, 1895); "having the clinical features described by Biermer and the blood

changes (megaloblastic) described by Ehrlich (Ehrlich, Schauman and most German observers); produced by many causes; one group—*secondary*—being produced by all sorts of known causes, but another group the *primary*—still mysterious in origin. "After all these cases have been dealt with (due to obvious causes), we have still to deal with cases of pernicious anæmia in which not a single point can be got out of the history throwing any light on the origin of the disease; in which neither clinical observations nor necropsy reveal any changes in the organs to which the severe disease can be referred—"primary," "essential, cryptogenetic anæmia. *It is not to be doubted that even among these are many forms differing entirely from one another in their origin and pathogenesis.*" (Lazarus and Ehrlich, 1900.)

The Unity of Addison's Anæmia.

The chief effect of the hæmolytic studies of this period was to largely re-establish the original conception as to the "unity" of the disease. This will be shown later by extracts from the conclusions of representative English and American observers well acquainted with the disease, both in the preceding period (1870-88) and in this period. (*See* Chapter VI; also Map 1, p. 65.)

It will be seen from these how much the steadily increasing belief in the *unity* of Addison's anæmia is intimately bound up with the degree of acceptance of the writer's studies (1888) regarding the constancy and special characters of its hæmolytic changes, their gastro-intestinal site, and toxic character.

The chief point of interest is that all observers (and the number is large) who have been able to confirm his observations and the still larger number who have been able to accept his conclusions—even those who disagree with them (Henry, 1889)—have seen in the class of facts relating to hæmolysis "the strongest argument in favour of this anæmia being an independent form of disease characterized by hæmolysis." (Henry, 1889.)

The history of the subject shows that the different interpretations put by Quincke (1876-83) and Hunter (1885-88) respectively, upon the pigment changes—the former denying, the latter asserting their constancy and pathognomonic importance, have had as much influence on the later work and conception as the original widely different etiological conclusions of Addison and Biermer. This will be brought out clearly in a later section.

(*See* Chapter XII.)

As regards *Etiology*, the conclusion come to by the writer (1888) that the hæmolytic changes in the disease were constant and

distinctive, "marking it off from other forms of anæmia clinically resembling it," has from first to last been the basis of his view, that this anæmia is not due to ordinary causes, but is of a special character ; it has prevented him seeking for its causes in ordinary factors, such as operate in general anæmia ; it has led him to look for some deeper causes, and keep his attention fixed on those forms of anæmia admitted by all to be "without discoverable cause," "primary," "cryptogenetic" ("Addison's Anæmia").

The position assigned to Addison's anæmia in the group of severe anæmias by the writer since 1888—as the outcome of the various studies he has given to the subject during the past twenty-one years—is represented diagrammatically in the Frontispiece Scheme ; and the character of the observations is represented and detailed in Scheme II (and described by other observers, p. 57).

The Author's Conception.

SCHEME II.

It will be seen that the whole superstructure of *etiology* built upon Biermer's foundation has been removed ; that most of the conditions and disturbances, *e.g.*, gastric and intestinal lesions, diarrhœa, &c., regarded as causes, are really effects of the infective agencies underlying the disease—they belong to the *pathology* of the disease and not to its etiology ; that the *clinical* features include the various disturbances in the gastro-intestinal tract which have been regarded as causes, and in addition a very definite group of hæmolytic symptoms which have been and constantly are overlooked, as also a very definite and constant group of *febrile* and *nervous* symptoms denoting the effect of the toxins of the disease on the body and the nervous system respectively.

Underlying all this great pathological and clinical characterization are the *infective factors* indicated at the bottom of the Scheme. One of them—the *septic*—is common to this and many other severe anæmias according to the author's observations ; the other is a *specific infection* of drain source, whose contraction is almost immediately marked by the *hæmolytic* and *glossitic* (or gastric or intestinal) lesions characterizing the disease.

The result is to satisfy him that Addison's anæmia is in truth a very remarkable disease, of a *specific infective hæmolytic nature*, in which both clinical observations and necropsy reveal definite hæmolytic and infective processes as a constant feature of the disease, and in which a very definite series of points can be got out of the history throwing light on the mode of origin of the disease, the source of the infection in the alimentary tract, and the lesions of the tongue, stomach, and intestine connected with it.

Infective Nature.—It is not merely a special form of anæmia, but a definite specific, hæmolytic, *infective disease*, localized to the alimentary tract — with characteristic mode of onset, clinical features and course, hæmolytic and infective lesions.

Symptoms.—So far from the *anæmia* being the sole feature of the disease and the cause of all its symptoms, there are *always* four other groups, *hæmolytic*, *gastro-intestinal*, *febrile* and *nervous* —striking and characteristic, and far more instructive than the actual anæmia—caused not by the anæmia itself but by the infective agencies underlying the disease.

In my experience they are to be found in combination in every case of Addisonian anæmia ; they are all related to one another, although sometimes one or other may be specially prominent ; and they have one marked feature in common, namely, *periodicity*—the same feature which, as can be seen, characterizes the activity of the local lesions presented by the tongue. (Stomach and intestine.)

Etiology. — The conclusion come to by Biermer, so largely accepted by nearly all later observers—namely, that all ordinary causes of anæmia are potential causes of this disease, if only they are severe enough—has, in my experience of the disease, neither clinical nor pathological basis. (1) The disease cannot, in my experience, be produced by ordinary anæmia-producing factors, *not even by sepsis*, however severe, and cases of this kind can be successfully excluded, both during life and after death, by the absence of the characteristic groups of symptoms and pigment changes I have described. (2) According to my observations, not one of the many causes above described are capable, however severe, singly or collectively, of producing the *whole* features and lesions of Addison's anæmia. Consequently, not one of them can be regarded as the real cause of that anæmia. The great majority of these so-called "causes" are really symptoms and effects of the infective processes underlying the disease. The etiological superstructure built upon Biermer's foundation represented in the accompanying schemes (Schemes I and III) must therefore be removed.

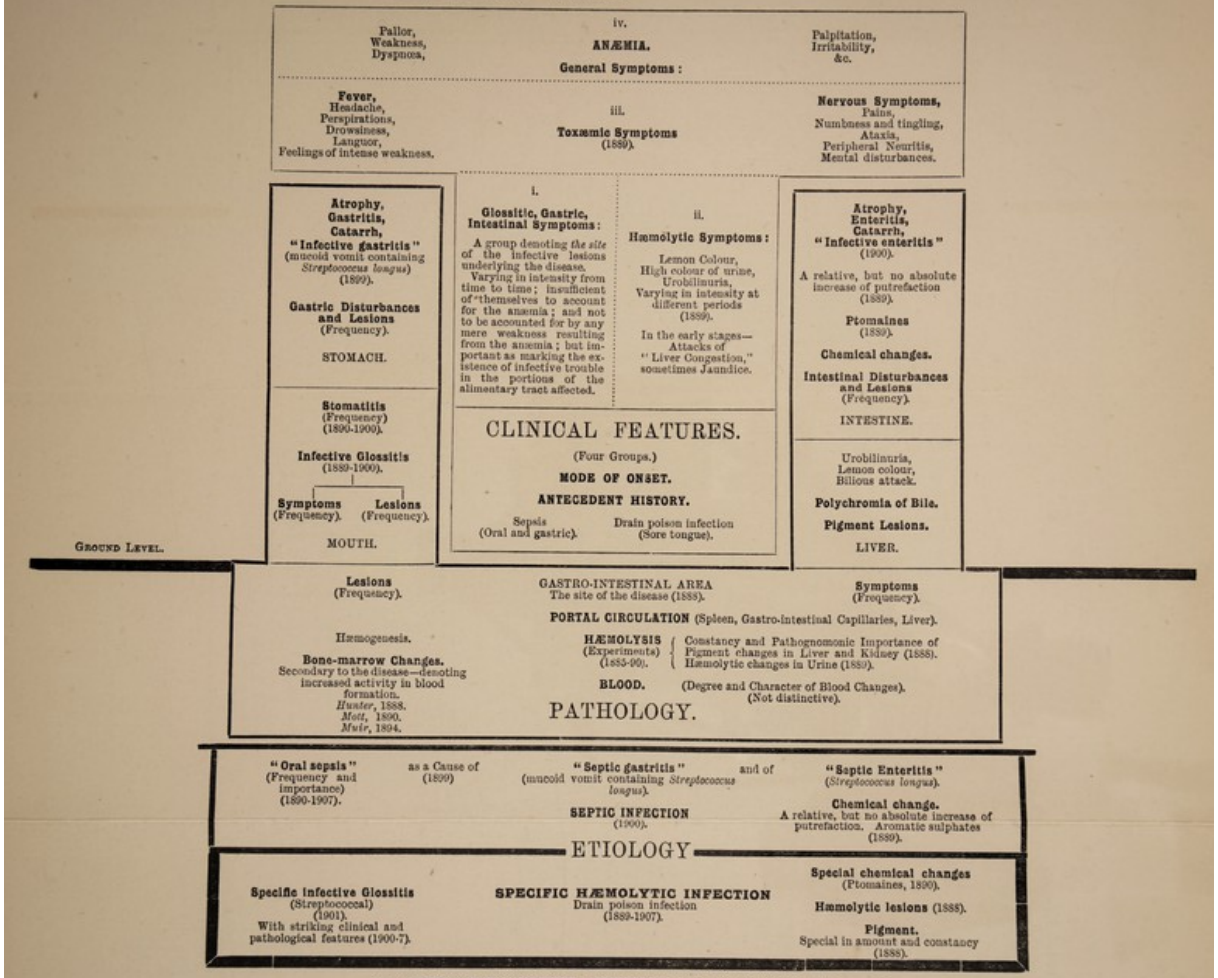
My endeavour has been to expose more and more the bed-rock of hæmolysis underlying Addison's anæmia (1888-1900).

The result has been not only to expose this but to reveal two sets of infective factors : (1) A *specific* (hæmolytic) *infection* whose site and lesions (the tongue, stomach, and intestine), approximate time of contraction, and probable source I have been able to

SCHEME II.

THE OBSERVATION AND INTERPRETATION OF ADDISON'S ANÆMIA. (HUNTER, 1885-1903.)

Period 1. "Its Unity, Hæmolytic Nature, Gastro-intestinal Site, Toxic Cause, and Toxic Clinical Features." (1885-90.)
Period 2. "Its Infective Origin and Lesions." (1890-1903.)



"A SPECIFIC INFECTIVE (HÆMOLYTIC) DISEASE." (HUNTER.)

Biermer's etiological foundation is weak both clinically and pathologically, and the superstructure built upon it by later observers (*see* Schemes I and III) must be removed (*see* p. 79); and replaced by new facts and old facts in new relations, as summarized in above Scheme.

The disease is a specific entity; the *primary etiological factor* is a *specific hæmolytic infection* of drain source, giving rise to a specific infective glossitis, gastritis, and enteritis, with sepsis of the alimentary tract as a potent predisposing factor. The *pathological edifice* raised upon these foundations is special, constant, and pathognomonic, and comprises (1) lesions in the gastro-intestinal area; (2) hæmolysis occurring in the portal circulation and evidenced by pigment changes in the liver and kidney, and hæmolytic changes in the urine; and (3) changes in the bone-marrow, denoting increased hæmogenesis. The *symptoms* are characteristic and can be arranged in hæmolytic and gastro-intestinal groups, which are inseparable from the pathological conception of the disease, and are surmounted by groups of symptoms referable to toxæmia (viz., fever and nervous disturbances) and anæmia respectively.

The essential changes of Addison's anæmia are not blood changes any more than the fever or diarrhœa is the essential change in typhoid fever; or any particular manifestation of scarlet fever—for example, angina, rash, or desquamation—the essential change in that disease. To so regard them is to miss the whole striking clinical, pathological, and infective characterization presented by this disease.

To face p. 42.

lay partly bare ; and (2) while doing this to lay completely bare a great stratum of *septic infection* traversing the foundations of Addison's anæmia and forming to a large extent the foundation of those forms of severe anæmia ("*Septic Anæmia*") which often clinically resemble Addison's anæmia (*see* Frontispiece), but differ from it by not presenting the hæmolytic or bone-marrow changes characteristic of Addison's anæmia. This septic type, according to my observations, is one of the commonest and most overlooked forms of anæmia. In varying degrees it frequently complicates other forms of anæmia (cancerous, loss of blood, nephritic, intestinal, &c.), giving them an intensity and a character which clinically resemble Addisonian anæmia. The severest forms are in my experience the most pronounced of all anæmias—they are more commonly mistaken for Addisonian anæmia than any other form. The characters of this anæmia will be fully described in a later section of this work. (*See* p. 82 and vol. ii.)

Plurality of Addison's Anæmia.

The opposite teaching regarding the *plurality* of all so-called "pernicious anæmias," including Addison's anæmia, is based upon (1) Biermer's and Quincke's etiological work ; (2) denial of the constancy and pathognomonic importance of the pigment changes ; (3) the hæmatological studies of Ehrlich regarding "megaloblastic degeneration" of the blood and bone-marrow denoting reversal to an embryonic type of blood formation as the chief criterion of "pernicious anæmia" ; (4) the studies of Schauman (1894) regarding bothriocephalus anæmia. This teaching is the prevailing one among Continental observers, *e.g.*, Birch-Hirschfeld (1892), Wiltschur (1893), Schauman (1894-1900), Ewald (1896), Eichhorst (1898), Ehrlich and Lazarus (1900), Grawitz (1896-1901), Ziegler (1902) ; and its influence is also shown in the conclusions of certain English and American observers, viz., Stockman (1895), Bramwell (1899), Henry (1889), Pepper and Stengel (1896), Gulland (1905), Osler (1903) ; Ewing (1904).

All who have adhered to the conclusion of Quincke that the pigment changes are not distinctive, but only denote hæmolysis as a feature of *some* cases ; or regard them as the result of extravasations (Stockman, 1895 ; Lazarus, 1900) ; or make no mention of them in their cases (Grawitz, 1896, and most German observers) ; or regard disturbance in blood formation as the essential feature of the anæmia with or without an increased

destruction (Russell, 1889 ; Earl and Purser, 1889 ; Henry, 1889 ; Ehrlich, 1892 ; Grawitz, 1896 ; Ewing, 1904 ; Gulland, 1905 ; Eichhorst, 1891 and 1898) ; all these observers have continued to regard the disease as merely "a group of symptoms, not an etiological unity" (Schauman, 1900) ; "not a disease *sui generis*, but a frequently occurring group of symptoms met with in very different conditions of disease" (Lazarus, 1900) ; "the result of well-recognized debilitating causes aggravated by bleedings" (Stockman, 1895) ; "a clinical condition — any profound and apparently causeless anæmia characterized by peculiar alterations in the blood and tending to pursue a progressive or pernicious course" (Bramwell, 1899) ; "a form of cachæmia which may arise from causes known or unknown" (Pepper and Stengel, 1896).

This conception is specially asssociated with the work of Ehrlich.

The position assigned to Addison's anæmia by Ehrlich (1892), Schauman (1894, 1898), Grawitz (1896 and 1901), many English (Stockman, 1895, Gulland, 1905) and American observers, is an even more subordinate one than that given to it by the first German observers of progressive pernicious anæmia. This position is shown in Scheme III, and in Map 2, p. 66.

SCHEME III.

It will be seen that the *etiological superstructure* is more imposing than before, and that it has been increased by a big slab variously entitled "Toxic," "Enterogenous," "Auto-intoxication"—admittedly largely taken from the present writer's work in 1888. The *pathological portion* has undergone change, great pathognomonic importance being attached to *megaloblastic degeneration* in the blood and in the bone-marrow as the "essential" feature not only of Addison's anæmia but of a whole group of other so-called megaloblastic anæmias.

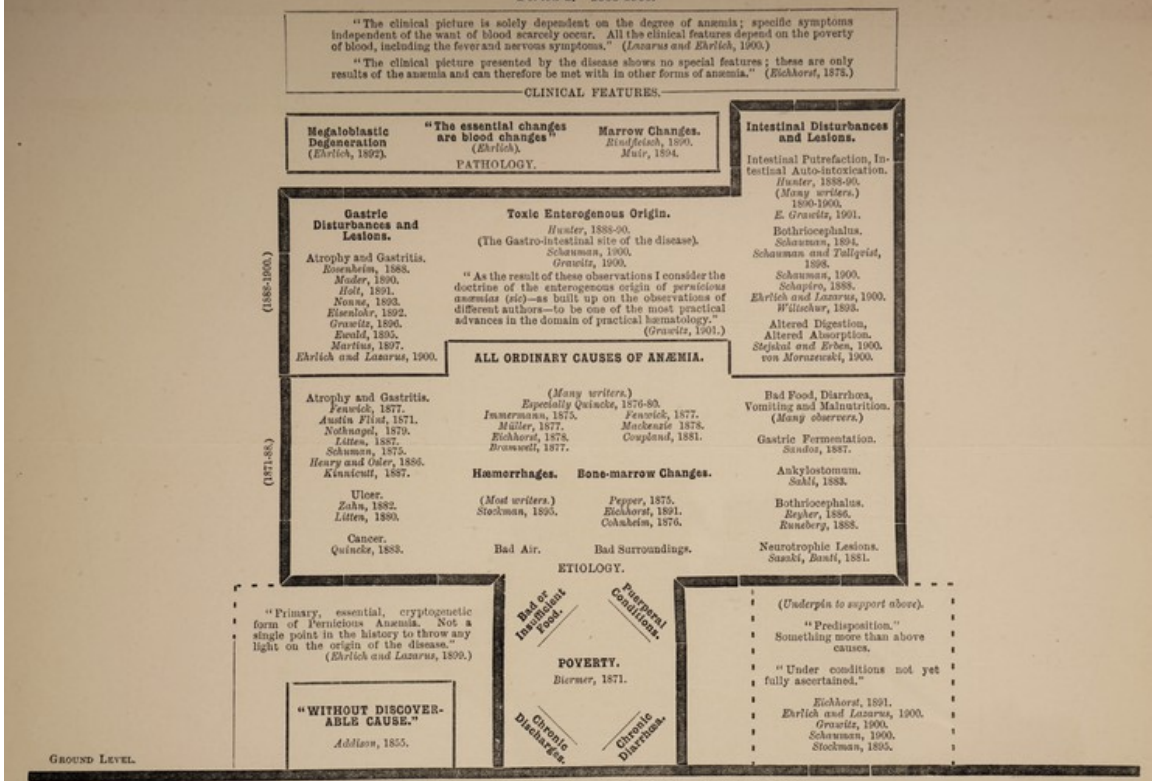
It will be seen that what they term the primary, essential, cryptogenetic form of "progressive pernicious anæmia" is relegated by them to a subordinate position ; and the degree of information possessed regarding it as the outcome of the extensive hæmatological observations of the last fifteen years, to which Ehrlich, German observers, and most English and American observers attach special importance, is thus described in Ehrlich and Lazarus's work (1900) :—

> The form of anæmia in which not a single point can be got out of the history to throw any light on the origin of the disease—in which both clinical observation and necropsy fail to reveal any changes in the organs to which this severe disease can be referred.

SCHEME III.

LATER OBSERVATION AND INTERPRETATION OF "PROGRESSIVE PERNICIOUS ANÆMIA" (1888-1900).

Period 1. 1871-1888.
Period 2. 1888-1900.



"PROGRESSIVE PERNICIOUS ANÆMIA." (BIERMER, 1871.)
"MEGALOBLASTIC ANÆMIA." (EHRLICH, 1892.)

Professor Grawitz (1896-1901):—

"The view that absorption of toxic products from the digestive tract is the cause of primary anæmia is represented chiefly by W. Hunter on the ground of clinical and experimental observations. According to Hunter, there occurs in pernicious anæmia a *destruction of red corpuscles in the capillaries of the portal vein*—probably produced *by the absorption of toxic substances from the stomach and intestine*—possibly as the result of bacterial action." (1896.)

"I consider the difference of pernicious anæmias from simple forms of transitory anæmia is due to the malignant direction taken by blood formation."

"That there are many points still dark in this difficult subject is certain—notably the *extraordinary persistence and progression of the disease* after, *to all appearance, the cause is removed*. As is known, Ehrlich (*Verhandlungen des Vereins für Innere Medizin*, 1899, p. 227) refers this to the anatomical changes in the bone-marrow as evidence either of megaloblastic degeneration or failure in regenerative function." (1901.)

Professor Ehrlich and Dr. Lazarus (1899):—

"The famous address by Biermer (1871), in which the name 'progressive pernicious anæmia' was first used, forms the starting point for our description of the disease. . . . Under this symptom-complex Biermer thus *groups together* essential, idiopathic, primary conditions of anæmia with those of known etiology and pronounced secondary character. . . . *The essential changes* which define progressive pernicious anæmia are *blood changes*. According to Ehrlich the blood of typical cases of pernicious anæmia differs from that of simple anæmia in showing, more or less numerously, red corpuscles which exceed the normal in size, whereas in simple anæmia only red corpuscles are met with whose diameter is normal or smaller than usual. The appearance of megalocytes in the blood, as also the appearance of their nucleated precursors the megaloblasts, show that *the regeneration of the blood is no longer following its usual physiological course*—it is following a type never found under normal circumstances in adults, a type resembling that found in embryonic life (p. 91). These distinctions are so important and far-reaching that it becomes necessary to separate the megalocytic and megaloblastic anæmias from the normocytic and normoblastic, *even if this division does not correspond clinically with Biermer's division of pernicious anæmia from other forms of anæmia*. We come, then, to the result that we are here concerned with the conditions characterized by the features described by Biermer and Ehrlich. But we *must continuously keep in mind that we have not to speak of a disease sui generis*, but a frequently occurring group of symptoms met with in very different conditions of disease (p. 92). . . . In diagnosis the point of greatest importance is to discover megaloblasts in the blood. Their discovery often requires great patience. A positive result—the presence of undoubted megaloblasts in conjunction with an increase of megalocytes—is *proof positive of the existence of pernicious anæmia*; since it demonstrates without doubt that the *blood formation* in the *bone-marrow is following a type which is abnormal for adults*."

Dr. Schaumann, "*Pernicious Anæmia in the Light of Modern Toxic Hypothesis*" (1900):—

"As regards the term 'pernicious anæmia,' I hold the same views as Immermann, Quincke, Lichtheim, Müller, and the other authors who consider that the disease is not an etiological unity but only a symptomatic group which can be produced by causes of all kinds. I regard, therefore, as pernicious anæmia not only the so-called idiopathic, or primary, or better, cryptogenetic cases where the disease develops without any recognizable cause, and apparently spontaneously, but also those in which a definite etiological cause for the anæmia is to be found. Among such causes are the following: (1) Intestinal parasites; (2) gastro-intestinal disturbances of all kinds; (3) pregnancy and puerperium; (4) repeated hæmorrhages; (5) infective processes (syphilis, malaria, enteric fever); (6) intoxications (carbonic-oxide poisoning). If I have to define my position in a few words—I consider that we must regard as pernicious anæmia those cases of severe anæmia which correspond to the clinical picture described by Biermer and possess the blood condition described by Ehrlich, irrespective whether such cases occur in individuals previously healthy, or in those already affected with disease, and irrespective whether the anæmia runs a fatal course or not (p. 233)."

The Author's Conclusions.

So far as Addisonian anæmia is concerned, the great etiological superstructure built upon Biermer's foundation must be removed. (*See* pp. 41, 42, 70, 79.)

The clinical, megaloblastic, diagnostic and prognostic criteria above described are inaccurate and misleading, and seriously interfere with its early diagnosis and its effective treatment. (Pp. 72 and 172.)

To face p. 44.

CHAPTER V

Period IV (1900-8).

"*Addisonian Anæmia—a Specific Infective Disease.*" (Hunter.)

Early in 1900 a fresh set of observations were recorded by the Author, and extended and confirmed by a further series in 1903, in direct continuation of his former series in 1888-90. These related to: (1) *certain infective lesions* (glossitic, gastric and intestinal) present in Addisonian anæmia; and (2) the important part played by a form of *sepsis* hitherto completely overlooked (namely, that derived from the mouth—"Oral Sepsis," as he designated it) as a great factor in causing lesions and catarrhal conditions of the stomach and intestine ("septic gastritis" and "septic enteritis" respectively) favourable to the contraction of Addisonian anæmia. (This sepsis is itself the cause of a common form of anæmia—"Septic anæmia," as the author has entitled it.) Not producible by this sepsis, and once it is contracted persisting even after complete removal of the "oral sepsis," he found a peculiar condition of *Glossitis* of an infective nature accompanying Addisonian anæmia, coming and going in the most persistent manner, and always marked by increased hæmolysis and by exacerbations of the anæmia. To this glossitis he has attached great pathogenetic significance, which it will be the object of this work to make clear. The result of the further observations on seventy-five cases of the disease is to satisfy him of the great individuality of this anæmia and its title to rank among the group of specific infective diseases. Its relation to other forms of anæmias is represented in Frontispiece Scheme.

The general character and scope of the observations may here conveniently be brought out by the following account by Professor E. Grawitz. (The words in brackets are the present writer's additions.)

("Zur Frage der enterogenen Enstehung schwerer Anämien," *Berlin. klin. Wochenschr.*, June, 1901.)

> The subject of the origin of pernicious [Addisonian] anæmia has been recently enriched by observations of W. Hunter, who in a series of such cases has found

> [a peculiar recurrent and infective] inflammation of the [tongue and] mucosa of the mouth, and has brought these inflammations into etiological relationship with pernicious [Addisonian] anæmia. As is known, W. Hunter was the first to draw attention to the destruction of corpuscles caused in the portal circulation by the absorption of toxic products from the intestine. As a sequel and outcome of this view he considers that [the infection responsible for] this severe [recurrent] stomatitis [and glossitis] is swallowed, infects the stomach and intestine [creating local infective lesions, difficult to detect *post mortem* on account of the extreme bloodlessness of all the tissues, but visible in the tongue during life], the poisons of which become absorbed and act destructively on the blood-corpuscles. These infective processes, he considers, explain the occurrence of the fever symptoms met with in pernicious [Addisonian] anæmia, as also the atrophy of gastric and intestinal glands met with in many cases of pernicious [Addisonian] anæmia.
>
> Hunter accordingly defines pernicious [Addisonian] anæmia as a chronic infective disease, caused by infection of certain parts of the digestive tract, especially the mouth [tongue], also the stomach and intestine; and he goes so far with this thought as to recommend in treatment the use of antistreptococcic serum along with local treatment of the mouth, stomach and intestine.
>
> My own experience is that no general significance can be attached to these mouth inflammations in this relation [special *glossitis*], since in the relatively large number of cases which have come under my notice I have not met with a single case in which there has been any noteworthy primary stomatitis [*glossitis*]. On the other hand, secondary stomatitis, with severe hæmorrhages into the gums, can arise in pernicious anæmia as the result of the general cachæmia prevailing.

(*Compare* Chapter XV, p. 114.)

The whole subject of the historical development of this disease may be concluded by the following opinions (1903) of an observer acquainted alike with its origin and its latest developments—the late Sir William Gairdner, of Glasgow—who wrote as follows (1903):—

> I feel personally much *edified* by your two papers in the *Lancet* (1903), the last of which I have just read. The dim and distant beginnings of my own knowledge of the subject extend back to the time when I was doing "Periscope" (Reviews) for the *Edinburgh Monthly Journal of Medical Science*; and somewhere away back in the late forties (1849) there is to be found an abstract of Addison's

paper on suprarenal disease which brings in the "Idiopathic Anæmia" idea. And although in my *Clinical Medicine* in 1862 I have alluded to several cases which I believed, and believe, to be of this kind, the elaborate memoir of Biermer (*i.e.*, Müller) found me unprepared to do more than look with vague astonishment on the vast superstructure he had erected, and which I was disposed to attribute to local predominancy in his field of observation of what I held to be a rare and very peculiar disease. I now see exactly what it really was—that the peculiar German faculty of working up *casuistic* in forms determined *a priori*, led Biermer astray as it has done many others. All that I have seen personally since then makes generally for your view of the case; although I have not seen quite enough to lead me to generalize on this subject, and am not likely now, in retirement at 79 years of age, to do any more upon the subject.

The name of Addison's Anæmia, had it been adopted generally in this country and on the Continent, would have saved a world of trouble—as the provisional name of "Bright's Disease" did, in its day, and does to some extent even now. I wish I could say I had taken note of the *glossitic* phenomena you describe, but I am afraid I am of the number of those who have passed over things very much within view, and shall now have no opportunities of repairing my omissions. If you can make that point, *i.e.*, the *glossitis*, clear, as being of the frequency you describe, you will have won your case as against all gainsayers."

(For sequel, *see* Chapter XV, p. 114.)

Summary.—The first period (1820-70) in the history of this disease may be fittingly designated that of "Idiopathic Anæmia"; the second (1870-88) that of "Idiopathic Pernicious Anæmia," and the third (1888-1900) that of "Hæmolytic and Toxic Anæmia." The period now entered upon will best find its appropriate name in that of "Addisonian Anæmia." This is the title which, in the writer's judgment, best connotes this remarkable disease historically, clinically, and etiologically. The title "Progressive Pernicious Anæmia" connotes, on the other hand, as will presently be seen (Chapter X), nothing but confusion—historical, etiological, clinical, pathological, diagnostic and prognostic—without its equal in the history of any disease or group of diseases. In the interests of clinical medicine the term "pernicious" should once and for all be dropped.

PART III

ETIOLOGY AS THE CHIEF PROBLEM OF THE DISEASE

CHAPTER VI

Relation of Addisonian Anæmia to other Forms of Anæmia.

The position assigned to Addisonian anæmia in relation to other forms of anæmia by representative observers is summarized in the following section.

Period I (1822-70).

(1) Dr. Combe (1822) :

- Anæmia
  - Symptomatic
  - ? *Idiopathic* — "A very peculiar disease. . . . If any train of symptoms may be allowed to constitute Anæmia a generic disease, the following may be considered an example of it in its *most idiopathic form.*"

(2) Dr. Addison (1855) :

- Anæmia (*Etiological*)
  - Ordinary — *Causes:* Loss of blood. Exhausting diarrhœa. Chlorosis. Purpura. Renal disease. Miasmatic disease. Glandular disease. Strumous disease. Malignant disease.
  - "*Idiopathic Anæmia*" (Addison's Anæmia) — "Without any discoverable cause whatever — apart from usual causes of the anæmic state. . . . A very remarkable disease."

PERIOD II (1870-88).

(3) PROFESSOR BIERMER (1868 and 1871):

"PROGRESSIVE PERNICIOUS ANÆMIA."

Anæmia (*Clinical and Anatomical*) — Secondary — Idiopathic — "Some cases of idiopathic and secondary anæmia *complicated by fatty degeneration of the heart and blood-vessels.*" (1868.) — "Found amongst *poor* people, especially among women among whom, in addition to poverty, puerperal conditions appear to be favouring causes. Insufficient and unsuitable feeding, unhealthy surroundings, chronic discharges — especially persistent diarrhœa — sometimes also hæmorrhages, usually preceded the disease and caused it. The most common cause according to his observations was chronic diarrhœa, with or without gastric disturbance. *A spontaneous origin without clear etiology is the exception.*" (1871.)

(*a*) *Opening words of Biermer's account* (1871):—

"Professor Biermer gave an address on a form of *progressive pernicious anæmia*, often observed by him, *which* was *complicated* by *fatty degeneration in the heart and vessels.* He had already described the peculiarities of this form of disease in a preliminary communication in 1868. It was only rarely that the disease originated spontaneously—without a cause." (The italics are in the original.)

(*b*) *Biermer's preliminary communication* (1868) above referred to:—

"Professor Biermer made a preliminary communication on fatty degeneration of the heart and of the vessels as a result of anæmia. He had observed many cases of idiopathic and secondary anæmia caused by great loss of blood, chronic diarrhœa, and such like (among these was one of splenic anæmia), which after some time had become complicated by fatty degeneration of the heart and vessels . . . . The occurrence of these degenerative changes in the cases observed was, he thought, due to the defective condition of the blood of anæmic patients."

(*c*) *Biermer on Etiology* (1886): In a discussion of Professor Runeberg's paper on *Bothriocephalus* anæmia and its identity with progressive pernicious anæmia:—

"Professor Biermer doubted the identity of the anæmia caused by the *Bothriocephalus* with the real pernicious anæmia. In none of the numerous cases of pernicious

anæmia observed by himself in Zurich and Breslau had he ever found tapeworms. *He emphasized the fact* that the true pernicious anæmia had a quite definite pathological anatomy, but *that its etiology was for the present unknown.*"

"One cannot emphasize too strongly Biermer's statement, 'A perfectly spontaneous origin without clear etiology is one of the rarities.' It is absolutely necessary that we should hold fast to this statement if we desire to be clear as to the degree and character of the services which Biermer has rendered to the subject. From the etiological standpoint there are as many forms of pernicious anæmia as there are causes to be found." (Eichhorst, 1878.)

It is for German observers to reconcile these various contradictions: (1) between Biermer's views in 1868-71 and in 1886; (2) between Biermer's statement in 1886 and that of Eichhorst in 1878 as to the chief merit of Biermer's work; (3) between Eichhorst's statement on the one hand, that

"the chief merit of Biermer's work was that it *brought together* various forms of anæmia, both idiopathic and symptomatic, in virtue of their having clinical features in common" (Eichhorst, 1878); and

Strumpell's statement on the other, that

"the chief merit of Biermer's work was that he discovered 'a primary form of anæmia without recognizable cause'";

and lastly, (4) between the statement of Strumpell (1899) that

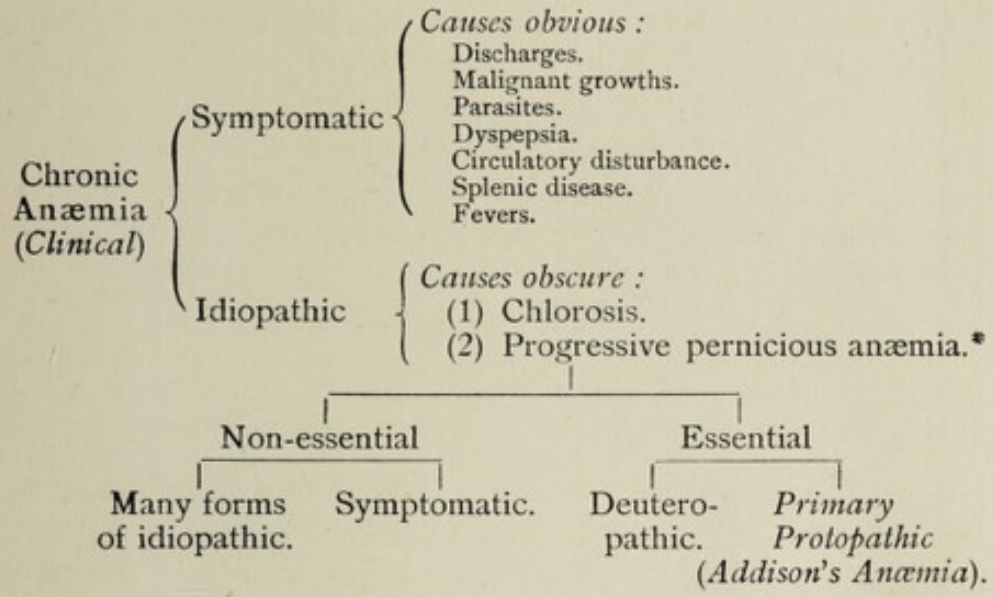
"the credit of being the first to study the above (primary) anæmia as a special disease belongs to Biermer";

and Eichhorst's contrary conclusion (1878):—

"We come to the result that the primary anæmia was first described in England both in the form of single cases and as a definite clinical disease."

(4) Professor Immermann (1879):

- Anæmia (*Pathological*)
  - Hypoplastic (*Anhæmatosis*) — *e.g.*, Anæmia of inanition, Chlorosis.
  - Consumptive (*Hæmophthisis*) — *e.g.*, Anæmia of hæmorrhage, Anæmia of pathological discharges.
  - Complex
    - (1) Known etiology, but complex pathogeny, *e.g.*, Fevers.
    - (2) Known pathogeny, but unknown etiology.
    - (3) Unknown etiology and pathogeny, *e.g.*, *Essential Pernicious Anæmia* (*Addison's Anæmia*).



* (1874) Immermann : "A peculiar form of severe anæmia . . . . to be separated from chlorosis, leukæmia and other pathological processes, as *an independent form of disease* for which Biermer's title appears the most suitable. The etiology is so far dark . . . the essential (? specific) cause is unknown."

(1879) "When I spoke in my first communication of "a special disease" I used this simply as a synonym for a "species" or "form" of disease—but only in a clinical-anatomical sense. The idea that all cases of essential pernicious anæmia must have one etiology is absurd. By pernicious anæmia is to be understood *nothing more than the highest form of anæmia however produced*—essential or non-essential, idiopathic or symptomatic."

(The contradiction here given to his first conclusion is complete.)

(5) "Pernicious Anæmia : A New Disease" (!) (1874).

[Title of Editorial article in the *Medical Times and Gazette*, ii, 1874, p. 681 ; Review of Immermann's paper, 1874 ; see also *Brit. and Foreign Med. Chir. Review*, ii, 1874, p. 487—first notices of Biermer's work in English literature.]

> The acuteness of a Swiss observer seems to have added another to the list of diseases with which the present century has enriched our text-books. Dr. Biermer, of Zurich, has described an affection which differs from ordinary simple anæmia in a marked manner, and which appears to be a disease *sui generis* in the sense defined above. . . . We are not aware that any case has as yet been reported in Great Britain (!), but no doubt there soon will be many observers on the look-out for it, and new light will be thrown on its etiology and course. For the sake of poor suffering humanity we must, however, hope that so serious a malady may only be due, as Immermann supposes, to special local influences, and that its distribution has not a wide range.

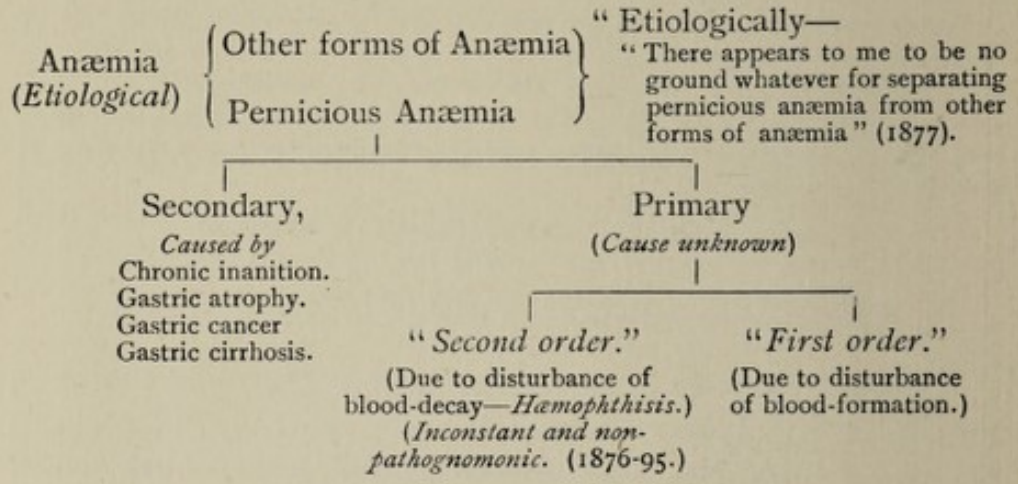
[The extraordinary confusion in identity and nomenclature of Addison's anæmia dates from this period. It is largely traceable, in the writer's judgment, to the single circumstance that Immermann's subsequent (1879) withdrawal of and apology for his first definition of Biermer's anæmia as "a disease of unknown cause" was never noted by English observers. So far as the writer knows, it has never been drawn attention to till now.]

(*See* Map 2, p. 66.)

(6) Dr. Pye-Smith (1875):

[A paper in *Virchow's Archiv* recording two cases, under the title of "Idiopathic Pernicious Anæmia," and calling attention to the apparent identity of Biermer's anæmia with that described by Addison as Idiopathic Anæmia.]

(7) Professor Quincke (1876-83 and 1895):



Professor Quincke (1876-80):

"If we summarize the facts recorded (1876) it thus appears that the conditions of the blood and other organs in pernicious anæmia are by no means alike in all cases; that the disease, therefore, most probably arises in very different ways; that we therefore have not to do with any single diseased process, but that pernicious anæmia, like anæmia generally, represents the product of various diseased processes and at the same time the highest form, the most extreme stage, of anæmia. One might, therefore, in a certain sense, parallel it with uræmia, jaundice, septicæmia, &c., which also present definite clinical pictures, and can yet spring from most different disease conditions. Two types: In individual cases the features of the

disease can vary (according to its mode of origin) by presenting certain of the features of the original cause. And in this connection one must remember that deficient blood-formation (*anhæmatosis*) and increased destruction of blood elements (*hæmophthisis*) form the two types, which, however, can be combined with one another and in this way alter the character of the clinical features. Examples of the first type would be those cases in which chronic inanition, gastric atrophy, or trophic disturbance of blood-forming organs are present; examples of the second variety *perhaps* those cases which show an increase of iron in the liver. On such a view of pernicious anæmia it is clear that the boundary line between it and the more intense forms of simple anæmia cannot be quite a sharp one. (1876.)

"The result of the present further observations (on eleven cases) serves to confirm the view expressed in my former—that pernicious anæmia, like anæmia generally, is the product of very various morbid processes and represents the highest form of anæmia. Etiologically there appears to me to be no ground whatever for separating pernicious anæmia from other forms of anæmia. (1877, p. 17.)

"Pernicious anæmia is essentially a clinical picture, and if one strives to distinguish between primary and secondary forms I do not think it justifiable to exclude all cases with obvious anatomical lesions as not belonging to the disease. Since we know that the picture of the disease can be presented by cancer of the stomach (Eisenlohr), or cirrhosis of the stomach (Nothnagel), we must regard these as causes of secondary progressive pernicious anæmia; while those cases which arise through disturbances of blood-formation, or disturbance of blood decay, are to be separated off as primary forms of the first and second order. In actual cases it will often remain doubtful to which group the case is to be referred." (1880, p. 586.)

Pigment changes (1876-83): Number of cases 9. In 5 marked; in 2 slight; in 2 absent.

1895 (Observations by Stühlen, a pupil of Quincke):—

"Even to-day the clinical picture presented by pernicious anæmia shows very little that is satisfactory, and very little certainty as regards the disease itself with the exception of the changes in the blood, the great anæmia and general weakness of the patient. *Post-mortem* changes are limited in most cases to the blood-forming organs, and yet are hardly ever considerable. Quincke was the first to draw attention to the high percentage of iron in the liver and other organs in *some* cases of pernicious anæmia. The number of cases since investigated, only eleven (!), is too small (!) to say whether this increase of iron is constant and pathognomonic.

"So far as we can even now judge this is not at all probable, since the pathogenesis of the disease appears to be a very variable one. Since further, siderosis occurs in other diseased conditions ('a very common occurrence in different diseased conditions'—Quincke, 1895) as Quincke and Peters have shown, this condition of the liver cannot be regarded as pathognomonic of pernicious anæmia."

(8) PROFESSOR EICHHORST (1878) :

Anæmia (*Etiological*)
- Ordinary.
- Progressive Pernicious Anæmia — "From the etiological standpoint there are as many forms as there are causes to be found."*

Secondary *or* Deuteropathic, *or* Symptomatic	*Primary* or *Essential*, or *Idiopathic* (*Addison's Anæmia*)
Caused by : Mental overstrain. Poverty. Bad air. Deficient food. Pregnancy. Puerperium. Diarrhœa. Vomiting. Hæmorrhages. Discharges. Syphilis. Malaria. Enteric fever.	("We come to the result that the primary form was first described in England, both in the form of single cases and as a definite clinical disease.")

* "One cannot emphasize too strongly Biermer's statement : "A perfectly spontaneous origin without clear etiology is the exception." It is absolutely necessary that we hold fast to this statement if we desire to be clear as to the degree and character of the services Biermer has rendered to the subject. From the etiological standpoint there are as many forms of pernicious anæmia as there are causes to be found. (1878.)

"Biermer's progressive pernicious anæmia is nothing more than a well-characterized clinical picture which can have very different causes. . . . The *causes* of the anæmias (*sic*) are but little regarded in Biermer's expositions ('treten wesentlich in den Hintergrund'). In view of the preponderating interest attaching to the clinical and anatomical features, Biermer both in his earlier and his later communications grouped together and united the primary (idiopathic) and secondary (symptomatic) forms of anæmia under the new name of progressive pernicious anæmia."

[The contradiction here involved between the statements (1) that etiology was but little emphasized by Biermer, and (2) that Biermer's statement on this subject constitutes "one of the chief services he has rendered to this subject" is to be noted, and compared with similar contradictions in Biermer's and Immermann's views.]

(9) Dr. Sidney Coupland (1881):

- Anæmia (*Clinical*)
  - Symptomatic
    - Simple.
    - Pernicious (*e.g.*, Wasting diseases)
  - Idiopathic (primary)
    - *Pernicious** (*e.g.*, *Addison's Anæmia*)
    - Simple (*e.g.*, Chlorosis).

"Destined to be merged again into one when etiology is perfected."

* *Same author* (1898): "Dr. Hunter's contention for the specificity of pernicious anæmia as a disorder consisting in hæmolysis, affords so far a satisfactory explanation of the phenomena. It has further enabled us to eliminate from the category of pernicious anæmia many anæmias which are strictly secondary, closely as they may simulate the primary disease in clinical features, blood changes and visceral lesions. Nor is it warrantable to include within the class such cases as those associated with the presence of intestinal parasites unless it can be shown that they depend on the same kind of hæmolysis as that which underlies the primary malady. Pernicious anæmia signifies, then, a definite group of clinical and pathological phenomena dependent upon a special form of blood-destruction or hæmolysis, induced by toxic agents absorbed from the gastro-intestinal tract."

(10) Dr. Pye-Smith (1883):

Causes:	*Anæmia of:*
Anæmia (*Etiological*)	
Hæmorrhages.	
Exhausting discharges	Recurring pregnancy. Long-continued lactation. Chronic leucorrhœa. Chronic albuminuria. Recurrent diarrhœa. Chronic dysentery.
Inanition	Stricture of œsophagus. Chronic dyspepsia. Gastritis. Gastric ulcer.
Increased destruction of corpuscles	Acute rheumatism. Phthisis. Chlorosis. Typhus. Other acute diseases.
Effects of drugs and poisons	Mercury. Lead. Alkalies. Syphilis. Malaria.
Changes in glands	Spleen. Lymph glands. With or without leukæmia.
"Without recognizable cause . . . not depending on known loss of blood constituents, or on diminished income, or on increased destruction of formed elements"	"*Idiopathic anæmia*" of Addison.
"Primary—essential autochthonous"	"Without any symptoms and without any lesions that cannot be referred to the anæmia, and without discoverable cause."

(11) Dr. Bristowe (1880-90) :—

Anæmia (*Clinical*)
- General.
- Idiopathic
  - Chlorosis.
    - "A form of Anæmia coming on independently of any organic lesion or specific dyscrasia." (1880-84.)
    - "Pathology not at all understood. (1884.)
  - *Idiopathic*, *Essential*, or *Progressive Pernicious Anæmia (Addison's Anæmia).*

"It seems to me impossible at the present time to make any trustworthy distinction between the chlorosis of girls and pernicious anæmia except such as depends on the age and sex of the patients and the effects of treatment. Nevertheless, I believe, as most physicians do, that there is a fundamental difference between them; and moreover, I suspect that the group of affections now grouped together and labelled "pernicious anæmia" will hereafter be found to belong to several categories." (1888.)

"Dr. W. Hunter has very carefully investigated the subject, and shows that pernicious anæmia is distinguished from all other forms of anæmia by the fact of the excessive presence of iron in the liver—due to the more or less continuous destruction of red corpuscles in the spleen or liver, or at anyrate within the portal circulation, and for reasons he gives, caused by some poison manufactured in and absorbed from the alimentary canal. He believes that chlorosis is due to imperfect and inadequate blood-formation, and is—pathologically—altogether a different disease from pernicious anæmia, a view in entire accordance with their characters." (1890.)

Period III (1888-1900).

(12) Dr. William Hunter (1888-90) :

Anæmia (*Clinical and Pathological*)
- Secondary *or* Symptomatic.
- Primary *or* Idiopathic
  - Chlorosis.
  - "Pernicious Anæmia"
    - *Addison's Anæmia.*
    - "Septic Anæmias." (1900)

Pathogeny
- Hæmolytic nature (1885)
  - Pigment changes (*Constant and pathognomonic*) (1887)
  - Bone-marrow changes (*Secondary to the hæmolysis and hyperplastic in character*) (1888)
- Gastro-intestinal site (Results of experiments) (1885-90)
- Toxic cause (*Increase of aromatic sulphates; presence of ptomaines*) (1890)
  - Toxic symptoms. Glossitic and Gastric Lesions (*Infective origin*) (1890)
    - Septic infection (1890-1900)
      - (Oral, gastric and intestinal. An important predisposing factor)
    - *Specific hæmolytic infection*
      - "*Glossitic hæmolytic Anæmia* (*Addison's Anæmia*)

(*a*) "Dr. Hunter's observations dispel some illusions. They demonstrate that, strictly speaking, pernicious anæmia has a *place apart from secondary anæmias* due to wasting diseases, repeated blood loss, or disease of the organs of nutrition. When in such cases the anæmia becomes, as we were wont to say, "pernicious," this is not, according to his views, by any normal sequence of events, but by the intervention of a new factor—the supervention of a malignant process of blood-destruction which accelerates the fatal issue. In support of his contentions Dr. Hunter details the results of many experiments upon the effects of hæmolytic agents. . . . Certainly he has succeeded in making out a very strong case for his view, which, more than any other yet advanced, would seem to harmonize best with the clinical facts of this remarkable malady." (Editorial article, *Lancet*, 1888.)

(*b*) "In my opinion these observations (now recorded) bear out strongly the views, and strongly support the conclusions arrived at in Hunter's recent studies regarding the hæmolytic nature of the disease. To my mind these studies have very definitely shown that *the essential features of pernicious anæmia are excessive destruction of blood corpuscles, the seat of disintegration being the portal system*, more especially that contained within the liver and the spleen, the process seeming to commence by a liberation of hæmoglobin in the spleen which is carried to the liver to be disposed of. The marrow changes are secondary to the disease, with a reversion to the embryonic type." (Dr. Mott, 1889.)

(*c*) "The opinion now prevalent of the nature of pernicious anæmia (that it is due to excessive hæmolysis) is largely due to the elaborate investigations of Dr. William Hunter (1888). The arguments of Hunter in favour of the *independent nature of the disease* are the most powerful that have yet been advanced. Hæmolysis is undoubtedly increased, but this is, in my opinion, the result of the defective blood-formation underlying the anæmia." (Dr. F. P. Henry, U.S.A., 1889.)

(*d*) "Whether or not pernicious anæmia is a distinct pathological entity is still a much disputed question. Henry (1887, also 1889) takes the ground that it is the final stage of several forms of symptomatic anæmia and of chlorosis, a view similar to that held by Quincke, Osler, Eichhorst, and Coupland. Hunter is one of the strongest of the more recent supporters of the *independence of the disease*, and has done much to establish these views. He shows very conclusively that such conditions as the presence of intestinal worms, atrophy of the gastric mucous membrane, and malignant disease, to all of which the disease has been ascribed, are repeatedly met with in cases presenting none of the appearances of pernicious anæmia; and, conversely, that cases of pernicious anæmia are repeatedly seen in which no such changes are to be found. These facts in connection with the clinical symptoms, but especially with the characteristic conditions of the blood during life, and the equally pathognomonic change in the liver after death, justify the belief that the disease is an independent one, due to some cause not operating on other forms of anæmia. The nature of this cause is a subject still very obscure." (Dr. Crozier Griffith, U.S.A., 1890.)

(*e*) "As check observations, the livers from a number of different diseases—especially those attended by anæmia—were examined. In not a single instance was the characteristic pigment found in amount at all comparable with that seen in pernicious anæmia, nor did it present the characteristic arrangement. In most cases it was entirely absent, or present in very small quantity.

"It would seem to be a just conclusion to regard pernicious anæmia as a *a truly independent affection*—probably due to the entrance into the portal circulation from the intestine of some certain hæmolytic agent—the origin of which is unknown, but that it is possibly of the nature of a ptomaine." (Drs. Griffith and Burr, U.S.A., 1891.)

(*f*) "The iron in the liver is in excess in pernicious anæmia, in striking contrast to the condition in cases of secondary anæmia. This, Hunter states, is a special and characteristic lesion. A. J. Scott examined (1892) the livers in forty-five consecutive autopsies without finding, except in pernicious anæmia, the special distribution of pigment." (Professor Osler, 1892-1903.)

(*g*) "Dr. Hunter is confirmed in his observations by the writers whose analyses he quotes, and also by others who have since found a great quantity of iron in the liver. . . . The important stride recently made is, then, that we have discovered that there is a great increase of iron in the liver in pernicious anæmia, and that this is very probably due to the fact of increased destruction of hæmoglobin (red corpuscles) somewhere in the portal system or its annexa. *We have thus learnt the probable seat of the disease.* . . . In favour of the view that the origin of the blood destruction is in the stomach and intestines, the frequency of gastro-intestinal symptoms is urged by him (1890). . . . To see if any support can be lent to this view from the presence of such symptoms during life, I have carefully collected (1890) all the reports of cases in Guy's Hospital since the time of Addison. . . An analysis of these cases (twenty-nine in number), showing that vomiting and diarrhœa are very common in pernicious anæmia, to a certain extent supports the view that the seat of the blood destruction is in the wall of the gastro-intestinal tract." (Dr. Hale-White, 1890.)

"The first step, and a very difficult one in the case of a rare disease, is the recognition of it as a clinical entity. Addison did this for pernicious anæmia.

"The next step is to advance our knowledge, that we can prophesy that if a patient has this or that assemblage of symptoms, a constant characteristic condition will be found *post mortem*. *During the last few years this advance has been made in the case of pernicious anæmia;* and now if you diagnose the disease during life, you imply that at death it will be found that the quantity of iron in the liver is greatly increased; and if at the *post mortem* this is not so, your diagnosis will have been wrong, just as you would be wrong if, having diagnosed cirrhosis of the liver during life, you should find that the liver was healthy." (Dr. Hale White, 1894.)

(*h*) "On the other hand, Dr. William Hunter, on the strength of remarkable investigations—as I think, too little known by us—has come to opposite conclusions. He has, by a series of very interesting investigations, made it probable that in the cases observed by him we are dealing with a *chronic auto-intoxication*. He believes that the absorbed toxins lead to a destruction of blood and deposition of iron in the spleen and liver, and this observation of Hunter has since been confirmed by others. That auto-intoxication is the first and original cause of pernicious anæmia must still remain a question. But the impression cannot be avoided that the lighter and severer attacks (of toxæmia), such as occurred in my patients (1895) and have been described by Hunter in his cases (1889), represent *a form of auto-intoxication produced by changes occurring in the gastro-intestinal tract.*" (Professor Ewald, 1895.)

(*i*) "The view that absorption of toxic products from the digestive tract is the cause of primary anæmia is represented chiefly by W. Hunter on the ground of clinical and experimental observations. According to Hunter, there occurs in pernicious anæmia *a destruction of red corpuscles in the capillaries of the portal vein—probably produced by the absorption of toxic substances from the stomach and intestine*—possibly as the result of bacterial action." (Professor Grawitz, 1896.)

(*j*) "With regard to the morbific agent that causes this blood-destruction in the portal system, Dr. William Hunter, of Cambridge, than whom probably no one has done more to elucidate the pathology of this obscure disease, as the result of a careful investigation, ventures the following conclusion: 'The special factor required to initiate the symptoms peculiar to pernicious anæmia is the presence

under certain favourable conditions of organisms of specific nature (a specific infection) within the gastro-intestinal tract.' We wish that this would stand the test of further investigation, but as yet it is not proven." (Professor MacPhedran, Canada, 1890.)

"Certain ptomaines (poisons) not present in health have also been found in the urine (Hunter, 1890). Hence the view has been expressed (by him) that pernicious anæmia is due to some *special micro-organism* in the intestine producing certain ptomaines which cause destruction of corpuscles in the portal blood, with the attendant symptoms. That there is some truth in this should not be a matter of surprise, as later physiological research (by him) has shown that the *chief seat of the normal destruction of the red corpuscles is in the intestinal mucosa.*" (MacPhedran, 1892.)

(*k*) "With regard to the exact nature of the poison generated, Hunter suggests it may be of cadaveric nature, absorbed from the alimentary tract. The research is, however, specially valuable in *fixing the seat of the disintegration of the corpuscles in the portal circulation, and its important annexa, the spleen and liver.*" (Professor Halliburton, 1890.

"(*l*) It has been urged against this theory that gastro-intestinal lesions of all sorts are common and bacteria plentiful in the intestine, and that therefore pernicious anæmia should be commoner than it is. But I take it that the whole pith of the theory is that there is a special micro-organism which may, for all we know, be very rare." (Dr. Hale White, 1890.)

(13) Professor Muir (1894):

"*Bone-marrow Changes.* — The condition of the bone-marrow even taken alone, would indicate *an increased regenerative activity*. . . . Moreover, if we examine the condition of the liver, we find it *is exactly in the case in which the liver contains most pigment that the bone-marrow changes are most advanced*, and the disease has run the most prolonged course. Taking all the facts, we cannot but conclude that these five cases form a group of examples of the same disease, and that in all the changes in the marrow are of similar nature, and *secondary to the disease*. . . . It would appear that when the increased demand has lasted for some time there is a return to a sort of embryonic condition in which nucleated red corpuscles of larger size are formed; and it is probable that they are formed in such numbers or of such size that they do not lose their nucleus in the normal manner, which undergoes degeneration (megaloblastic degeneration). *The reversion is not a primary pathological condition, but a process compensatory to the long-continued drain.* (1894.) These changes are chiefly of the nature of degenerations, and are to be referred principally to *direct toxic action*, and they can be produced experimentally by the injection of micro-organisms, especially pure cultures of staphylococcus." (1901.)

(14) Professor Stockman (1895):

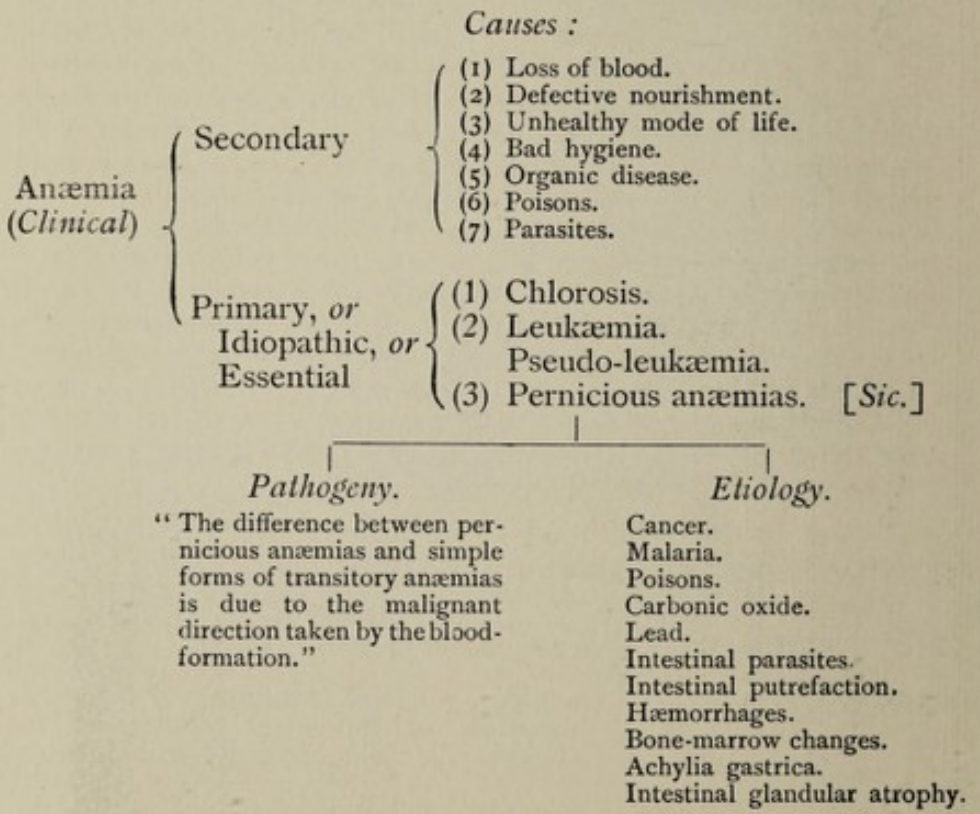
		Causes:
Anæmia	Ordinary	Well-recognized debilitating causes.
	Pernicious	The same, aggravated by degenerative changes in the whole vascular system, which permit the occurrence of minute internal bleedings, more rarely of external ones also, leading ultimately to excessive anæmia and death.

"The evidence seems convincing that pernicious anæmia follows usually on well-recognized debilitating causes. These bleedings are, to judge from the exacerbations and partial remission of symptoms, more numerous at one time than at another; and according to the amount of blood loss the case progresses rapidly or slowly. . . .

"In some cases which I have examined after death, the hæmorrhages have been so few that I have doubted very seriously whether they could ever have been very numerous; but taking into account their rapid absorption, and the probability that with extreme anæmia their number must diminish just before death, I believe in such cases they had previously been much more numerous. (*See* p. 113.)

"As has been previously pointed out, *the causes of the initial anæmia are still imperfectly known, and cases sometimes occur in people who are apparently healthy and living under good conditions*. Hunter may be correct in holding that a cadaveric (bacterial) poison breaks down the blood in some cases; and, if this be so debilitating conditions with hæmorrhages need not necessarily precede the 'pernicious anæmia.' It is possible, too, that degenerative changes in the small vessels may occur spontaneously in certain people. But conclusive evidence is wanting on all these points. As I have previously pointed out, the capillary hæmorrhages found *post mortem* may be very few in number; and this might lead us to adopt Hunter's view, that in some cases at least a blood-destroying body may be the cause of the condition; but the course and history of such cases lead me to believe that hæmorrhages have been more frequent previously and have become absorbed."

(15) PROFESSOR GRAWITZ (1896-1901):



(16) PROFESSOR EHRLICH (1892-1900) :

Anæmia (*Hæmatological*)
- Normoblastic — All secondary anæmias.
- Megaloblastic
  - Progressive Pernicious Anæmia ("Biermer's Anæmia") — ("The conditions characterized by the clinical features described by Biermer and the blood changes described by Ehrlich.")

Secondary.	*Primary.*
Caused by :	*Cryptogenetic.*
Poverty.	*Idiopathic.*
Bad hygiene.	*Essential.*
Cancer.	("Neither the history nor the clinical features, nor the *post-mortem* changes, throw any light on the origin of the disease, or reveal any changes in the organs to which the disease can be referred.") (*Addison's Anæmia.*)
Diseases of bone-marrow.	
Loss of blood.	
Bad nourishment.	
Malaria.	
Typhoid fever.	
Lead poisoning.	
Bothriocephalus latus.	
Gastric and intestinal lesions.	
Pregnancy and lactation.	
Mental overstrain.	
Syphilis.	
Vomiting and diarrhœa.	
Discharges.	

(17) DR. SCHAUMAN (1900) :

Anæmia (*Etiological*)
- Ordinary
- Pernicious Anæmia — "The disease is not an etiological unity, but only a symptomatic group which can be produced by causes of all kinds."

Secondary	*Idiopathic.*
Definite etiological causes, e.g.,	*Primary.*
Intestinal parasites.	*Cryptogenetic.*
Gastro-intestinal disorder.	("Without recognizable cause—apparently spontaneous in origin.")
Pregnancy and puerperium.	(*Addison's Anæmia.*)
Repeated hæmorrhages.	
Syphilis, Malaria, Enteric fever — Infective processes.	
Intoxications, *e.g.*, Carbonic oxide.	

(18) DR. BYROM BRAMWELL (1899) :

Anæmia (*Clinical*)
- Secondary, *or* Symptomatic — *Causes :*
  - Loss of blood.
  - Presence of poisons.
  - Defective nutrition.
  - Well-defined organic disease, *e.g.*, cancer of stomach.
- Primary
  - Chlorosis.
  - Pernicious anæmia ("a clinical condition").

"Before I became acquainted with Hunter's observations, I was in the habit (with, I suppose, most other clinicians and pathologists) of regarding the great diminution in the number of red corpuscles, which is the essential characteristic of pernicious anæmia, as the result of defective blood-formation. . . He regards the changes in the bone-marrow as secondary to the blood destruction; and with this opinion I entirely agree, so far as the great majority of cases are concerned.

"At the same time, I think it quite possible that future observations may show that a condition of blood identical with the *clinical condition which we term pernicious anæmia* may perhaps in rare instances be due to a *primary* lesion of the bone-marrow.

"He allows that there is defective blood-formation, but he explains this defective formation as the result of the excessive strain thrown on the blood-forming tissues —the bone-marrow—in consequence of the excessive blood-destruction which he argues is the essential cause of the anæmia. This argument seems to me to be a satisfactory explanation; but the question is, whether it represents the whole truth. It is quite possible, I think, that in many cases of pernicious anæmia the diminution of red corpuscles is the result both of excessive blood-destruction and defective blood-formation.

" . . . To cases of the kind in which there is an excess of iron in the liver—the Hunterian type of the disease, as I am in the habit of terming it—a double cause of the bloodlessness is present, viz., increased blood-destruction in the portal circulation, and too rapid and therefore defective blood-formation in the bone-marrow.

"Until further information is obtained, the question whether the condition termed pernicious anæmia may result from a variety of causes, or whether it is a single clinical entity, the cause of which is always one and the same, should be left an open one.

" . . . In concluding this discussion on the pathology of pernicious anæmia, I may add that during the past six months I have had the opportunity of observing, both during life and after death, a considerable number of typical cases of the disease, and that *in all of them an excess, and with one exception a very large excess, of iron has been present in the liver.* A careful consideration of these and of the other cases under my notice during the past two years, has led me to believe that Dr. Hunter's conclusions as to the nature and causation of the disease are correct, in the vast majority of cases at all events. Whether all cases of pernicious anæmia are due to one and the same cause remains, I think, to be proved by future observations."

(19) DR. CABOT (1901):

Anæmia (*Clinical*)

Secondary — "The cause obvious; on its removal the anæmia ceases."

Causes:

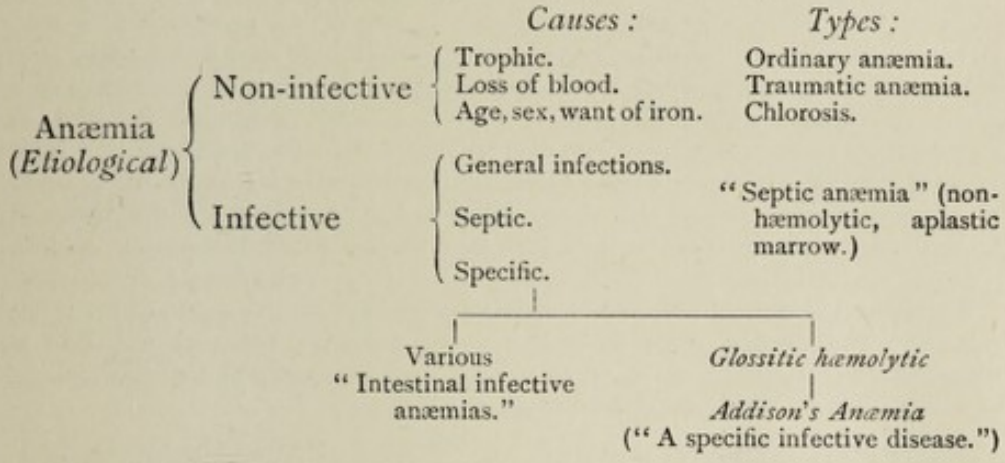
(1) Infective and febrile diseases, acute or chronic.
(2) Malignant disease.
(3) Chronic suppurations.
Nephritis.
Chronic dysentery.
Cirrhosis of the liver.
(4) Bad hygiene.
Pregnancy
Lactation.
(5) Intestinal parasites.
(6) Poisons (lead, arsenic, &c.).

Primary — "The causal factor unknown, or insufficient to produce so severe an anæmia."

Chlorosis.
Pernicious Anæmia.
("Evidence is accumulating in support of Hunter's view that pernicious anæmia is due to excessive blood destruction produced by toxic substances absorbed from the gastro-intestinal tract.")
(*Addison's Anæmia.*)

Period IV (1900-8).

(20) Dr. W. Hunter (1900-7) (*See* Frontispiece.)



"(1) By the aid of the schematic table (Scheme II) he summarized his own observations and conclusions (1885-1903), showing, as it appears to him, that the disease is a specific entity; that the *primary etiological factor* is a *specific hæmolytic infection* giving rise to a specific infective glossitis, gastritis, and enteritis, with sepsis of the alimentary tract as a potent predisposing factor; that the *pathological edifice* raised upon these foundations is special, constant, and pathognomonic, and comprises lesions in the gastro-intestinal area, hæmolysis occurring in the portal circulation and evidenced by pigment changes in the liver and kidney, and hæmolytic changes in the urine; changes in the bone-marrow, denoting increased hæmogenesis; that the *symptoms* are characteristic and can be arranged in hæmolytic and gastro-intestinal groups, which are inseparable from the pathological conception of the disease, and are surmounted by groups of symptoms referable to toxæmia and anæmia respectively." (Scheme II.)

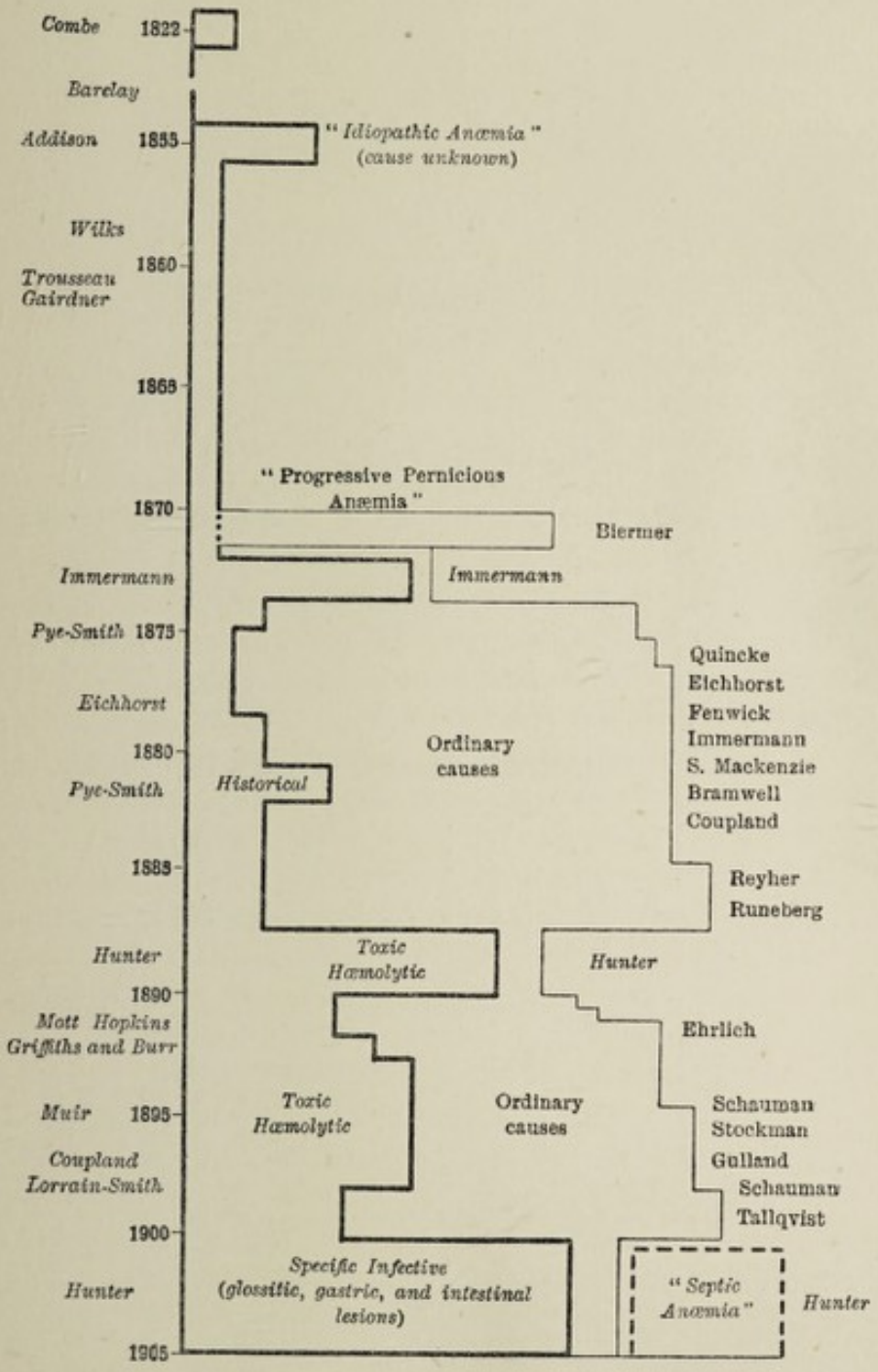
"(2) Dr. Hunter has arrived at very definite and clear conclusions regarding the real nature of pernicious anæmia. . . . We must refer our readers to the text of his paper for his close and searching criticism of recent literature on pernicious anæmia, merely remarking that the criticism appears to us to be sound. . . . The great advance made mainly by Dr. Hunter's investigations has been in the direction of revealing the true nature of Addison's 'idiopathic' anæmia. By his researches on hæmolysis and his observations on the clinical and pathological characters of this form of anæmia Dr. Hunter has given an explanation of the disease which is thoroughly in accord with modern scientific hæmatology. . . . Addison's anæmia is a definite entity, specific, infective, hæmolytic, presenting characteristic local lesions (especially a peculiar form of glossitis). . . . . There is no gainsaying the advantage of arriving at so definite a conclusion, and we must hasten to recast our nosology accordingly. For the practical outcome of such considerations is the total reversal of the situation as it was when Biermer wrote (1871) on 'progressive pernicious anæmia.' . . . Now we learn that the only condition entitled to be termed 'pernicious anæmia' is just that which was neglected by those observers, and that it alone possesses a single and well-defined etiology. It is in the demonstration of this definite character that so much is owing to Dr. Hunter, and we doubt not that by following up his line of enquiry much will be gained, not only in the direction of clearness of conception, but in the treatment of this grave disease." (*Lancet* Editorial, 1903.)

"(3) Inasmuch as we have no other explanation for the megaloblastic transformation of the bone-marrow than *the presence of some toxic substance*, we will assume the cause of the megaloblastic reaction to be the formation of toxins which have the capability of influencing the marrow in *a specific manner*." (Lazarus, 1899.)

"To the mind of the writer this latter theory approaches most closely *the true solution of the question of pathogenesis*, namely, that of *the absorption of a toxic substance, probably of intestinal origin, which acts on the circulating blood, producing hæmolysis*, and through the circulation *also on the marrow*, resulting in a *faulty hyperplasia*. That *this toxin is a result of gastro-intestinal infection*, as suggested by Hunter, *seems not improbable*. There are other evidences of a toxic substance circulating in the blood—notably the symmetrical lesions found at times in the spinal cord—which practically all investigators agree are the result of a toxin, and not of the anæmia *per se*, as they are not found in even the severest types of secondary anæmia. With a circulating toxin—for example, ricin—there is destruction not only of red cells in the circulation, but also of some at least in the marrow. The marrow responds in this emergency with nucleated red cells of normoblastic or megaloblastic type, depending upon the extent of the destruction." (Bunting, U.S.A., 1905, and August 10, 1907.)

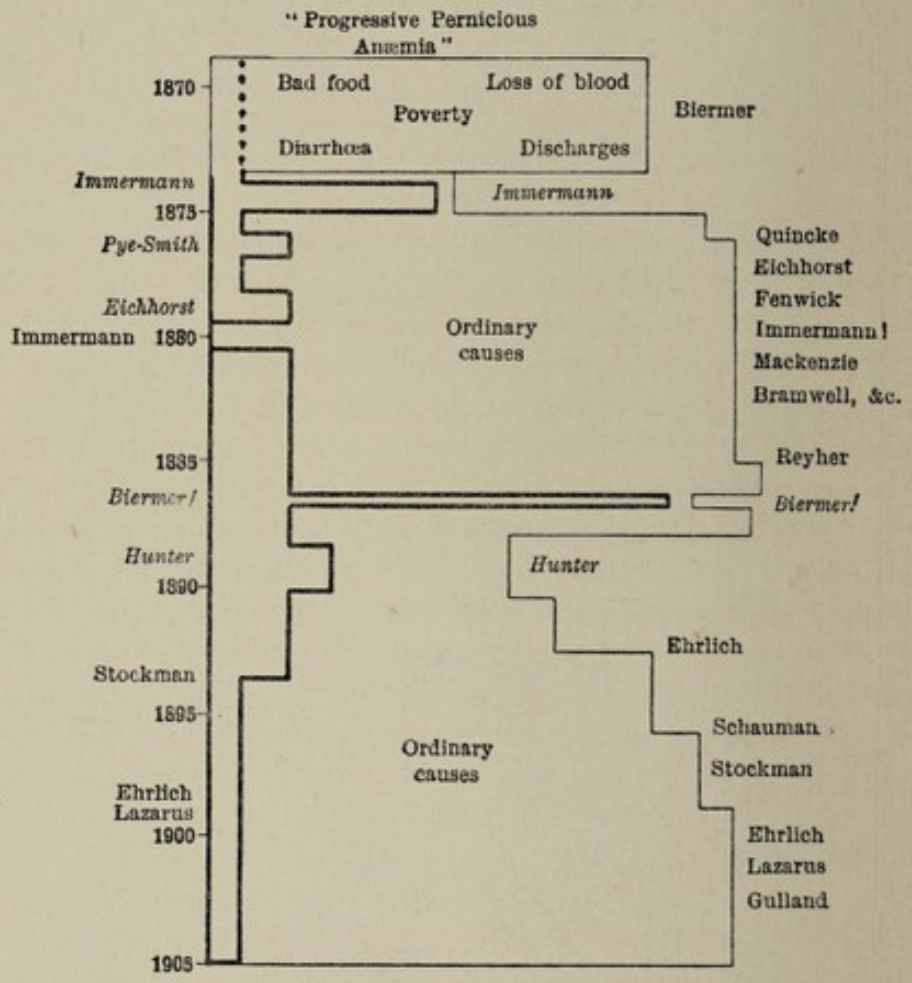
The above observations and conclusions of Dr. Bunting regarding the nature of the bone-marrow changes afford, in the author's opinion, the most complete confirmation of his whole interpretation of the pathology of this disease from 1888 onwards. They fully confirm the interpretation upon the marrow changes by himself (1888), by Mott (1890), and more especially by Muir (1894-1901). At the same time they entirely dispose of the contention of Ehrlich (1892) and all who have followed him, namely, that the bone-marrow changes (with megaloblastic degeneration) denote some "primary," "developmental" failure in blood-forming powers. For Dr. Bunting's experiments conclusively show that *the whole of these changes, including megaloblastic degeneration, can be induced experimentally in a few days (!) by the injection of certain hæmolytic agents (!).*

MAP 1.



CHRONOLOGICAL MAP showing the etiological position assigned to Addisonian Anæmia in relation to "Progressive Pernicious Anæmia" by English (and other) observers throughout its history. The dark outline represents the former; the clear outline represents the latter. (*See* Chapter VII.) The map shows (1) the steadily increasing recognition of the individuality of Addisonian Anæmia from 1888 onwards; (2) the effect of Ehrlich's megaloblastic criteria from 1892 onwards in once more enlarging the group of anæmias termed "pernicious" (*see* p. 78); and (3) the outcome, according to the author's observations (1900-5) of these megaloblastic criteria. (*See* p. 75, and pp. 175-6.)

MAP 2.



CHRONOLOGICAL MAP showing the etiological position assigned to Addisonian Anæmia in relation to "Progressive Pernicious Anæmia" by German (and other) observers throughout its history. The dark outline represents the former; the clear outline represents the latter. It is regarded as a limited and subordinate form of the larger group entitled to be called "pernicious" or "megaloblastic" anæmias. (*See* p. 78, and p. 96.) The author draws particular attention to: (1) The first view of Immermann in 1874, identifying Addisonian anæmia with "progressive pernicious anæmia" (*see* p. 88), and the consequent adoption of that *name* for Addisonian anæmia (*see* p. 90); (2) Immermann's repudiation in 1879 of his first view, out of deference to Biermer, Quincke, and Eichhorst's teaching (*see* p. 91); (3) Biermer's repudiation in 1886 of his own former teaching and that of his chief exponents, both before (1876-86) and since (1886-1906).

CHAPTER VII

Relation of Addison's "Idiopathic Anæmia" to "Progressive Pernicious Anæmia."

(*With Maps* 1 *and* 2.)

The foregoing classifications bring out the great complexity and wide diversity of opinions which have prevailed regarding this anæmia since its first description in 1822 and 1855. It will be seen that, wherever or under whatever name the particular form of anæmia had in view by Combe and Addison is considered, the fact about which all are agreed is the one which induced these observers to draw attention to it originally, namely, its cryptogenetic origin—its unknown cause. Short of that great fact, the classifications seem to reveal nothing but divergence of opinion and differences of conception—in some notable instances remarkable confusion in conception, observers contradicting themselves flatly at different periods. It is little wonder that the history of the disease has proved—to those who have ventured to deal with it—almost as difficult a task to unravel as that of the nature of the affection itself. On this point the present writer may perhaps claim to speak with authority, in virtue of the exceptional interest he has taken in the disease, and the work which he has devoted to it during the past twenty years. Despite his general acquaintance with its whole history, it has only been during the last three or four years, by repeated perusal and study of its earlier literature, that he has found it possible to trace to its source the precise circumstances which led English observers—quite erroneously as he finds—to identify Biermer's anæmias with Addison's anæmia, and to adopt generally for the latter the name "pernicious anæmia" which was given to the former. (*See* Chapter X.)

The point which he is at present concerned to bring out is not any explanation or reconciliation of the views of the exponents of Biermer's anæmias, but one of a more important nature, namely this—that from the very first the conception of "progressive pernicious anæmia" practically undid what Combe and Addison had attempted to do. It *brought together different forms of severe anæmia*

by virtue of superficial clinical, pathological, and etiological resemblances ; whereas, the sole object of Addison's accounts was to *separate one form from all others* on account of the absence of any obvious or sufficient cause. The difference between the two conceptions may be put thus : that even if Addison had never written, it would still remain for some observer to make a much needed contribution to Medicine, by separating the anæmia which he had in view from the heterogeneous group of anæmias now termed " progressive pernicious anæmia." For the result of the author's investigations here recorded is to show that the anæmia which he described is not only a " remarkable " form of anæmia, as they thought, but also *a remarkable infective disease*—nosologically, etiologically, clinically, and pathologically, deserving to be marked off from other forms of " progressive anæmia " as sharply and clearly as " enteric fever " is now definitely marked off from all other forms of " continued fever."

If it has been his good fortune to be able to throw any light on this complex disease, it is largely due to the circumstance that he was led (1885) to interest himself in its pathology as the result of experimental studies (" Transfusion," and " Nature and Seats of Blood Destruction," 1885-86), without any knowledge whatever of its highly complex controversial history. For many years the question of who first described it, or how their conceptions differed, appeared to him matters of quite subordinate interest, in view of the fact that no two observers seemed to agree as to what constituted the disease. If at this time he had any prejudice at all as regards the English " idiopathic " and the German " progressive pernicious " view of the case, it was in favour of the latter. The conception involved in the latter left the question of pathology completely open ; whereas the Addisonian conception, as afterwards defined (1883), viz., that " the disease must be without any lesions other than those due to the anæmia," appeared to prevent any possibility of light being thrown upon it, since the very fact of ascertaining any class of lesion to which this could not apply would *ipso facto* exclude the case altogether from the rank of this anæmia.

In the light of these early preconceptions (1885), the conclusions eventually reached and embodied in the accompanying summary as to the relations of Addison's anæmia to Biermer's progressive pernicious anæmia are of additional interest ; they may possibly have the more weight with German observers, on account of a criticism made by a reviewer on his former work, viz.,

"In his history of the observation and interpretation of the disease, the author appears to us perhaps to err on the side of generosity to Biermer."

AUTHOR'S CONCLUSIONS REGARDING THE RELATION OF "IDIOPATHIC ANÆMIA" ("Addison's Anæmia") TO "PROGRESSIVE PERNICIOUS ANÆMIA" ("Biermer's Anæmia" of German Writers).

"PROGRESSIVE PERNICIOUS ANÆMIA." ("Biermer's Anæmia.")	"IDIOPATHIC ANÆMIA." ("Addison's Anæmia.")
Conception.	*Conception.*
(1) The famous address by Biermer in 1871, in which the name "progressive pernicious anæmia" was used for the first time, forms the starting point for our description of the disease. (Ehrlich and Lazarus, 1900; Grawitz, 1906; Strumpell, 1890).	(1) The accurate accounts of Combe in 1822, and Addison in 1855, in which the latter termed the condition "idiopathic anæmia," form the starting point for the account of the disease here given.
(2) "The chief merit of Biermer's work—the great and invaluable service which he has rendered—is that it *brought together* into one common group and under one title a number of different forms of anæmia possessing certain characteristic features in common." (Eichhorst, 1878.) After a verbatim report of Biermer's address, we read these words: "Under the above symptom-complex, Biermer thus grouped together: (1) Essential, idiopathic, primary conditions of anæmia, and (2) those of known etiology and pronounced secondary character." (Lazarus, 1900.)	(2) The chief merit of Addison's work was that it *separated* one form of anæmia from all others on the ground of its being a "remarkable form," a remarkable disease. The chief result of Biermer's work was that his observations excited general attention and stimulated observation. Its great demerit was that it *brought together* widely different forms of anæmia on account of superficial clinical and anatomical resemblances.
(3) "A perfectly spontaneous origin, without clear etiology, is one of the rarities," (Biermer, 1871)—emphasized as correct by Eichhorst: "We cannot emphasize too much this statement if we desire to be clear as to the merits of Biermer's work. It is therefore clear that, from the etiological standpoint, there	(3) In one important point—the essential point according to Addison—Biermer's observations were at variance with Addison's description. According to Addison, the chief feature of the disease was that it occurred without any discoverable cause whatever, and "apart from the usual causes or concomitants of

are as many forms of progressive pernicious anæmia to be distinguished as there are causes to be found." (Eichhorst, 1878, p. 31.)

the anæmic state." Biermer, on the other hand, described it as "specially prevalent among *poor* people—poverty, puerperal conditions, insufficient and unsuitable food, unhealthy surroundings, discharges, especially persistent diarrhœa, sometimes also hæmorrhages, usually preceding the disease and causing it." The influence of this teaching of Biermer as opposed to the original teaching of Addison has continued to be felt in all later work.

Priority.

(4) "The question of priority resolves itself into this—Who first drew attention to the anæmia, to its fatal course, and to the absence of any anatomical changes as the essential etiological feature? To Biermer belongs this credit." (Eichhorst, 1878.)

Priority.

(4) The claim here put forward and reiterated by almost every German writer, that "to Biermer belongs the credit of having been the first to study it as a special disease" (Strumpell, 1899); "that he first described it clinically and anatomically, thereby introducing it into pathology"; "that he first made known its whole symptom-complex to the medical world" (Grawitz, 1896); that all subsequent works dealing with this anæmia are based directly or indirectly, consciously or unconsciously, on Biermer's work"—these claims cannot for a moment be admitted by any observer acquainted with the facts. As Professor Eichhorst writes (1878): "We come to the result that this, the 'primary' form of pernicious anæmia, was first described in England, both in the form of single cases and as a definite clinical disease."

Etiology.

(5) "One has to distinguish between (i) *primary*, *essential*, *idiopathic* forms, and (ii.) *secondary*, *deuteropathic*, *symptomatic* forms caused by (*a*) pregnancy and childbirth; by (*b*) disturbances of digestion; (*c*) hæmorrhages and discharges; (*d*) unhealthy surroundings. (Eichhorst, 1878.)

"In a number of cases (the fewer) the disease occurs with-

Etiology.

(5) "I do not recognize any primary or secondary forms of this disease any more than I recognize primary or secondary forms of typhoid fever or tuberculosis. In all cases it has its special (infective) etiology. As an infective disease it may occasionally, like typhoid or tuberculosis, occur in those who are already the subjects of other diseases. In such cases it can

out recognizable cause—*idiopathic*, *primary* form ; while in others recognizable causes precede it—*deuteropathic*, *symptomatic* form. In the latter group a feature is the gross disproportion which exists between the causes and the effects. . . . In short, a kind of predisposition is essential to the development of the disease." Eichhorst, 1878-91.)

(6) "Occurrence, causes and origin." Factors discussed : (i) More common in certain localities than in others ; (ii) more common in women than in men ; (iii) age ; (iv) heredity ; (v) constitution of the patient ; (vi) life circumstances ; (vii) *bothriocephalus* anæmia (designated as "progressive pernicious anæmia with a known etiology") ; (viii) syphilis ; (ix) intestinal disturbances ; (x) atrophic processes in stomach or intestine ; (xi) cancer of the stomach ; (xii) bone-marrow changes. (Ehrlich and Lazarus, 1893-9.)

(7) "After all these cases have been described there remain cases of pernicious anæmia in which not a single point can be got out of the history that throws any light on the origin of the disease—cases in which clinical observation and *post-mortem* examination alike fail to reveal any changes in the organs to which the severe disease can be referred—it is these which must be characterized as 'primary,' 'essential,' 'crypto-genetic' anæmia.

"It is not to be doubted that even among these there are many forms which are entirely different from one another in their origin and pathogenesis." (Lazarus, 1900, p. 107.)

be diagnosed during life and after death by the characteristic clinical features and pathological changes which I have described. What interest the so-called 'secondary' forms have, arises largely from the circumstance that they include a large number of the real 'primary' forms, their so-called causes being in fact the symptoms, effects and lesions of the real disease.

(6) The conclusion of Biermer, almost unanimously accepted by subsequent observers, that all ordinary anæmia-producing factors, if only severe enough, are potential causes of this disease (in so-called "secondary" forms) has in my experience neither pathological nor clinical basis. The disease with all its characteristic hæmolytic changes and clinical features and course cannot in my experience be produced by such factors alone, however severe they may be. No fact in connection with the etiology of the disease stands out more clearly in my own mind than this one. (1888-1900.)

(7) This is *Addisonian Anæmia*. It is to this anæmia that the author's conclusions as to its hæmolytic (1888) and infective nature (1900) refer, and to which his statement applies that "both clinical observation and necropsy reveal definite infective and hæmolytic lesions invariably associated with the disease, and a very definite number of points can be got out of the history, which throw light both on the mode of origin of the disease, and on the sources of infection."

Pathology.

(8) Pigment changes are neither constant nor pathognomonic. (Quincke, 1876-95, and all German observers.)

"The essential feature of the anæmia is megaloblastic degeneration of the bone-marrow, denoting a reversal to an embryonic type of blood-formation as the characteristic feature of the conditions." (Ehrlich, 1892.)

Pathology.

(8) From all those anæmic conditions which appear *clinically* most closely analogous to Addisonian anæmia—the anæmia of septic disease, of wasting disease, and of loss of blood—Addison's anæmia is sharply and clearly distinguishable by its pigment changes—the large excess of iron contained in the liver (1888) and the kidney.

The anæmia of Addison's anæmia is the result of greatly increased hæmolysis taking place in the portal blood, and caused by the absorption of a specific hæmolytic poison from the digestive area. (1888.)

Megaloblastic degeneration is a secondary effect—the result of the action of the poison on the bone-marrow. There is no anæmia in which the blood-forming powers are more active, and the powers of recovery more remarkable than in this disease.*

* (*See* Charts 3 and 4, p. 148.)

Infective Nature.

(9) Regarding the isolated observations of Klebs, Frankenhauser and Petrone and Perles, as to the presence of flagellate and leptothrix organisms in the blood :—

"All these observations have had the fate that, after being published by their authors, they have not been confirmed either by the authors themselves or by others." (Ehrlich and Lazarus, 1900.)

Infective Nature.

(9) "The disease is not merely a special form of anæmia, but a well-marked infective disease, with typical mode of onset and definite site of infection. It is characterized not merely by (i) anæmia, but also by definite local and general effects, viz. (ii) hæmolytic ; (iii) glossitic and gastro-intestinal ; (iv) toxic (febrile and nervous)." It is of hæmolytic nature, gastro-intestinal site and toxic origin.

These poisons are not of digestive origin (*e.g.*, poisonous food products), nor are they the outcome of mere putrefactive (bacterial) action (1889). They result from a *Special Infection* localized to the *mucosa* of the alimentary tract (1889-1900). No portion of the *mucosa* of this tract from the lips to the anus is safe from the infection. But one of its most easily recognizable sites is the tongue, where it occasions

a glossitis (1889), presenting clinical and pathological features of a striking and distinctive character, of great persistency (1900), often for considerable intervals of time becoming quiescent, but always liable to resume their activity; causing in the early stages and at periodic intervals definite lesions with marked soreness and tenderness of the tongue; in the later stages both these features tend to disappear in the absence of local inflammatory reaction, owing to the profound anæmia which prevails.

A similar infection (with similar variations in gastric and intestinal symptoms) may be found in the mucosa of the stomach and intestine, the actual seat of injury being determined by local pre-existing septic lesions of the mucosa.

The infection is of *drain origin* with marked hæmolytic action. In a large number of cases its time of onset can be determined by the occurrence of a peculiar infective glossitis with tenderness of tongue.

In the contraction of this infection, oral, gastric, or intestinal sepsis is a factor of paramount importance: (i) By creating catarrhal (in severe cases ulcerative) conditions of the mucosa of the mouth, stomach, or intestine, which enable the special infection to take root (1899); (ii) by occasioning a concurrent septic condition, which greatly facilitates the persistence of the real infection after it has taken root (1900), and the removal of which greatly promotes recovery. (1900-7.) (*See* Charts 3 and 4, p. 148.)

The typical mode of development of this anæmia is thus in my experience a history of antecedent oral, gastric, or intestinal trouble which extends usually over many years, caused by, or associated with, sepsis—with or without some "septic" anæmia. This is suddenly followed by a rapidly developing anæmia which is out of all proportion to the actual extent or severity of the symptoms or lesions connected with the mouth, tongue, stomach, or intestine. The sudden development of the severest anæmia, marked by hæmolytic changes (urobilinuria), *glossitis*, &c., denotes the introduction of a new factor (not a special predisposition of the patient), viz., a definite contraction of the hæmolytic infection. Once the infection is contracted the history is no longer merely one of oral, gastric or intestinal trouble, as it was before, but one of intense anæmia with all the characteristic (anæmic, hæmolytic, gastro-intestinal, febrile and nervous) features of Addison's anæmia.

Unity or Plurality.

(10) "The name *progressive pernicious anæmia* denotes no one condition, no special disease. There are varieties of the disease differing in etiology and in pathology." (Eichhorst, 1878.)

"We must continually keep in mind that we have not to speak of a disease *sui generis*, but of a frequently recurring group of symptoms met with in very different conditions of diseases." (Ehrlich and Lazarus, 1900, p. 91.)

Unity or Plurality.

(10) Addison's "Idiopathic Anæmia" is a specific infective disease, with characteristic and constant etiology and pathology. It is a disease *sui generis*, with characteristic clinical features, and clinical course, and it should be distinguished by its own name of *Addisonian Anæmia*.

Clinical Features.

(11) The clinical picture presented by the disease shows no special features; these are only results of the anæmia, and can therefore be met with in other forms of anæmia. (Eichhorst, 1878.)

"The clinical picture is dependent alone upon the degree of anæmia; specific symptoms independent of the want of blood scarcely occur." (Eichhorst, 1891, p. 23.)

"All the clinical changes depend upon the poverty of the blood. The fever and nervous symptoms are likewise secondary and anæmic—the former being caused by irritation or perhaps paralysis of the heat moderating centres; the latter on similar causes, more rarely on hæmorrhages." (Eichhorst, 1891, p. 34.)

Clinical Features.

(11) "So far from the anæmia being the sole feature of the disease, and the cause of its symptoms, it is only one of the symptoms.

"There are three other groups—hæmolytic, glossitic and gastro-intestinal, febrile and nervous—no less striking and characteristic, and even more distinctive than the anæmia itself.

"These are caused not by the anæmia, but by the infective agencies underlying the disease, and they display a remarkable periodicity in their occurrence." (1888-1900.)

Diagnosis.

(12) "The essential changes are blood changes, especially the presence of megaloblasts. The discovery of megaloblasts is proof positive of the existence of pernicious anæmia. The most important point in diagnosis is the discovery of megaloblasts." (Ehrlich and Lazarus, 1892-

Diagnosis.

(12) It is the existence of the four groups of features above described that constitutes the complete clinical picture presented by this anæmia. The essential changes are not the blood changes, and megaloblasts are neither constant nor pathognomonic. In many stages of the

1900, and many other observers since 1892).

disease they are not present—or, as admitted by Ehrlich, are so few in number that they have to be searched for through several slides with the aid of an oil immersion lens—and even then, when discovered, it may be doubtful whether they are megaloblasts or normoblasts. Moreover, megaloblasts are found in other forms of anæmia (lead poisoning). (*See* p. 174.)

The author bases his diagnosis not on the presence or absence of megaloblasts, but on the whole assemblage of features above described—especially on the glossitic and hæmolytic phenomena. In every case, without a single exception, analyses of organs *post mortem* have confirmed the accuracy of the diagnosis made during life. (*See* p. 110.)

"*Megaloblastic Anæmia*" and "*Progressive Pernicious Anæmia.*"

Ehrlich's distinctions are so important and far-reaching that it becomes necessary to separate the megalocytic and megaloblastic anæmias from the normocytic and normoblastic, *even if this division does not correspond clinically with Biermer's division of pernicious anæmia from other forms of anæmia.* We come, then, to the result that we are here concerned with the conditions characterized by the features described by Biermer and Ehrlich. But *we must continuously keep in mind that we have not to speak of a disease sui generis*, but a frequently occurring group of symptoms met with in very different conditions of disease (p. 92). (Lazarus, 1900.)

I consider that we must regard as pernicious anæmia those cases of severe anæmia which correspond to the clinical picture described by Biermer and possess the blood condition described by Ehrlich, irrespective whether such cases occur in individuals previously healthy, or in those already affected with disease, and irrespective whether the anæmia runs a fatal course or not. (Schauman, 1900.)

Megaloblastic Criteria and Addisonian Anæmia.

I regard the extension here given to the title "pernicious" as—*happily for clinical medicine*—the *reductio ad absurdum* of the fitness of that name for any anæmia. For it is pathologically *wide enough to include* an anæmia (tapeworm) which has nothing progressive or pernicious about it in the literal sense of these terms. And it is *narrow enough and clinically erroneous enough* to exclude (1) many cases of Addisonian anæmia through long periods of their course when no megaloblasts are present in the blood; and (2)—what is even more remarkable—it excludes from the rank or title of "pernicious" the form of anæmia which next to Addisonian is actually the severest, and is most commonly mistaken for that anæmia, viz., "Septic Anæmia." *For the blood type of this anæmia is normoblastic.* (*See* Map 1, p. 65; and p. 176).

CHAPTER VIII

Relations of Addisonian Anæmia to "Septic Anæmias."

Addisonian Anæmia.

Nature.—The disease is not merely a special form of anæmia, but a definite and—in regard to mode of onset and site of infection—a well-characterized *specific infective disease of hæmolytic nature* localized in the alimentary tract—one in whose contraction long-lasting *sepsis*, oral and gastric, plays an essential and important antecedent and concurrent part.

Symptoms.—So far from the anæmia being the sole feature of the disease and the cause of all its symptoms and lesions, it is only one of the symptoms. There are always three other groups—*glossitic and gastro-intestinal*, *hæmolytic*, *febrile and nervous*—far more characteristic, and in regard to the site of infection far more instructive, than the anæmia itself, caused not by the anæmia but by the infective agencies underlying the disease.

Diagnosis.—The disease can be diagnosed even in its early stages—with certainty—*during life*, by considering (1) its mode of onset with special reference to the *glossitic* and *hæmolytic* symptoms; (2) the degree of blood change, which in a few weeks or even days invariably follows these symptoms, as well shown in Charts 1, 2, 4, pp. 147, 148; (3) the characteristic groups of symptoms which I have described; and *after death* by the no less characteristic hæmolytic changes in the liver, bile, kidneys, and spleen.

Etiology.—The clinical foundation of our knowledge was, in my judgment, laid deep and broad by the first describers, Combe (1822) and Addison (1855), when they originally characterized the disease as insufficiently accounted for by the usual causes of the anæmic state. The different conclusion of Biermer for the condition he termed "progressive pernicious anæmia," and since then termed "Biermer's Anæmia"—so largely accepted by the great majority of later observers (namely, that all ordinary anæmia-producing factors, if only severe enough, are potential causes of the disease, and that Addison's anæmia is only one form of this condition) has, in my experience, neither etiological nor pathological basis. Addison's anæmia cannot, in my experience, be produced by such factors alone however severe they may be; and cases of this

kind can, I consider, be successfully excluded—during life by the absence of the characteristic grouping of clinical features, and still more easily after death, by the absence of the pigment changes which I have described. I, therefore, do not recognize any primary or secondary forms of this disease, any more than I recognize primary or secondary forms of typhoid fever or tuberculosis.

The question as to the value of Addison's and Biermer's conceptions respectively is not the narrow one of priority of observation as has been too often and too hastily assumed, but the far more important one of the existence or non-existence of a special disease. The conclusion reached by the author as the result of the twenty years close investigation he has given to the subject is that the anæmia first described by Addison (1855) as "idiopathic" is in every way a "remarkable" disease entitled to separate recognition. It is a remarkable chronic infective disease, whose antecedents, mysterious mode of origin, infective and hæmolytic lesions, and clinical features, and intensely grave characters, fully entitle it to all the interest which it has aroused.

On the other hand, the investigations here detailed which have led to the above conclusions have also made it clear that whatever real interest attaches to Biermer's anæmias is derived almost solely from the circumstance that they include a far larger proportion of cases of the real Addisonian (idiopathic) anæmia than its chief exponents imagine.

(1) The so-called "primary," "cryptogenetic" forms are by no means always Addison's Anæmia. Many of them are "Septic Anæmias."

(2) But many of the forms termed "secondary" are true Addisonian anæmia. The so-called "causes"—gastric and intestinal disturbance and the like—to which they are referred, are, in the judgment of the writer, quite erroneously so designated, and are really among the chief symptoms. They have as much right to be termed its causes as the diarrhœa or other gastro-intestinal disturbances of typhoid fever have to be termed the causes of the fever and clinical course of that disease.

The foregoing constitute, according to my observations, the grave *Infective Anæmic Disease* here described.

"Septic Anæmias."

(1) "*Septic Anæmia.*"

In both the foregoing class of cases (Addisonian anæmia), oral, gastric, and intestinal *Sepsis* plays, according to the author's investigations (1900), an important antecedent and concurrent part

as a factor facilitating the contraction of the disease, although not itself able to produce the hæmolysis and clinical course characteristic of the disease. (*See* p. 82.)

But sepsis is in certain cases able, according to the writer's observations, to produce a degree of anæmia more than any other resembling in severity Addisonian anæmia, but differing from it in certain notable respects, particularly in the absence of hæmolysis, of bone-marrow changes, and clinically in the favourable course of the anæmia if the septic cause be removed in time. To this anæmia he has given the title "Septic Anæmia"; and, according to his experience, many cases of this anæmia are *constantly* included within the group termed "pernicious anæmia," and indeed not a few within the Addisonian group termed "primary" or "cryptogenetic." (*See* Vol. ii.) Severe cases have from time to time been described under the title of "Aplastic anæmia." (Vol. ii.)

(2) "*Megaloblastic Anæmias.*"

"Progressive pernicious anæmia" as defined by its most recent exponents (Ehrlich and Lazarus, and Schauman), *excludes this "septic" anæmia* (*sic*) although it includes such cases as were never contemplated by Biermer himself, still less by the observers of "idiopathic" anæmia. For according to its latest definition it is "an anæmia characterized by the clinical features described by Biermer, and the blood changes (megaloblastic) described by Ehrlich, even if this division does not correspond clinically with Biermer's division of pernicious anæmia from other forms of anæmia." (Lazarus, 1900; Schauman, 1900.) Such a definition, in the writer's opinion, represents the final stage of degradation which this progressive pernicious anæmia of Biermer has reached. For it can then be held to include such widely different forms of anæmia as easily curable tapeworm anæmia, and the severest and most fatal forms of Addison's anæmia; and what is equally striking, if adhered to, it would in his experience certainly exclude many cases of the true primary or Addisonian anæmia, which often for lengthy periods of their course show no megaloblasts in the blood. (*See* p. 174.)

(3) "*Tapeworm Anæmia.*"

Lastly, it includes a form of anæmia of which observers in this country have no experience, and which indeed, is almost a local variety limited to Finland—the form of anæmia associated with the intestinal parasite, *Bothriocephalus latus*. To this form the greatest importance is attached by the exponents of "Biermer's

anæmia." It is declared to be "progressive pernicious anæmia with a known etiology." (Ehrlich and Lazarus, 1900.) It is even asserted that apart from Schauman's very extensive observations regarding this anæmia our knowledge of the etiology of progressive pernicious anæmia would be absolutely *nil*. The present writer cannot admit that this claim is in any sense justified. His earlier observations regarding the hæmolytic nature, gastro-intestinal site, and toxic origin of Addison's anæmia which form the basis of all his subsequent work, were carried out (1885-8) and confirmed by many others (1888-94) some years before Schauman's first studies (1894), and ten years previous to the later studies of Schauman and Tallqvist (1898). And his later studies (1890-9) regarding the infective nature and the *rôle* of sepsis in the true Addisonian anæmia were carried out in typical forms of that anæmia, and their accuracy would not be in the slightest degree affected if bothriocephalus anæmia had never existed. (*See* p. 177.)

Insufficiency of Ordinary Causes.

To a degree which they themselves have never recognized or acknowledged, the whole etiology of "Pernicious" anæmia as built up by its workers has from the very first largely rested on Addison's foundation; that is to say, whenever its so-called causes have one and all been absent, the anæmia has been summarily disposed of by being termed the Addisonian variety—"primary, cryptogenetic"—and no further attempt has been made to throw light on its nature or mode of origin. Moreover, even for the large group of "causes" which they consider responsible for the anæmia—*e.g.*, worms, gastric disturbance, intestinal disturbance, hæmorrhages, &c.—all the chief exponents of "progressive pernicious anæmia" have to admit that these causes are not themselves sufficient, but that "something over and above" is required. (*See* Scheme III.)

(1) "A gross *disproportion between cause and effect*," "a kind of *predisposition*," are essential features. (Eichhorst, 1891; Lazarus, 1900; Grawitz, 1901; Schauman, 1900.)

(2) "*Something over and above*, which transforms the worm from a comparatively harmless inhabitant of the intestine to an important disease-producer . . . under certain conditions not yet fully ascertained"—such is the admission that has to be made by Lazarus (Ehrlich and Lazarus) with regard to the anæmia caused by the bothriocephalus, which he just immediately before declared to be "progressive pernicious anæmia with a known [*sic*] etiology, . . . fully [*sic*] explained in its etiology if not also in its pathogenesis."

(3) "We cannot explain these blood diseases without assuming the existence of *an individual predisposition*; . . . many points still dark in this difficult subject,

notably *the extraordinary persistence and progression of the disease after to all appearance the cause is removed.*" Such is the admission of Professor Grawitz, one of the strongest and most recent (1901) upholders of the theory of the gastro-intestinal origin of the disease from auto-intoxication—its cause being "a vicious circle" of blood changes, gastro-intestinal lesions, altered digestion and absorption, and auto-intoxication, the auto-intoxication causing the blood changes, these causing the atrophy of the glands, this atrophy producing altered digestion and absorption (which in turn increases the anæmia), and this latter causing the auto-intoxication. And yet, curiously enough, the disease persists and progresses after all these "causes" are removed. A similar *predisposition* is admitted by Dr. Schauman to be necessary for the occurrence of the severe anæmia (which more than any other observer he has studied and thrown light upon) associated with bothriocephalus anæmia, "since there are a great number of men whose blood is not in the slightest degree affected by the worm, *although the worms of these men contain*, as shown by Dr. Schauman and Dr. Tallqvist, *the same toxic bodies as other worms.*" (1900.)

(4) "*The causes of the initial anæmia are still imperfectly known*, and cases sometimes occur in *people apparently healthy and living under good conditions.* . . . In some cases after death hæmorrhages have been so few that I have doubted very seriously whether they could ever have been very numerous, . . . so very few that this might lead us to adopt Hunter's view that in some cases at least a blood-destroying body may be the cause of the condition" Such is the admission of Professor Stockman, the most recent and chief upholder of the view that the disease is due to the ordinary causes of anæmia aggravated by internal hæmorrhages. (1895.)

Put together, all these admissions and qualifications form an "underpin" of remarkable size and strength for an erection whose foundation, declared to be a solid one, is "that a spontaneous origin *without clear etiology* is the exception."

(*See* Schemes I and III.)

Conclusion.

Ordinary etiological factors cannot account for the extraordinary and mysterious severity of Addisonian anæmia. It has a special etiology underlying it.

If the author has been able to throw any light on the nature and etiology of the severe conditions of anæmia comprised within Addison's and Biermer's widely different conceptions it is largely due to two circumstances: (1) It was his good fortune to approach the subject (1885), not from the surface, where his attention would probably have been engrossed by the conflicting views—historical, clinical, and etiological—connected with the disease, but from the ground (physiological and pathological) underlying the whole group of these severe anæmias. (2) While working there he came almost accidentally, as it were, upon a great bed-rock of hæmolysis underlying Addison's anæmia (1885), and in endeavouring to expose its size and relations (1886-7) he no less suddenly found the whole superstructure built upon Biermer's different foundation

tumbling about his ears. For instead of a bed-rock of hæmolysis, such as he found *in all cases* of Addison's anæmia, he found, underlying the alleged ordinary causes of this anæmia, a mass of rubble of various kinds, of which hæmolysis was quite the *least* prominent constituent. In consequence of these observations he was able to recognize and to point out very early (1888) the existence of the great "underpin," which the chief builders upon Biermer's foundation are recognizing only now (1891, 1895, 1900, 1901). (*See* Schemes I and III, pp. 28 and 44).

"With regard to all these so-called causes—malnutrition, gastritis, loss of blood, cancer (*et hoc genus omne*)—it is necessary to assume that there have been superadded *certain other factors* essential to Addisonian anæmia *on which its severity and unusual course depend.* [In the case of *Bothriocephalus latus some pathological factor other than the presence of worms must be at work* to explain, on the one hand, the frequent presence of worms without anæmia; on the other hand, the occurrence even in Finland of cases of "pernicious" anæmia—specially intractable cases too—without any worms.] For these reasons I am compelled to conclude for malignant disease and other alleged ordinary causes that *their presence alone* cannot be held as sufficiently accounting for the Addisonian anæmia *occasionally* associated with them." (1888.)

Further experience only served to confirm the conclusions then come to. "In my own mind no fact stands out more clearly in connection with the etiology of the disease than that none of the above causes, *not even sepsis*, can of itself produce Addison's anæmia with its characteristic hæmolytic changes, clinical features, and course." (1900.) On the contrary, my endeavour has been to expose more and more the bed-rock of hæmolysis underlying Addison's foundation. (1890-1900.)

The pathological factor I drew attention to in 1888 was hæmolysis of unusual constancy and degree. My later observations reveal that the "something over and above" ordinary causes necessary to produce Addisonian anæmia is not "predisposition" or "a vicious circle" of changes, but (1) a *specific* (hæmolytic) *infection*, whose site and lesions (the tongue, stomach, and intestine), approximate time of contraction, and probable source I have been able to lay bare; and (2) while doing this they have laid bare a great stratum of *septic infection* which favours the contraction of Addison's anæmia, but forms to a large extent the foundation of those forms of severe anæmia which clinically most resemble Addisonian anæmia, viz., "Septic Anæmia." (*See* Frontispiece.)

CHAPTER IX

Infective and General Etiology.

Infective Etiology.

It is, I find, this septic infection which gives to certain anæmias the resemblances which have led them to be mistaken for Addison's anæmia. In them the "septic factor" is so predominant that I have for some time past distinguished them in my own mind by the title of "Septic Anæmia." The features of severe forms of this anæmia are : (1) The highest degrees of oligocythæmia of normoblastic type, usually with low hæmoglobin ratio, and *with very variable leucocytic characterization according to the presence or absence of other complicating infections ;* sometimes the existence of poikilocytes, normoblasts (and occasionally even megaloblasts, to which so much *distinctive* importance has erroneously, in my experience, been attached by Ehrlich and most observers) ; (2) hæmorrhages ; (3) grey yellow, anæmic complexion ; (4) very frequently the existence of oral, gastric, and intestinal sepsis and symptoms ; (5) fever ; (6) severe and fatal course which some cases may take ; (7) nervous effects and symptoms in many cases ; and (8) favourable prognosis if cause be removed in time ; it is distinguishable, however, from Addisonian anæmia by (9) absence of the hæmolytic changes and of the hyperplastic marrow changes found in Addisonian anæmia. The changes are essentially aplastic. (*See* p. 156.)

In Addison's Anæmia, on the other hand, the septic factor is, according to my observations, a most important antecedent and concomitant, *but not the only factor.* It precedes the disease, creating conditions of mucosa in mouth, stomach and intestines which permit *the contraction* of the *specific* (hæmolytic) *infection* underlying the real characteristic features of the disease. These features include a far more definite series of blood changes, of hæmolytic character and of greater severity than in septic anæmia. They include, moreover, other features which mark it off from septic anæmia : (1) Most important pathologically, an *intense hæmolysis*, accompanied by pigment changes in the liver, kidney, and spleen—these changes being, according to a series of forty analyses made in the author's cases during the last seven years, no less characteristically absent in "septic anæmia," even

the severest forms. (2) The occurrence of a *glossitis* possessing *peculiar clinical features*, as I described (1900), and even more *striking pathological characters* (*see* Plates, i-vii), and associated with a deep-seated *infection* of the tongue itself, as I have ascertained bacteriologically. (3) The contraction of this infective glossitis coincides approximately with the onset of the severe anæmia and its accompanying hæmolysis, so that in some cases with a clear history the patient can date the onset of his disease from a particular month when this glossitis was first noted. (4) The source of this hæmolytic and glossitic affection which thus, comparatively speaking, *suddenly* comes on is connected (when the history can be clearly obtained, viz., as many as 25 per cent. of cases) in all cases with an *exposure to drain poisons*. (5) The hæmolytic infection, once taken root in the mucosa and substance of the tongue, in the mucosa of the stomach, and in some cases in the mucosa of the intestinal tract, is extraordinarily persistent, healing up in one part for a time, then spreading to another—these variations in activity as they can be seen during life in the tongue being attended by an aggravation of all the features of the disease—viz., increased hæmolytic changes (marked by urobilinuria, lemon colour, attacks of "liver congestion," and sometimes by jaundice); glossitic, gastric, and intestinal symptoms; febrile and nervous disturbances; and, lastly, increased anæmia.

For purposes of clearness, and in view of the importance attached by the writer to the hæmolytic, glossitic, and gastro-intestinal lesions above described, the history of the observation and interpretation of these changes is given in full in the following Sections. (Part V, Pathology.)

Further consideration of the character of the glossitic and gastro-intestinal lesions will be given in Volume II of this work—dealing with the Pathology, Clinical Features, Diagnosis, Prognosis, and Treatment of this Disease.

General Etiology of Twenty-five Cases.

The facts in connection with the general etiology observed in twenty-five consecutive cases under the care of the author (1900-3) may be summarized as follows:—

Age varied from 32 to 72 years. The average age was 51 years, the majority of the cases being between the ages of 40 and 60 years.

Sex.—Nineteen cases were in men and six were in women.

(*Compare* Biermer's conclusion that his anæmias were most common in women.)

Station in Life.—There were seventeen private patients and eight hospital patients. (*Compare* Eichhorst's conclusion that he had never found Biermer's anæmias in a person in good circumstances of life.)

General health in all the cases was good.

Poverty.—In no case did this play any part in the production of the disease, nor did *bad food* or *insufficient food*. As one of the hospital patients put it, he had always been careful about what he ate and drank, and had been in a position to gratify his wishes in those respects. (*Compare* Biermer's opposite conclusion.)

Pregnancy or *Puerperal Troubles.*—In none of the six cases in women did pregnancy or puerperal troubles play any part.

Loss of Blood.—In no case was there any previous loss of blood, and in the few cases—the very small minority—in which epistaxis occurred this was only slight in amount and not very frequent in occurrence ; it occurred only after the disease was already well developed, and was not a factor in its original production.

Malignant Disease.—In none of the twenty-five cases was there reasonable ground for suspecting malignant disease, and in none of the seven cases examined *post mortem* was any malignant disease found.

Gastric or Intestinal Disturbance.—A history of antecedent gastric or intestinal disturbances, as I shall presently show, was found in every case. In no case were these of sufficient character or intensity to account for the supervention of such an intense degree of anæmia. The various disturbances connected with this tract have an important significance, which I have brought out, not as causes of the disease but as symptoms of the gastric and intestinal infective lesions presently to be described associated with the disease.

Chronic Discharges and Suppurations.—In no case were there any discharges or suppurations sufficient of themselves to originate the anæmia. But in twenty-four of the cases there was a well-marked history of antecedent "oral sepsis." (*See postea*, vol. ii.)

Anatomical Lesions.—In all the cases observed during life, twenty-five in number, and in the cases, seven in number, in which *post-mortem* examinations were obtained, I found (1) striking *hæmolytic changes*, and (2) certain infective *lesions* in the *tongue*, *stomach*, or *intestine*, either singly or associated with each other. The most notable of these was (i) a peculiar form of *glossitis* presented by every case, and not found in any class of case resembling

Addisonian anæmia ; (ii) *gastritis* or *gastric atrophy*, more or less in every case, and most intense in three cases ; (iii) a patchy *enteritis* —in one case croupous—in three cases. With regard to these, the point to be emphasized now in view of the significance I shall subsequently attach to them is : in no case were these lesions either in anatomical character or severity sufficient of themselves to *originate* the intense anæmia by any interference with nutrition they may have been capable of producing. (*See* Plates, Chapters XV-XVIII.)

Summary.—In all the twenty-five cases the anæmia might well have been described in Addison's own words—viz., as " occurring without any recognizable cause whatever ; cases where there has been no previous loss of blood, no exhausting diarrhœa, no chlorosis, no purpura, no renal, splenic [miasmatic], glandular, strumous, or malignant disease, . . . and without any organic lesion that could properly or reasonably be assigned as an adequate cause of such serious consequences." (1855.) On the other hand, to not one of the cases could Biermer's description of the etiology of " progressive pernicious anæmia," which has so largely influenced the views of most subsequent observers, be applied. "A spontaneous origin *without clear etiology* is the exception." In all the foregoing cases an apparently spontaneous origin was, on the contrary, the rule *without exception.*

Conclusion.—The first clear conclusion in regard to the etiology of these twenty-five cases was this : that even *on clinical grounds* the disease could not reasonably be ascribed to the ordinary causes of anæmia, since (1) it originated without the presence of these ; and (2) each and all of these are often present in severest degree without causing the anæmia. In that respect Addison's original etiological foundation has been proved, so to speak, even to the naked eye—*i.e.*, clinically—as far as my own work is concerned, to have been much more solidly laid than that of Biermer. *Some other factor* was required to account for the disease in all these cases.

With regard to these twenty-five cases—and the same applies to *fifty other cases* since observed—no better description of their general etiology could be given than the one originally given by Professor Immermann (1874) in his first (and most important) paper on Biermer's anæmia. He wrote (the italics are the present writer's) :—

> The etiology of *this independent form of disease* is still dark. We only know certain helping causes and predisposing factors, *but not the essential* (*? specific*) *cause.* If the causes are such as Biermer describes, the wonder is why more people do not

suffer from the disease. It is *quite inexplicable* to me why social misery, pregnancies, diarrhœa, epistaxis, and the like should relatively often cause the disease in Zürich, as Biermer describes, while in neighbouring Basle the same conditions hardly ever produce the disease. I have only met five cases among 7,000 patients, and none of these had been in poor circumstances.

The astonishment here expressed was the same as that felt by another great physician—Professor (Sir William) Gairdner, of Glasgow—who had been acquainted with Addison's anæmia from 1849 onwards :—

Although in my "Clinical Medicine" in 1862 I had described one case and alluded to several cases which I believed, and still believe, to be of this kind, the elaborate Memoir of Biermer (*i.e.* Müller, 1877) found me unprepared to do more than look with *vague astonishment* on the vast superstructure he had erected, and which I was disposed to attribute to local predominancy in his field of observation of what I *held to be a rare and very peculiar disease*. I *now* [1903] see what has happened. (*See antea*, Chapter V.)

The effect of Biermer's work is thus described by another independent observer—a student in 1861. Professor Sir T. Clifford Allbutt, Regius Professor of Medicine in the University of Cambridge, writes (1908) :—

Of my St. George's teachers Dr. Barclay was one ; but my vivid recollection is of the great interest taken in Addison's anæmia—as distinct, of course, from Addison's disease—by Dr. Bence Jones, whose keen intellect was specially manifest in diagnosis. So far as the clinical phenomena are concerned, my recollection is that no very considerable points were overlooked, although, of course, the toxic hypothesis, as you understand it, was unimagined.

I do definitely remember forming the opinion at the time, and probably teaching it in my lectures, that Biermer had *thrown Addison's definite conceptions into confusion*. Such being the case, I did not take very much trouble, with my pupils or in my own work, to give any special consideration to Biermer's point of view.

Inexplicable confusion and astonishment were thus the effects produced on the minds of great clinical physicians by Biermer's etiology. This being the case, the question arises how it was that Biermer's anæmia was so quickly identified with Addison's anæmia ; why the name "pernicious" or "progressive pernicious" given by Biermer was taken over by English physicians for something which they regarded as different from Biermer's anæmias. The author has sought to reveal this by a close perusal of the literature of this period—with interesting results, which will now be described. It turns out that the identification was a huge mistake, for which Immermann and an unknown editorial reviewer in an English journal are jointly responsible.

PART IV

NOMENCLATURE

CHAPTER X

Origin of Confusion in Nomenclature.

To the problem as to the real nature of Addison's anæmia Biermer's account added another of a totally different and altogether subordinate kind, which from that time onward up even to the present date has proved a perfect curse to the whole subject. This was the problem of *Conception* and *Nomenclature;* of the identity or non-identity of "idiopathic anæmia," and "progressive pernicious anæmia" — of Addison's conception with Biermer's conception; controversy as to what Biermer's conception really was; as to what he wrote; as to what he really meant; and as to what his various interpreters have imagined to be his meaning.

The result has been a confusion without its equal in the history of the interpretation of any disease—one which has proved a source of infinite trouble to every worker at the subject, as the present writer's experience has shown. He thought to free himself from this confusion by stating in the preface of his former work that his observations referred to the anæmia described by Addison and to that alone; but all in vain. And hence in this work he has decided—for the first time in the literature of the subject—to keep apart the two subjects of "Addison's anæmia" and "Biermer's progressive pernicious anæmia." For the confusion which prevails applies to the latter, not to the former; and how great and widespread that is, the following extracts from some of the writings of the leading exponents of Biermer's anæmias will show.

The author has carefully examined the early history of the subject in this relation, and has come to the conclusion that the premature and erroneous assumption of the identity of "idiopathic

anæmia" with "progressive pernicious anæmia" made by English and Continental observers alike is traceable to four circumstances: (1) The confusion as to Biermer's meaning, shared by Biermer himself, his words lending themselves to a double interpretation; (2) the first interpretation put upon Biermer's work by Immermann (1874); (3) the circumstance that the first English account of the work of Biermer was taken not from Biermer himself, but from the first account of Immermann (1874); (4) the second interpretation put upon Biermer's work by Immermann (1879), characterizing his first one as "absurd"—*a change of opinion never noted by English observers.*

Biermer's Account (1871).

(1) The chief cause of the subsequent confusion that arose was undoubtedly the want of precision and clearness in the first words of Biermer's address (1871), as to the anæmia with which he was dealing. He entitled it "a form of *progressive pernicious anæmia*" (the italics are his), as if the latter were a well-known condition, and he was dealing with a special "form" of it. His subsequent clinical and anatomical account referred to that form. But on the other hand, his account of the etiology was such as could apply not only to that but to every other form of severe anæmia. The result was that while a few subsequent observers, *e.g.*, Strumpell (1899), have considered the particular "form" to be the condition he designated "progressive pernicious anæmia," the great majority of German observers have, with greater plausibility, contended that "Biermer's anæmia," "progressive pernicious anæmia," was any severe form of anæmia produced by the various causes which he described. (Quincke, 1877; Eichhorst, 1878; Birch-Hirschfeld, 1892; Ehrlich and Lazarus, 1892-1900.)

Immermann's First Account (1874).

(2) In 1874 Professor Immermann reported three cases, and summed up his conclusions as follows:— (*See* Maps, pp. 65 and 66.)

There exists a peculiar form of severe anæmia distinguished by its progressive pernicious course, and its almost invariably fatal termination. The affection is one to be separated from chlorosis, leukæmia, and other pathological processes as *an independent form of disease*, for which Biermer's title appears to be most suitable. The etiology of the disease is so far dark, inasmuch as we only know certain "helping causes" and predisposing factors, but not the essential (? specific) cause. The geographical distribution presents interesting differences. All the symptoms are a result of the poverty of the blood.

The references here to "a peculiar form . . . *of unknown (? specific) cause* . . . to be separated . . . as an independent form of disease . . . with almost invariably fatal termination," were an exact parallel to those of Addison's original account—"a very remarkable form of anæmia . . . this very remarkable disease . . . presenting in every instance the same character, pursuing a similar course, and, with scarcely a single exception, followed after a variable period by the same result." If, as Immermann asserted, this was the condition termed by Biermer "*progressive pernicious anæmia*," then clearly this anæmia and Addison's *idiopathic anæmia* were one and the same condition, and the condition might be entitled "idiopathic," "progressive pernicious," or "essential," or all three combined. And so it was interpreted by Dr. Pye-Smith (1875) and, following him, other English observers when their first knowledge of Biermer's work was conveyed to them through this article of Immermann, as a glance at the various titles given to the condition in the period immediately following shows. (*See* p. 27.)

First English Accounts (1874).

(3) The earliest accounts of Biermer's work in English medical literature were the following :—

(i) A review of the foregoing in the *British and Foreign Medical Chirurgical Review*, ii, 1874, p. 487. ("Anæmia Progressiva Perniciosa," by Professor Immermann, of Basle, *Deutsch. Archiv. f klin. Med.*, xiii, 1874.)

Biermer was the first to observe and group together a set of cases of progressive and fatal anæmia which partook of certain features and altogether exhibited a pathological unity. In the paper before us Immermann reviews the collected (fifteen) cases of Biermer and Gusserow and adds two more from his own practice. The paper is accompanied by clinical details of three cases of this inveterate form of anæmia, with diagrams of the variations of temperature recorded, and the particulars of the examination made after death. The humoral origin of the fever is shown by Immermann to be countenanced by the phenomena both of chlorosis and leukæmia.

(ii) An editorial article in the *Medical Times and Gazette*, ii, 1874, p. 681, under the prominent title, "Pernicious Anæmia : A New Disease," on the same paper.

The acuteness of a Swiss observer seems to have added another to the list of diseases with which the present century has enriched our text-books. Dr. Biermer, of Zurich, has described an affection which differs from ordinary simple anæmia in a marked manner, and which appears to be a disease *sui generis* in the sense defined above. . . . We are not aware that any case has as yet been reported in Great Britain (*sic*), but no doubt there soon will be many observers on the look-out for it, and new light will be thrown on its etiology and course. For the sake of poor human

nature we must, however, hope that so serious a malady may only be due, as Immermann supposes, to special local influences, and that its distribution has not a wide range.

Even if any shadow of doubt had existed—as it did not—among English observers as to the correctness of Immermann's interpretation, that also would have been dispelled by the first German ("casuistic") account which appeared the following year by Scheby-Buch (1876), where the condition was termed "essential anæmia." The conclusion of this paper was in the following clear terms :—

All things taken together, it appears to me certain that the so-called *progressive pernicious anæmia* represents *an independent disease*, which hitherto has not yet been sufficiently marked off; whose chief symptom is a severe anæmia which generally, if not always, ends fatally ; that as yet anything adduced as explaining it is insufficient ; and that it must remain for the future to throw light on the disease.

The attitude of German writers towards this "independent disease," as thus interpreted by Immermann and Scheby-Buch, was clearly the same as that of Addison towards his "idiopathic anæmia," or of Gairdner (1862) towards "this most mysterious form of disease."

Thus by 1876 the identity of "idiopathic" and "progressive pernicious" anæmia seemed complete, and was accepted as such, thanks to Immermann's interpretation of Biermer's account. (*See* Maps, pp. 65 and 66.)

It has now to be pointed out that from this year which seemed to establish the identity of the anæmia referred to in the English and the Swiss account, dates the subsequent pernicious confusion connected with the history of the disease. The writer traces the confusion to four circumstances :—

Quincke's Account (1876).

(4) In that year the title "progressive pernicious anæmia" *suddenly, and quite unnoticed by English observers*, underwent a complete degradation owing to Quincke's interpretation (1876). Instead of being regarded as "an independent disease" . . . "a peculiar form of anæmia," it was asserted with the utmost emphasis to be :— (*See* Maps, pp. 65 and 66.)

Only an extreme form of ordinary anæmia—the possible result of many causes —a mere symptomatic condition like jaundice, uræmia, septicæmia, &c., which present definite clinical pictures, but spring from most different diseased condition ; and that as regards etiology, there is no ground whatever for separating pernicious anæmia from other forms of anæmia. (Professor Quincke, 1876, 1877.)

Eichhorst's Account (1878).

(5) This great and sudden change was completely accepted and endorsed by Professor Eichhorst in his important monograph (1878) ; and this endorsement was accompanied by a criticism of Professor Immermann's view destined to have much weightier consequences than Eichhorst could ever have imagined. According to Eichhorst,

> The chief characters of the new clinical picture drawn by Biermer under the name "progressive pernicious anæmia" are those of a deep-seated anæmia ending fatally, and showing fatty degeneration of the several organs as the only *post-mortem* change. The causes of the anæmia were only of secondary importance in Biermer's exposition. Immermann, on the other hand (1874), lays special stress on etiology, whereas the causes of these anæmias are placed in the background in Biermer's accounts.
>
> *The progressive pernicious anæmia of Biermer is nothing more than a well-characterized group of symptoms which can have very different causes; the progressive pernicious anæmia of Immerman on the contrary is, as he himself states, "a special disease."* (Eichhorst, 1878, p. 17.)

Immermann's Withdrawal of His First Interpretation.

(6) By these criticisms, and by the views of Quincke, Professor Immermann seems to have been most unduly affected. He hastened to characterize as "absurd" all that he had previously said about the special character and independent nature of this disease. (*See antea*, p. 51.) He did not note that Eichhorst, in stating that Biermer had not emphasized etiology (p. 17), contradicted himself subsequently (p. 31) by asserting that

> One cannot emphasize too much Biermer's etiological statement. "'A spontaneous origin without clear etiology is the exception.' From the etiological standpoint there are as many forms of progressive anæmia as there are causes to be found, and it is absolutely necessary we should hold fast to this statement if we desire to be clear as to the degree and character of the services Biermer has rendered to the subject."

Immermann passed this by unheeded, and weakly yielded to Quincke's and Eichhorst's views in the conclusions already seen (p. 51) *which unfortunately passed unnoticed by English observers*, and received no editorial comment as his first conclusions (1874) had done. Instead of "progressive pernicious anæmia" he now termed it "essential pernicious anæmia," and constantly spoke of "pernicious anæmias." He now wrote (1879) :— (*See* Map, p. 66.)

> From the anatomical and clinical standpoint, one must agree with Quincke that under the name "pernicious anæmia" is to be understood nothing more than the highest degree of anæmia apart altogether from the way it has arisen.

Biermer's First Account (1868).

(7) Lastly, and perhaps most important of all, there can be no doubt that Biermer's original conception, properly examined, was far more in accordance with this later interpretation of Quincke, Immermann, and Eichhorst, than it was with that put upon it in the first instance by Immermann.

Nowhere, from first to last, in his accounts did Biermer even hint that he was separating one rare form of anæmia from a group of commoner anæmias. On the contrary, in his preliminary communication (1868) he expressly stated that what he had done was to *group together* both "idiopathic and secondary forms of anæmia" solely in virtue of one pathological process complicating them both, viz., fatty degeneration in the heart and vessels.

Nowhere in this first account did he emphasize the *unknown cause* of his "progressive pernicious anæmia," the chief feature of Addison's conception. On the contrary, the chief point in etiology he emphasized was that "an obscure etiology was the exception," and he was at pains to describe as the causes of the disease the conditions which Addison and all observers of "idiopathic anæmia" (1855-70) considered to be absent or quite insufficient to account for the great anæmia.

In his account (1868) "the peculiarities of his form" were the following :—

> Professor Biermer made a preliminary communication on fatty degeneration of the heart and vessels following on anæmia. He had observed several *cases of idiopathic and secondary anæmia which had become complicated after a time with fatty degeneration of the heart, arteries and capillaries.* These cases were in patients of middle age, anæmic in consequence of great losses of blood, chronic diarrhœa, and such like. (One case was an example of so-called splenic anæmia.) The symptom-complex was of this kind, that very marked heart symptoms (bruits, &c.), venous pulsation, œdema without albuminuria, sometimes capillary hæmorrhages (one total blindness through retinal apoplexy), syncopal attacks, and sometimes swelling of spleen, became added to the anæmia. The author was of opinion that in these cases a law operated similar to that concerned in the necrobiotic fatty degeneration after arrested supply of blood, or defective supply of blood (*e.g.*, by emboli) ; he considered that the occurrence of the degenerative changes in these cases was due to the defective blood condition of the anæmic subjects.

In this communication Biermer struck firmly the keynote of his whole subsequent conception. The cases he had in mind were "patients anæmic in consequence of great losses of blood, chronic diarrhœa and such-like." The anæmia Addison had in view was, on the contrary, "remarkable" inasmuch as all such causes were absent. Biermer *grouped together* by special

name "idiopathic" and "secondary" anæmias on the ground of one complication common to them all, fatty degeneration of vessels. The whole point of Addison's conception was that on account of the absence of recognizable cause he was led to *separate one form* of anæmia—"idiopathic"—from all others.

Biermer's Repudiation of his First Interpretation and of his Exponents' Interpretation (1886).

(8) Biermer's original description of the multiple origin and causation of his anæmia having been fully endorsed, and emphasized as the greatest merit of his work, it only remained, in order to complete the confusion, for Biermer himself to repudiate this interpretation, and contradict both himself and his exponents. This is exactly what happened! For in the only communication known to me (1886) as to his views on this controversy, he emphatically repudiated any such interpretation, and spoke of the "real pernicious anæmia," which he had described as "a perfectly definite anatomical condition whose etiology remained so far (1886) quite unknown," adding that this "real" form was not to be confounded with other forms of severe anæmia, such as that produced by tapeworms, due to known causes.

It is a curious example of the irony of fate that what is termed "Biermer's anæmia" by all later German observers is "a group of symptoms produced by causes of all kinds" (Schauman, 1900); and among its various forms "the one which in its etiology, if not also in its pathogenesis, is fully explained is bothriocephalus (tapeworm) anæmia. This form of anæmia is progressive pernicious anæmia with a known etiology." (Ehrlich and Lazarus, 1900.)

> There is no reason on the grounds of etiology for separating from other forms of severe anæmia, and entitling as "true" pernicious anæmia those cases in which no cause is discoverable, since by this criterion the diagnosis can only first be made after death. (Birch-Hirschfeld, 1892.)

In other words, the conception associated with Biermer's name, for which his description is responsible, is the conception which in his last words on the subject he desired to repudiate.

Nevertheless, it is still alleged (*see* pp. 26 and 70) that the fame of having firmly grasped (*sic*) and defined with greatest clearness (*sic*) the whole essential features of these diseases (*sic*), and made it (*sic*) known to the medical world belongs to Biermer!

Conclusion.

The identification of "Addisonian anæmia" with "progressive pernicious anæmia," made in 1874 by English writers when Biermer's work was first brought to their notice, was a huge mistake, the origin of which has proved almost as difficult to trace as the nature of the disease itself. The result of a very exhaustive analysis of the whole history shows that the mistake arose largely from a single circumstance, viz., that the first account of Biermer's work was taken, not from Biermer, but from Immermann (1874), who described it as "of *unknown cause*"; and that Immermann's later recantation (1879) and apology for having so described it was never noted by English observers, and has completely escaped notice, till now drawn attention to.

Yet, curiously enough, among all the early Continental writers and observers of this disease, there is no one whose criticisms and comments display, in the judgment of the present writer, a deeper insight into and keener appreciation of the real problem which this anæmia presents than those of Professor Immermann (1874 and 1878). Had he adhered to the position he took up in 1874, instead of yielding, unfortunately, to Quincke's views and Eichhorst's criticisms, the result would have been a great service to the subject.

It is to be particularly noted that Immermann's complete change of opinion (1879, *see* p. 91) was not in reference to the *facts of Addisonian anæmia* (*see* p. 85), but solely in reference to Biermer's *name of "progressive pernicious anæmia,"* and the etiology which Biermer, Quincke, and Eichhorst described *in connection with that name.*

While patients have continued to die of the *disease*—Addisonian Anæmia, physicians and pathologists have from that time forward wrapt themselves in fiercest controversy regarding the *name*—progressive pernicious anæmia.

CHAPTER XI

Necessity for Abandonment of the Name of "Pernicious."

To distinguish this remarkable disease from the mixed group of "symptomatic conditions due to many causes," described and spoken of as "progressive pernicious anæmia," and by many as "pernicious anæmias," has thus become an even greater necessity than it was when Addison first described it. "Addisonian Anæmia" would best describe it, and spare the patient the needless cruelty of the name pernicious which both he and everyone dealing with this grave disease bitterly resent. The term "idiopathic" has been given a generic significance, and cannot now be restricted to one form of anæmia, even if it were any more satisfactory than such terms as "primary," "essential," "protopathic," "cryptogenetic," which it is not. The author has always employed the title "pernicious anæmia" as referring to the rare form of anæmia had in view by Addison, occurring "without discoverable cause"; and it has become quite a task each time to explain that it is this form, and not the "progressive pernicious anæmia" of Biermer, "due to many causes," that is meant. For many English writers, and the great majority of Continental writers, use the title "pernicious anæmia" in a generic sense as including all forms of "severe anæmia"; and the result is to add a perpetual confusion about nomenclature to what is already sufficiently mysterious, viz., the nature of the individual conditions of anæmia described.

The Name "Pernicious."

To change the title "pernicious," sanctioned alike by authority and long use, and generally associated in the English-speaking profession with the form of anæmia termed "idiopathic," by Addison, is a step not to be lightly undertaken. But, on the other hand, those who were first responsible for the recognition of a grave disease have the best right to give it a name which connotes it and nothing else.

The history of this disease already given and the history of the subject of nomenclature just referred to clearly show that the name "pernicious" connotes nothing definite—either historically (for even on that point Biermer and his exponents are not

agreed), clinically, pathologically, etiologically, diagnostically or prognostically.

It is a product, from first to last, of grouping together various anæmias on account of superficial clinical, pathological and hæmatological resemblances. The process by which this has been done is correctly described by Sir William Gairdner in his striking commentary (*see* p. 47), namely, that of working up *casuistic* into groups determined *a priori*. This was done in the first instance by Biermer (1871)—the particular condition he emphasized *a priori* being "fatty degeneration of the circulatory apparatus" due to many causes. It was followed up by Quincke (1876)—the particular condition he emphasized *a priori* being that "all sorts of causes" *must* be held responsible for Biermer's anæmia, and, *therefore*, any pathological differences, *e.g.*, pigment changes observable in particular cases, must be subordinated to this etiological generalization. (*See* pp. 52 and 103.)

It was completed by Ehrlich's work (1892), emphasizing "megaloblastic degeneration" as a feature of certain forms of anæmia, and (again *a priori*) forthwith identifying this change as "*the special feature* of 'progressive pernicious anæmia,' *even if this does not correspond clinically with Biermer's pernicious anæmia.*" [*Sic.*]

"*The progressive pernicious anæmia of Biermer is nothing more than a well-characterized group of symptoms, which can have very different causes;* whereas the progressive pernicious anæmia of Immermann is, as he himself states, 'a special disease' of unknown (? specific) cause,"—so Eichhorst wrote in 1878, and most observers have since maintained.

Nevertheless, it is still pointed out in this relation by Professor Eichhorst (1898), whose claim to speak with authority is indisputable, "it appears to be nothing more than fair to hold to the name selected by Biermer, since Biermer was (in a sense) the first to rediscover the disease, and the name he gave it is the most appropriate and instructive that could be given" (!). Thus despite all the above definitions Biermer's anæmia is still spoken of as "a disease (!)"—although Eichhorst was the first to call Immermann sharply to account for having so termed it (!) By a parity of reasoning it would be equally just to entitle "fatty degeneration" a disease.

Biermer was (in a sense) the first to rediscover the disease (!), so it is still claimed—although (*a*) Eichhorst himself admitted (1878) that the Addisonian form was first described in single cases and as a general disease by English observers long prior to Biermer; and

(*b*) Biermer himself, and exponents of his anæmias, did not realize the importance of this form (which he afterwards termed the "real, true" anæmia) until Dr. Pye-Smith drew their attention to it in 1875. (!) (*See* Map 1, p. 65 ; also p. 21.)

Lastly, despite its continually changing connotation, the name "pernicious" is the most appropriate and instructive that could be given (!)—although the most typical form, so called according to German interpretation, is tapeworm anæmia, which has nothing pernicious about it, using that term in its literal sense.

Surely in the interests of clinical medicine, not to speak of common-sense, the time has come to put an end, once and for all, to this truly pernicious confusion. To the patient who is suffering from the "real true" thing, the name of his disease is a gross cruelty, and has to be hidden from him ; to the patient who has not got the real disease it is a misnomer and a farce ; to the medical profession it is a cause of endless confusion—a scrap-heap into which is cast at the will of each observer any and every form of anæmia he chooses. A full acquaintance with it satisfies the writer that one-half, or more, of the value of the literature of the subject is completely discounted by doubts as to the nature of the varying conditions to which the name pernicious is indiscriminately given.

The Name Addisonian.

On the other hand, there is no doubt as to what the anæmia termed "*Addisonian*" by English observers connotes clinically and etiologically. It was because the anæmia arose without discoverable cause and was so severe, that they were led to differentiate it from all other anæmias ; and, according to the author's results, this differentiation has been more than justified, since, in his judgment, the condition they described is a well-marked independent infective disease.

If the definition attached by German observers to the title "pernicious anæmia" then connotes something widely different, it is not permissible, but only perpetuates confusion, to reserve this title for the particular form termed "*Addisonian*," by English observers. The name of the Infective Disease, termed Addison's anæmia, must be left to English Medicine, where it was first described.

Nor does it suffice to term it "idiopathic or primary pernicious anæmia," and other forms "secondary"—any more than it would suffice to call the disease characterized by typhoid lesions of intestines, "idiopathic or primary enteric fever," to distinguish it from all the other forms of intestinal ulceration (septic, dysenteric, tuberculous, &c.), which may likewise be accompanied by some degree of fever, and which might just as fitly be termed, by way of distinction, "secondary enteric fevers."

Progress is made by having regard to all features, not by finding features of similarity between and grouping together forms of disease superficially resembling one another. For the future, then, it would be well, since the title "progressive pernicious anæmia" or "pernicious anæmia" connotes nothing definite, to remove the term pernicious from Clinical Medicine altogether—to place under the title of "Addisonian Anæmia" that Form of Disease which we know as the "Idiopathic Anæmia of Addison," and under their own appropriate names of "Septic," "Parasitic," "Chlorotic," "Traumatic," &c., the anæmic conditions connected with these various factors. If, for purposes of clinical characterization and teaching, some general title is required for forms of anæmia presenting resemblances to Addisonian anæmia, then the title "Septic" now suggested would be the most appropriate. It is under that general title that these forms will be considered in a later portion of this work.

There is no real reason why the terrifying and extremely confusing name "pernicious" should be attached to any anæmia, any more than to many other diseases—of liver, or kidney, or lungs, or heart, from which it is out of regard to the patient properly withheld, however severe they may be, and however grave may be their outlook.

So far as observer and patient alike are concerned, the most important requirement is a name which will accurately connote the *Nature* of his disease without reference to its prognosis. The title, which in view of the facts here described, best fulfils this purpose, would be the general title of "*Infective*," instead of the misleading and false name of "Pernicious." Whether the anæmia be found to be of the "Addisonian" or the "Septic" type, this title would accurately describe its main etiological character. It would also, in either case, greatly facilitate effective treatment, by drawing attention to their infective causes, and the necessity for their removal.

PART V

PATHOLOGY

Section I—HÆMOLYTIC LESIONS

CHAPTER XII

The Hæmolytic Lesions.

As already stated, the history of the subject shows that the different interpretations put by Quincke (1876-83) and Hunter (1885-8) respectively upon the pigment changes — the former denying, the latter asserting their constancy and pathognomonic importance—have had as much influence on the later work and conception as the original widely different etiological conclusions of Addison and Biermer.

Constant and Pathognomonic.

As regards *Etiology*, the conclusion come to by the author that the hæmolytic changes in the disease were constant and distinctive, "marking it off from other forms of anæmia clinically resembling it," has from first to last been the basis of his view, that this anæmia is not due to ordinary causes, but is of a special character; it has prevented him seeking for its causes in ordinary factors, such as operate in general anæmia, and has led him to look for the deeper causes operating in those forms of anæmia admitted by all to be "without discoverable cause," "primary," and "cryptogenetic" ("Addison's Anæmia").

As regards *Pathology*, the result has been to invest the subject of hæmolysis with quite a special interest for most English and American observers. This is shown in many ways: (1) by the amount of attention since 1888 given to these pigment changes; (2) the number of analyses made—over 80; (3) the frequent references to these changes and to their importance in the interpretation of the disease. Conclusions regarded at the time of their first publication (1888) as most disputable are now constantly found stated among the most obvious facts relating to the disease—*e.g.*, "the essentially hæmolytic nature of the disease," "the portal site of the hæmolysis," "the gastro-intestinal site of the disease," "the toxic cause," and "the special nature of this anæmia."

For a time, indeed, it seemed as if the most debated points in connection with the disease had been settled—as if there was a general consensus of opinion that we had to deal not with a general anæmia (the conclusion in the second period of its history) but with a truly independent form of anæmia, as Addison had surmised. This, at least, appeared to be the case as far as English and American observers were concerned. The trend of opinion among German writers could not be so easily gathered, since under the influence of Ehrlich's hæmatological studies (1892) and of Schauman's work (1894) on bothriocephalus anæmia their attention had been devoted almost exclusively to hæmatological studies, and they had come to accept megaloblastic degeneration as the criterion of the latter form of anæmia—the best and "fully explained" example of "pernicious anæmia." It was not until the almost simultaneous publication of Ehrlich's and Lazarus's monograph on "Anæmia" (1899) and the author's monograph on "Pernicious Anæmia" (1900) that it became evident how widely the conceptions formed by German writers and himself regarding this anæmia differed. At the time (1895-1900) when he had found further facts (glossitic, gastric and intestinal infective lesions) denoting more than ever the independent nature of this anæmia and its infective nature, all the chief German observers (Eichhorst, 1891; Ehrlich and Lazarus, 1900; Schauman, 1900; and Grawitz, 1901) were asserting, with more emphasis than even Quincke and Immermann had done, that it "was not a disease *sui generis*, but a mere group of symptoms, due to many causes, and having only one constant and pathognomonic feature — to wit, megaloblastic degeneration of the blood and bone-marrow."

How intimately the conception formed regarding the unity of the disease is bound up with the interpretation put upon its hæmolytic changes is brought out in a more obvious and concrete way by the striking contrast between the amount of space devoted to the subject of hæmolysis in the author's monograph on "Pernicious Anæmia" (1901)—the first one on the disease in the English language — and in Ehrlich's and Lazarus's "Die Anämie," Part II, published the same year (1900). In the former no fewer than 150 out of a total of 450 pages are devoted to studies connected with hæmolysis, and these have since (1903) been supplemented by the author by thirty-three further analyses in this anæmia and other diseases. (*See* p. 110.)

As pointed out by the author, the degree of these pigment changes is of utmost importance in the diagnosis of the disease.

He states indeed (1900) that the whole of his later conclusions regarding the special infective nature of this anæmia incorporated in his treatise "have as their basis his pathological observation regarding the hæmolytic nature, the gastro-intestinal (portal) site, and special character of the hæmolysis; without this basis it would not be justifiable to attach to the symptoms and lesions connected with this tract the special significance which he has been led to attach to them."

The interpretation put upon the pigment changes has equally influenced the conception of others regarding the nature of this mysterious anæmia. All observers who have been impressed with the importance of hæmolysis as the striking feature of this anæmia (Mott, 1889; Crozier Griffith, 1891; Hale White, 1894; Gowland Hopkins, 1893; Muir, 1894; Coupland, 1898; and many others) have seen in the class of facts relating to hæmolysis, toxic nature and gastro-intestinal site (1888) the strongest argument in favour of this anæmia being a remarkable independent form of anæmia of mysterious origin, as was the conception of its original describers. (*See* Extracts, pp. 57, 58, 59.)

Inconstant and Non-pathognomonic.

On the other hand, all who have adhered to the conclusion of Quincke that the pigment changes are not distinctive, but only denote hæmolysis as a feature of *some* cases; or regard them as the result of extravasations (Stockman, 1895; Lazarus, 1900); or make no mention of them in their cases (Grawitz, 1896, and most German observers); or regard disturbance in blood-formation as the essential feature of the anæmia with or without an increased destruction (Russell, 1889; Earl and Purser, 1889; Henry, 1889; Ehrlich, 1892; Grawitz, 1896; Ewing, 1904; Gulland, 1905; Eichhorst, 1891 and 1898)—all these observers have continued to regard the disease as merely "a group of symptoms, not an etiological unity" (Schauman, 1900); "not a disease *sui generis*, but a frequently occurring group of symptoms met with in very different conditions of disease" (Lazarus, 1900); "the result of well-recognized debilitating causes aggravated by bleedings" (Stockman, 1895); "a clinical condition—any profound and apparently causeless anæmia characterized by peculiar alterations in the blood and tending to pursue a progressive or pernicious course" (Bramwell, 1899); "a form of cachæmia which may arise from causes known or unknown" (Pepper and Stengel, 1896).

In Ehrlich and Lazarus's work (1899) the whole subject of these pigment changes is dealt with in three paragraphs, and thus summarily characterized and interpreted:—

"In a certain connection, as yet not quite explained, with the tendency to hæmorrhages there is the abnormal richness in iron (siderosis) of internal organs, missed only in a few cases of pernicious anæmia. It must, however, be clearly pointed out that according to the *post-mortem* reports it has also been frequently shown that the organs which in one case were rich in iron contained in a parallel case the least. (Immermann.) An increase of iron is found in the first instance in these organs which are the seats of formation and destruction of the blood elements, *e.g.*, in the spleen [where, according to Hunter, it is least marked and sometimes absent], the bone-marrow, the lymph glands, and in specially high degree the liver. Further, iron is found where it is normally absent—in the epithelium of the kidney and pancreas."

The whole subject of these pigment changes is dealt with in half a page of three paragraphs, and no analyses are given. The subject of the liver is dealt with in one paragraph; that of the spleen also in one paragraph, the only change described being "a simple hyperplasia" [hæmolytic changes are not even mentioned, although this organ, according to Hunter (1888), is one of the chief seats of active hæmolysis].

The influence of Quincke's teaching on German work (1883-1902) has thus been most marked, both as regards etiology and pathology. Just as his views (1876-7) regarding *etiology* profoundly influenced all the work of the period 1870-88 (Immermann, Eichhorst, Bramwell, Stephen Mackenzie, Coupland and others), so they have continued to influence and even dominate all later German work and conceptions (Ehrlich, Lazarus, Grawitz, Schauman, and others). No less marked has been the influence of his *pathological teaching* regarding the non-pathognomonic character of the pigment changes on views of German observers. With but few exceptions (and these only dating from 1895, *i.e.*, Schauman and Tallqvist, 1898; Quincke and Stuhlen, 1895), the whole subject has in German literature since 1883 received relatively little and superficial attention. The presence or absence of pigment changes is not noted in the individual cases recorded (since 1888), as it constantly is in English literature. Observations and analyses regarding the existence and degree of the pigment changes (to which since 1888 so much importance

has been attached by the author and other English and American observers) are comparatively few in German literature.

The neglect of the subject in German work of this period is perhaps most striking in the case of the anæmia—bothriocephalus—whose relation to pernicious anæmia has been so keenly discussed by German writers from 1886 onwards, since it has come to be regarded by them as "pernicious anæmia with a known etiology" (Lazarus, 1899). Thus Schauman, to whose important work we owe most of our knowledge regarding this anæmia (one hardly known outside Finland), in his important monograph in 1894, discussed fully the two alternative conditions of (1) failure in blood-formation, and (2) increased blood-destruction as the essential nature of this anæmia, and gave his adhesion to the latter as the most probable. He made no mention, however, of pigment changes as having any bearing on the matter, whereas the whole question of the nature of this anæmia could, according to the author (1888), have been definitely settled by observations and analyses regarding pigment changes similar to those he adduced for Addison's anæmia in 1888. It was not till 1895, and then by Professor Stockman, of Glasgow, that two analyses were made, showing increase of pigment denoting increased hæmolysis (or as Professor Stockman would interpret it, the existence of hæmorrhages) in this anæmia. It is only within the last few years, from 1898 onwards, that the subject of hæmolysis in connection with this form of anæmia has received the attention and elucidation at the hands of Schauman and Tallqvist (1898), presently to be noted (p. 175).

Such, then, has been the influence of Quincke's teaching regarding these pigment changes which he was the first to describe (1876); so slight was the importance attached to them by German observers that when twenty years later (1895) his pupil, Stuhlen, at his request again made them the subject of further study—he wrote "that since that time (1876) the observations were too few—*only eleven* (*sic*)—to decide whether the changes were pathognomonic or not—probably not, since the disease may be the result of the most various causes."

Yet, by that period (1895) the acceptance of their pathognomonic importance was almost general in English literature as the result of the author's teaching and numerous confirmatory observations of others. Their distinctive character has been accepted as one of the most fundamental facts relating to the disease by the great majority of English and American observers from 1888 onwards.

Truly, as Professor Ewald remarks (p. 58), English and American work appears to be "too little known" to German observers.

CHAPTER XIII

OBSERVATION AND INTERPRETATION OF THE HÆMOLYTIC PIGMENT CHANGES (1876-88).

PERIOD II (1876-88).

Observer.	No. of Cases.	Nature of Observations.	Relation to the Anæmia.
1876-83. Quincke, with Peters (1882)	9	In 5 marked. In 2 slight. In 2 absent. *Inconstant and Non-pathognomonic.* Five analyses: average percentage of iron, 1·098. Three analyses in other diseases: average percentage of iron, 1·494.	Significance uncertain; administration of iron during life could nor be excluded. (1876.) A feature of *some cases* perhaps denoting (1) hæmophthisis or (2) diminished excretion of iron as a result of marasmus; *absent in others*, denoting anæmatosis (failure in blood-formation) as their special feature (this class the one of first order). (1880-3.)
1895. (Description of the above observations given later (1895), by Quincke and his pupil, Stuhlen (1895).	—	"The deposition of iron in the liver cells and capillaries is, as Peters and I found, a very common occurrence in different diseased conditions — in pernicious anæmia, in many cachectic conditions, in febrile diseases, and in acute intestinal catarrh of children." (Quincke, 1895.)	"In the five more severe cases of siderosis, the breaking down of corpuscles must have gone on not only in proportion to the cachexia, but in more marked degree, so that their disappearance was perhaps the starting point of the disease and created a real *hæmophthisis*. Later on—with the advancing marasmus of the whole body and of the liver cells—a siderosis of the liver has occurred." (1880, p. 215.)
1895. Stuhlen (at Quincke's request).	6	(With control observations in eight other conditions.) "The number of cases investigated since 1876 is too small—only 11 (!)—to say whether this increase of iron is constant in pernicious anæmia. This is not at all probable, since the pathogenesis of the disease appears to be a very variable one. Since, moreover, siderosis occurs in other diseases, as Quincke and Peters have shown, *this condition of the liver cannot be regarded as pathognomonic of pernicious anæmia.*"	"The condition found in pernicious anæmia can be compared with that found by Quincke after transfusion." (*Compare* Hunter's opposite results, *postea.*)

1877. Rosenstein...	1	Analysis for iron: Liver, 0·518 per cent.; spleen, 0·227 per cent.	"More probably due to administration of iron than to increased death of red corpuscles."
1877. Müller	—	(No observations.)	"No pathogenetic significance whatever; depends probably on the free administration of iron as a medicine."
1877. Lépine	—	"Deposit of granules of sulphide of iron in some organs is not peculiar to pernicious anæmia."	"If this depended on increased destruction of corpuscles one could not understand why it should only be found in the portion of the pancreas touching the intestine."
1878. Eichhorst	—	(No observations.)	"In all cases recorded, there is the suspicion that the increase is an artificial one, due to the overloading of the liver with iron preparations."
1879. Immermann	2	"In one case pigment was abundant, in another absent." "A questionable discovery, not pathognomonic for pernicious anæmia, since it is neither found in all cases, nor does it occur only in pernicious anæmia. I have found it in typhoid fever."	—
1878. Stephen Mackenzie ...	1	"Parenchymatous inflammation of the liver with hæmorrhages into the softened areas."	"The excess of iron found in the liver by Quincke possibly stood in some relation to these extravasations, but it has to be borne in mind that these cases had been taking iron medicinally."
1881. Coupland	—	—	"The observations of Quincke require to be confirmed. The excess of iron is probably due to iron administered medicinally."

Observer.	No. of Cases.	Nature of Observations.	Relation to the Anæmia.
1881.			
Stahel	1	Iron: In the liver, 0·614 per cent.; in the spleen, 0·091 per cent.	"Very unlikely that the great excess of iron is due to medicine." (Possible relation to blood-destruction or to character of the anæmia not mentioned.)
	(Analyses in 9 other diseases.)	Average of iron: In the liver, 0·083 per cent.; in the spleen, 0·171 per cent.	
1882.			
Graanboom	? 1 (of doubtful nature which he regarded as a form between pernicious anæmia and leukæmia.)	Excess of iron in the liver, 0·396 per cent. Average in five other diseases, 0·081 per cent.	"The result of our investigation in respect of the high percentage of iron in Case 1, as well as in respect to the great differences between different organs, and between the same organs in different diseases appears to favour the view that the greater part of the iron belongs to the parenchyma as such." (No other comment or conclusion.)
1883.			
Pye-Smith	—	No observations. (No mention of pigment in his own account of the liver changes; first observation of such changes in Guy's Hospital was November, 1888.) (*See* Hale White, 1890.)	Quincke's observations. "Possibly due to administration of iron, perhaps to blood-destruction." Addison's anæmia does not depend on increased destruction of red corpuscles, but it shows the same evidences of such destruction as syphilis, malaria, and poisoning by lead and mercury in the deep colour of the urine, the peculiar lemon tint of skin, and quite possibly in the excess of iron in the viscera.

1885-6. Hunter (Gold Medal Thesis, University of Edinburgh, April, 1886). "The physiology and pathology of transfusion, and the Fate of extravasated blood."	1	Very large excess of iron in the liver; little or none in the spleen. Experimental observations regarding nature and seats of blood-destruction in health, after transfusion, and after extravasation of blood. The great excess in the liver and the peculiar distribution of pigment between liver and spleen in pernicious anæmia *not* producible by transfusion or extravasation of blood, but most closely produced by chemical agents, such as phosphate of soda.	If pernicious anæmia be due to some weakness of the red corpuscles, their destruction ought to go on, and pigment be found in all the usual organs, especially in the spleen. But none is present in the spleen in this case, whereas it is extremely abundant in the liver. In pernicious anæmia we have to do with an organism whose blood corpuscles are being destroyed with unusual rapidity. The conclusion seems unavoidable that excessive destruction of blood (on the part of the liver) is a far more important factor in the production of forms of anæmia, characterized by their perniciousness, than has hitherto been considered probable or even possible. So far as my observations at present go, I am inclined to refer the great majority of cases of anæmia, if not all of them, to one or other of two conditions: either to diminished production of corpuscles or to increased destruction. Chlorosis exemplifies the former—probably induced by faulty assimilation of iron. But the case is quite otherwise in other cases of anæmia, such as those to which the name "progressive" or "pernicious" have been applied. In the two cases we have to do with entirely different conditions. The latter, so far as my observations show, must be regarded as the result of an excessive destruction of red corpuscles mainly within the liver, as evidenced amongst other things by the extraordinary amount of blood pigment within the liver cells in that disease. Confirmation of this view of the pathology of pernicious anæmia can only be obtained after examination of the various organs in a great number of cases. The material for such a study, I have hitherto, unfortunately, not been able to obtain. (April, 1886.) (The material of nine cases obtained, and the experimental investigations continued till 1890, with reference to the nature and seats of blood-destruction in health and disease, and the peculiar excess and distribution of pigment in pernicious anæmia). (Results recorded in 1888.)

Observer.	No. of Cases.	Nature of Observations.	Relation to the Anæmia.
1886.			
Zaleski	1 (with 3 analyses in other conditions).	Iron in liver, 0·623 per cent. Average of iron, 0·083 per cent.	All the previous analyses have a very limited value, since in all of them hitherto no attention has been paid to the varying quantity of blood in the organs examined. This error applies especially to the liver. *Conclusions:* Iron is a constant and integral constituent of the liver tissue, its quantity varying within very wide limits. The whole of it is exclusively in the form of organic compounds, either albuminates or nucleo-compounds; since it varies greatly in quantity, the *term "pathological siderosis" introduced by Quincke has really no meaning.* (No mention of blood-destruction, or of the pathology of pernicious anæmia.)
1886.			
Silbermann	—	"On the pathogenesis of essential anæmias." (No mention of pigment changes.) The two chief questions regarding blood diseases: (1) the place and nature of blood-formation; and (2) the importance of hæmoglobin for the red corpuscles as well as for the whole bodily metabolism. The general effects on the body of blood-destroying agents on the body have not, I consider, received adequate attention; and it is with these I am concerned, more especially with the power of hæmoglobin in causing fibrin-ferment intoxication. These observations give, in our opinion, a full and satisfactory explanation of the nature of certain blood diseases. Experiments with laked blood, glycerine and pyrogallic acid. The effects that followed he ascribed to the formation of fibrin-ferment, with stagnation of blood in the venous system or arterial anæmia. By gradual injections of small doses, an anæmia of a very severe character, closely resembling pernicious anæmia, producible.	We have in pernicious anæmia to do with a blood exceptionally rich in fibrin ferment; and it is this that explains all the characteristic symptoms of the disease, pallor, systolic murmurs, a typical fever, severe digestive disturbances, &c. The primary part of the process is hæmoglobinæmia, and the circulatory disturbances resulting therefrom; the secondary part is defective blood-formation. It *is through* the *disturbance of blood*-formation (*hæmatopoiesis*) *alone, that* the *anæmia*, the *weakness, systolic murmurs are to be explained.* These new points of view are applicable to other forms of anæmia. For we believe that *the essential anæmias differ from each other not in nature, but only in degree.* This applies especially to certain forms of chlorosis and of primary simple anæmia. If we imagine that in these anæmias the red corpuscles are in any manner (by bad food, disease, discharges) injuriously affected, so as to cause hæmoglobin to escape into the plasma, we have then a hæmoglobinæmia of moderate degree and all the consequences above described will follow, including a defective blood-formation. To the question, "what it is that leads to this increased destruction of blood, and to the hæmoglobinæmia, no precise answer can be given, since the *process may be the result of very different diseases.*

1888. Hunter (*Lancet*, Sept. and Oct.): "An investigation into the pathology of pernicious anæmia." Also (*Practitioner*, Aug., 1888): "Is pernicious anæmia a special disease?"	9	*Microchemical Observations.* Excess of pigment in liver, little or none in spleen. Constant in all, and of great pathognomonic and pathogenetic importance. Far in excess of that met in other conditions at all resembling it. Experiments (1885-90) to explain this peculiar excess, and distribution of pigment; the nature and seats of blood-destruction in health and disease; the absence of hæmoglobinuria in this anæmia. *Results.* (1) *The hæmolytic nature.* (2) *Portal (gastro-intestinal) site.* (3) *Toxic cause.* (4) *Bone-marrow changes denote excessive regenerative activity secondary to the hæmolysis of the disease.* *See* PART VII (*postea*). "The blood changes and the pathological changes mark this anæmia as due to excessive destruction of blood—they prove it to be *hæmolytic*, not *hæmogenic*, in its origin." [The term "hæmolytic" was here purposely selected to designate an *active destruction* of blood, as distinct from a mere *wasting* denoted by the term hæmophthisis. It was the first time it was used in relation to anæmia.]	The excess cannot as hitherto be regarded as an accidental condition, the result of some accidental weakness of the corpuscles common to this and other severe anæmias. On the contrary, it appears to me to indicate—*and this I regard as one of the most important results of my study of the morbid anatomy of the disease*, that (1) a destruction of blood occurs in pernicious anæmia, far greater than that met with in any form of anæmia clinically resembling it, or liable to be mistaken for it—notably the anæmia of wasting disease and loss of blood. (2) The liver plays an important part, if not in the destruction itself, at least in the disposal of the hæmoglobin set free. The relation between liver and spleen (as regards amount of pigment they contain) appear to be disturbed in a very striking way in this anæmias, viz., the great increase in the liver is unaccompanied by any proportionate increase in the spleen as is usual in all other diseases. Sometimes there is no excess at all in the spleen. After transfusion, on the other hand, I have always found a very large excess in the spleen, with little or no excess in the liver. This peculiar distribution in pernicious anæmia accentuates the importance of the condition of the liver as one of the most essential pathological changes in this disease. These conclusions receive support from the few analyses already made—*if Quincke's analyses be excluded.* The foregoing observations appear to me to denote that *the essential nature* of *the blood change* is *excessive blood-destruction.*

CHAPTER XIV

The Hæmolytic Nature of the Disease.

Period III (1888-1900).

The reader is referred for full confirmation of the foregoing conclusions to Chapter VI, pp. 57, 58, 59, and 64; also to the author's work on "Pernicious anæmia," (1901, pp. 98-100), for the following and other analyses made during this and the preceding period.

Summary of Analyses (1888-1900).

Condition.	No. of Cases.	Average Percentage of Iron, in Milligrammes. Liver.	Spleen.
Health	4	80	231
Loss of blood ...	3	19	23
Wasting diseases ...	4	53	115
Addisonian anæmia	12	325	175

Period IV (1900-8).

Results of 40 Analyses made in Author's Cases (1888-1908).

Condition.	No. of Cases.	Average Percentage of Iron, in Milligrammes. Liver.	Kidney.	Spleen.
Health	2	86	4	90
Loss of blood ...	1	39	—	—
Ulcerative phthisis ...	2	78	13	481
Gastric cancer ...	4	46	11	378
Severe sepsis ...	13	64	21	136
Addisonian anæmia	18	290	54	113
		344		

Results.

Analyses of the liver, spleen, and kidney in eighteen cases show (1) the large excess of iron, and (2) the peculiar distribution between the liver and the spleen—the reversal of that usually obtaining—to which importance is, in the author's judgment, to be attached. (1888.) The contrast between the results obtained in Addisonian anæmia and those obtained in twenty-two other control

analyses made in other conditions of profound anæmia is exceedingly striking. In Addisonian anæmia the average percentage of iron in the liver and kidney combined was 344 milligrammes, whereas in health it was 90, in profound sepsis 85, in cancer of the stomach 57, and in ulcerative phthisis 91 milligrammes.

(1) It will be noted that the kidney is always included among the organs analysed. This is a point to which I have attached more and more importance during the past twenty years, for reasons which the present series of analyses bring out. They show that the excess of iron present is not always equally distributed between the liver and kidney. In some cases—*e.g.*, Cases 6 and 10—the percentage in the kidney was as large as 133 and 256 milligrammes, the percentage in the liver being 363 and 140 respectively (to ensure absence of any error I had the analyses in these cases repeated). If in the latter case the analysis of the kidney had not been made, the moderate percentage in the liver would not have accurately represented the amount of blood-destruction that had occurred. The varying percentage in the kidney in different cases is notable. It depends, as explained by the writer in 1888, on the overflow of hæmoglobin from the portal circulation :—

> If the destruction is slight the products of it present within the portal circulation are completely disposed of by the liver before reaching the general circulation. If it is excessive at any one time the evidences of hæmolysis extend to the general circulation. Hæmoglobin in the form described passes into the general circulation and is excreted through the cells of the convoluted tubules of the kidney. The most likely cases, therefore, in which to find pigment in the kidneys will be those in which the progress of disease has been marked by specially severe exacerbations—in which, therefore, the destruction has been very great. (1888.)

In Case 10 a notable exacerbation of this kind had occurred during the patient's last relapse, the blood corpuscles falling in the course of three or four weeks from 83 to 32 per cent., and the hæmoglobin from 82 to 35 per cent.

(2) The analyses bring out also in a striking way the second point which was drawn attention to in 1888 as one of the marked features of the hæmolysis in this disease—*the peculiar distribution of pigment between the liver and spleen.* In health and in most diseases the spleen usually contains a higher percentage of iron than the liver (as these analyses show, than the liver and kidney combined), sometimes from six to eight times higher. In Addisonian anæmia, on the other hand, as will be seen, in every case without exception this relation was reversed. The percentage in

the liver alone exceeded that of the spleen, sometimes more than fivefold, *e.g.*, liver 360 ; spleen 69.

(3) I draw particular attention to the analyses in thirteen cases of *profound Sepsis* and *Septic Anæmia*. They prove conclusively that sepsis alone, however severe, cannot cause the pigment changes characteristic of Addisonian anæmia. Case 21 is a typical example of what the author has termed "septic anæmia," the form of anæmia oftenest mistaken for Addisonian anæmia. It was sent to him as such a case, and it resembled this in the general features and appearances, in the degree of its oligocythæmia, and in the presence of marked gastro-intestinal symptoms and extreme oral sepsis. But the urine showed no hæmolytic changes, and there was no history of the glossitis which the author regards as characteristic of this anæmia, and he therefore declared it to be "non-pernicious," and probably of the type of "septic anæmia." A trace of albumin subsequently appeared in the urine, and the patient died from uræmia two months later. At the necropsy I found a large perinephritic abscess in the left loin connected with a calculous pyonephrosis, of which there were no symptoms during life. The pigment changes contrast in a most striking way with those of Addisonian anæmia, viz., *liver* 12 ; *spleen* 95 milligrammes ; so also do the gastric changes. (Plate XI.)

(4) The four analyses in *Gastric Cancer* (35-38) are also of special interest in view of the very prevalent view that gastric cancer may simulate Addisonian anæmia and be a cause of that anæmia. Case 35 was a typical case of this kind, presenting the lemon colour of Addisonian anæmia. The low percentage of iron in the liver is very striking, viz., *liver* 46 ; *spleen* 378 milligrammes. Case 36 was a case of cancer involving the whole body of the stomach. The high percentage of iron in the spleen, viz., 1,330 (as also in the cases of ulcerative phthisis), is noteworthy. It is the condition typically found in long-standing wasting disease depending on inanition. It denotes, for reasons explained by the author in his studies on blood-destruction ("Pernicious Anæmia," 1900), a long chronic process of decay of the red corpuscles, not an acute active hæmolysis.

If Addisonian anæmia could be produced by inanition—the result of gastric atrophy, achylia gastrica, &c., as so many maintain, the distribution of blood pigment between the spleen and the liver would be that illustrated in these last-mentioned analyses rather than the one just drawn attention to in Addisonian anæmia.

Conclusion.

There exists a form of anæmic disease, rare in individual experience, but by no means uncommon in incidence, possessing the clinical features and the mysterious origin described by Addison (*Addisonian Anæmia*). This form is always marked by an extensive hæmolysis as a constant pathological feature. This hæmolysis is not a terminal feature. On the contrary, as will afterwards be seen, it is one of the initial features, and marks its progress from first to last. A similar hæmolysis is no less characteristically absent from those forms of anæmia met with in this country which most closely resemble Addisonian Anæmia, viz., "Septic Anæmia."

The "Hæmolysis" here referred to has nothing to do with extravasations, as the author's experimental studies and chemical analyses (1888, 1895, 1900) conclusively show. As a matter of fact, extravasations are far more common in "Septic Anæmia"—in which such pigment changes are absent, than in Addisonian Anæmia—in which they are constantly present. The statements about their frequency or importance in Addisonian Anæmia are not borne out by the pathological or clinical facts. The results in two cases may illustrate this :—

	Percentage of Iron, in Milligrammes.		
	Liver.	Kidney.	Spleen.
Addisonian Anæmia without any extravasations ...	515	43	23
Septic Anæmia with extensive purpura... ...	69	14	105

To the onlooker, the difference between Professor Ehrlich's and the author's pathological interpretations may appear to be the comparatively slight one — that while the former emphasizes defective blood-formation, the latter emphasizes excessive hæmolysis, as the essential feature of the blood process. In reality, the difference is of a far more fundamental character, *in relation to etiology*. For Ehrlich's interpretation has, as is admitted (*see* p. 44), thrown no light on the origin or causation of Addisonian anæmia, but has only served to group it with a number of other forms of anæmia. The author's hæmolytic interpretation, on the other hand, has by successive steps led to the following results : (1) The recognition of the portal blood as the chief seat of the hæmolysis ; (2) of the gastro-intestinal tract as the seat of the processes which induce this hæmolysis ; (3) the toxic character of these processes ; (4) and, finally, the recognition of their infective character, and of the lesions in the tongue, stomach, and intestine underlying them.

PART VI

PATHOLOGY (*continued*)

Section II—INFECTIVE LESIONS

CHAPTER XV

The Glossitic Lesions of Addisonian Anæmia.

(*With Plates I—VII.*)

Clinical Introductory.

The observation and interpretation of the glossitic lesions form a new chapter in the history of this disease. The history of these observations is summarized in the accompanying tables. The lesions found by the author are represented and briefly described in the accompanying Plates (I—VII). Since they can be best observed during life, they will be more fully described in Volume II of this work dealing with the clinical features of the disease.

The two important points to which the author here would draw attention are: (1) that the glossitic changes are of varying intensity in different cases—sometimes of an acute and subacute inflammatory character, followed later by degenerative and atrophic changes—at other times more chronic; and (2) that they are closely similar to those met with in the mucosa of the stomach, and, less commonly, of the intestine. (*See* Plates VIII—XVII.)

The clinical observations have been made on *seventy-five* well-marked cases of Addisonian anæmia, which have been under my care during the past seven years. I have made a close study of the *glossitis presented by every one of these cases without exception*, and never observed in any other conditions—its mode of onset, its appearances, its persistence, and above all, its periodicity. In seven cases I have made a similar study of the histological changes presented in such cases; and I have examined three cases bacteriologically, taking the cultures from the *interior* of the tongue free from any contamination with the organisms of the

mouth. These observations have been controlled by similar ones on tongues derived from all sorts of diseases, especially those marked by extreme oral sepsis.

The glossitis here described is not due to "oral sepsis." I have not found it in any of the thousands of cases of that condition which I have closely observed, both in my general experience as a hospital physician, and in my special experience as a fever physician dealing with septic stomatitis of every degree and variety. Moreover, it is not due to anæmia *per se*, for it is characteristically absent in the severest forms of "septic anæmia," however great the degree of sepsis which may be associated with it. Moreover, when once contracted, it persists even after removal of all oral sepsis—even in the absence of any teeth. Plate I, fig. 2, was from a case of this latter kind. The patient had no teeth, and she never complained of her tongue; yet the condition found was that shown in the plate; and a most virulent streptococcus organism was obtained in pure culture from the interior of her tongue.

Although it is not producible by ordinary "oral sepsis," it is most intensely aggravated by such sepsis. The open wounds which it creates (*see* Plates III—VII) leave its lymphatics in free communication with the "oral sepsis"—which, until drawn attention to by the author in 1900, has throughout its history invariably accompanied the disease. The result has been that in addition to the specific hæmolytic infection underlying the glossitis and its hæmolytic anæmia, the patient subject to Addisonian anæmia has always had to contend with an intense "septic anæmia" as an invariable complication of his real Addisonian hæmolytic disease. As I shall subsequently show (p. 156, also Charts, p. 148), the action of this septic infection on the bone-marrow is the reverse of that of the Addisonian hæmolytic infection. It is intensely depressant and aplastic; on its removal the power of recovery of Addisonian anæmia is markedly increased. (*See* Charts, p. 148.) The characteristic effect of the Addisonian infection, on the other hand, is hyperplastic and regenerative. The co-existence of "septic anæmia" is thus, and has hitherto been, the fatal handicap to the patient suffering from Addisonian anæmia. He has really been in the grip of two severe anæmias—one the Addisonian—characterized by increased blood-destruction, with marked powers of blood-formation; the other, the "septic," characterized by defective blood-formation.

On removal of the latter, the effect is immediate (*see* Chart 3,

p. 148); if removed in time before the patient's powers of recovery are completely exhausted, the effect may be permanent. (*See* Chart 4, p. 148.)

The course of Addisonian anæmia, *once freed and continuously kept free* from sepsis, is then seen; and it is such as to make the name pernicious quite unjustified even on prognostic grounds. The case was observed in 1900, fully recorded in my work on "Pernicious Anæmia" (1901, pp. 329-336), and again described six months later in the *Trans. Roy. Med. Chirurg. Soc.*, London, 1901. He has been kept under closest observation for the past eight years, with instructions always to report himself *whenever he had a return of his glossitis.* Throughout the period he has remained to all appearance a stout, healthy-looking man, two and a half stones (35 lb.) heavier than when he first came under treatment. It will be seen, however, from his blood chart (the number of his red corpuscles) that at the end of his first year after recovery (1901) he had a considerable relapse, from which he rapidly recovered; at the end of his second year (1902) a more considerable relapse, with once more rapid recovery; and at the end of his third year (1903) a still more marked relapse, from which he still more rapidly recovered. Since then, for the last five years, his blood has remained stationary at close on 100 per cent., and his hæmoglobin at 100 per cent. to 110 per cent. *The first symptom in each of the relapses was a return of his glossitis*, invariably followed by all the other features of Addisonian anæmia, namely, gastric and sometimes intestinal discomfort, urobilinuria, and lemon colour; extreme sense of weakness, and marked nervous (peripheral) disturbances.

The similarity between the blood-curves of his threatened relapses (the last one in 1903 was the only one which confined him to bed for a week or ten days) and those of the cases shown in Charts 1 and 2, p. 147, marked by glossitis and precisely the same class of features is exceedingly striking.

The same remarkable powers of recovery are shown in all cases. The only difference was one of *vital importance to the patient;* viz., that these powers only sufficed to carry the patient over one relapse (Chart 1, p. 147), or with diminishing strength over a longer period (Chart 2, p. 147), *thanks to their continuous impairment by the co-existing septic infection.* In Case 5, on the other hand (Chart 3), they were more marked from the very outset, more durable, and, up to the present time, permanent (*i.e.*, eight years later), *thanks to the complete removal of all sepsis, and to continuous attention to ensure its non-recurrence.* (Chart 4, p. 148.)

These new facts connected with the improved prognosis and treatment of this grave disease will be fully described in Volume II of the work. They are here touched on for a definite purpose, viz., to enlist the interest of the profession in the class of *Infective Lesions* to which attention has now to be drawn.

The problems of blood-destruction (*Hæmolysis*) are difficult and controversial enough ; but inasmuch as I have dealt with them fully in my former work on " Pernicious Anæmia " (1901), I have felt free to summarize them in the manner already seen. The points of importance in this relation are :—

(1) That the experimental study of that process led me back (1888) for the first time in the pathology of this disease to the *gastro-intestinal tract as the site of the diseased processes underlying it*, and to *toxic causes* as the etiological factor in producing the blood changes ;

(2) That this great generalization—based originally on experimental results—has been amply confirmed for all other severe anæmias—so much so, that Professor Grawitz (1901) is able to affirm " that the doctrine of the enterogenous origin of pernicious anæmias (*sic*), as built up on the observations of different authors, is one of the most practical advances in the domain of hæmatology." (*See antea*, Scheme III, p. 44.)

The problems of blood-formation (*Hæmogenesis*) are, if possible, even more difficult and controversial ; and the author has endeavoured to make them clear to himself and to others in the concluding section of this work.

The ordinary observer may reasonably beg to be excused from even endeavouring to penetrate the mazes which both these processes present to him. He may hesitate to enter, with the certain result of stumbling about in mists of historical controversy ; of getting himself entangled in the thick undergrowth and boggy places of pathological research (the difficulties of " hæmolysis," and the pitfalls of " megaloblastic degeneration ") ; of being bewildered by the number and variety of diagnostic and prognostic sign-posts ; and always of floundering in deep waters of etiology. But when it is made clear to him, as I have succeeded in making clear to myself, that right through the middle of this maze there run deep hidden channels of *Infection*, marked by certain sign-posts (*glossitic*, *gastric*, and *intestinal*), which can be recognized, although hitherto they have been much hidden by the thick under- and overgrowth around them ; that the most important of these sign-posts (*glossitic*) is the one which can be earliest recognized and kept in sight from

the first to the last, the great importance of this line of exploration becomes obvious. When it is further made clear, in ways which I have already indicated, that by following these channels of infection to their sources—a double source is discoverable—one, the *hæmolytic*, not easy to trace, but, nevertheless, in my opinion traceable; the other, the *septic*, easily traceable, and *easily cut off;* and that by cutting off this latter much of the etiological and pathological mystery which have wrapped this disease in darkness can be made to disappear, and the prognostic outlook, both for the patient and the observer, can be made clearer and brighter, then the interest of those called on to deal with this grave disease may be fully claimed for the consideration now to be given to the subject of the *Infective Lesions.*

I have endeavoured to simplify the subject, and make the various observations clearer, by arranging them in tabular form. Their further interpretation will form part of Volume II of this work.

It will be seen that the point of departure of the author's interpretation of these lesions dates from 1888. The interpretation here placed upon the glossitic lesions has been controlled in the way already mentioned. That of the gastric and intestinal lesions has been controlled by a general experience of over 1000 *post-mortem* examinations, and by the histological examination of many cases of diseases of the stomach and intestine, carried out by the methods and with the precautions here described. The work has been carried out in the Pathological Department of Charing Cross Hospital. The photographs here shown of the tongue and intestine are those of specimens prepared by the author, and now in the Museum of that Department.

[*Note.—The histological changes are destroyed in the usual post-mortem method of examining the stomach, viz., by douching it with a stream of water, and roughly handling its surface. To study them, the surface of the mucosa must not be touched by anything, but left intact with all its mucus adhering to it; fixed down by pins on cardboard; hardened, with surface upwards, in Kaiserling's fluid or in Müller's fluid and formalin. Portions from different parts of the stomach must then be embedded in paraffin and examined.* Had attention been confined to the portion shown in fig. 15 and in fig. 19, none of the striking lesions shown in figs. 16, 17 and 18 would have been discovered.]

(*See* PLATES.)

CHAPTER XVI

THE OBSERVATION AND INTERPRETATION OF GLOSSITIS IN ADDISON'S ANÆMIA.

Observer.	No. of Cases.	Character of Observations.	Interpretation.
1851. Dr. Barclay on "Death from Anæmia" (two cases). The first recorded subsequent to Combe's (1822) and prior to Addison's account (1855).	1	In his second case :— "Soon after her confinement she had a sore mouth, for which she applied for advice, and was ordered to leave off beer and meat, and confine herself to slops. To this she attributed her debility, as she had continued to suckle her child, and had never been able to get up her strength properly." (The chief gastro-intestinal symptom in the case was diarrhœa.)	No observations of author. Patient's statement, "to this she attributed her debility!"
1877. Hermann Müller (sixty-two cases of "Progressive Pernicious Anæmia).	5	"In some cases (20, 23, 29, 38, 39) there was a peculiar stomatitis, viz., there formed in the mouth, especially on the tongue and under the tongue, small ulcers of whitish colour, about the size of a split pea, very resistant to local treatment, disappearing spontaneously or with temporary improvement in general health, recurring again without special cause, to the great discomfort of the patient, since they were very painful and made eating difficult—now and then, indeed, almost impossible." Full references in Cases :— Cases 20 and 23, "Stomatitis." ,, 29, "Complains of very painful spots on tongue which render eating almost impossible." ,, 38, "Small ulcers in mouth which render eating almost impossible." ,, 39, "Stomatitis, small ulcers on the tongue and on the mucous membrane of the mouth."	"It seems reasonable to assume that this stomatitis had some connection with the alteration in the blood, that certain chemical products in the blood mixing with the secretions of the mouth, caused irritation and ulceration in a manner similar to that described by Mosler (1866), for the parotid secretion in other diseases."

Observer.	No. of Cases.	Character of Observations.	Interpretation.
1877-80. Quincke (31 cases)	4	Tongue red and sensitive.	No remarks.
1878. Eichhorst (91 collected cases)	1	(Mention of the above observations of Müller.) In one of his own seven cases. Case 4: "Tongue very fissured on the surface."	"Possibly, on account of the pain caused, they are not without significance."
1883. Laache ("Die Anämie"), eleven cases.	3	Case 3: "Tongue smooth, clean, without sign of papillæ. It is considerably hacked at edges and painful here. Some small excoriations in both angles of the mouth. The teeth partly fallen out, the remainder very carious." Later: "He complained not so much of weakness, as of the mouth, which is sensitive and tender (one sees, as before, fissures in angle of mouth; the tongue is smooth, clean, hacked at edges). He mentions he has of late lost all taste, and that he had no sense of smell for several years." Two months later: "Tongue and throat, to a considerable degree, smooth and polished."	No remarks.
		Case 4: The illness began with sudden onset of diarrhœa. "At same time he became 'skinless' (*hautlos*) in mouth" (mouth feeling skinned).	
		Case 10: History.—"In course of last winter and spring his appearance became bad, and at the same time he had a feeling 'of a wound' in mouth and down the throat which prevented him taking anything but cold, fluid, and bland foods."	
1883. Pye-Smith	1	"Tongue pale, sodden, and tender."	No remarks.

1889.

W. Hunter, "A case of Pernicious Anæmia" which was made the subject of extended observations on: (1) urinary changes, excretion of urobilin, blood pigment, iron, aromatic sulphates and diamines; (2) its toxic clinical features; (3) gastric and glossitic symptoms; (4) pigment changes in liver, kidney and spleen; (5) subacute gastritis and atrophy of stomach; (6) their probable infective nature and relation to drain infection.

1

October, 1888. The condition of his tongue troubled him much. Great tenderness on mastication, especially when hot or stimulating food or drinks of any kind were taken. He described the tenderness on swallowing as extending down the throat to the stomach. Tongue extremely raw and flabby, deeply indented by the teeth, presenting a red and fiery appearance, with here and there scattered patches of a more inflamed character, the intervening portions of mucous membrane being smooth, as if devoid of papillæ. The inflammatory redness extended to the anterior pillars of the fauces. There was no uneasiness or tenderness of, or any symptoms connected with, the stomach itself.

March, 1889. Gums very spongy, and some of the teeth loose. Condition of tongue much the same as that previously described; it is not quite so raw-looking, but presents a more atrophied appearance, the mucous membrane being smooth and free from papillæ. At parts over the dorsum and along the edges there are patches of more fiery redness; some under the tip of the tongue showing small inflamed vesicles full of serum. The whole tongue is tender and mastication is both painful and difficult. No acidity or uneasiness in stomach after food; occasional flatulence, bowels irregular, requiring the use of mild laxatives, looseness at times, especially at nights, alternating with constipation. Under treatment a rapid and distinct improvement took place, as regards the condition of the mouth and tongue. The change of treatment took place on March 10. The effect was already obvious on

Relation to Gastric Lesions. — *Post mortem*, marked inflammatory changes, both old and recent, in the mucous membrane of the stomach. The inflammation was localized and at certain parts of the most intense description; the changes in the glandular cells and the infiltration with leucocytes recalling at once the similar appearances frequently presented by glandular structures, like the kidney, when the seat of a localized infection.

Furthermore, the swollen pinkish, translucent appearance of the small lymphatic glands, lying on the wall of the stomach itself — under ordinary circumstances scarcely visible to the naked eye—pointed to some recent, as well as chronic, trouble in the stomach wall itself.

There was, moreover, a definite history of infection in the case, the patient's weakness dating from the time he was exposed to insanitary influences.

I am disposed therefore to regard the gastric mucosa as the seat, not only of the primary infection, but also of the subsequent development of the infection; the *affection of the tongue noted during life being probably of the same nature as that of the stomach.*

The infection was favoured in the first instance by some unhealthy condition of the stomach and tongue. For it is interesting to note that some years previous to the onset of his illness he had suffered from some affection of the stomach designated "gastritis" and that although the condition of his tongue never troubled him till after the onset of his illness, he expressly stated, that *for some time before* he had suffered at times from some uneasiness in the tongue.

Successful infection having once occurred (favoured doubtless by these conditions) the history was no longer one of gastric trouble, but one of steadily-increasing weakness, with all the symptoms we have learnt to regard as characteristic of pernicious anæmia.

Observer.	No. of Cases.	Character of Observations.	Interpretation.
1889.			
The Author (*continued*) ...		March 20. The tongue was flabby and smooth on the surface, but much less so than before. It had lost its former angry red appearance, and was now much paler, and the inflamed patches were less marked, and the vesicles had entirely disappeared. From this time onward he ceased to have any further trouble with his tongue. Its condition was better than at any time during the previous year and a half. The sponginess of the gums had disappeared and the teeth became firm. The tongue always continued to present a smooth flabby appearance; but the tenderness on eating was entirely lost; instead of being a painful effort to take even bland food and drinks, he could take all kinds of food and even condiments without the slightest discomfort.	The evidence adduced in the foregoing case supplements, and also confirms, the conclusions thus arrived at. In the light of the observations made in the case as to the presence of ptomaines in the urine, for whose formation the action of specific micro-organisms is necessary, the toxic character of the clinical features, and the character of the gastric and tongue lesions, I draw the conclusion that the special factor required to initiate the symptoms peculiar to the disease—pernicious anæmia—is the presence under certain conditions of organisms of specific nature within the gastro-intestinal tract. These conditions may, I conceive, be either local and more permanent—malignant disease, various forms and degrees of gastritis with atrophy of gastric glands, or general and more removable—an unhealthy condition of mucous membrane of stomach and intestine induced by the presence of intestinal parasites or by prolonged bad nourishment. [My later observations (1890-1900) revealed that the unhealthy conditions of mucosa of stomach and intestine, which seemed necessary for successful infection to occur, were due to sepsis—"oral sepsis," "septic gastritis" and "septic enteritis."]
1895.			
Ewald	1	A severe case, apparently rescued by transfusion. "The patient was repeatedly troubled by a very annoying tongue affection. There formed, especially on edges of the tongue, but also on the inside of it, on inner surface of lips and cheeks, small round vesicles or papillæ of size of a pin's head, which soon disappeared leaving behind whitish spots, surrounded by a zone of congestion. They remained some days, and disappeared without attaining any greater size than that of split peas. Deeper ulcerations never occurred."	"I have repeatedly seen this condition, which may best be termed erythema bullosum, as Rosenthal (1894) calls it, in very anæmic, especially nervous, patients. It has a certain resemblance to the condition described by Jacobi as 'chronic neurotic stomatitis,' and is quite extraordinarily persistent. I would not term the condition one of *pemphigus*, since pemphigus characters were quite absent, nor yet herpes." The most suitable name for it would be "follicular stomatitis." (Relation to pernicious anæmia not touched on.)

1900. Hunter, "Pernicious Anæmia," a chronic infective disease: Relation to oral and gastric sepsis. And "Pernicious Anæmia," 1901.	12	(1) A *glossitis* characterized by great tenderness, presence of sores, periodicity (seven cases); the glossitis forming one of the chief subjects of complaint (4 cases); and seeming to be connected with the origin of the disease, either preceding the weakness, or most troublesome early in the disease (seven cases). (2) Gastric or intestinal symptoms in all cases. (3) History of "Oral Sepsis" in all cases. "Oral Sepsis," as a cause of "Septic Gastritis and Enteritis," (a great predisposing factor, favouring *the contraction* of Addisonian anæmia, but not capable by itself of producing that disease). *The glossitis is not producible by ordinary "oral sepsis,"* however severe that may be. But once it is contracted, it is greatly aggravated by such sepsis—the open sores on the tongue which it creates (*see* Plates III, IV, V) placing the lymphatics of the tongue in direct communication with this sepsis	"The mode of onset, character and progress of the glossitic conditions denote their infective nature, and the special significance attaching to them is that their existence points to an infection of a definite character, localized to the alimentary tract. "The characters are not those of an ordinary (septic) glossitis; they suggest an infection much more deep-seated and severe; and one of its most noted features—periodicity—recalls one of the most striking characters of the disease itself." This remarkable periodicity I desire to emphasize. It irresistibly suggests the thought, that if an infective process so severe and distressing in its character can affect one portion of the mucosa of the alimentary canal, and yet disappear without leaving any obvious lesion, or at most a slight atrophy, a similar infective lesion affecting other portions of the mucosa of the alimentary tract lower down might cause grave symptoms, and yet leave no obvious lesion behind. In other words, an infection similar to that found in the tongue may well exist lower down; especially in the stomach, possibly in some cases in the intestine. *Such an infection of the tongue, stomach, or intestine, singly or combined, I consider to be the true pathogeny of this disease;* and to be evidenced by, and accountable for, the most striking features of the disease, viz.:— (1) Hæmolysis of a special character originating in the portal area. (2) The prevalence of gastric and intestinal symptoms, *e.g.*, vomiting and diarrhœa during life. (3) The frequency with which morbid lesions when discoverable are confined to the gastro-intestinal tract, especially to the stomach—gastritis, atrophy of glands, &c. (4) The febrile and nervous symptoms of the disease.

Observer.	No. of Cases.	Character of Observations.	Interpretation.
1900.			
Hunter ... ... Examination of the Literature of 165 recorded cases.	8 Reference to the mouth.	(1) "Tongue partly raw and fissured." (2) "A burning sensation in the mouth." For past year troubled with sore gums. (3) "Inflammation of the gums, buccal mucous membrane, and side of tongue." (4) "Stomatitis troublesome." (5) "A deeply drilled-out ulcer on the tongue." (6) Mouth very rough and dry for some time. (7) Tongue sore. (8) "Later on, tongue and mouth very sore."	No remarks.
1901.			
Grawitz	—	Reference to foregoing observations of present writer. (*See antea*, p. 45.)	"My own experience is that no general significance can be attached to these mouth inflammations in this relation ['oral sepsis,' special glossitis], since in the relatively large number of cases which have come under my notice, I have not met with a single case in which there has been any noteworthy primary stomatitis [glossitis]. On the other hand, secondary stomatitis, with severe hæmorrhages into the gums, can arise in pernicious anæmia, as the result of the general cachæmia prevailing."

1903. Hunter, "The Infective Nature and Etiology of Pernicious Anæmia." (*Lancet*, 1, 1903.)	25	(1) Clinical observations on 25 cases regarding (*a*) "Oral Sepsis." (*b*) "Glossitis." (*c*) "Gastric and intestinal symptoms." (2) Pathological, chemical and bacteriological observations on the tongue, stomach, and intestine, in 7 cases, controlled by similar observations in many septic conditions. The occurrence of a *glossitis* possessing *peculiar clinical features*, as I before described (1900), and even more *striking pathological characters*, as I have since found, and associated with a deep-seated pure streptococcal *infection* of the tongue itself, as I now have ascertained bacteriologically (in three cases) (*see* Plates I, II, VII). The *glossitis is not* of a *terminal character*. For as a matter of fact, it is most marked in the earlier stages when inflammatory reaction is possible. In the later stages it becomes *less marked and obvious owing to the extreme anæmia* of all the tissues. *The same applies to the lesions in the stomach and intestine.* (*See* Plates I—VII).	Full confirmation of writer's former observations and interpretation of 1889-1900). A glossitis similar to that above described—not observed in any other condition—not even of extremest oral sepsis. The contraction of this infective glossitis coincides approximately with the onset of the severe anæmia and its accompanying hæmolysis, so that in some cases with a clear history the patient can date the onset of his disease from a particular month when this glossitis was first noted. The source of this hæmolytic and glossitic affection which thus, comparatively speaking, *suddenly* comes on is connected—in all cases when the history can be clearly obtained (20 to 25 per cent.)—with an *exposure to drain infection*. The hæmolytic infection once taken root in the mucosa and substance of the tongue, in the mucosa of the stomach, and in some cases in the mucosa of the intestinal tract, is extraordinarily persistent, healing up in one part for a time, then spreading to another—these variations in activity as they can be seen during life in the tongue being attended by an aggravation of all the features of the disease—viz., increased anæmia, increased hæmolytic changes (in the urine), increase of glossitic, gastric, or intestinal symptoms, and increase of toxic (febrile and nervous) disturbances.
1908.	50	Glossitis in every case. (*See* p. 114.)	*Fullest confirmation of above observations and conclusions.*

CHAPTER XVII

Observation and Interpretation of the Gastro-intestinal Lesions.

Among the lesions occasionally found in cases presenting the clinical features of Addisonian anæmia none have excited more interest or controversy than those found in the stomach and intestine. Like most other lesions found in this disease, they have been variously regarded by those describing them. They have either been interpreted as of no importance—the *result* of anæmia itself—or as its possible *cause* on account of the disturbances in nutrition they may produce. An additional interest has been attached to them on another and different account, namely, that the presence of such lesions in certain cases of this disease has been held by observers to prove that this form of anæmia can be caused by various lesions ; and, consequently, that Addisonian anæmia has no right to be regarded as a disease at all—it is merely an extreme condition of anæmia producible by various causes, among which gastro-intestinal lesions form a prominent group.

Number of Observers and Observations.

Observers who have found such lesions and who have been led to study and record them in the history of the disease from Addison's time (1855) down to the present number some thirty. The actual number of cases so recorded, which form the basis of all the varying conclusions arrived at regarding this class of lesion, is only some sixty. Only a few of these have been histologically examined.

The following table gives the observer, date, number of cases examined, nature of the lesions found, the relation of these to the anæmia, the probable cause of the lesions themselves.

(1) *Nature of the Lesions.*

On this point there is a general agreement amongst observers.

In the case of the *Stomach* the changes described are : (1) varying degrees of fatty degeneration of glandular cells, with or with-

out (2) inflammatory changes, and especially (3) atrophy of the gastric tubules, these changes being accompanied by changes, atrophic or fibrotic, in the other coats of the stomach. As to the relation to one another of these changes, there has been a divergence of views. Some have regarded the process as essentially a degenerative one—an atrophy (Fenwick, Quincke, Nolen, Henry and Osler, Eisenlohr, Ewald, Martins, Grawitz, Max Koch); while others have regarded the process as an inflammatory one leading to atrophy. (Nothnagel, Lewy, Kinnicutt, Rosenheim, Hunter, Mader, Holt, Nonne, Hayem, Fletcher, Faber and Bloch.)

In the case of the *Intestine*, changes have not been so frequently found.

The number of cases recorded in the literature from 1855 to 1888 (Periods I and II) in which some slight lesion was found, varying from atrophy to diphtheritic colitis, was only some seven, recorded by as many observers. The number in the third period (1888 to 1900) was only ten or twelve, six of these being cases recorded by Dr. Hale White (1890) from the records of Guy's Hospital from Addison's time up to 1890. The conclusion come to by Faber and Bloch (1900) as the result of a careful study of four cases was that there was no constant or characteristic lesion. It is not even proved, according to them, that intestinal atrophy occurs, the appearances of atrophy being to a large extent artificially produced, and depending largely on the degree of distension of the gut.

Despite the absence of obvious changes in this tract, the experimental and anatomical observations of the Author in 1888, confirmed by his clinical and chemical observations in 1890, pointed clearly to this tract as *the seat of the toxic processes* underlying the hæmolysis of the disease. This conclusion was subsequently accepted by practically all observers (*see* pp. 55-59) and confirmed in a most striking way by Schauman's and Tallqvist's observations ten years later regarding the hæmolytic action of substances extracted from the bodies of the tapeworm, *Bothriocephalus latus*. (*See* p. 79.) "*We have thus learnt the probable seat of the disease*" was Dr. Hale White's conclusion after a detailed review of the Author's work of 1888-90 (*antea* p. 58); and his careful analysis of the reports of the cases (twenty-nine in number) in Guy's Hospital since the time of Addison, showing that vomiting and diarrhœa are very common, was held by him to support to a certain extent this view. So also Professor Grawitz, 1896 and 1901, and Professor Ewald, 1895 (*see antea* p. 58, and Scheme III, p. 45), and many others. (*See* pp. 56-59.)

Quite apart from the rarity of lesions in this tract or their apparent insufficiency to explain this severe anæmia, the Author from 1890 onward kept his attention closely fixed on the alimentary tract. The results are described in the following summary (1890, 1899, 1900 and 1903, pp. 135-142), and in the accompanying Plates. The outcome was the new series of observations recorded in 1900 relating to the two classes of infective lesions present in this tract, which he then described, viz.: (1) *Glossitis*, with *infective gastritis*, and occasionally *infective enteritis;* and (2) "Oral Sepsis" as a cause of a form of "septic gastritis" and "septic enteritis" common to this and many other conditions. (*See* Scheme II, p. 43.)

The lesions are represented and briefly described in the accompanying Plates. Their anatomical and infective characters will be more fully considered in Vol. II of this work, dealing with the morbid anatomy of the disease.

(2) *Their Relation to the Anæmia.*

This is the subject which more than any other has engaged the interest of most observers, as a glance down the column dealing with this aspect of the subject sufficiently reveals. Most observers, basing their conclusions on the individual cases studied, consider the lesions to be a possible *cause* of the anæmia, on account of the disturbance in nutrition they may occasion. Some, on the other hand, consider them to be the *effect* of the anæmia.

The conclusion formed by the author early in the course of his investigations (1888) was that they were neither cause nor effect of the anæmia; they had rather the character of an infective inflammation, and this infection was probably related to the onset of the disease. This conclusion, it is to be noted, was based largely on the results of the pathological, experimental, chemical and clinical investigations he had previously recorded demonstrating the special hæmolytic nature of the disease, the portal site of this hæmolysis, and therefore the probable gastro-intestinal site of the processes occasioning it. (1888.) The conclusion formed the starting point of the author's further study and interpretation of these lesions.

(3) *The Cause of the Gastric and Intestinal Lesions.*

This has engaged the attention of observers least of all. Henry and Osler thought that abuse of alcohol in their case had probably played a part in producing the gastric atrophy they

described. Morley Fletcher (1899) thought that the extensive intestinal lesions he found in his case might be caused by some *neurotrophic* disturbance, such as that described in the intestinal nerve plexuses by Sasaki and Banti.

On the other hand, it was the possible cause of the gastric lesion that from the first (1888) most interested the author. In the first case he described (1890) he came to the conclusion, for reasons then stated: (1) that the gastric changes were of an *infective* nature, this infection being in some way related to the hæmolytic anæmia; (2) this infection took root in a mucosa previously the seat of some gastritis. As to the nature of this he had at that time no clue. The observations made between 1890-1900, and recorded (*Lancet*, January, 1900) regarding (1) the prevalence of "oral sepsis" in this disease, (2) the existence of "septic gastritis," (3) the relation of the two to one another, viz., "oral sepsis as a cause of septic gastritis," showed that the gastritis preceding the onset of the disease was also of infective origin, viz., due to septic infection.

The observations now to be recorded demonstrate the histological characters and infective nature of the gastric and intestinal lesions found present in all cases. They are an extension of those above referred to. They relate especially to the prevalence and infective character of certain infective lesions in the stomach and intestine similar to those I have described for the *glossitis* to which I have been led to attach so special a significance.

Nature of Author's further Observations.

The observations now to be recorded have been made on seventy-five well-marked cases of Addison's anæmia which have come under my notice during the past seven years. They have been of the following character: (1) Special observations on the mode of onset, naked-eye characters and appearances of the glossitis found in every case without exception, and never observed in any other conditions; with histological examination of the tongue in seven cases, and bacteriological investigation of the tongue in three cases; (2) complete histological examination of seven cases; (3) chemical analyses of the liver, spleen and kidneys in a series of eighteen cases, confirming the diagnosis during life; with control analyses in twenty-two other diseases—two of health, thirteen of severe septic conditions, four of cancer of the stomach, and three of ulcerative phthisis. (*See antea*, p. 110.)

CHAPTER XVIII

THE OBSERVATION AND INTERPRETATION OF THE GASTRO-INTESTINAL LESIONS OF ADDISONIAN ANÆMIA.

Observer.	No. of Cases.	Nature of Lesions and Observations.	Relation to the Anæmia.	Probable cause of Lesions.
1855. Addison, "Idiopathic Anæmia."	1	No observations. Healed ulcers in colon and rectum in one of his cases, 1857.	I have failed to discover any organic lesion that could properly or reasonably be assigned as an adequate cause of such serious consequences.	—
		PERIOD II	(1870-88).	
1871. Biermer, "Progressive Pernicious Anæmia." And Müller, 1877.	3	No inflammatory changes found. The mucous membrane of the digestive tract usually shows no pathological changes except an extreme degree of pallor, or one finds here and there small areas of hyperæmia. The Peyer's patches are usually prominent, but are not swollen. (Müller, 1877.) In one case numerous punctiform and branched ecchymoses in the intestine, and small hæmorrhages with an ecchymosis of the size of a florin in the stomach. In another, extreme pallor, circumscribed patches of hyperæmia, small scattered extravasations, and superficial follicular ulcers (of the size of peas), in the large intestines. In two cases ulcers were found in the lower part of the small intestine resembling hæmorrhagic erosions.	The only organic lesions so far found in some cases which might be blamed for the disease were follicular ulcers of the colon. Biermer, 1870.	The erosions obviously resulted from hæmorrhages. Any other explanation of the ulceration could not be thought of, since they had nothing dysenteric or tuberculous about them. (Müller, 1877.)

1870-7. S. Fenwick, *Lancet*, 1870-1.	7	Well-marked, extensive atrophy of the secretory tubules of the stomach. No evidence of chronic inflammatory condition—a slow degenerative process—not an inflammatory one.	The fatty state of the gastric tubules is often the cause instead of being merely the consequence of the malady. The anæmia is the direct result of this glandular disorganization and the imperfect secretion of gastric juice consequent upon it. All the most prominent symptoms are most easily explained on the supposition that the various tissues are starved of their nourishment. Some of the cases Dr. Addison had in view were instances of atrophy of the stomach, but it was equally certain that not all those at present grouped under the head of pernicious anæmia were of this nature.	No remarks.
1871. A. Flint	—	"On severe anæmia."	Some cases of obscure and profound anæmia depend upon degeneration and atrophy of the glands of the stomach.	—
1873. Ponfick	—	Fatty degeneration of gastric glands in severe anæmia.	—	—
1875. Schauman	1	A case of progressive pernicious anæmia, the gastric mucosa almost entirely deprived of epithelium and the glands very few, and ill developed, also small hæmorrhages and an increase of fibrous tissues.	—	—
1876. Burger	1	Degeneration of gastric and intestinal tubules.	—	—

Observer.	No. of Cases.	Nature of Lesions and Observations.	Relation to the Anæmia.	Probable cause of Lesions.
1876.				
Quincke	1	In one case the mucosa of the stomach very thin; microscopically, the glands appear very few in number.	The atrophy formed perhaps the starting point of the disease in this case.	—
	1	Diphtheritic colitis.	—	—
1879.				
Nothnagel	1	The atrophy of the gastric glands, and an enormous thickening of the walls of the stomach and marked cirrhosis ventriculi.	In this case the atrophy of the stomach is the cause of the anæmia, the essential and chief alteration. "To his knowledge, Fenwick was the first who had associated distinct clinical features with this atrophy."	The cirrhosis, the primary lesion; the atrophy secondary to the cirrhosis, the latter being the result of a gastric catarrh of which there was a nine years history. Whether the atrophy is secondary to an interstitial change in the mucosa, or could occur as an independent disease, he could not determine. He thought it very improbable that we were dealing merely with the effects of an ordinary catarrh.
1877.				
Bramwell	1	"Slight intestinal ulceration."	—	No remarks.
1878.				
Eichhorst	7	Any essential variation from the normal could never, with certainty, be discovered. Only in Case 3 the glandular cells appeared to be slightly fatty. In one of his seven cases the mucosa of the intestine, the upper part of the jejunum, the lower part of the ileum, and the whole of the colon swollen, and œdematous with small hæmorrhages on the edges of the villi.	Changes described can only have a secondary significance, and are to be regarded as results of the anæmia.	No remarks.

1882. Nolen	2	The walls of stomach thin, the glandular cells degenerated, and in some places no glands at all.	The glandular condition is the essential cause of the anæmia which therefore ought to be called secondary.	No remarks.
1883. Pye-Smith, *Guy's Hospital Reports*, 1883.	—	Analysis of 103 recorded cases. Fatty degeneration of the gastric glands frequently observed; occasionally infiltration of leucocytes between the tubules (a muco-gastritis); and sometimes (two cases) a thickening of the mucosa with atrophy of the tubules. Intestine pale, and œdematous with occasional petechial or hæmorrhagic erosion.	The anæmia is primary, essential, without any lesions other than those due to the anæmia.	No remarks.
1886. Henry and Osler ...	1	Atrophy of the gastric mucosa with complete destruction of the peptic glands over the greater part. Towards the pylorus, where the atrophy was less advanced, a small-celled infiltration between the tubules such as occurs in all forms of slow intestitial inflammation.	A careful study of the case justifies, we believe, the conclusion that a primary atrophy of the mucous membrane does occur; and bears out the suggestion of Flint, Nothnagel, and others, that certain of the cases of progressive pernicious anæmia depend upon the profound alteration in the gastric tubules.	It seems natural to conclude that the abuse of alcohol extending over many years played a part in the causation of the atrophy. In Fenwick's cases there was no history of alcohol.
1886. Lewy	1	Extensive degeneration of the gastric mucosa.	—	The result of ulcerative processes which had caused hæmatemesis.

Observer.	No. of Cases.	Nature of Lesions and Observations.	Relation to the Anæmia.	Probable cause of Lesions.
1887. Kinnicutt	2	*Case* 1. In extensive areas of mucosa not a trace of tubules could be seen, elsewhere fatty degeneration of cells of tubules, hyaline degeneration, and small-cell infiltration, fibrous tissue not increased, submucous coat normal. *Case* 2. Almost complete destruction of the tubules of the stomach. The more superficial portion least involved; the greatest destruction affected the deeper portion of the tubules. The atrophy probably supervened upon an inflammatory process.	A primary degeneration and atrophy of gastric tubules occurs, and extensive destruction of secretory structure may be regarded as causal in a certain number of cases of pernicious anæmia. Gradual destruction of the glandular tissues of the stomach, consequent impaired nutrition and fatty changes in the other viscera would seem to represent the probable sequence of events in the two cases. The supposition of a creeping ulceration in explanation of the gastric lesion is untenable. The general and very dense small-celled infiltration points strongly to the probable dependence of this atrophy upon an inflammatory process.	—
1888. Rosenheim ...	2	*Case* 1. Atrophy of gastric mucosa, the glands divided up by interstitial growth. Many of them cystically degenerated. *Case* 2. Mucosa very thin, and glands very few. The atrophy, the result of an intermediate process of catarrh and inflammation (similar changes found in gastric cancer—11 out of 16 cases).	The atrophy may exist for years without severe symptoms, the intestine taking on vicarious functions. When it reaches such a degree as to arrest secretion of HCL altogether, or when any further complication occurs in the digestive tract, even if it be of a similar character, then results the clinical picture peculiar to pernicious anæmia.	No remarks.
1888. Hunter	—	An investigation into the pathology of pernicious anæmia, anatomical and experimental observations establishing the hæmolytic nature, *gastro-intestinal seat*, and toxic cause of the disease. Confirming the results of these experiments, I would now point out that *all the various morbid processes alleged as causes are found exclusively in connection with the gastro-intestinal tract.*	*The gastro-intestinal tract, the seat of the disease* (experiments). *None of the conditions described*, whether malignant disease or other gastro-intestinal lesions, *can be regarded as the essential anatomical causes, or account for the extreme* (*hæmolytic*) *blood change characterizing the disease. Some other pathological factor* necessary to explain the hæmolysis. [*See antea*, p. 57, (*d*), p. 58, (*g*).]	The Author, 1888. *Toxic causes* responsible for the blood changes. *These observations attach a new significance to the frequency of gastro-intestinal symptoms and lesions.* The very number and variety of the lesions make it difficult to assign essential importance to any one of them. Some of them may possibly be as much the result as the cause of the anæmia. I am, therefore, unable to attribute essential pathological importance to these lesions, whatever may be their importance as *predisposing* or *etiological* factors.

1890. Hunter	1	Microscopically, marked inflammatory changes both old and recent, in the mucous membrane of the stomach, varying in degree at different parts, disappearance of gastric glands, replacement by fibrous tissue and proliferating connective tissue cells, subacute and chronic inflammatory changes in submucosa and its vessels. The inflammatory changes are of a localized character, the changes in the glandular cells, and the infiltration with leucocytes recalling at once the appearances presented by glandular structures, *e.g.*, the kidney, when the seat of a localized infection; *similar inflammatory and atrophic lesions observed in the tongue during life, dating from the onset of the anæmia.*	However important atrophy or other changes in the mucosa may be as etiological factors, they cannot (for reasons given, 1888) be regarded as the essential lesion (anatomical) underlying the hæmolysis of this anæmia.	*Two forms of gastritis presented by the case:* (1) *An earlier gastritis* of unknown cause six years before the onset of the disease, without anæmia. (2) *A more recent, acute and subacute gastritis* (*and glossitis*) dating from an exposure to drain infection, and co-incident with the onset of the anæmia. *The real cause of the disease was this latter infection. I am disposed to regard the gastric mucosa as the seat of the later infection; the affection of tongue noted during life being probably of the same nature as that of the stomach.* The contraction of this infection was favoured by some unhealthy condition of the stomach. *The earlier gastritis was a factor favouring the contraction of this later infection.* Successful infection (from a drain source) having once taken place in the gastric and tongue mucosa, the history was no longer one of gastric trouble, but of this "anæmia" with its characteristic (hæmolytic and toxic) features, and clinical course. "*The special factor required to initiate the symptoms peculiar to this anæmia is the contraction* (*under certain favouring local conditions*) *of a specific infection within the gastro-intestinal tract.* [From this time forward the object of the writer's enquiries, 1890-1900, was to ascertain the causes of (1) this earlier gastritis, (2) the nature and relationship to the disease of the glossitis and gastritis. The results were recorded in 1899-1900.]

Observer.	No. of Cases.	Nature of Lesions and Observations.	Relation to the Anæmia.	Probable Cause of Lesions.
1890. Hale White ...	6	Analysis of *post-mortem* records of Guy's Hospital, 1855-90. Stomach and intestines absolutely healthy in 11 cases. In two cases appearances described are often met with in healthy intestines; in 11 cases the gastro-intestinal tract may be taken as healthy, for the autopsy was made and recorded very carefully, and yet no mention made of stomach or intestine. In six cases something found. (1) Cæcum œdematous, one or two blackish small spots on the mucous membrane, almost diphtheritic looking. (Case 13.) (2) Large intestine, numerous cicatrices of ulcers or ulcers newly healed, and a little recent diphtheritic inflammatory exudation in parts. (3) Mucous membrane of stomach, especially the pylorus, was thickened. (Case 15.) (4) A cicatrix of a small healed ulcer a foot above the cæcum. (Case 24.) (5) A few follicular ulcers in colon. (Case 25.) (6) Several scars in lower part of small intestine. (Case 29.) In none of these cases is there any record of a microscopical examination of the stomach and intestine.	It is impossible to say in the present state of our knowledge whether the slight lesions observed (in 6 out of 29 cases) are of much importance. But it is clear that for the future attention must be directed to the point. In favour of the view (of Hunter) that the origin of the blood-destruction is in the walls of the stomach and intestine, the frequency of gastro-intestinal symptoms is urged by him (1888). An analysis of the foregoing cases showing that vomiting and diarrhœa are very common in pernicious anæmia to a certain extent supports the view that the seat of the blood-destruction is in the wall of the gastro-intestinal tract.	—

1890. Mader	2	*Case* 1. Mucosa of stomach and intestine hæmorrhagic. *Case* 2. Chronic gastritis with small-celled infiltration and atrophy of the mucous membrane.	—	—
1890. Mott	1	The mucous membrane covered with a thick layer of glairy mucus. Microscopically no definite changes, and the glands of the cells appeared normal.	—	The thick layer of glairy mucus could be explained by the severe vomiting (probably cerebral in origin) which occurred during the last three days of life.
1891. Holt	1	A child aged 2 [a doubtful case]. The stomach contained a quantity of brownish mucus, and there were a few small ecchymoses in the mucous membrane and evidences of acute or chronic gastritis.	—	—
1892. Eisenlohr	1	Atrophy of stomach and intestinal mucosa. Atrophy of gastric glands with small-celled infiltration, in the intestine the glands and villi had completely disappeared.	These changes had led to a profound disturbance of nutrition which had declared itself clinically as pernicious anæmia.	The process is a primary genuine atrophy.
1893. Nonne	1	Mucosa and submucosa of stomach showed small-celled infiltration around the glands, but the glands themselves not atrophied.	--	--

Observer.	No. of Cases.	Nature of Lesions and Observations.	Relation to the Anæmia.	Probable cause of Lesions.
1894. Schauman on "Bothriocephalus Anæmia," Thirteen cases.	—	In all cases, secretion of the stomach diminished. Changes are found in stomach and intestine, identical with those found in pernicious anæmia, but not in all cases. The mucosa of stomach had a smooth surface, and presented the same pallor as most of the other organs. In 3 cases, local hyperæmic patches were observed. The intestinal mucosa equally pale. In 6 cases, the solitary follicles in lower part of ileum, and in 3 cases the Peyer's patches were slightly swollen. In 7 cases, intestinal wall markedly thinner than normal. Whether this was dependent or not upon glandular atrophy could not be determined since I have to regret that I had not time to make any histological examination.	The superficial ulcers found in one case scarcely stand in any generic relationship to the anæmia. In that case small tuberculous lesions were found in the lungs, and hence the suspicion cannot be avoided that they were also of tuberculous nature, although no miliary granulation could be seen.	—
1896. Hayem	2	(*Case* 1.) Lesions of stomach in pernicious anæmia. A general atrophy of the stomach, with thinning of walls. (*Case* 2.) Signs of gastritis without atrophy.	—	—
1896. Pepper and Stengel	2	Gastric changes.	It is probable that in this case the anæmia was the result of disturbed digestion, or of fermentations in stomach or duodenum.	—

1895, 1896, 1898. Ewald	7	"Anadenia Ventriculi." Atrophy of the mucosa of stomach and intestine.	The changes in the intestinal tract were so severe that they afforded a perfectly sufficient explanation of the extraordinary anæmia the patient presented. The gastric atrophy not the result but the cause of the anæmia. Dr. Hunter has arrived at opposite conclusions. He has shown that it is probable that in the cases observed by him we are dealing with a chronic auto-intoxication. That auto-intoxication is the first and original cause of pernicious anæmia must still remain a question. But the impression cannot be avoided that the lighter and severer attacks (of toxæmia), such as occurred in my patients (1895), and have been described by Hunter in his cases (1889), represent *a form of auto-intoxication produced by changes occurring in the gastro-intestinal tract.*	—
1897. Martius	2	Seventeen cases of "Achylia gastrica: its causes and consequences," of which two were anæmic and died with the clinical features of pernicious anæmia. In all cases there was complete absence of gastric secretion. In the two cases there was pronounced atrophy of gastric and intestinal mucosa.	Total arrest of gastric secretion arising from atrophy of the mucosa can lead to a considerable degree of anæmia; but for the development of this a necessary condition seems to be a similar atrophy of the intestinal mucosa. No ground for the view that an intestinal intoxication is necessary as a cause of the anæmia. Disturbance of absorption is sufficient of itself to cause the anæmia.	—
1896. Grawitz	2	Microscopic examination of stomach showed atrophy of glands; in one case marked, the other moderate.	Still uncertain whether these atrophies are not secondary to the anæmia.	—

Observer.	No. of Cases	Nature of Lesions and Observations.	Relation to the Anæmia.	Probable cause of Lesions.
1898.				
Max Koch... ...	5	Changes in stomach and intestine in pernicious anæmia. Observations confirmed those of Ewald and Martius.	The changes are not the cause, but the result of the pernicious anæmia.	—
1899.				
Morley Fletcher ...	1	Old inflammatory lesions of colon causing thickening and fibrosis of submucosa; and a more recent coagulation necrosis of the mucosa in patches associated with great hyperæmia and in places hæmorrhages.	—	Possibly caused by some neurotrophic disturbance.
				"SEPTIC GASTRITIS."
1899.				
Hunter	—	Observations on vomit, in a case of severe gastritis thought to be cancer, but traced to infection from three suppurating teeth, and entirely cured by removal of these teeth. "*Oral sepsis*" as a cause of "*septic gastritis.*"	This *sepsis not* the cause of the hæmolytic anæmia. But it is a most potent cause of the gastric (and intestinal) lesions and disturbances which precede the anæmia. It thus favours the contraction of the specific hæmolytic infection (of drain source) which underlies this anæmia. (*See* p. 82.)	*The mucosa of stomach continuously exposed in such cases to infection by influx of pus organisms from suppurating teeth may eventually become infected.* The irritant catarrh originally set up, may become eventually *a septic catarrh;* if this influx is kept up, the catarrh becomes chronic, and leads to the usual results of a glandular catarrh, viz., glandular atrophy with increase of fibrous tissue.
		PERIOD	IV (1900-8).	
1900.				
Idem.	7	The chronic infective nature of pernicious (Addisonian) anæmia. Its relation to infection from mouth and stomach (7 cases.) In all of these a definite history of "glossitis," with gastric or intestinal trouble marking the onset (contraction) of the disease, and preceded by a history of "*oral sepsis.*" In one case microscopic observations	*The lesions found are neither the cause nor the effect of the anæmia, but concomitant results* (with the anæmia, the hæmolysis, the bone-marrow changes, the febrile symptoms, nervous symptoms and lesions) *of the specific infection underlying the disease. The infection spreads from point to point of the mucosa; and at*	(1) *Sepsis*, oral, gastric and intestinal, *plays an important part in creating conditions, and in some cases lesions of mucosa, favourable to the contraction and persistence of the specific hæmolytic infection underlying the disease. Its removal does not necessarily check the disease once it has been firmly contracted;*
Lancet, Jan., 1900.				

		on the vomit, demonstrating intense inflammatory and infective changes, "*septic gastritis.*" Numerous confirmatory observations in 25 cases, 1900-3.	*the time of death the lesions are generally hidden by the profound degree of anæmia, and can only be discovered by careful histological examination. They are very obvious, and can be well studied during life in the tongue.* (*See* Plates I-VII.)	but (as subsequent observations, 1900-7, conclusively show) *it does modify materially the course of the disease, and, if effected early in the course of the disease, may arrest its progress.* (*See* p. 116.) (2) *The real cause of the disease is, however, a* specific infection (*with marked hæmolytic properties*) *derived from drain sources, and contracted only under above favourable conditions. This infection is located in the mucosa of the tongue, stomach, or intestine, or in all three combined.* (*See* Plates.)
1900. Faber and Bloch ...	4	"On the pathological changes in the digestive tract in pernicious anæmia, and on so-called intestinal atrophy." In all cases, deficient or arrested secretion of HCL. In two cases marked changes, viz., a diffuse inflammation of the mucosa with destruction and atrophy of the glands. *Case* 3. No free HCL; mucosa atrophied, and the seat of a diffuse round-celled infiltration. *Case* 4. Stomach mucosa everywhere the seat of a diffuse inflammation, with irregular, small-celled infiltration, most marked in the deeper layers. Collected 33 cases in which the gastric juice has been examined, in all it was diminished, and in most it was completely absent. Intestinal changes, apparently atrophic, in two cases.	The gastro-intestinal changes are limited to a diffuse inflammation of the gastric mucosa, accompanied by more or less glandular atrophy. That the gastric change is not the cause of pernicious anæmia can be regarded as certain; and the most natural thought is that it is secondary—a result of pernicious anæmia, as Max Koch and Müller have concluded. No constant or characteristic lesion in intestinal tract. It is not proven that intestinal atrophy occurs in pernicious anæmia. The appearances of atrophy are, to a large extent, artificially produced; they depend largely on the degree of distension of the gut.	It is possible that the gastric condition and blood change have a common cause, whether of toxic or infective nature. It is also possible that, although no anatomical changes are to be found in it, the contents of the intestinal tract may be the seat of abnormal processes. (*Cf.* Hunter's conclusions *antea* in 1889). It must remain for further investigations to show how these inflammatory processes in stomach arise. (*Cf.* Hunter's observations, *antea*, 1889 to 1900.)

Observer.	No. of Cases.	Nature of Lesions and Observations.	Relation to the Anæmia.	Probable Cause of Lesions.
1903. Hunter	25	Observations on 25 cases, with complete histological examination of seven cases. There are two classes of lesions which I consider of importance in this relation—(1) a *Hæmolysis* of special degree and character, well shown by the analyses in the present series of seven cases: and (2) *a glossitis, observed in every case*, having the peculiar relation to the onset of the anæmia and clinical characters suggestive of its being of an infective nature, described by me in 1890 and 1900. Histological examination in seven cases shows that it has even more striking pathological features, and in all the three cases bacteriologically examined these are associated with, and presumably dependent upon, a deep-seated pure streptococcal infection of the substance of the tongue. *Anatomical lesions.*—In all the cases observed during life, and in 7 cases in which *post-mortem* examinations were obtained, I found certain infective *lesions* in the *mouth, tongue, stomach*, or *intestine*—either singly or associated with each other. These were: (1) a special form of *glossitis* (in every case), (2) a *gastritis* causing finally gastric atrophy (more or less in every case) and most intense in three cases); and (3) *enteritis, e.g.*, marked croupous enteritis, patches of congestion and catarrh, follicular enlargement, and patchy colitis (three cases); (4) "Oral Sepsis" preceding or existing (24 cases).	*Gastric or intestinal disturbance.*—A history of antecedent gastric or intestinal disturbance was found in every case. In no case were these of sufficient character or intensity to account for the supervention of such an intense degree of anæmia. *The various disturbances connected with this tract have an important significance*, which I have brought out, *not as causes of the disease but as symptoms of the gastric and intestinal infective lesions* presently to be described *associated with the disease.* *Anatomical lesions.*—With regard to these the point to be emphasized now in view of the significance I shall subsequently attach to them is: *in no case were these lesions, either in anatomical character or severity, sufficient of themselves to* originate *the intense hæmolytic anæmia by any interference with nutrition they may have been capable of producing.*	The result has been to expose *two sets of infective factors:* (1) a *specific* (hæmolytic) *infection* whose site and lesions (the tongue, stomach, and intestine), approximate time of contraction, and probable source I have, I think, been able to lay partly bare; and (2) a great stratum of *septic infection* traversing the foundations of Addison's anæmia, and forming to a large extent the foundation of those forms of severe anæmia which clinically most resemble Addisonian anæmia. (*See* Frontispiece.) **These conclusions fully confirmed by observations on a further series of fifty cases seen since 1903.**

PLATES

(I—XVII)

ILLUSTRATING THE INFECTIVE LESIONS OF ADDISONIAN ANÆMIA

To face p. 142.

GLOSSITIC LESIONS.

PLATE I.

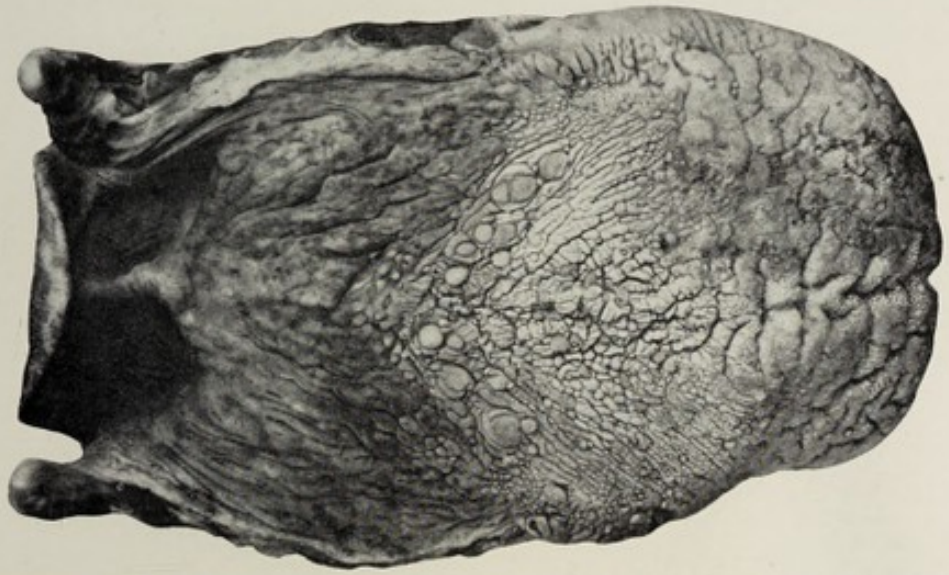


FIG. 1.—Tongue from a patient, aged 65, who died of a wasting disease ; normal in size, appearance, and on histological examination.

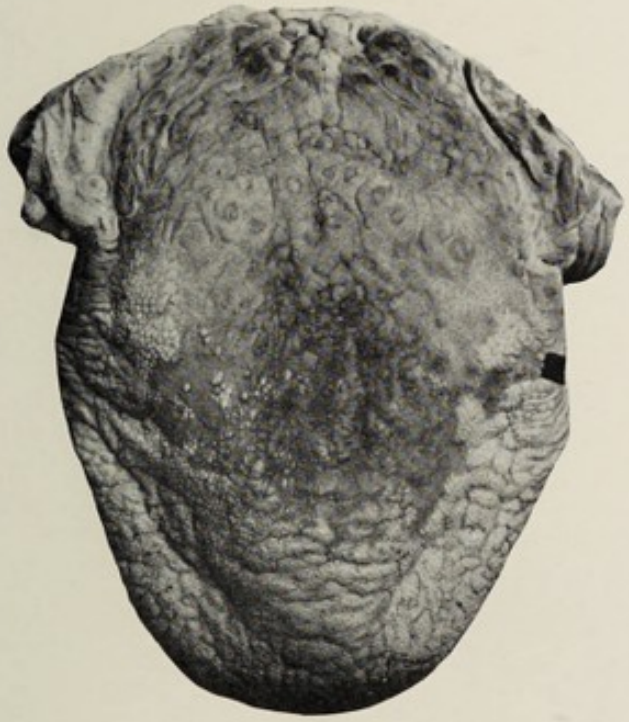


FIG. 2.—Tongue from a case of Addisonian Anæmia, slightly sore from time to time throughout illness. *Post mortem*, it presented nothing obviously abnormal. After preparation with Kaiserling fluid it shows the above striking atrophic appearances on the dorsum, and the subacute inflammatory appearances both on dorsum and on its edges.

Post Mortem.—Cultures made from its interior after death grew a pure culture of a *Streptococcus longus* of great virulence. (*See* Plate VII, fig. 14.)

To face p. 144.

PLATE II.

FIG. 3.—Tongue from a case of Addisonian Anæmia, which was the seat of recurrent inflammation throughout the illness. Both to the naked eye and on histological examination it shows intense chronic inflammatory and atrophic changes.

FIG. 4.—Tongue from a case of Addisonian Anæmia, the seat of intense inflammation during the early part of the illness. *Post mortem* it showed nothing obviously abnormal, resembling closely the tongue shown in fig. 1, Plate I, from a patient of the same age. On being prepared with Kaiserling fluid, it shows the most extreme degree of chronic inflammatory and atrophic changes. (*See* Plate V, figs. 9 and 10.)

PLATE III.

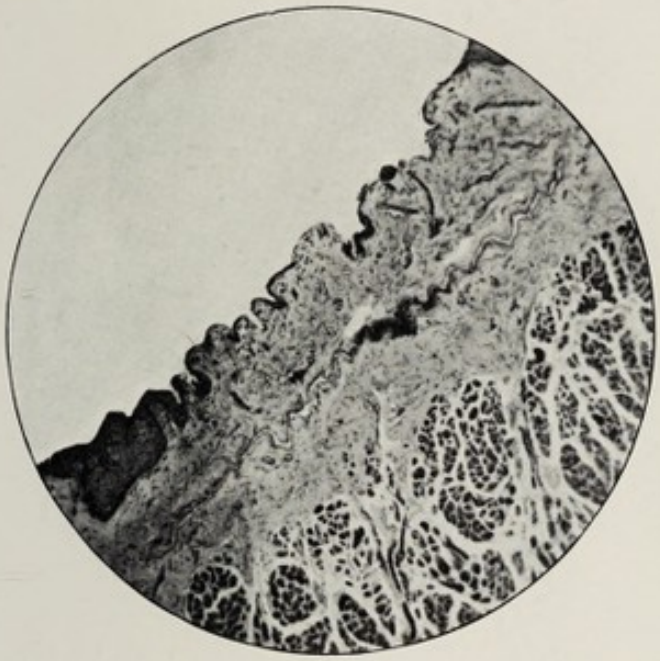


FIG. 5.– Tongue from a case of Addisonian Anæmia running an acute course of three to four months. *Post mortem* it showed nothing obviously abnormal, but it was painful during life, and histological examination shows the appearances represented in this figure and in the following figures, 6, 7 and 8. At the part shown the epithelium is removed by ulceration, and the underlying layer of tissue is chronically inflamed.

FIG. 6.—Another portion of surface of the tongue from the same case. It is to be noted that the muscle of the tongue is still well preserved. (The open spaces seen at several places are artificial.) Further, that at such portions of tongue as are here shown (figs. 5 and 6, also 7, 8 and 9), the cavity of the mouth with its sepsis is in direct open communication with the lymphatics of the tongue.

PLATE IV.

FIG. 7.—Another portion of the tongue from the same case, more highly magnified. At one part there is a deep fissure, at the base of which there is a considerable degree of inflammatory change, viz., small-celled exudation and proliferation in the tissues and in the walls of the blood-vessels.

FIG. 8.—Another portion of the tongue from the same case, showing still deeper fissures, detaching a considerable piece of the mucosa. The inflammatory and necrotic changes are here very intense, the latter predominating. The tissue is loaded with coccal organisms (streptococcal), staining badly with Gram's.

PLATE V.

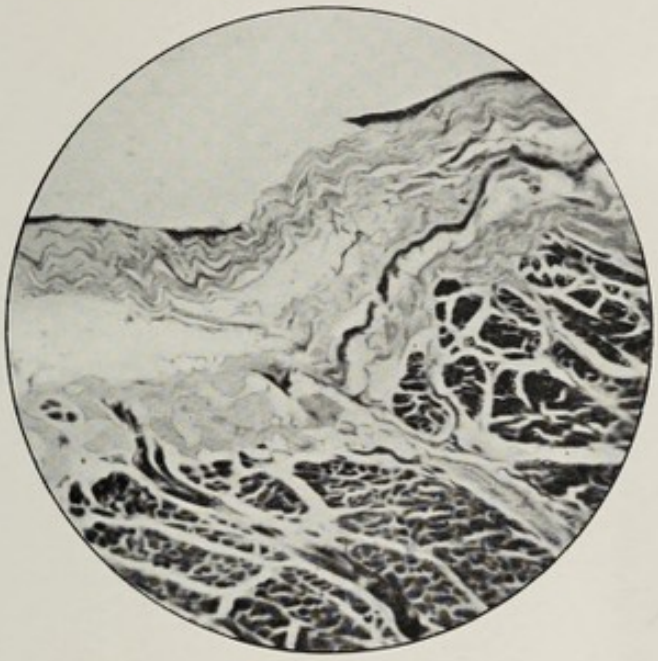


FIG. 9.—Tongue from the case of Addisonian Anæmia shown in Plate II, fig. 4. The extreme atrophy of the epithelial covering is to be noted, and the chronic fibrous appearance of the underlying tissue.

FIG. 10.—Another portion of above tongue (shown in fig. 4). It shows the most extreme degree of inflammatory and atrophic change. The epithelial covering of the tongue, which under this magnification ought to fill half the field, is reduced to a thin, almost fibrous layer; and the entire muscle substance has undergone atrophy and been replaced by fat occupying the clear spaces (and removed in course of preparation).

PLATE VI.

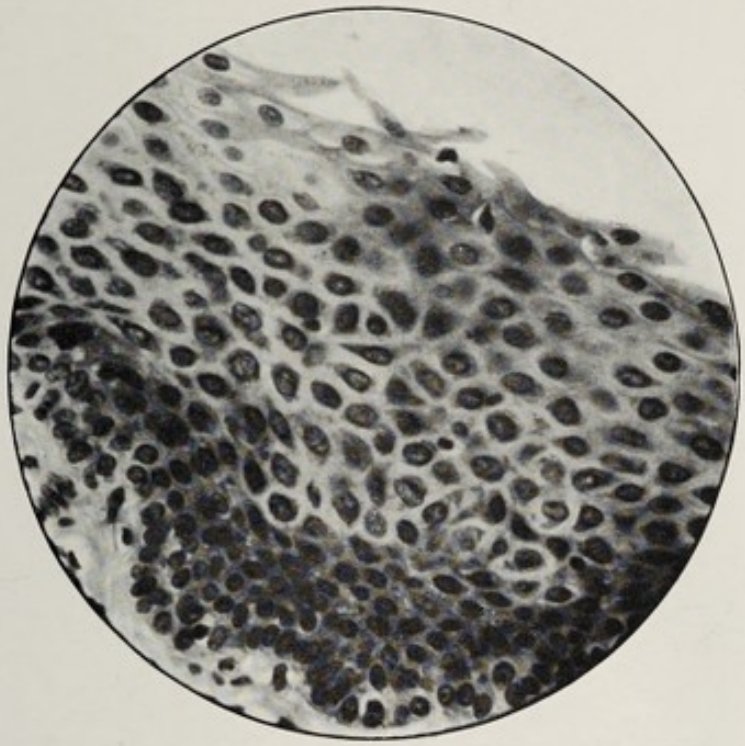


FIG 11.—Section showing normal appearance and thickness of epithelial covering of the tongue (from a patient who died with severe sepsis).

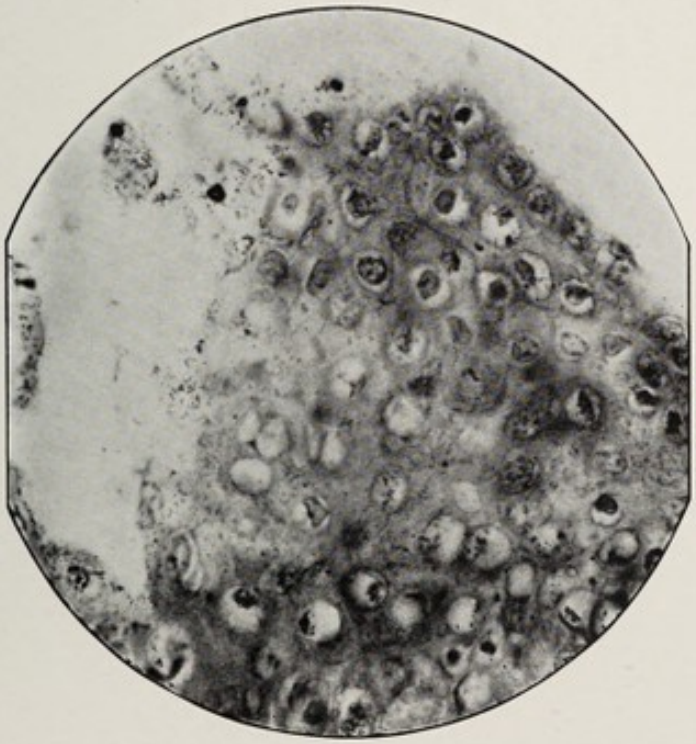


FIG. 12.—Section showing the degenerative changes (mucoid and necrotic) presented by the epithelial covering of the tongue in Addisonian Anæmia, in the neighbourhood of the infective lesion shown in fig. 3 and subsequent figures.

PLATE VII.

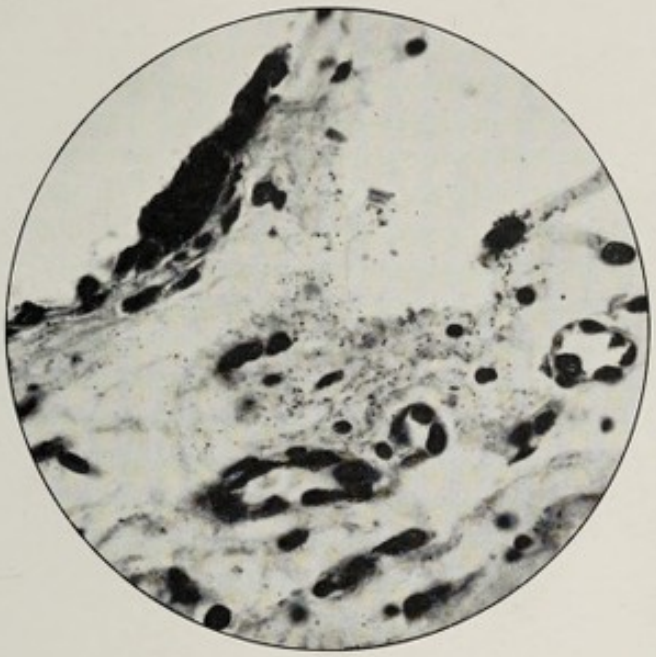


FIG. 13.—High power view (× 1,000) of one of the lesions shown in Plates III. and IV. It shows (1) the invasion of the substance of the tongue by streptococcal organisms; (2) the mixed degenerative and low inflammatory changes (around blood-vessels) produced by this infection; and (3) the ulceration of the epithelial covering.

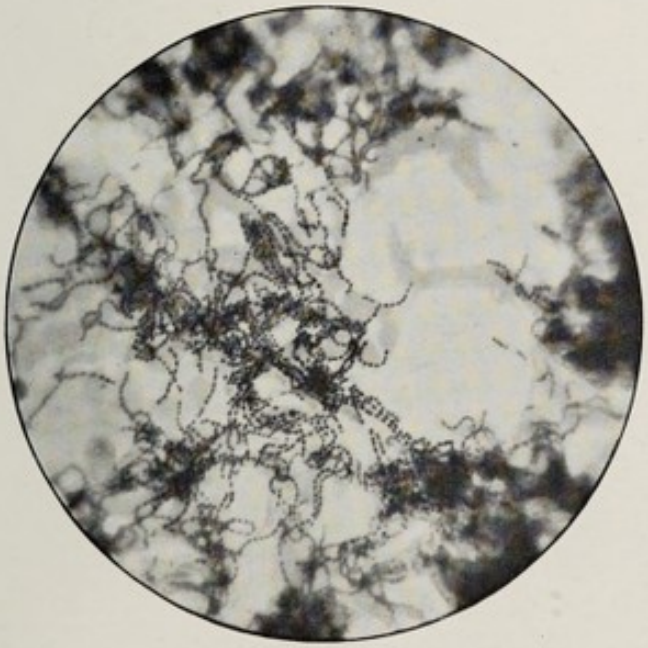


FIG. 14.—Streptococcal organisms obtained in pure culture from the *interior* of the tongues shown in figs. 2, 3 and 4. They have the characters of *Streptococcus longus*. and are in chains of 30, 40, 60 and 100 cocci. They proved exceedingly virulent to mice.

PLATE VIII.

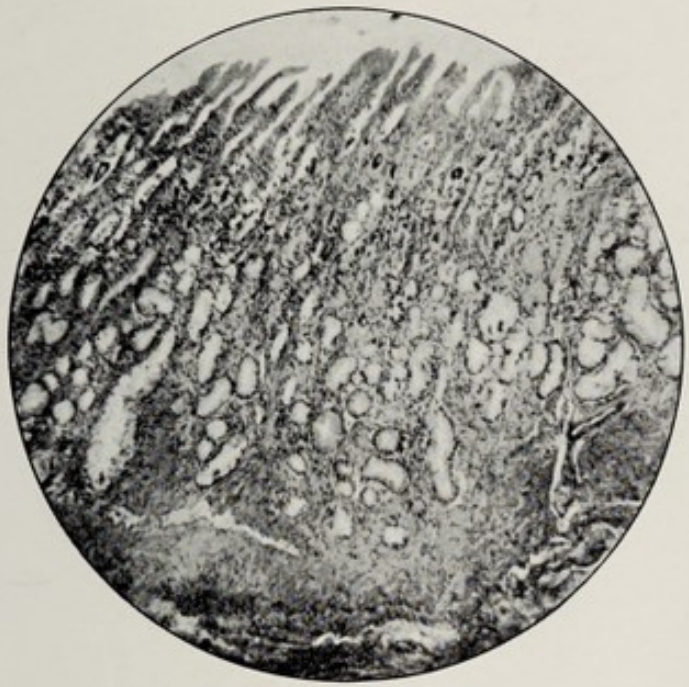


FIG. 15.—Mucosa and submucosa of stomach from a case of Addisonian Anæmia which died in an early stage, and showed the tongue lesions represented in Plates III and IV *antea*. It shows normal thickness and appearances; the epithelium of the opening of the tubules having fallen out from maceration.

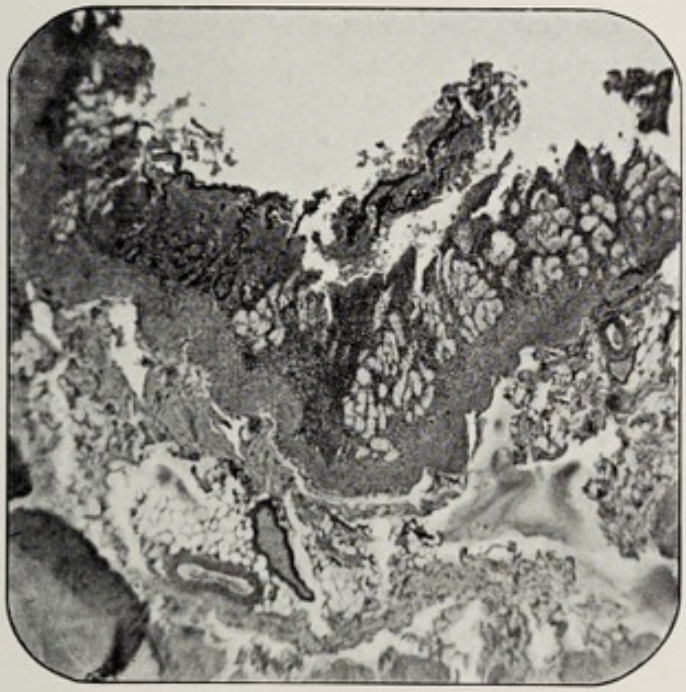


FIG. 16.—Mucosa and submucosa of stomach from the same case as above, from another portion of the surface. It shows intensely inflammatory and ulcerative and necrotic changes—affecting at one point (to the left) the whole of the mucosa; at another part (to the right), glands can still be seen at the lower part of the mucosa. The inflammatory and necrotic exudation shown on the surface, both in this figure and in the following figures, 17 and 18, is loaded with streptococccal organisms, and is thrown off as blood-stained and mucoid vomit during life. The histological characters of this vomit are identical with those of the exudation on the mucosa of the stomach, and the streptococci correspond with those found in the tongue.

PLATE IX.

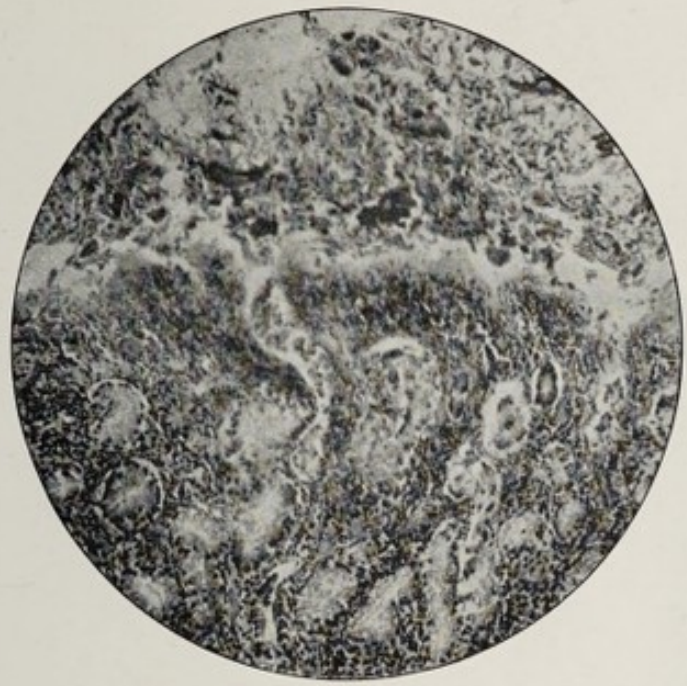


FIG. 17.—Another portion of the gastric mucosa from same case as the preceding. The changes are of a more acute inflammatory character, with small-celled infiltration around the tubules. Note the exudation on the surface.

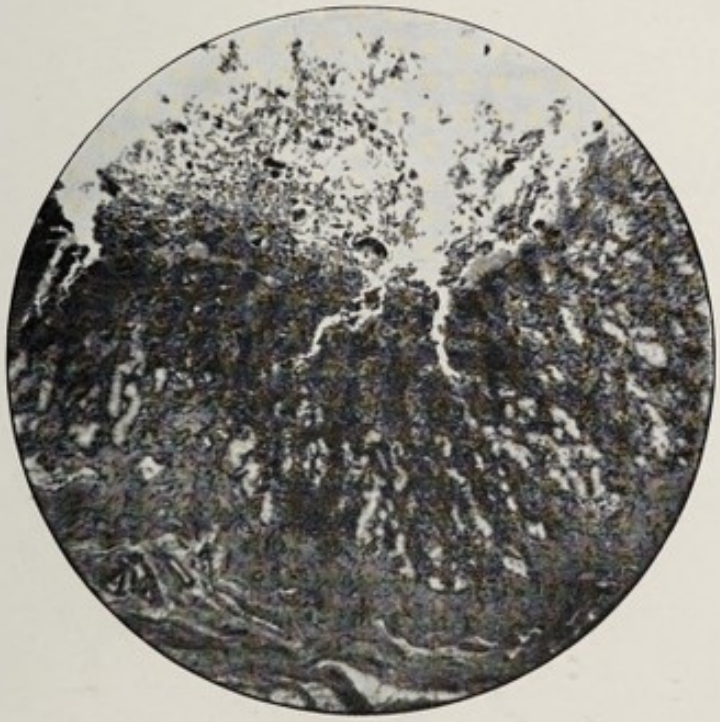


FIG. 18.—Another portion of the mucosa from the same case. The inflammatory changes are more marked, but they are accompanied by more ulceration and necrosis, extending, as will be seen, at one part through nearly the entire thickness of the mucosa.

PLATE X.

FIG. 19.—Portion of healthier mucosa from the preceding case, showing normal thickness and appearance, in contrast with the extraordinary degree of atrophic change represented in the following fig. 20, under the same magnification.

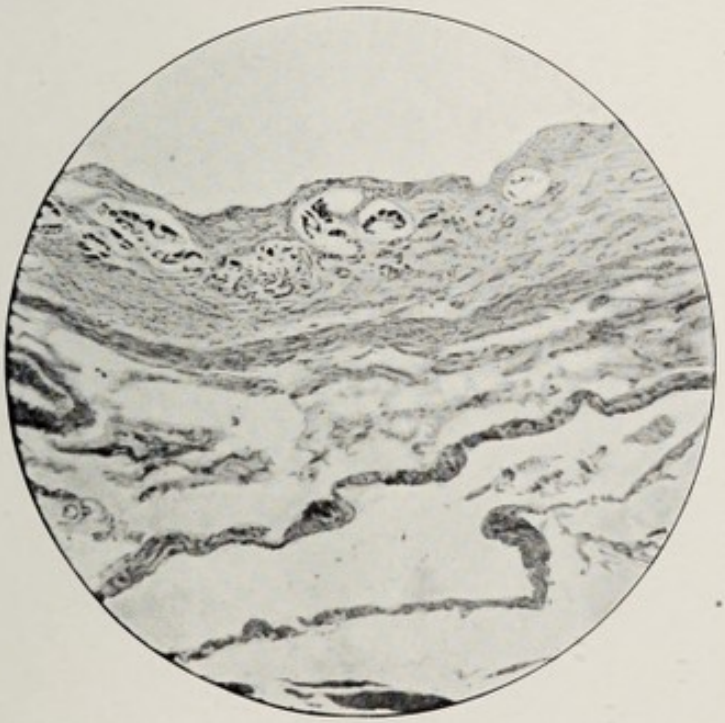


FIG. 20.—Mucosa and submucosa of stomach, from a chronic case of Addison's Anæmia (three to four years duration). It shows the extreme atrophy typically presented by such cases, as first fully described by Dr. Fenwick. The almost entire absence of secreting tubules is to be noted, and the more or less thickening of the submucous coat, which such cases often present.

PLATE XI.

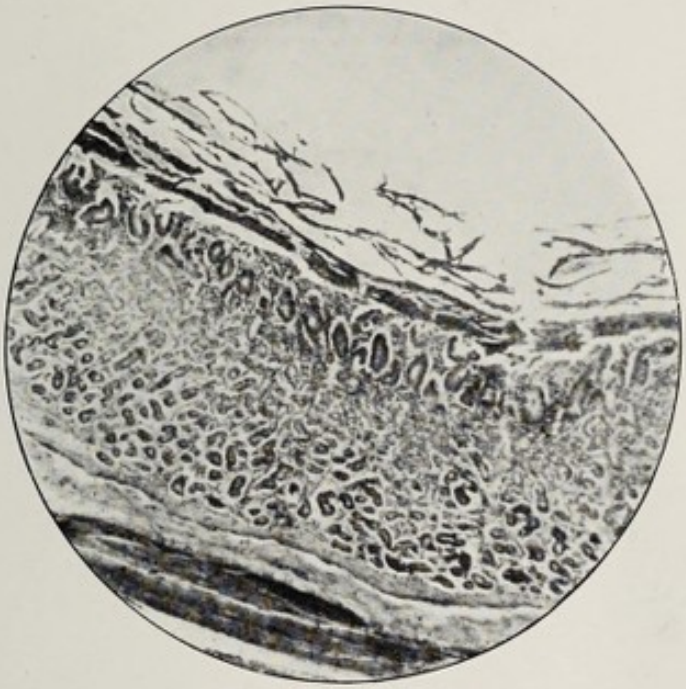


FIG. 21.—Mucosa and submucosa of stomach from a severe case of "Septic Anæmia" (Case 21, see p. 111) in a man, aged 72. Notwithstanding the extreme anæmia and the age of the patient, the appearances are normal, the glandular cells, including those of the ducts, being well preserved, with a thin layer of mucus on the surface. These appearances contrast in a striking way with those presented by the gastric mucosa in Addisonian Anæmia.

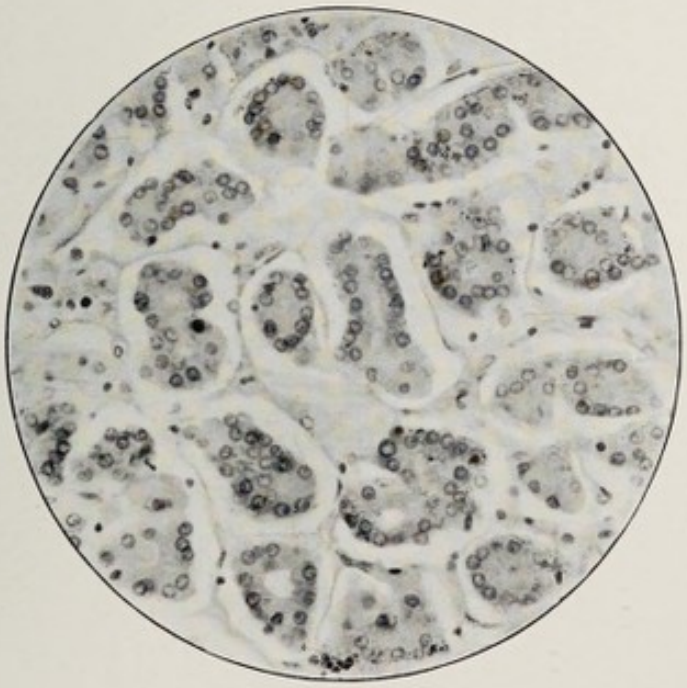


FIG. 22.—High power view of the glands in the above case. The gland cells are in all respects normal, and there is an entire absence of inflammatory change. Compare appearances in fig. 23.)

PLATE XII.

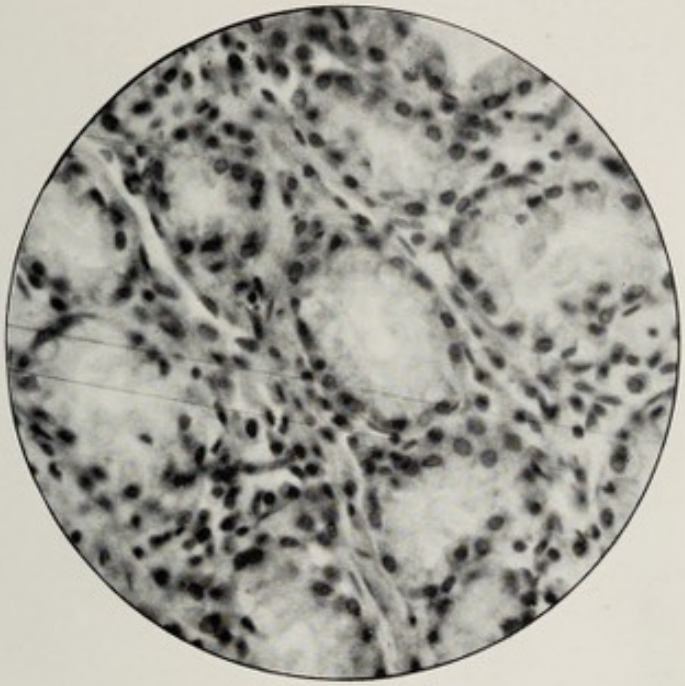


FIG. 23.

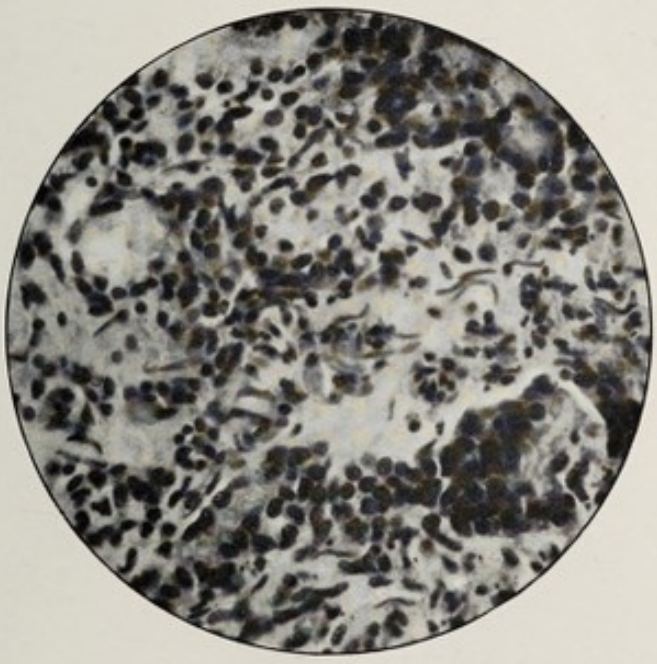


FIG. 24.

FIGS. 23, 24, 25 represent in a continuous series the inflammatory changes from their first appearance (fig. 23) around the healthy glands to the final disappearance of the glands, and their replacement either by fibrous tissue or by extreme atrophy. (Fig. 20.)

PLATE XIII.

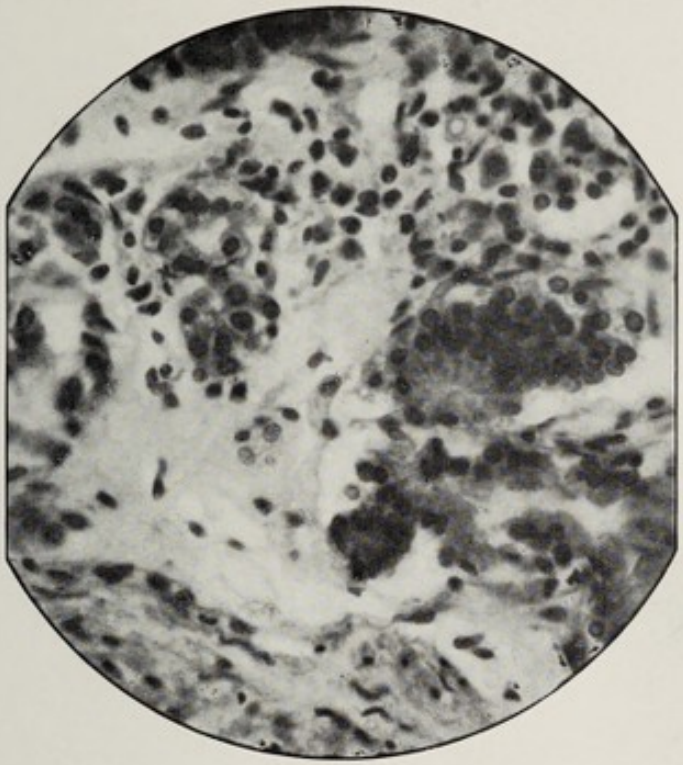


FIG. 25.

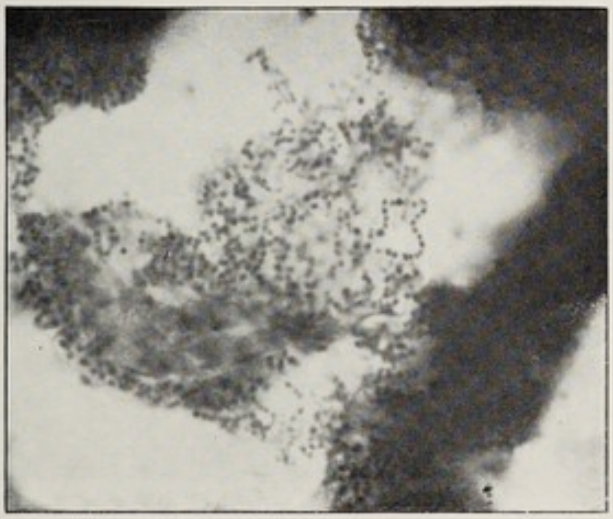


FIG. 26.—A zoogloea mass of streptococcus organisms in the inflammatory exudate thrown off from the stomach in a case of Addisonian Anæmia. Similar masses are found in the inflammatory and necrotic exudate of the gastric lesions shown in figs. 16, 17, 18.

INTESTINAL LESIONS.

PLATE XIV.

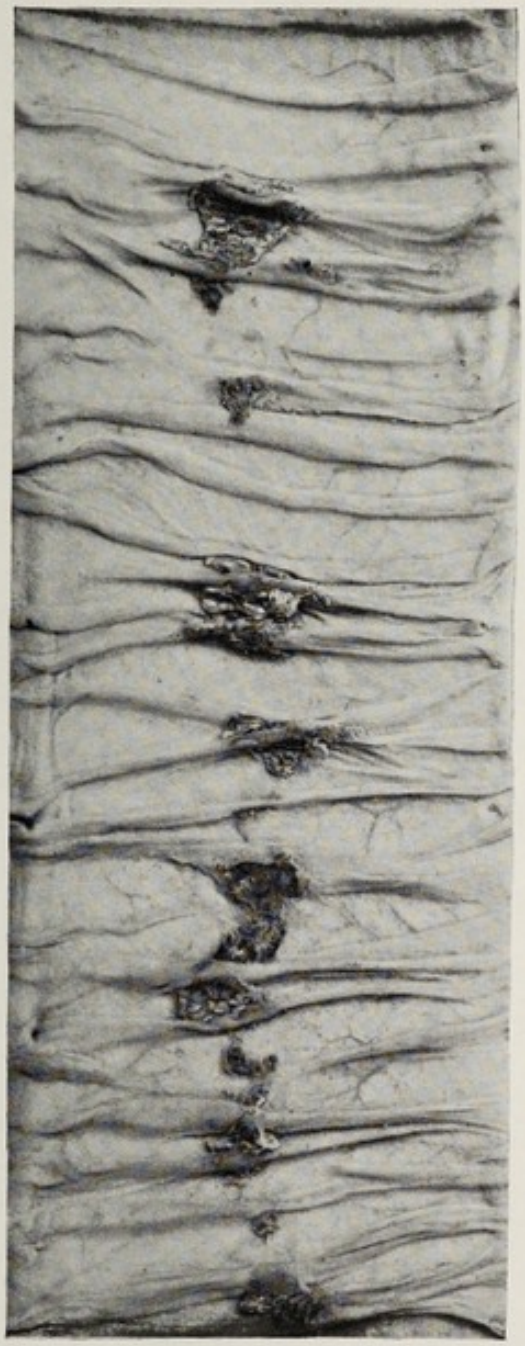


FIG. 27.—Lesions shown in jejunum in a case of Addisonian Anæmia with marked cord symptoms (combined degeneration). Patches of croupous enteritis are here shown, situated on or near the valvulæ. If the larger ones were not present, the smallest might readily escape notice, especially if, as is often the case, the intestine is washed out with a strong stream of water before it is opened or examined.

INTESTINAL LESIONS.

PLATE XV.

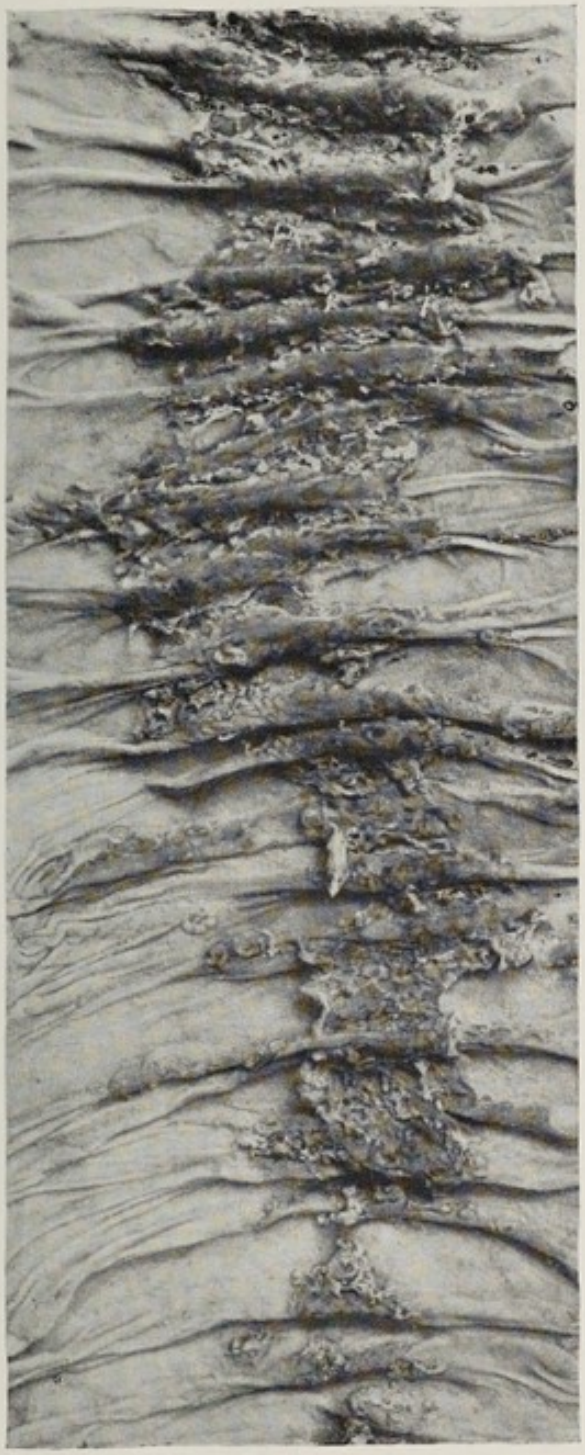


FIG. 28.—Another portion of the intestine from the same case as the preceding. It shows still more intense croupous enteritis. Here again it is to be noted that the slighter lesions seen at the bottom or at the margins of the bigger sloughs might easily escape notice if unaccompanied by the grosser lesions.

INTESTINAL LESIONS.

PLATE XVI.

FIG. 29.—Another portion of the jejunum from the same case as the preceding, showing well-marked inflammatory changes, less defined in character than those shown in Plates XIV and XV. Patches of inflammatory congestion, still less defined than those here presented, are very commonly present in the intestine in Addisonian Anæmia. It is only in cases which die in the early stages of the disease that these inflammatory lesions are *obvious*. In the later stages, the tissues are so bloodless, that nothing can be seen by the naked eye. This also applies to the lesions of the tongue and of the stomach.

PLATE XVII.

FIG. 30.

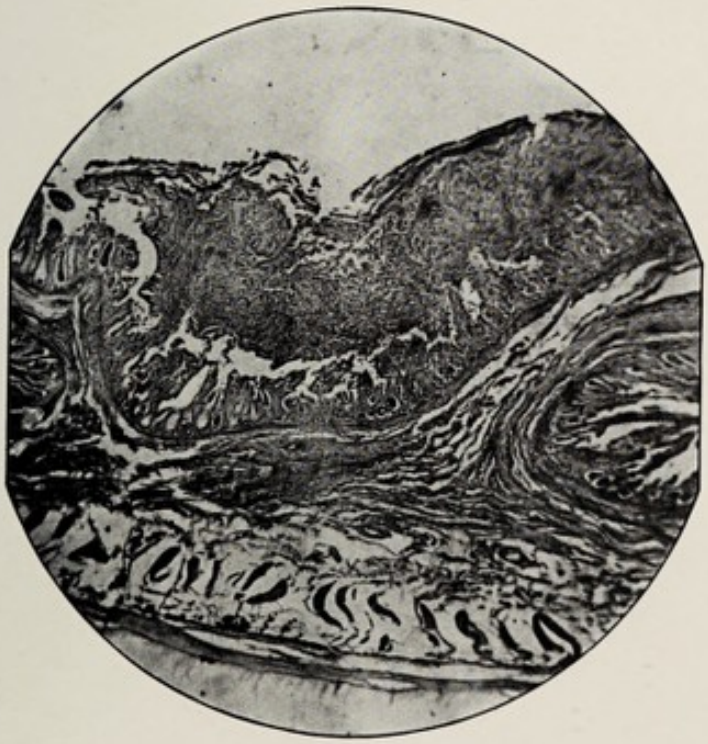


FIG. 31.

FIGS. 30 AND 31.—Section of intestine from foregoing case, showing the character and relation to the valvulæ of one of the smallest lesions present in the intestine.

PART VII

PATHOLOGY (*continued*)

DISTURBANCES IN THE BLOOD-FORMING PROCESSES IN ADDISONIAN ANÆMIA

CHAPTER XIX

Clinical Introductory

The Regenerative and Compensatory Powers of the Disease.

The lesions, hæmolytic and infective, so far described are of an intensely retrogressive character. In the case of the former class, they are intensely destructive, for, as will afterwards be seen, the hæmolysis is frequently so intense that the number of corpuscles may be reduced from the normal 5,000,000 to as low as 1,000,000 and even lower in the course of a few weeks. If hæmolysis of such a character and intensity were the only pathological blood feature of this disease, it would not run the subacute or chronic course which it generally does. (Charts 1 and 2.) It would terminate in a few months or almost weeks as it sometimes, though rarely, does. Fortunately for the patient, a series of compensatory processes come into play which give this disease its usually longer course, and are of themselves of a more striking and remarkable character than any observed in any other disease of equal intensity. Next to the profound degree of the anæmia, the two most prominent features presented by the blood are :—

(1) The extraordinarily severe and persistent character of the blood-destruction—hæmolysis.

(2) The no less striking powers of recovery.

Both these features are more marked than in any other form of anæmia. It is not uncommon to find a patient's blood reduced

from the normal standard to 20 or 30 per cent. in the course of a few weeks, accompanied by all the clinical evidences of intense blood-destruction, namely, high colour of urine, urobilinuria, lemon colour, biliousness, and occasionally jaundice. No less striking is the rapid recovery of the blood when the hæmolysis is arrested. The percentage of corpuscles and hæmoglobin often rises from 20 or 30 per cent. up to 80 or 90 in the space of a month or two—in some cases in the writer's experience, in the course of three to four weeks. (*See* Charts 3 and 4.)

This remarkable power of recovery is a natural feature of the disease and its most hopeful one. From the point of view of treatment, however, it is often misleading, since the particular treatment in use at the time of its occurrence is wrongly credited with having produced it—with having cured the disease. It misleads, moreover, in another way with unfortunate results ; for so remarkable is the recovery that doubt is cast, both by the doctor and the patient, on the accuracy of the original diagnosis. The patient feels and looks so well that he resumes his ordinary occupations and habits of life and gives up all treatment. There follows, in a period varying from six to nine months, the usual relapse, fatal in about three-fourths of the cases (Chart 1). In a certain number, however, recovery again takes place, although more slowly and less complete in character ; the patient remains well for another period of three to six months, when a second relapse occurs. Even this is survived by a few (Chart 2), and the writer's experience satisfies him that, under suitable treatment, this number is steadily increasing (*see* Chart 4).

The above features of the disease are very striking and constant. They will be fully described in a later section of this work.

It is necessary, however, to draw attention to them in this place, since they have an important hearing on the correct interpretation of the bone-marrow changes now to be described.

The powers of recovery and the course of the disease in individual cases are represented in the accompanying four charts. The alternating relapses and degree of recovery shown in *every case* of the disease are illustrated by the history of one case. (Chart 2.) The increased and more durable powers of recovery *after removal of the septic factor* are strikingly shown in Charts 3 and 4.

CHART I

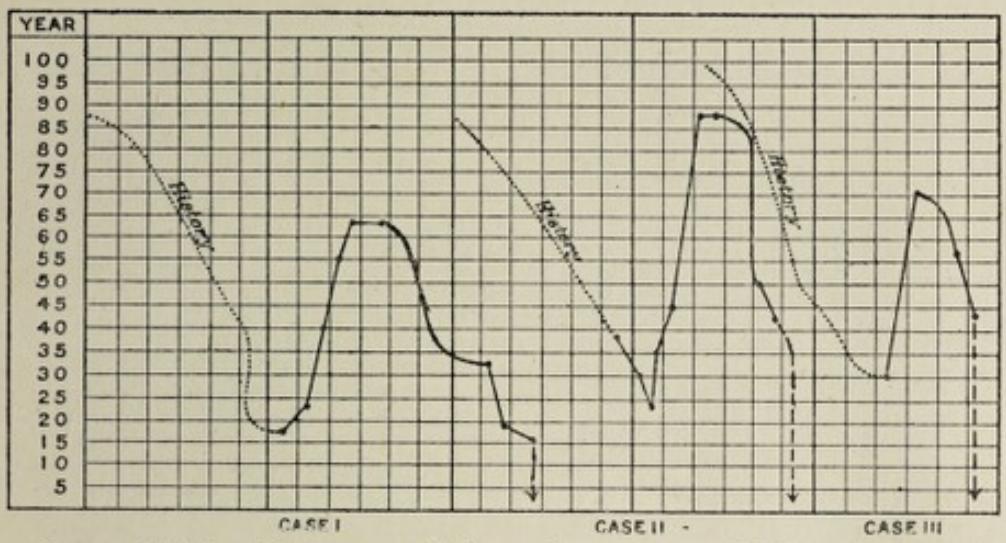


CHART I—The clinical course of three subacute cases of Addisonian Anæmia as it generally appears to the observer, showing the great natural powers of recovery of the disease, followed by relapse in three to four months.

CHART II

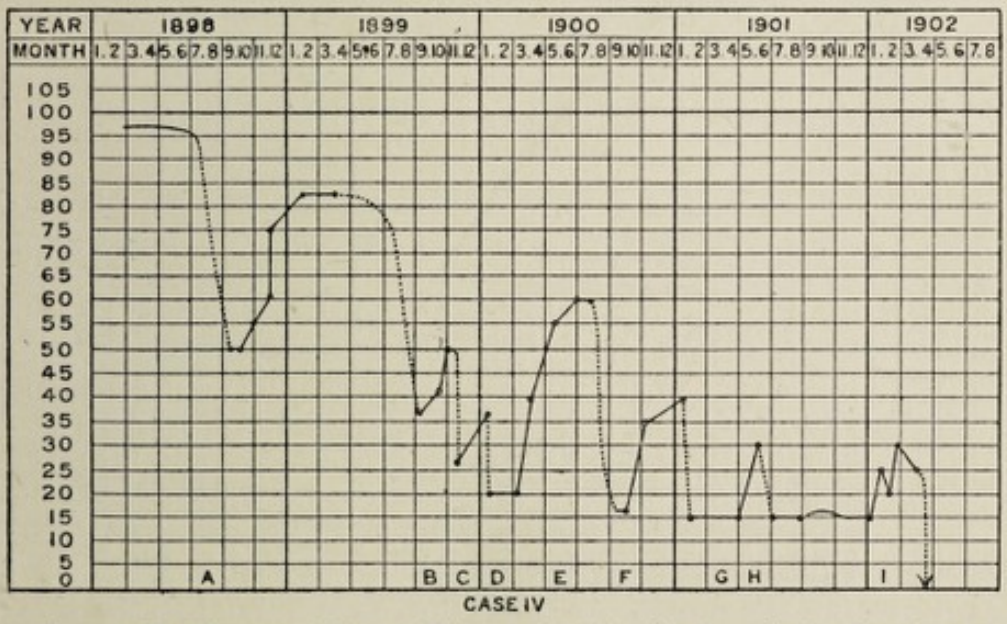


CHART II—The actual Natural History of Addisonian Anæmia (a chronic case), as it appears when observed from the commencement to the end—showing the still greater powers of recovery in the earlier stages (A B C) before the disease is recognized. Stages A B C, when the disease is amenable to successful treatment and arrest—pass unrecognized, and are regarded as "failing health." At stage D, the anæmia becomes more marked, and the patient is confined to bed for a short period, but recovers quickly; he again relapses (F). From that time onward there is much searching of blood for megaloblasts, which are as often absent as present. (*See* p. 174.)

CHART III

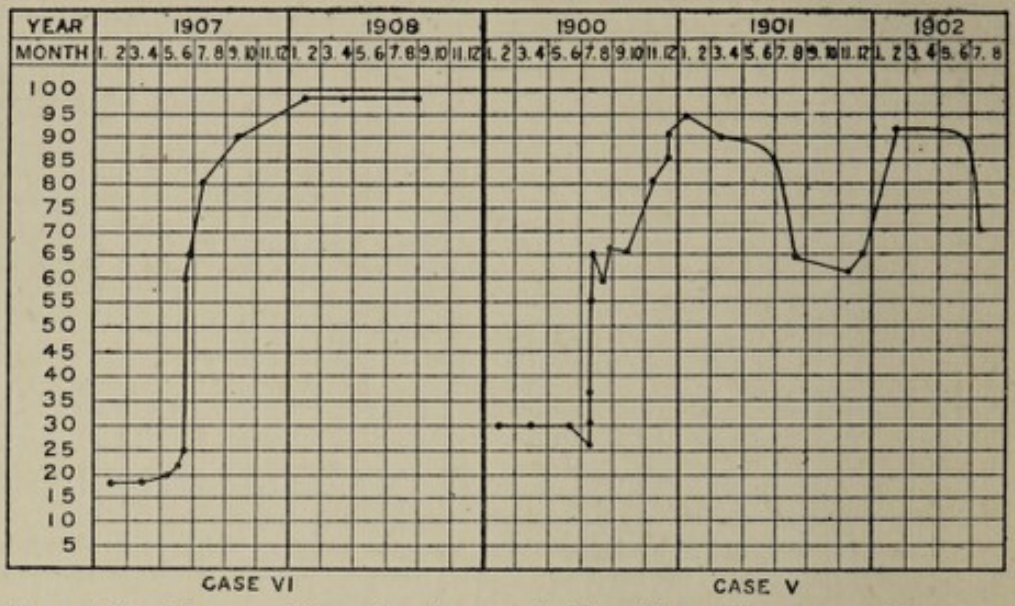


CHART III—Two cases illustrating the remarkable and immediate power of recovery of Addisonian anæmia on removal of the Septic Factor.

CHART IV

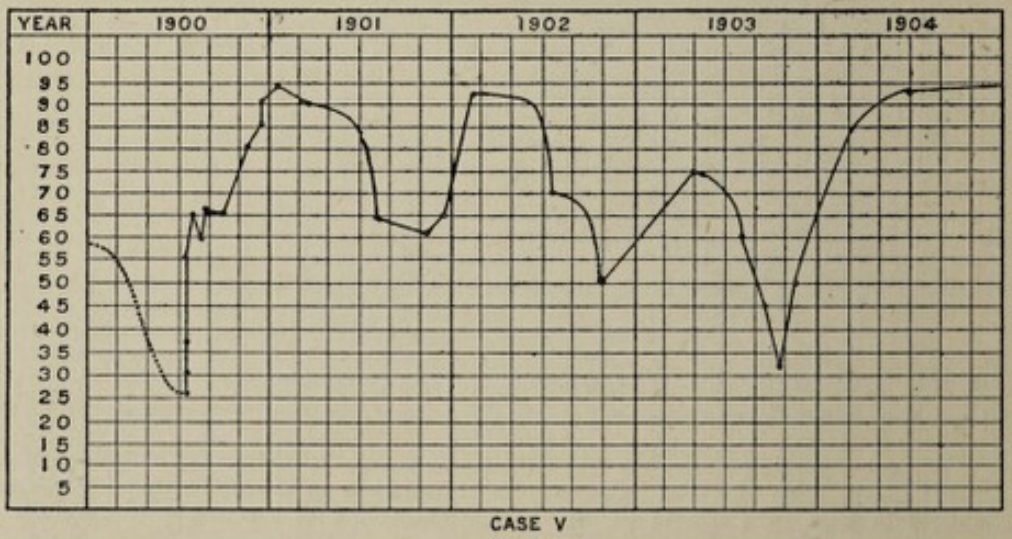


CHART IV—The subsequent history of the above case of Addisonian Anæmia (Case V, Chart III), successfully freed and *kept free* from Sepsis. The patient has remained well for the past eight years without further relapse since 1903. The last mentioned was the only relapse which confined him to bed for a week. (*See antea*, p. 116.)

CHAPTER XX

The Changes in the Bone-marrow

The observation and interpretation of the changes found in the bone-marrow form an interesting and important chapter in the history of this disease. The changes are of a striking character. The bones are abnormally rich in blood-forming (red) marrow, not only the vertebræ and the flat bones of the head and pelvis, where such marrow is normally present, but also the long bones, which normally contain yellow marrow. Microscopically there is a large increase of lymphoid tissue, showing young nucleated red cells—normoblasts and megaloblasts—in great numbers, sometimes also many cells enclosing red corpuscles.

Since their first description by Pepper (1875), and Cohnheim (1876), and Osler (1877), they have excited much attention, apparently denoting some profound disturbances in blood-formation as the possible cause of this severe anæmia. They have been variously interpreted. While many observers (Pepper, 1875 ; Cohnheim, 1876 ; Rindfleisch, 1890 ; Ehrlich, 1892-1900 ; Engel, 1898 ; Grawitz, 1895 ; Bramwell, 1899 ; and most recently Gulland and Goodall, 1905) have regarded them as primary, and important evidence of a defective blood-formation as the cause of the disease —its "myelogenous" variety—others (Neumann, 1877 ; Hunter, 1888 ; Mott, 1890 ; Muir, 1894 ; Askanazy, 1895 ; Pappenheim, 1901) have looked upon them as secondary—as important evidence of an exaggerated blood-forming function of a compensatory character—as an endeavour on the part of the bone-marrow to compensate the excessive destruction of blood taking place elsewhere (Hunter, 1888 ; Mott, 1890 ; Muir, 1894).

The "myelogenous origin" of pernicious anæmia was the original view regarding the nature of this anæmia almost universally held by observers up till 1888, when the "hæmolytic origin" was definitely asserted by Hunter (1888). It is the view still held by many observers, especially Ehrlich (1888-1900), to whom, as also to Stockman (1895), the pigment changes in this disease "stand in close relation" to the tendency to hæmorrhages observed in many cases of this disease.

Certain other observers have explained the relation between the bone-marrow changes and the hæmolysis in another way, viz., "hæmolysis is increased, but it is because of defective blood-formation." (Russell, 1889; Henry, 1889; Gulland and Goodall, 1905; Ewing, 1904.)

Nature of the Changes.

These have been most fully studied and described by Professor Muir (1894). Their chief feature is the enormous number of *nucleated red corpuscles* ("erythroblasts"), in some cases constituting as many as one-quarter of the total number of red cells. Some of these are of very large size, reaching 20 μ in diameter. They show a great variety in the appearance of the nuclei, some containing one spherical or irregular nucleus, others two or more nuclei, and in many the nucleus is rosette-shaped or broken up into fragments—a condition never seen, according to Muir, in the adult marrow in the normal state, either due to degenerative changes in the nucleus or to broken-down mitotic figures. In severe cases there is not only an extension of the red marrow, but a striking alteration in the microscopic characters of the erythroblasts (nucleated red cells) of the nature first described by Rindfleisch (1890), but according to Muir scarcely so extreme.

In cases (four out of five in number described by Muir) the nucleated red corpuscles are increased in number, but in none is there so great a proportion of the large forms. In a few cases (one out of five) nearly all are of normal size, with spherical nuclei, most of them of homogeneous structure. According to Muir's studies, it appears clear that all intermediate forms can be found between the normal nucleated red corpuscles (Ehrlich's "normoblasts") and those large forms (Ehrlich's "megaloblasts" and "gigantoblasts"), and that the latter do not constitute a distinct class of cell, as some writers following Ehrlich (1891-2) conclude. This last-mentioned conclusion of Muir's is important; for, as will be afterwards seen, the view that megaloblasts are a totally distinct class of cell from the normoblasts forms the basis of all Ehrlich's teaching that "megaloblastic degeneration" of the bone-marrow is the essential "cause" and distinguishing feature of pernicious anæmia.

The *ordinary red corpuscles* ("normocytes") show the same variations in shape and size as are found in the blood in Addisonian anæmia. It is an important point, however, according to Muir, that in none of his observations were any found corresponding in

size ("megalocytes") with the largest nucleated forms—another important divergence from Ehrlich's teaching that megalocytes are a distinct variety of red cells, and are formed from megaloblasts.

The *colourless marrow cells* undergo a proportionate diminution in number (Rindfleisch, 1890; Muir, 1894); otherwise they do not appear to undergo any alteration (Muir).

The *eosinophile cells* appear to be less numerous in the newly formed marrow than in the normal marrow. (Muir.)

The *giant-cells* are always few in number and of comparatively small size. (Muir.)

Pigment cells and *corpuscle-holding cells* are present in considerable numbers in most cases (Osler, 1878), but not in all (Hunter, 1888; Muir, 1894). The pigment is both in the free condition and also within cells, most of it giving the iron reaction, though some did not (Hunter, 1888; Muir, 1894); but it is never in any great excess (Hunter). Muir found it most abundant in the case in which the progress of the anæmia was most rapid before the death of the patient.

The *structural changes in the marrow* described by Muir accompanying the above-mentioned changes include disappearance of the fat from most places and its replacement by a highly cellular tissue, with vascular arrangements somewhat similar to those found in normal marrow. One curious fact specially noted by Muir is that in the venous sinuses and in the parenchyma the red corpuscles are closely packed together as in the normal blood, whilst many of the veins contain merely a fine fibrinous network with only a few scattered red corpuscles. In other words, the extraordinary poverty of the blood as regards red corpuscles found in the general circulation does not extend to the tissue of the marrow (Muir)—an observation which only applies to the spleen among all the other organs of the body (Hunter, 1888); also Combe, 1822 (p. 19).

The other structural change is *absorption of the bone trabeculæ*, which appears to take place by a simple softening and atrophy apart from any special cellular agency. There is no evidence of erosion by osteoclasts, no proliferation of bone corpuscles, and no layer of leucocytes in special relation to the bone. (Muir.)

Such, then, are the marrow changes as described by Muir, and beautifully illustrated in the plate which accompanies his paper. The important point in connection with the pigment changes in the liver and other organs described and regarded as pathognomonic of the disease (Hunter, 1888) is the one drawn attention to by Muir (1894), viz., that "it is exactly in the cases in which the liver

contains most pigment that the marrow changes are most advanced and the disease has run the most advanced course."

Their Relation to the Anæmia.

Secondary and Compensatory.

The bone-marrow changes are secondary and compensatory to the hæmolysis, not causal (the author, 1888). Such is the view taken, among late observers, by Mott (1890), Muir (1894), Askanazy (1895), and Pappenheim (1901). The conclusions of Muir (1894) are of special weight, since more than any other observer he has made the bone-marrow the subject of extensive studies :—

> The earlier changes can only be interpreted as an extension of blood-forming tissue of compensatory nature, due to blood-destruction, the increase of the numbers of nucleated red corpuscles and transformation of yellow marrow being similar to those produced by hæmorrhage, and also found in other diseases.
>
> The further changes found in advanced cases—the occurrence in large numbers of large nucleated red corpuscles (gigantoblasts) reaching 20 μ or even more in diameter —are also secondary, and are due to a long continuance of the same conditions, the nucleated red corpuscles showing a return to an embryonic type.

These conclusions of Muir (1894) (as also of Mott in 1890 and the author, 1888) are entitled to the more weight inasmuch as they are formed with due regard to the class of facts drawn attention to in 1888 (p. 110) pointing to excessive hæmolysis as the essential and original blood feature of this disease. Nothing illustrates better the extraordinary possession which Ehrlich's teaching has taken of the minds of many observers than the fact that most of them who have investigated the subject only refer to increased hæmolysis as a possible consequence of defective blood-formation. In face of the large mass of facts, already described, denoting excessive hæmolysis as the great feature of the disease, it appears to be as idle and as logical to ascribe the disease to defective blood-formation, or "megaloblastic degeneration of the bone-marrow," as it would be to ascribe the real cause of the fall of a nation whose manhood had all been killed off in a long-sustained, terrible struggle, to the immaturity and juvenility of its youth whom it pushed to the front (the blood) ; or to the evidences of haste and hurry of preparations which were shown in its arsenals at home (the bone-marrow).

In view of the extraordinary degree of controversy connected with the interpretation of these marrow changes, the history of their observation and interpretation is hereafter given in full.

Primary and Causal.

The marrow changes are primary and causal (Cohnheim, 1876 ; Pepper, 1875 ; and most observers of earlier period (excepting Neumann, 1877) ; Rindfleisch, 1890 ; Ehrlich, 1892 ; Gulland, 1905 ; and many observers in later period).

The class of observations of this period which have most materially influenced the conceptions of Continental observers regarding the nature of the marrow changes in this anæmia and other severe anæmias have been, not those relating to its hæmolytic nature, but the hæmatological studies of Professor Ehrlich (1888-92) and his followers regarding the presence of megaloblasts and their significance. They are held to denote a "megaloblastic degeneration of the bone-marrow"—the result of defective blood-formation—as the essential feature of all so-called "pernicious anæmias," including Addisonian anæmia—their so-called "myelogenous origin," with this blood change as its chief manifestation.

By a curious coincidence, the period (1888-94) marked by the first assertion and confirmation of the pathognomonic importance of hæmolysis in this anæmia was marked on the Continent by the first assertion of the above conclusion by Ehrlich and his followers, to wit, the pathognomonic importance of megaloblastic degeneration of the blood and bone-marrow as the essential feature of their "progressive pernicious anæmia," denoting a reversal to an embryonic type of blood-formation as the chief feature—even cause—of this anæmia. The two opposing conceptions of the nature of this anæmia met in full conflict in 1892, when Ehrlich formulated his views on the subject at full length in an important discussion on "Severe Anæmias" held in Wiesbaden, the hæmolytic view being represented by Professor Birch-Hirschfeld, who based his conclusions largely on the work of the author. Reference should be made to this discussion by those desirous of understanding clearly the after-historical development of this subject. From that time onward up to the present two opposing schools have fought for mastery in relation to the pathogeny of this anæmia, the "hæmolytic" school represented by the Author (1888) and the "megaloblastic" school represented by Ehrlich (1892). The two schools gradually drew away from one another so far that in 1900 two monographs professing to be on the same disease "pernicious anæmia" could be published, one by Ehrlich and Lazarus (1899), wherein everything is said of megaloblastic degeneration and its importance, and hardly any mention made of hæmolysis, and the

other by the author, in which nearly two-thirds of the book were devoted to hæmolysis and no mention made of this change, except the conclusion originally formed (1888) that the bone-marrow changes were secondary to the disease. His later observations (1890-1900) regarding the infective *etiology* of Addison's anæmia were made without any reference to the presence or absence of megaloblasts in the blood.

The importance attached to megaloblastic degenerations by Ehrlich and his school has had the effect of extending the title "pernicious" to forms of anæmia quite other than those had in view by Addison and English physicians under the title "idiopathic anæmia," and quite other than those contemplated by Biermer under his title of "progressive pernicious anæmia." As already seen, the condition termed "progressive pernicious anæmia" by Biermer, and since commonly termed "Biermer's Anæmia" by German writers, never was identical with Addison's Anæmia. It was reduced by the choice of Biermer's exponents to being

nothing more than a mere group of symptoms met with in very different conditions of disease and produced by many causes.

The effect of Ehrlich's work is to carry the degradation a stage further, since the latest definition of it (1900) is

"the condition characterized by the symptoms described by Biermer and the megaloblastic blood changes described by Ehrlich (Biermer-Ehrlich Anæmia), even although, it is added, this does not correspond clinically with Biermer's division of pernicious anæmia from other forms of anæmia." (Lazarus.)

Of this definition of "megaloblastic degeneration of the marrow" as *the* criterion of Addisonian anæmia, it may here be said that it is wide enough to include lead poisoning and sufficiently loose to let many cases of the truest Addisonian anæmia escape through its meshes. For at many stages of this anæmia megaloblasts may be entirely absent from the blood; or, as Ehrlich himself admits, so few in number that it is necessary to search through many fields with the aid of an oil immersion to discover one; and even if this one be discovered it may be exceedingly difficult to decide whether it is a small megaloblast or perhaps only a large normoblast. Enough has been said to show that in view of the importance attached to it, the historical development of "megaloblastic degeneration" in relation to the whole subject of Addison's Anæmia requires to be dealt with in full detail, and this will be done in the following chapters.

For on his observations Ehrlich has based a whole series of generalizations—clinical, pathological, diagnostic and prognostic, regarding anæmias generally and "progressive pernicious anæmias" more particularly, which have received a wide acceptance.

Their effect has been: (1) to greatly stimulate interest in purely hæmatological studies in this disease, in many cases to the almost complete exclusion of all the other features; (2) to perpetuate and give strong support to the conception that this anæmia is not a disease but only a group of symptoms (to extend in one direction and to restrict in others the class of cases entitled to be termed pernicious) and to affirm once more that "progressive pernicious anæmia" is only a group of symptoms, which may have the most diverse causes, characterized by the clinical features described by Biermer and the blood changes described by Ehrlich ("Biermer-Ehrlich Anæmia").

Lastly, as will be afterwards shown, while professedly lending strongest support to "Biermer's anæmias"—by identifying them with "megaloblastic anæmias"—the work of Ehrlich has put an end for all time to the historical group, as described by Biermer, by removing from it the chief forms which, with Addisonian anæmia, originally constituted that group. [*Sic.*]

(*See* p. 174 and Map 1, p. 65.)

Toxic and Infective Causes of the Marrow Changes.

As will be made clear, the chief point of interest regarding these marrow changes has proved to be not embryological or pathological, but etiological, precisely as the author early recognized (1887) to be the case for the hæmolytic changes of the disease. Professor Muir's later extensive observations (1901) reveal that the toxins of various infections produce marked changes in the bone-marrow. His results were obtained by experiments on rabbits, and have, he states, been fully confirmed by his observations on the marrow of the human subject in various diseases.

The two *chief* functions of the bone-marrow, as judged by the relative proportion of cells and the number of mitoses in them, are the production of red corpuscles and of finely granular leucocytes. Either of these functions may be called into greater activity, and the marrow becomes correspondingly altered. The condition resulting from increased drain on finely granular leucocytes I have called the *leucoblastic* type of bone-marrow, in contrast to the erythroblastic, which results from hæmorrhage.

Other changes in the bone-marrow are chiefly of the nature of degenerations, and are to be referred principally to direct toxic action. The giant-cells in particular are very sensitive to such action; in severe conditions, *e.g.*, poisoning with diphtheria

toxin, pneumococcus septicæmia, &c., they may be nearly all in a degenerated condition within forty-eight hours. On the other hand, when leucocytosis has occurred with a minimum of toxic condition the giant-cells may present a normal appearance. Well-marked degeneration may also occur in the finely granular myelocytes, constituting the great majority of the marrow-cells; and when there has been a condition of severe poisoning, a considerable number of them may be seen lying free in the blood of the venous sinuses and veins, a fact of interest, since in such conditions a few myelocytes may be found in the circulating blood before death, usually accompanied by a few nucleated red corpuscles. Along with these changes there is an increased amount of blood in the marrow, and the vascular channels are widened and engorged. The changes found in these severe toxic conditions may be thus summarized: extensive degenerative changes in the giant-cells, degeneration to a less extent in the finely granular myelocytes, diminution in the number of the polymorphonuclear leucocytes, increased amount of blood, passage of myelocytes and erythroblasts into the blood-stream.

Such are the changes in the marrow which can be experimentally produced by the injection of micro-organisms, especially pure cultures of *Staphylococcus pyogenes aureus*. When the infection was slight, with little or no disturbance of the general health, the changes found were chiefly of a formative or reactive nature. When the infection was more severe, so that a fatal result followed, there were, in addition, changes of a degenerative type produced by toxic action.

It will be seen to what a remarkable extent these important observations (1901) confirm the view of the marrow changes taken by the author (1888) regarding their secondary or compensatory character. They also confirm in a remarkable way his later conclusions (1900) regarding the infective nature of the etiological factors underlying this disease, one of these infections being of septic nature. Lastly, they have been still further confirmed (1905-7) by a striking series of experiments made by Dr. Bunting. These show that this megaloblastic change can be induced *in a few days* by certain hæmolytic agents. (*See antea*, p. 64.)

During the past seven years the author has been able to confirm his etiological conclusions (1900) regarding the infective origin of this disease, and extend them in a direction of great practical importance to the patient. (*See* Chapter XV.) I find, namely, as the result of clinical observations in its treatment, that it is the *septic* (staphylococcic and streptococcic) infection which retards blood-formation. On its removal (*see* Charts, p. 148) the powers of recovery are exceedingly striking, more marked, and more durable than has ever hitherto been the case. The disease still persists, but can be compensated for years by the increased regenerative activity of the bone-marrow excited by the action of its own hæmolytic poisons. (*See* Chart 4, p. 148.)

BLOOD-FORMATION

CHAPTER XXI

The Earlier Observation and Interpretation of the Marrow Changes

Period II (1875-88).

Changes in the bone-marrow were first described by Pepper (1875) and Fede (1875). *Pepper* described the change as a *hyperplasia of the marrow*, with production of lymphoid cells similar to that found in some cases of leucocythæmia, and regarded the disease as a "medullary form of pseudo-leukæmia.

Cohnheim (1876) independently confirmed and was the first to point out the chief histological features. He found the *bone-marrow intensely red*, without being hæmorrhagic, extending into the shafts of the long bones, almost devoid of fat, and showing, histologically, large numbers of *nucleated red corpuscles* with single or double nucleus, with increase of marrow cells and large red corpuscles. He considered the change to be *a return to an embryonal type of blood-formation*, with a holding back of immature nucleated red corpuscles, in the bone-marrow, and thought it to be *the primary factor in the disease.*

Neumann (1877) confirmed Cohnheim's discovery, but interpreted the changes quite differently; they were, he considered, merely *compensatory to the anæmia*, and *were similar to those found in other anæmic conditions, and after hæmorrhage.*

Eisenlohr (1877) confirmed these observations as to the presence of nucleated red corpuscles, small yellow microcytes (2 μ in diameter), and larger and smaller blood-corpuscle-holding cells. But he found *similar changes in a case of carcinoma of the stomach*, and on the strength of this concluded that *cancer of the stomach might be one of the many causes of this anæmia.*

Osler and Gardner (1877) described similar changes, with, in addition, large numbers of *blood-corpuscle-holding cells*, and took the same view as that of Pepper.

Riess (1881) directed attention anew to the presence of *blood-corpuscle-holding cells.* He found them in five out of seven cases, and concluded that a destruction of red corpuscles took place in the bone-marrow.

Litten (1881) reminded him, however, that he and others had found such cells in the bone-marrow in the most varied acute and chronic diseases, as well as in pernicious anæmia; and he, therefore, could not regard them as characteristic of any one form of anæmia.

Mullendorff (1881) found them present in two cases, and Osler (1882), who first described them, found as the result of further investigations on seventy-five cases of other diseases that they were often present, especially in phthisis, pneumonia,

typhoid fever, ulcerative endocarditis, and they therefore were not characteristic of any one disease.

Dr. Pye-Smith (1883), reviewing these bone-marrow changes described up to this time, expressed the opinion that cases showing such changes "must be separated from those of idiopathic (Addisonian) anæmia."

His colleague, *Dr. Fagge* (1886), discussing the subject in his "Text-book of Medicine," took a less extreme view. For his own part he preferred to adopt Immermann's hypothesis, that the medullary changes, when they were present, were a result of the disease rather than a cause of it, and perhaps indicated an effort on the part of the bones to take an unusually active part in the generation of red discs *in compensation for the failure of the spleen and lymph glands to maintain the blood in a normal condition.*

In 1886, *Geelmuyden* (Christiania) made a very careful investigation of the bone-marrow in various diseases, including three cases of "pernicious" anæmia. Out of forty cases of various diseases he collected from the literature, nucleated red cells were found in 78 per cent. of cases, and pigment cells in 44 per cent.; fatty marrow in 18 per cent., and lymphoid marrow in 82 per cent. In twenty normal cases which he himself examined nucleated red cells were present in 91 per cent. and pigment cells in 64 per cent. But in "pernicious" anæmia the numbers present were far in excess of those met with in health. He concludes that the lymphoid change in the bone-marrow of the long bones was in all probability *a secondary compensatory process, the result of the anæmia;* this change was not a specific one, but was found in other diseases, and consisted in the replacement of fatty marrow by a lymphoid blood-forming marrow.

Litten and *Orth* (1887) agreed with Neumann; they succeeded in producing *similar conditions in animals by bleeding.*

In 1880, *Professor Ehrlich* made an interesting contribution to our knowledge of the blood changes in anæmia. Up to that time, he stated, there existed in the literature of "pernicious" anæmia only two cases in which *nucleated red corpuscles* were found in the blood during life. But by his methods he had *found them in all forms of severe anæmia,* irrespective of whether they were traumatic or essential. He distinguished three forms: (1) *Normoblasts,* forms of the size of red corpuscles; (2) *megaloblasts,* forms which were the precursors of giant red cells; (3) *micro-* or *poikiloblasts,* a very rare occurrence.

"It was specially important to note that in simple traumatic anæmias and in leukæmia normoblasts were almost exclusively found; while in 'progressive pernicious anæmia' in *the great majority of cases* [*sic*] megaloblasts were found. Further, in anæmic blood a degeneration of the red corpuscles can be found leading eventually to their destruction, shown by a more violent staining of the hæmoglobin, instead of a pure orange, with eosin and methylene blue. These changes could also be observed in simple traumatic anæmia, even a short time after bleeding. These observations, he held, were fitted to throw a certain light on the nature of "pernicious" anæmia. Degeneration and regeneration run together even in uncomplicated anæmias; on the prevalence of one or other process depended whether the simple anæmia passed on to recovery or became the 'progressive pernicious' form."

It requires to be specially noted that the case on which these observations were made was a case of general sarcoma, termed by him "pernicious anæmia," not a case of Addisonian anæmia in any sense. [*Sic.*] He distinguished three forms of nucleated red corpuscles in the blood: (1) One of small size with deeply staining nucleus, "normoblasts"; (2) one of larger size, "with faintly staining nucleus, megaloblasts," the precursors of giant red cells, "macrocytes"; and (3) microblasts or poikiloblasts, a rare occurrence; and he specially noted that while in ordinary anæmias normoblasts were almost exclusively to be found, in "pernicious anæmia" megaloblasts were found in *the great majority of cases.* [*Sic.*]

In 1888, in a further brief communication bearing the title, "On a Case of Anæmia, with Observations on Regenerative Changes in the Bone-marrow," he made some further observations; and inasmuch as these communications form the basis of all his subsequent conclusions, his own summary of them (1888) may be given. It is again to be noted that his next two cases were, by his own admission, not entitled to be called even "pernicious," still less Addisonian anæmia.

I have only published two cases—one showing the very rare combination of "pernicious" anæmia with periosteal sarcoma [*sic*], the other showing a peculiar and quite isolated condition of the polynuclear variety of leucocytes.

I record a third case: A woman, aged 21, admitted for metrorrhagia [*sic*], very anæmic, but no trace of lemon tint; very numerous retinal hæmorrhages. Death. *The case was one not of "pernicious" anæmia* [*sic*], but of secondary traumatic anæmia.

Blood.—I suggested the name "schistocytes" as a better name than "poikilocytes." I have attempted to show in former works that the so-called poikilocytes arise in this way: that portions of them become cut off and continue to functionate in the blood as independent corpuscles, a process which I regard as a compensatory act to provide a larger respiratory surface. As schistocytes I designate all those elements, apart altogether from their character, which are so small that they can only be looked upon as parts of red corpuscles. In support of this view I may state that neither in the blood nor the blood-forming organs have I ever found nucleated precursors of poikilocytes (*i.e.*, poikiloblasts). In this case the greatest number of leucocytes were lymphocytes (80 per cent.), with only 14 per cent. of polynuclears, a change in proportion only met with when the bone-marrow and spleen are not functioning in normal manner. In favour of this view it is to be noted that the eosinophile cells were entirely absent; there was also an entire absence of nucleated red corpuscles. As I have shown [*sic*] *one can determine the character of an anæmia better from that of the red nucleated corpuscles than in any other way.* [*Sic.*]

In secondary anæmia nucleated red corpuscles of normal size—normoblasts—are found, while in "pernicious" anæmia a much larger form (gigantoblasts) are present, representing an embryonal type of blood-formation. *I am accustomed to consider the examination of an anæmic blood complete only when I have determined the form of the nucleated red corpuscles, and as the result of several years experience I regard this criterion as the most trustworthy in the differential diagnosis of anæmia,* because similar cells were found in embryonic blood. [*Sic.*] I localize the seat of this "pernicious anæmic" change to the bone-marrow for three reasons: (1) because

they were found here in large numbers; (2) because the polynuclear leucocytes, which I consider arise in the bone-marrow, were few in number; (3) because the eosinophile cells, which also arise in the bone-marrow, are almost absent from the blood. *The nature of "pernicious anæmia" in my view is that nucleated cells normally present in the blood are replaced by an embryonic type of nucleated cell—the megaloblast; and this is a sure sign of the "pernicious" nature of the anæmia.*

The conclusion come to by the author (1888) regarding the bone-marrow changes in his "Investigation" was of a different character :—

> They point to an excessive activity on the part of this tissue in blood-formation. So far from denoting any interference with blood-formation, the presence of nucleated red corpuscles rich in hæmoglobin indicates undoubtedly some marked necessity for increased blood-formation; but their large numbers and richness in hæmoglobin (along with the high hæmoglobin ratio in the corpuscles of the blood) seem equally to indicate that the demand is being fairly met by the bone-marrow even up to the last or very near the last. *Failure in blood-formation plays, therefore, I consider, little or no part in the production of "pernicious (Addisonian) anæmia."*

It was not the primary factor in the production of the anæmia, but merely secondary to the hæmolysis. He based these conclusions largely on his observations regarding : (1) the existence of hæmolysis as the cardinal feature of the disease (*see* p. 109); (2) changes he found in the bone-marrow in animals after excision of the spleen—namely, he always found a marked lymphoid hyperplasia, very rapidly produced. The essential nature of the blood change was not failure in blood-formation but excessive blood-destruction.

"*The observations now recorded* (*v. antea*, p. 109) *appear to me to denote for the reasons detailed that the essential nature of the blood change is excessive blood-destruction.*"

Such was the conclusion arrived at (1888) as the result of the work then recorded. The essential blood change was hæmolytic. The bone-marrow changes were compensatory, not causal; they denoted a big and, for a long period, successful effort on the part of the blood-forming tissues to replace the blood continuously being destroyed. So far from being unfavourable, the conditions in Addisonian anæmia were rather favourable than otherwise to blood-formation.

Issue was thus fairly joined with the view up to that time generally prevalent that disturbance of blood-formation was the cause of this anæmia. For the first time in the history of the disease the bone-marrow changes were brought into relation with the hæmolytic changes presented by the disease.

CHAPTER XXII

The Later Observation and Interpretation of the Marrow Changes

Period III (1888-1900).

The later history of the observation and interpretation of these changes shows the influence of the foregoing teaching of Ehrlich and Hunter respectively. They may be divided into two groups, according as the various observers interpret the marrow changes to be : (1) the primary cause of the blood-changes, denoting the "myelogenous origin" of the disease ; or (2) merely compensatory, the effects of the disease, secondary to the hæmolysis and the toxic agencies underlying that hæmolysis.

As the result of careful observations, *Dr. Mott* (1890) took the same view of these changes as the author in three cases of pernicious (Addisonian) anæmia showing well-marked pigment changes. The changes were secondary and compensatory ; the larger nucleated red cells denoted a reversal to an embryonic type of blood-formation.

In 1890 *Professor Rindfleisch* made some observations (in one case) destined to form, in Ehrlich's hands, the basis of the view regarding "megaloblastic degeneration" as the essential "cause" of "pernicious" anæmia. The marrow showed an extraordinary number of nucleated red corpuscles ; but what specially arrested his attention was their large size, many of them larger than the large corpuscles of the frog's blood. He concluded that in place of the normal changes ending in the formation of normal red corpuscles (viz., the extrusion of their nuclei), there was a formation of very large, ill-formed cells which retained their nuclei and swelled up to form very large, but for functional purposes very worthless, giant-cells. This he considered to be the fault of the blood-formation in "pernicious" anæmia. He agreed, therefore, with Cohnheim—the pathogeny of this anæmia was to be sought for in diseased processes in the bone-marrow.

Rindfleisch's teaching received the keenest support from *Professor Ehrlich* (1892), who saw in it an important confirmation of

his own observations (1880 and 1888), and on the strength of it developed his conception still further. He confirmed Rindfleisch's observations regarding the mode of formation of red corpuscles. He considered that in "pernicious" anæmia blood-formation took place by megaloblasts, which lost their nucleus by fragmentation and atrophy, whereas in all other conditions the red corpuscles were formed from normoblasts by extrusion of their nuclei. The presence of megaloblasts he described as a characteristic feature of "pernicious" anæmia. He had frequently seen free nuclei in anæmic blood, and stated that such nuclei were capable of surrounding themselves by new protoplasm, and becoming transformed again into nucleated red corpuscles. The normoblasts represented an extraordinarily useful type of cell, since a single normoblast could produce successive crops of new red corpuscles. They were the only type found in the blood-forming organs of healthy animals.

The megaloblasts are two to four times larger than normoblasts, very rich in hæmoglobin, the nucleus larger but not so darkly staining. The nucleus never becomes extruded, but undergoes degeneration, breaks down and gradually becomes absorbed. I have never found this type in the normal adult organism of men or animals, but I have found it in the embryo, and regard it therefore as a return to an embryonal type of blood-formation, and all conditions in which these appear in the adult organism are, in my judgment, to be grouped together as denoting a reversion to the embryonal type.

The occurrence of megaloblasts I consider to be the proof that the type of blood-formation is no longer normal, but has become embryonic in character; and this change is in many ways an unfavourable one. First, this type of regeneration is a much slower one than the normoblastic. Such rapid regeneration as I and v. Noorden have above described is quite impossible in "pernicious" anæmia. Moreover, the largeness of the corpuscle diminishes the respiratory capacity of the blood-cell. The high hæmoglobin ratio so often observed in "pernicious" anæmia is to be explained by this embryonic type of blood-formation, viz., through the type of megaloblasts.

It suffices to establish the "pernicious" character of the bone-marrow change if, instead of the whole, only considerable portions of bone-marrow have undergone this megaloblastic change. . . . It is possible to diagnose a "pernicious" anæmia from the character of the blood changes. Megaloblasts and megalocytes are the criteria which denote the existence of megaloblastic degeneration, *the chief cause of "pernicious" anæmia* (p. 50). [*Sic.*]

We must consider it established that *the nature of "pernicious" anæmia is to be found in the specific alteration of the bone-marrow now described.* How this is brought about it is not possible to say. It is possible that certain poisons affect in this way the bone-marrow. This would be the really primary "pernicious" anæmias; while in the secondary forms, the change in the hæmopoietic system only occurs later on as the result of the already existing anæmia.

The chief point to be noted in the above observations of Ehrlich is this: that he now asserted that the megaloblastic changewas not only a reversion to an embryonic type, but was also a "degeneration" and the "chief cause" of pernicious anæmia.

In 1893, as the result of a careful embryological study, *H. F. Müller* gave full adherence to Ehrlich's view of "pernicious" anæmia. He concluded that Ehrlich's megaloblasts did really correspond with the type of nucleated red cell found in the embryo as first described by Hayem (1883) under the name of "nucleated giant corpuscles," and independently more fully described later by Howell (1890) under the name of "ancestral cells." As regards the relation of these observations to the pathogeny of "pernicious" anæmia, he thought that "pernicious" anæmia was the result of an abnormal hyperplasia of the erythrocytes, just as leukæmia was an abnormal proliferation of leucocytes. He adhered, therefore, to Cohnheim's view. The alternative view—which he stated to be that of Birch Hirschfeld and Maragliano—namely, that the cause of the disease was to be found in the blood-plasma, was declared by him to be a hypothesis. Not once in this whole consideration of the subject, either by Rindfleisch, Ehrlich, or himself, is the subject of blood-destruction as an alternative to abnormal blood-formation ever mentioned. His final summing up was :—

We must regard "progressive pernicious" anæmia as a *primary disease of the bone-marrow*, the essential feature of which is the reappearance of embryonal cells, by which at once the severe cachexia is produced and the area available for normal blood-formation is diminished.

In 1894 *Professor Muir* contributed very full and important studies regarding the bone-marrow changes in five cases of pernicious anæmia, especially valuable inasmuch as, unlike Rindfleisch, Ehrlich, and Müller, he took cognizance of the evidence of hæmolysis presented by his cases. At the outset he stated :—

Although a general statement is often made by writers that the alteration is similar to that met with in various other diseases and produced by the anæmia, I may here state that the changes described by Rindfleisch, and also observed by me in certain cases, are such as I have never found in any other diseased condition, and, so far as I can find, have never been recorded. There are therefore some cases (*i.e.*, Addisonian) of "pernicious" anæmia in which a peculiar lesion is present, and these must either form a distinct class or be merely examples in which compensatory changes have reached a remarkable degree.

His interpretation of these changes was the following :—

The changes are, I consider, correctly described as an extension of hæmopoietic tissue. The increase in the number of the nucleated red corpuscles and the atrophy of fat have been frequently produced by bleeding animals, and are found in the human subject after hæmorrhage, and, in my experience, in other diseased conditions attended by anæmia. *This condition of bone-marrow, even taken alone, would indicate an increased regenerative activity.* . . . Moreover, if we examine the condition of the liver, we find *it is exactly in the case in which the liver contains*

most pigment that the bone-marrow changes are most advanced, and the disease has run the most prolonged course. Taking all the facts, we cannot but conclude that these five cases form a group of *examples of the same disease*, and that in all *the changes in the marrow* are of similar nature, and *secondary to the disease*. . . . It would appear that when the increased demand has lasted for some time there is a return to a sort of embryonic condition, in which nucleated red corpuscles of much larger size are found; and it is probable that they are formed in such numbers, or of such size, that they do not lose their nucleus in the normal manner, which undergoes degeneration. *The reversion is not a primary pathological condition*, but a *process compensatory to the long-continued drain*.

In 1895 a very valuable study was contributed by *Askanazy*:—

The differences which exist between megaloblasts and normoblasts are of degree more than of kind. There is no sharp line of demarcation between them—one form may pass into the other. The megaloblasts represent the younger, the normoblasts the older forms. For it is in the former that mitotic changes are chiefly found; and the polychromatophile coloration which they show—regarded by Ehrlich and Maragliano as a sign of degeneration—is, according to Gabritschewsky, a characteristic feature of young cells—a constant feature, for example, of young red corpuscles of birds and reptiles, while absent from older forms.

Nearly the whole of the nucleated red corpuscles of the human embryo liver show the same changes. Hence it is that megaloblasts are specially found in severe anæmia.

For the severer the injury to the blood is, the greater the strain put upon blood regeneration, and the more numerous are the young, unripe corpuscles thrown into the blood, many of them showing mitotic changes. *The presence of these is therefore an expression not of a degenerative but of an excessive regenerative process. The bone-marrow strives to compensate the severe alterations in the blood.*

In the following year (1896) an extended embryological and morphological study was contributed by Pappenheim. He also distinguished two classes of nucleated red cells, but these two classes did not correspond with Ehrlich's normoblasts and megaloblasts, either anatomically or physiologically.

(1) *Anatomically.*—In respect of size of cell, and of the fate of the nucleus—which are the features Ehrlich lays stress upon—there are no fundamental differences between the two classes of cells—normoblasts and megaloblasts. Intermediate forms exist, and all stages of transition can be traced between the two forms—a transformation of "megaloblasts" into "normoblasts" and *vice versa*. There are gigantoblasts whose nuclei are smaller and more deeply stained than in most gigantoblasts; and normoblasts whose nuclei are larger and less deeply staining than those of most normoblasts (p. 624). The formation of red corpuscles in embryonic blood occurs *exclusively* by breaking up and disappearance of the nucleus within the body of the cell, irrespective altogether of the size of the cell—whether gigantoblasts, megaloblasts, or normoblasts.

In other words, the process which Ehrlich chiefly relied upon (1888) as denoting the degenerative character of his megaloblasts, viz., the disintegration of the nucleus within the cell, was in reality the normal method of blood-formation in early embryonic life.

The question whether pernicious anæmia is a reversal to an embryonic type of blood-formation was further examined by

C. S. Engel. (1898.) He supported Ehrlich's view with this qualification: that as his observations showed, embryonic blood-formation was not of the same type at all periods :—

Embryonic blood-formation is no single process. It differs at different periods. There are different forms of nucleated red cells in embryonic life. The nucleated red corpuscles of normal bone-marrow are identical with those found during the second and third periods of embryonic life; but they are not identical with the large embryonal cells found in the first third of embryonic life. The development forms found in "pernicious" anæmia, on the other hand, resemble the embryonic cells of this period. The term "reversion to embryonic blood-formation" would be right if we had no continuity in blood development from the earliest period of embryonic life to the end of life. *It would then be correcter to say, that in "pernicious" anæmia the developmental forms of the red corpuscles in the bone-marrow grow into large cells such as are met with in earliest embryonic life.*

His observations, however, did not confirm Ehrlich's emphatic teaching regarding the clinical and diagnostic importance of megaloblasts as *the* feature of the blood in "pernicious" anæmia :—

It is certain that *megaloblasts are not to be found in every case of "pernicious"* anæmia. In addition to cases recorded by other authors, I have myself observed four such cases, all ending fatally, the blood of which showed macrocytes, but no megaloblasts. . . Moreover, *they are not* distinctive of "pernicious" anæmia, for I have found them in the blood in the severe anæmia of children; and Hammerschlag (1894) has found them in the blood in several cases of chlorosis. . . . *Megaloblasts are not the characteristic feature of the blood in "pernicious" anæmia; . . . they are by no means the most essential . . . ; they denote merely the action of chemical products on the bone-marrow.* [*Sic.*]

Ehrlich having stated (1898), in reference to Pappenheim's observations, that they did not accord with the clinical facts, Pappenheim returned again to the subject (1901), ("Das Unterhalten des Knochenmarkes bei Winterschlaf," &c., *Zeitschr. f. klin. Med.*, 1901, vol. xliii, p. 363) :—

In anæmia *the process is essentially a compensatory one* (*i.e.*, secondary), *never a primary anomaly depending on a primary disease of the bone-marrow.* All anæmias are secondary, including even Biermer's, only it is cryptogenetic. [*Sic.*]

The kind of anæmia cannot be determined by the blood changes. If megaloblasts appear in the blood, we have to do with certain forms of anæmia. But their absence does not exclude these forms. The *appearance of these cells in the blood denotes an increased formation in bone-marrow;* nevertheless, they can be increased in the bone-marrow without appearing in the blood. There are anæmias with normal normoblastic blood-formation which can be fatal, and others essentially megaloblastic, *e.g.*, bothriocephalus, which are curable, so that the *identification of a term "pernicious" with a particular type of blood-formation is not justified.*

CHAPTER XXIII

The Significance of Megaloblastic Degeneration in Relation to Addisonian Anæmia

The observations of the last ten years establish conclusively that the blood-formation in Addisonian anæmia is of an embryonic type. But between this conclusion and the further one drawn by Ehrlich, and emphasized with every degree of force by him, to wit, that this constitutes the nature and the cause of this anæmia, there is, in my judgment, a very wide gap. This explanation of Addisonian (and other "pernicious") anæmia as a "megaloblastic degeneration"—a reversion to an embryonic type of formation—appears to have exercised a sort of fascination over the minds of many observers during the past ten years—easy to understand when regard is had to the weight of Ehrlich's authority, the simplicity and beauty of his methods, and the attraction which bold and sweeping generalizations always have. What is not so easy to understand is why Ehrlich should have been content to stop short at megaloblastic degeneration and not have seen that, at this point, the chief problem still remained, viz.: to find out the cause of this change, to explain why the bone-marrow should undergo such a change. By emphasizing time after time the view that this megaloblastic degeneration of the bone-marrow is the primary factor in the disease, he has, as it appears to the author, taken a far too limited view of the problem which this anæmia presents. It is no explanation of a deadly disease to assign as its primary cause something that exists in other conditions not at all deadly but eminently curable. It was in every way as reasonable on the part of Addison, Wilks, Biermer, and many of the early observers to suspect fatty degeneration of the heart, liver, or blood-vessels as the prime factor of the disease as it is to assign this *rôle* to a megaloblastic degeneration of the blood and bone-marrow.

When we come to examine more closely Ehrlich's bold generalizations—pathological, clinical, prognostic, and diagnostic—one cannot but be struck by their fascination.

(1) It is a bold *morphological* generalization to assert that there is some great fundamental difference between normoblasts and megaloblasts ; that it is quite easy to distinguish between a normoblast of large size and a megaloblast of small size ; that they represent fundamentally different types of blood-formation, megaloblasts in particular denoting degeneration and a diseased blood-formation.

(2) It is an interesting *pathological* generalization to deduce from this—that anæmias may be divided into two classes, the normoblastic and the megaloblastic.

(3) It is a still bolder and even more fascinating *clinical* generalization to identify these two groups of anæmia with the two great clinical groups of *simple* and *pernicious* anæmia respectively.

(4) It is a remarkably fine *diagnostic* generalization, greatly simplifying the problems which the diagnosis of anæmias presents—to allege that the diagnosis can be based on the examination of the blood alone, by having regard to the numbers, proportions, and characters of its cells, especially of its normoblasts and megaloblasts.

(5) Lastly, it is a simple *prognostic* generalization to assert that normoblastic anæmias have a good prognostic significance, while megaloblastic anæmias denote diseased blood-formation, and have a bad prognostic significance.

In all Ehrlich's works these bold generalizations are so interwoven as to give each and all of them a totally fictitious appearance of strength, and they are drawn from so many departments of knowledge—morphological, embryological, physiological, pathological, and clinical—that it is not easy for any one observer to gauge the strength of the component parts—unless he comes to the subject with some other clue as to the nature of these anæmias than that afforded by hæmatology.

As already stated (Chapter III), the author from the very first (1892) profoundly dissented from the interpretation put upon this or any other particular blood change as the essential feature of Addisonian anæmia. To mark this dissent, he made no mention of it in his work on "Pernicious Anæmia," in 1900, although at that time, and for some years previously, the literature of the disease was filled with blood counts and blood studies to the exclusion of almost every other feature of the disease. He dissented even more strongly on a number of grounds from the sweeping generalizations which Ehrlich had based upon his interpretation. These grounds were connected with the whole range of these generalizations—historical, morphological, pathological, clinical, diagnostic, and prognostic. The character of his objections on all these grounds will now be made clear.

Ehrlich himself (1898) states that his conclusions are based on two classes of facts: (1) *Morphological*, the different fate of the nucleus in normoblasts and megaloblasts respectively; (2) *Clinical*, the facts observed in disease. His view must thus stand or fall according to the strength of these two bases.

Historical Basis.

Historical.—Before these are considered there is, however, one point of importance which calls for attention, and which of itself throws an interesting sidelight on the whole of Ehrlich's interpretation so far as Addisonian anæmia is concerned. That point is the nature of the cases on which Ehrlich first made his observations. Attention has been drawn to this in the account just given (*see antea*, p. 159), and, so far as the author knows, for the first time. *The cases on which his first observations were made were not cases of Addisonian anæmia at all and had no connection with that anæmia.* The first was a case of sarcoma; the second was a curious case following metrorrhagia, which Ehrlich himself would not include even within the wide limit he gives to the title "pernicious"; and the third was a nondescript case which he could not classify at all. It was in connection with these three cases of ordinary anæmia that he recorded all the blood features which, by a bold generalization, he afterwards grafted on first to so-called "pernicious or megaloblastic and grave prognostic" anæmias, including among these the form known as Addisonian anæmia; and secondly, to so-called "simpler or normoblastic and good prognostic" anæmias. The remarkable outcome has been that the most typical so-called "pernicious and grave prognostic" anæmia is one—tapeworm anæmia—which has nothing prognostically pernicious about it. [*Sic.*] And to complete the confusion, the so-called "simple or normoblastic and good prognostic" anæmia is found by the writer to include the severest form of "septic anæmia"—the form which is most commonly mistaken in everyday practice for Addisonian anæmia, and, next to Addisonian anæmia, is, in the writer's experience, the most severe and fatal of all the anæmic conditions simulating Addisonian anæmia. Truly a remarkable product of megaloblastic and pernicious confusion. (*See* Frontispiece.) (Map 1, p. 65.)

Morphological and Embryological Basis.

As regards the *morphological* and *embryological basis* underlying all his conclusions, the following are the facts not in dispute: (1) Two types of nucleated red corpuscles are found in the embryo, one in early and the other in later embryonic life, as

shown by Hayem (1883) and Howell (1890) ; (2) the megaloblast, first described by Ehrlich in the blood of various forms of anæmia (1880), corresponds to one of these forms, viz., that met with in the first third of embryonic life (Engel, 1898) ; (3) the bone-marrow is the seat of formation of both these forms (Neumann [1877], Bizzozero). These facts have been amply confirmed by Rindfleisch (1890), Müller (1893), Muir (1894), Engel (1898), and many others.

So much for the morphological identity of megaloblasts with a certain type of embryonal cell. The points in dispute are as regards their significance in Addisonian anæmia. The answer to this depends entirely on the view taken of their physiological significance. The view taken by Ehrlich from the very first is that their significance is pathological, not physiological, and denotes disease and degeneration, not excessive activity and excessive growth. This view is based on two classes of fact : (1) In health and most simple anæmias the type of nucleated red cell met with is the small one normally found—the normoblast—while the megaloblast is often found in severe anæmias ; (2) that the normoblast shows no degenerative changes, its nucleus after extrusion being capable of surrounding itself with new protoplasm and forming a continuous series of non-nucleated red cells, while the megaloblast shows degenerative changes, its nucleus undergoing degeneration, and ultimately becoming absorbed. Normoblasts are on this view quite distinct from megaloblasts ; the former denote health and the latter denote disease and degeneration, so that the title " megaloblastic anæmia " has come to be considered synonymous with their presence and with the type of disease termed " pernicious anæmia."

It is necessary to consider these sweeping deductions more closely.

First of all, it is quite inexplicable on *a priori* grounds why a reversion to an embryonic type of formation should *ipso facto* be a degenerative process. It implies that a type prevalent in the embryo is absolutely morbid if met with at any time in extra-uterine life, that a fundamental difference exists between blood-formative processes before and after birth. This is the fundamental assumption underlying all Ehrlich's conclusions regarding the pathological significance of these megaloblasts. But it has to be pointed out that in the opinion of those who have made the bone-marrow the subject of closest embryological study, *e.g.*, Neumann (1881), Askanazy (1895), Pappenheim (1896), Engel (1898), there is no

justification for distinguishing thus sharply between the blood-formation of the embryo and of adults. According to Neumann there is no doubt that "embryonal cells" are to be found in the red marrow at every time, and there is therefore no ground for distinguishing between embryonal and post-embryonal blood-formation.

> . . . To satisfy oneself on this point, one need only compare the nucleated red cells in the bone-marrow of the embryo with those contained in the embryonic blood itself and in the bone-marrow of adults. The absolute identity of all these cases leaves no doubt that they all have a similar histological formation.

Other observers who express similar conclusions are Rindfleisch (1890) and Hayem (1889), and, most recently and fully of all, Askanazy (1895). The latter concludes, after full consideration of the subject : "If such an identity exists, it is not justifiable to speak of a megaloblastic degeneration of the bone-marrow in pernicious anæmia." So also Pappenheim (1896, *antea*) finds that the changes in the nuclei, which Ehrlich (1898) specially relies upon as evidence of degenerations, are normal features of embryonic blood-formation.

There is even dispute as to what constitutes a normoblast and a megaloblast. According to Pappenheim, all cells possessing particular nuclear structure may be termed megaloblasts, however small may be their size, and all cells possessing another kind of nuclear structure are normoblasts, however large their size. "The division of the two kinds of cells, according to their size, must therefore be given up"—that is to say, he disposes of the second criterion of Ehrlich's classification, viz., the size of the cell. The differences between the two classes, according to him, relate solely to thickness of nuclear fibrils and size of interspaces between the fibrils, and are of such a minute character that they can only be well seen during karyokinesis.

Ehrlich's morphological distinctions, then, receive no support from Pappenheim's work. Doubt is even cast on his pathological interpretation, to wit, that the presence of megaloblasts necessarily denotes degeneration. According to Pappenheim, in every stage of life both kinds of cells are produced (*i.e.*, the two types he describes), and they breed true :—

> In the early days of embryonic life the great majority of the cells are large (megaloblastic), and only a few are normoblastic ; in the later stages the reverse is the case. Hence it is that while common in early life, it is only found in adult mammals under pathological conditions. This type of cell represents, therefore, a more unripe form, and this explains the character of its nucleus, its large size, poorness in hæmoglobin, and the general instability of its cell. In the earliest

period of blood-formation it is this type of cell that is formed (p. 636). In these stages the reproduction of young cells is much more active. In later stages it gives place to the normoblastic type.

Degenerative Changes.—It is probably on account of their great sensitiveness that the first type is more liable to undergo degeneration, while the second type is more resistant. The commonest form of degeneration they are subject to is *cytolysis*, with swelling (hydrops of the nucleus). It is mostly unripe megaloblasts that show this change, but older cells of normoblastic type may also show this degeneration. The *polychromatophilia*, which Askanazy and Gabritschewsky regard as evidence of youth, is not to be regarded as such because it is found chiefly in megaloblasts; nor are the latter young forms because they show polychromatophilia. The latter is much more, as Ehrlich holds, a peculiar degeneration which attacks especially elements poor in hæmoglobin (anæmic degeneration). Most megaloblasts are thus poor in hæmoglobin; but so also are sometimes young normoblasts, and these can likewise show this degeneration. But there are not only many young forms of both megaloblasts and normoblasts without this degeneration, but also there are many cells of both types—both young and old—which can show this degeneration.

Ehrlich having stated in reference to the foregoing observations that they did not accord with the clinical facts, Pappenheim returned again to the subject (1901) in the terms already seen. (*See antea*, p. 165.)

But as a matter of fact, embryological conclusions similar to Pappenheim's were reached by Engel (1898), one of Ehrlich's own workers :—

If an embryonal character is to be asserted for megaloblasts and denied to normoblasts, the question arises, up to what size are we to consider nucleated red corpuscles as normoblasts, and beyond what size as megaloblasts? For everyone who has studied the subject has seen transitions form between the two. It must therefore be doubted whether any fundamental difference exists between normoblasts and megaloblasts; a conclusion also come to by Askanazy. The conclusion of Neumann, Bizzozero, and most authors—that the nucleated red corpuscles of normal bone-marrow are identical with (not totally distinct forms, as Ehrlich holds) those found in embryonic life—is quite correct, and one of the normal phenomena of their development is disappearance of their nuclei by karyolysis—the process which Ehrlich regards as degenerative.

Conclusion.

A type of blood-formation which prevails in the first third of embryonic life, when blood-formation is most active, is not necessarily a degenerative process. An equally natural view to take of the appearance of nucleated corpuscles—megaloblasts—resembling those of early embryonic life might well seem to be that some great strain is being put on the blood-forming powers, which the blood-forming tissues endeavoured to meet by calling out all its reserves of blood-forming functions, including those which have lain quiescent since early embryonic life.

Clinical and Pathological Basis.

Ehrlich's only reply to the overwhelming evidence thus adduced against his morphological views is that this evidence is not in accordance with clinical facts. Here he touches ground which it is possible for all of us to investigate. The result may be thus expressed—that his clinical and pathological generalizations unfortunately do not accord in any measure with the clinical and pathological facts. It is precisely because Ehrlich has seen fit to graft bold clinical generalizations on his morphological observations that his views have in my judgment contributed not to clearness but to confusion. By thus transferring the controversy from the morphological to the pathological domain, he by no means helps his case. For whatever real basis this whole conception of "megaloblastic degeneration" as the cause and nature of Addisonian anæmia ever had was morphological. Without this basis, his clinical generalizations have—in the writer's judgment—no standing whatever.

To assert that megaloblastic degeneration of the bone-marrow is the essential cause of Addisonian anæmia, or any other anæmia, is just as correct as to say that "normoblastic degeneration" is the essential cause of all other anæmias in which normoblasts may be found; or that "poikilocytotic degeneration" is the essential cause of the anæmias in which it is found, as distinguished from "normocytic" anæmias in which it is not found; or that "lymphocytic degeneration" is the essential cause of lymphatic leukæmia; or "myelocytic degeneration" is the essential cause of spleno-medullary leukæmia.

Such distinctions are merely other ways of stating that some forms of anæmia show megaloblasts, normoblasts, poikilocytes, normocytes, lymphocytes or myelocytes; and if such designations were confined to their proper domain—viz., the hæmatological—no great harm would be done. But when the attempt is made to identify arbitrarily such pathological groups with clinical groups of anæmia, the result is a terrible confusion; and this, in the writer's judgment, is the real effect of Ehrlich's work on the whole subject of this anæmia. His statement is that normoblastic anæmias correspond to simple anæmias, while megaloblastic anæmias correspond to the pernicious group; moreover, that normoblasts and megaloblasts have a corresponding diagnostic and prognostic significance. And this teaching has been eagerly accepted by many, especially hæmatological observers.

Thus Dr. Lazarus, in Part II of Ehrlich's and Lazarus' joint work on "Anæmia" (1900), p. 171, writes :—

> In diagnosis the point of greatest importance is to discover megaloblasts in the blood ; their discovery often requires great patience. A positive result—the presence of megaloblasts in conjunction with an increase of megalocytes—is *proof positive of the existence* of pernicious anæmia, since it demonstrates without doubt that the blood-formation in the bone-marrow is following a type which is abnormal for adults.
>
> Further, these distinctions between normoblasts and megaloblasts are so important that it is necessary to separate the megalocytic and megaloblastic anæmias from the normocytic and normoblastic, *even if this division does not correspond clinically with Biermer's division of pernicious anæmia from other forms of anæmia.* [*Sic*]. We come to the result that (in pernicious anæmia) we are here concerned with the conditions characterized by the clinical features described by Biermer and the blood features described by Ehrlich.

Dr. Schauman also writes (1900) :—

> If I have to define my position in a few words, I consider that we must regard as pernicious anæmia those cases of severe anæmia which correspond to the clinical picture described by Biermer and possess the blood condition described by Ehrlich, irrespective of whether such cases occur in individuals previously healthy or in those already affected with disease, or whether the disease runs a fatal course or not.

Nowhere in any of his articles does Ehrlich adduce any facts to support such sweeping generalizations. In truth, the facts do not in any degree support them. The result is merely to create a type of "pernicious" anæmia wide enough to include almost every anæmia met with. The most various kinds of anæmia may at times show megaloblasts in the blood, *e.g.*, lead poisoning, even chlorosis ; and it is perfectly certain that, if logically adhered to, this definition would oftentimes exclude the most pernicious of all forms—the so-called cryptogenetic or idiopathic or Addisonian group. For this latter, in the author's experience, may show at different periods every variety of blood change—absence of nucleated red corpuscles of any kind, large or small ; presence of normoblasts to the exclusion of megaloblasts ; or the latter so few in number that, as Ehrlich himself admits (1898) they have to be sought for through many fields of the microscope. Moreover, when found, they may be of such a nature that it is often very difficult, if not impossible, to say whether they are normoblasts or megaloblasts ; and to determine this point, according to Pappenheim, it would be necessary to examine closely the thickness of the nuclear fibrils and the relative size of the intranuclear spaces. [*Sic.*]

The logical outcome of such a classification based on the presence or absence of one particular element of the blood—to the exclusion of clinical and etiological features—is that which Ehrlich boldly faces :—

> Progressive pernicious anæmia is a mere group of symptomatic conditions produced by every kind of cause. We must continuously keep in mind that we have not to do with a disease *sui generis*. The essential changes are blood changes.

Diagnostic Significance.

As regards the *diagnostic significance* of these megaloblasts, this is so much emphasized by Ehrlich that, as he states, their presence alone decides the diagnosis. It suffices to say, certainly in my experience, that this significance can be but slight, since, as he himself admits, they may be found in other forms of anæmia ; and may be absent altogether, or replaced by normoblasts in typical Addisonian, the most severe of all anæmias.

As the result of twenty-one years close study and almost daily experience in dealing with this disease, the writer knows nothing more pathetic than the over-importance attached to any individual blood change, and to this one in particular, in its diagnosis ; while far more *essential features*, *e.g.*, glossitic, hæmolytic and febrile, by which it could in his experience have been recognized and dealt with at the outset of the disease, are continuously overlooked. Certainly in the case of this great blood-disease (and in my experience in that of most other obscure anæmias) hæmatological methods have been a good servant but a most untrustworthy and misleading master. In no disease is this better exemplified than in the grave malady now before us. To wait until the discovery of a few megaloblasts in the blood—possibly only after searching through several slides with the aid of an oil immersion—becomes "proof positive" of the existence of this disease is to wait until the doctor and even the patient and his friends have themselves suspected or even diagnosed the disease from its general features. So far as effective treatment is concerned, it is to miss the only hope which is held out to us in connection with its prognosis—namely, the opportunity of dealing with it in its earliest stages. In the writer's experience this stage extends on an average over a period of a year to a year and a half before the disease, as detectable by its alleged diagnostic blood changes, has been recognized. (*See* Chart 2, p. 147.)

Even after megaloblasts have made their appearance, they are constantly absent, sometimes for long periods, during the intervals of betterment, when nevertheless other features (glossitic, hæmolytic, &c.) show that the disease is still present.

As already stated, megaloblastic degeneration formed no part of my diagnostic or pathological conception of the essential nature of Addison's anæmia; and I profoundly dissented from the interpretation put upon it by Ehrlich (1892). To mark this divergence I purposely omitted any mention of this change in my work in 1900, although at this time the writings of other observers were full of it. The conclusion of Dr. Melland, a close observer of the blood changes in anæmias, is therefore of particular interest (1907) :—

I have laid no stress upon the presence or absence of nucleated red corpuscles in the diagnosis of pernicious (Addisonian) anæmia. Normoblasts may be found in considerable numbers in many forms of severe anæmia from various causes, and even the presence of a considerable proportion of megaloblasts is not absolutely conclusive, since they may be found in still larger numbers in leucocythæmia; and, further, we may come across cases of pernicious anæmia with all the characteristic changes in the blood, but with few or no nucleated red corpuscles, normoblast, or megaloblast.

Prognostic Significance.

Even less can be said for the *prognostic significance* assigned to megaloblasts and normoblasts respectively by Ehrlich, for the former are found in the most eminently curable forms of severe anæmia, to wit, that of bothriocephalus anæmia. On the other hand, I have found the blood with normoblasts very numerous per cubic millimetre in a profoundest anæmia ("septic anæmia"), ending fatally a fortnight later.

The facts relating to the form of anæmia here referred to exemplify more than others could do the extraordinary confusion created by these normoblastic and megaloblastic criteria of Ehrlich, so far as prognosis is concerned. For, as will be seen in a later volume dealing with "Septic Anæmias," the form of severe anæmia which in its general appearances and in its severity and fatality most closely simulates Addisonian anæmia and is most often mistaken for it (and without doubt constituted, although not recognized, the most important member of Biermer's "progressive pernicious anæmia" group, next to Addisonian anæmia), is the severest type of the form of anæmia described by the writer under the name of "septic anæmia," *This form is typically normoblastic in its type.* [*Sic.*]

CONCLUSION.

Thus, the hæmatological criteria so much emphasized by Ehrlich, and so strongly supported by other hæmatological observers, have led to the following remarkable results :—

(1) Addisonian anæmia, admittedly the severest and most fatal of all anæmias, is relegated by them to an altogether subordinate position amongst so-called "pernicious anæmias." [*Sic.*] (*See* Schemes I, III, and Map 2, p. 66.)

(2) "Septic anæmia," although in its severest forms the most pronounced of all anæmias, and the most severe and fatal next to Addisonian anæmia, is by these criteria thrust out from Biermer's "pernicious" (Ehrlich's megaloblastic) anæmias, since it is typically normoblastic in its type. [*Sic.*] (*See* Map 1, p. 65.)

(3) These two great forms being removed, there remains as almost the only and the most typical form of Biermer's original "epoch-making" pernicious group—tapeworm anæmia, which has nothing pernicious about it, clinically or prognostically, and is easily cured in a few weeks. [*Sic.*] (*See* Map 1, p. 65.)

Hæmatological criteria have thus thrust out from Biermer's "pernicious" group the only form, apart from Addisonian anæmia, which has in its literal sense anything pernicious about it [*sic*], *a fact to which attention is now drawn for the first time.* This outcome of hæmatological criteria, *when divorced from clinical and etiological facts*, is made clear in *Map* 1, p. 65. Apart from Addisonian anæmia, which is thrust aside as unimportant (Map 2), and the "Septic Anæmia" described by the author, which is thrust out altogether, since it is normoblastic in its type—"progressive pernicious megaloblastic anæmia" ("Biermer-Ehrlich anæmia") now remains poised on the narrow, slender pedestal of an anæmia (Bothriocephalus) which has nothing severe about it either clinically or prognostically, and is itself by no means always megaloblastic. (*See* p. 178.)

As regards the *pathological significance* of the megaloblastic change in relation to Addisonian anæmia, the observations of Muir (p. 163), Askanazy (p. 164), Engel (p. 165), Pappenheim (p. 165), and last, and perhaps most complete, of Bunting (p. 64), are overwhelmingly conclusive. The change can be induced experimentally in a few days by injection of hæmolytic agents. "*The marrow responds in this emergency with nucleated red cells of normoblastic or megaloblastic type, depending upon the extent of this destruction.*" (Bunting, 1907.)

The blood change is hæmolytic in its nature, toxic in its origin, with bone-marrow changes secondary and compensatory to this destruction. (The Author, 1888.) This conclusion is confirmed by the clinical facts of the disease recorded on pp. 145-148 ; also on pp. 116-118, and 156.

It is also confirmed by the observations of Schauman (1900) with regard to *Bothriocephalus* anæmia—at once the most megaloblastic and the most curable of all severe anæmias. He sums up as follows :—

"'Pernicious anæmia' is therefore in my opinion due in most cases to an excessive blood-destruction ; the insufficiency of blood formation is a relative—not an absolute—one. It is probable that the blood poison acts simultaneously on the blood and on the bone-marrow—destructively on the blood, formatively on the marrow, stimulating it to increased activity. *It is in my opinion doubtful whether the peculiar change in the marrow which Ehrlich terms megaloblastic degeneration plays any part in the final exhaustion of the bone-marrow.*"

Megaloblastic Degeneration in relation to Bothriocephalus Anæmia.

The facts relating to this anæmia will be considered fully in a later volume of this work dealing with the great group of "Septic Anæmias," of which it is in my judgment an interesting and most striking form. (*See* Frontispiece.) For the last twenty years and more, since it was first drawn attention to in 1886, it has flickered like a veritable *Will-o'-the-wisp* over the field of severe anæmic conditions—visible to the gaze of observers in Finland where it has its chief home, but only seen on exceptional occasions by observers in any other country.

The attention of these latter has, however, been continuously invited to and attracted by its interesting features, since they are alleged to be identical with those of the gravest of all anæmias —Addisonian Anæmia—especially in respect of its blood changes, first and most fully investigated by Dr. Schauman (1894). These resemblances have been specially dwelt on by Professor Ehrlich (1898) as constituting the strongest basis of his teaching regarding the importance and significance of "megaloblastic degeneration" in relation to the nature and diagnosis of so-called "pernicious" or "megaloblastic" anæmias.

According to Ehrlich, "all attempts to ignore or to deny the existence of any difference between megaloblasts and normoblasts are shattered by the outstanding clinical fact that the blood of

'pernicious' anæmia is megaloblastic, and the most typical form of 'pernicious' anæmia is *Bothriocephalus* anæmia."

The following conclusions of Schauman (1900), to whom Ehrlich and all other observers owe their knowledge of the blood changes of this anæmia, are therefore of particular interest.

"*The blood in Bothriocephalus anæmia is by no means always megaloblastic or even megalocytic.* In some cases by far the great majority are small forms. On review of all the facts, we cannot conclude that any essential difference exists between normoblasts and megaloblasts. Their presence or absence depends upon the nature of the specific poisons; sometimes only normoblasts, sometimes only megaloblasts, sometimes both varieties, may be found; and lastly, in some cases, forms intermediate in structure may be found. The most active blood-formation may be found without the appearance even of normoblasts. Even the appearance of these latter — so-called 'blood crises' — regarded by Ehrlich as of good prognostic significance, has not always that significance. For these 'blood crises' have been found by Askanazy (1895) in a case of gastric cancer, and by myself in a case of *Bothriocephalus* anæmia, ending fatally on the following day. On the other hand, in rapidly healing cases of this anæmia, I have almost always found megaloblasts in much greater number during convalescence of cases ending in recovery, than when the disease was at its height. *We are therefore forced to the conclusion that the megaloblastic change of the bone-marrow has not the bad prognostic significance which Ehrlich has wished to attach to it.* On the contrary, in my experience, and as Askanazy (1895) has also found, *the most complete recovery may occur in cases in which megaloblasts are most numerous.* Even the relative numbers of normoblasts and megaloblasts have no appreciable influence on the prognosis as Erhlich would have us believe. I investigated twenty-six cases of *Bothriocephalus* anæmia in this relation. Twenty of these cases showed both normoblasts and megaloblasts, five only megaloblasts, and one exclusively normoblasts. All the last six cases underwent complete recovery, while four out of the first-mentioned twenty cases ended fatally. *The prognosis in cases in which only megaloblasts are present is thus, to say the least, not worse than in those in which normoblasts and megaloblasts are present.* Having regard to all the facts, I conclude that *it is not the megaloblastic change in itself, but the fact that the cause of the increased blood-destruction in most cases*

of 'pernicious' anæmia is not removable, that determine the bad prognosis of this disease. It is indeed possible that the megaloblastic change is even a salutary one, lessening or delaying the deleterious influences of the poison of the disease.

"While these changes have an important place among the symptoms of severe anæmias, *they have not, from a diagnostic and prognostic point of view, the exclusive pathognomonic importance which Ehrlich desires to attach to them.*"

The whole of the clinical and diagnostic traditions connected with this process of so-called "megaloblastic degeneration"—which, thanks to Ehrlich's teaching, have gathered around so-called "pernicious" anæmias for the past fifteen years—must therefore, in view of the overwhelming evidence above adduced, be regarded as having finally broken down; and with them all the clinical, diagnostic, and prognostic generalizations which Ehrlich and others have based upon them. They have profoundly influenced the work and conceptions of many observers. (*See* p. 155.) In conjunction with the name "pernicious" and the original etiological teaching of Biermer, they have served more than other teaching to obscure the great etiological problem which Addisonian anæmia presents. Their effect has been (*see* Map 2, p. 66) to represent this most fatal and mysterious of all anæmias as a small and unimportant form of the group entitled to be called "pernicious" anæmias; and to place in the forefront of such anæmias a form which has least of all anything progressive or pernicious about it, but is the most curable of all severe anæmias.

So far as Addisonian anæmia—the severest of all blood-diseases—is concerned, megaloblastic blood changes are tardy in their appearance, inconstant in their presence, and clinically, diagnostically and prognostically misleading. Further, the importance attached to their presence or absence seriously interferes with its early recognition and successful treatment. By the time they appear in the blood, the disease has in many cases existed for a period of one to one and a half years. (*See* Chart 2, p. 147.) I attach no importance to their presence or absence in the diagnosis of this disease. The disease can be diagnosed *in its very earliest stages* by the glossitic, hæmolytic, febrile and nervous features already described. (*See* p. 74.)

EPILOGUE.

THROUGHOUT the extraordinarily vexed history—full of controversy—of the anæmic conditions here considered, two general views have been expressed as to the probable ultimate outcome of future studies regarding their real nature. One of these was, that "if the etiology of the essential anæmias should ever be made clear, we should be in the happy position of seeing these hitherto mysterious diseases ceasing to exist as pathological entities, and disappearing altogether from the field of special pathology." And the writer, Professor Immermann (1879), added: "Personally, I can only wish for comfort's sake, that not the first but the latter will be the case, and the sooner the better." Or, as another earlier observer (1881), Dr. Coupland, put it: "All varieties of 'pernicious anæmia' are destined to be merged again into one when etiology shall be perfected."

The other view was that expressed by Dr. Bristowe: "I suspect that the group of affections now (1888) grouped together and labelled 'pernicious anæmia' will hereafter be found to belong to several categories."

As has been made clear in the course of this work, and has been represented graphically in the frontispiece, the latter, and not the former, view has proved in my observation and judgment to be the correct one. Moreover, the form of anæmia known to all observers as at once the most severe and mysterious of all, viz., *Addisonian anæmia*, but relegated by German and other observers for forty years to a subordinate position among so-called "pernicious anæmias," is entitled to a prominent place, not only in the field of special pathology, but also amongst the group of specific infective diseases. As such, it is fully entitled to all the interest which it has aroused. At the same time, as I have endeavoured to make clear, the great etiological factor common to this Anæmic Disease and other Anæmic Conditions resembling it, is an infection extremely common and hitherto overlooked, viz., Septic Infection. To that extent the other surmise, that all forms of "pernicious

anæmia" were destined to be fused into one when etiology was perfected, has also been proved by the author's observations to be at least partially correct.

The unhappy, confusing and misleading traditions associated with the name "pernicious" and with the etiological and hæmatological criteria connected with that name by Biermer and Ehrlich respectively having been broken down and removed—as in my judgment they now are—the ground is left free for the *new facts* regarding the infective characterizations of this grave disease, and for the *older facts in new relations* which constitute the author's conception of its real character. This conception is represented graphically in the Frontispiece and in Scheme II, p. 42, and will be still more fully elaborated and strengthened by the additional etiological, and the full clinical, diagnostic and prognostic facts which I shall describe in Vol. II of this work.

But no facts however new, and no conception however clear, will avail to dispel the mystery of these severest anæmias, unless the misleading *name* of "pernicious" be definitely abandoned by the profession. That name—in the face of the facts here recorded—has precisely as much or as little significance in relation to anæmias, as the term "continued" formerly had in relation to fevers of such different characters as typhus, typhoid, and relapsing fever. The title "*Addisonian*," here given, definitely connotes the grave *Infective Anæmic Disease* here described, possessing the remarkable individuality and characterization here detailed; and *it connotes nothing else.*

The title "*Septic*," which I have here given, connotes, no less accurately and definitely, the great etiological factor common to all the severest *Anæmic Conditions* which most closely resemble Addisonian Anæmia, and are constantly being mistaken for it. It has the great additional advantage of facilitating their effective treatment, since it draws attention to their chief cause and the necessity for its removal.

These two great types of anæmia have hitherto been grouped together under the common title of "Pernicious" Anæmias, just as typhus and typhoid fevers were formerly grouped together under the common title of "Continued" Fevers. They are, however—like the latter—sharply distinguishable from each other by differences in symptoms, course, duration, lesions and *cause.* The difficulty of making the distinction has been greater in their

case than in the case of typhus and typhoid fevers. For some degree—sometimes a very high degree—of "Septic Anæmia" is frequently present in cases of Addisonian Anæmia, both obscuring and gravely complicating its real characters. According to the author's observations (*see* p. 115), it is this association—*to which he now draws particular attention*—which gives Addisonian Anæmia its peculiarly severe and intractable course. When dissociated—*as they can be by complete removal of the septic infection* (*see* p. 116), the striking hæmolytic, glossitic, and nervous features of Addisonian Anæmia remain in a much milder form. But the course of the disease is profoundly modified by the remarkable compensatory and regenerative powers brought into action by the disease. This course can be far more easily determined and more closely followed by the observation of these changes—especially the glossitic, febrile, and hæmolytic changes—than by observation of the blood changes.

In short, the results here recorded regarding the essentially infective origin of all severest anæmias—both Addisonian and "Septic"—satisfy the author, that in direct proportion to the degree of their recognition as diseases of infective nature—*and not merely as hæmatological anæmias*—they can be largely or wholly deprived of the characters which now render them severe. This result can even now be achieved in individual cases, as already seen. (*See* Charts, p. 148.) But it will only be properly achieved when due attention is given to their infective *as distinguished from their mixed and variable hæmatological* characterizations. The latter, regarded by themselves—*as they too frequently are, and have been for the past fifteen years*—are chiefly of interest as indications of the varying character and severity of the infective and toxic influences responsible for their production.

Anæmia in General.

The whole subject of anæmia may be likened to a great forest of unknown size: some of it more open, with little undergrowth, clear overhead, and easily traversed (simple anæmia); other parts of it much overgrown with rank, luxuriant vegetation, rendering exploration difficult (severe anæmia); and lastly, other portions so shrouded by mists of historical controversy, so full of thick growth and of hidden pitfalls, that it seems almost impossible to penetrate them, or even find out their precise boundaries and extent—where they begin or where they end (Addisonian anæmia).

I have endeavoured in the foregoing work to clear away the mists of historical controversy overhanging the subject of these severe anæmias ; to guide the observer through the thick undergrowth of pathological research (the difficulties of "hæmolysis" or the pitfalls of "megaloblastic degeneration") without losing sight of the great clinical and prognostic landmarks ; and lastly, to draw attention to the deep waters of infection responsible for the thick growth and boggy places of their pathological recesses. It is now possible to survey the general result.

At the one extreme of these anæmic conditions may be placed the anæmia of hæmorrhage—"traumatic anæmia"—and at the other admittedly stands the condition historically known to English observers under the title of "Addison's idiopathic anæmia," and to German observers as the "primary," "essential," "cryptogenetic" form of "progressive pernicious anæmia." (*See* Frontispiece.)

Addisonian Anæmia.—Whatever views may be held by observers as to this anæmia, all are agreed that it represents without exception at once the severest, the most fatal, the most mysterious form of all blood diseases ; and to prevent any confusion arising as to the anæmia here referred to, I have given this its proper title of "Addisonian anæmia."

Progressive Pernicious Anæmia.—For a host of reasons here detailed the title "progressive pernicious anæmia," or "pernicious anæmia," should now be definitely abandoned ; for that title is now given indiscriminately to various forms of anæmia in virtue of certain features common to all, but without any regard to the two characters of "progressiveness or perniciousness" which ought to characterize any anæmia so called. Its chief form is alleged to be "tapeworm anæmia," which has nothing progressive or pernicious about it, and can be got rid of by a few doses of an anthelmintic ; Addisonian anæmia, which all observers agree is most mysterious in origin and most severe in its characters, and generally progressive in its course, is held to be a subordinate form.

Primary and Secondary Anæmias.—By way of further clearing the ground, the use of such terms as "primary" and "secondary," so often applied to two great classes of anæmia, should now be given up. For all forms of anæmia are really secondary ; and the term "primary," even when employed clinically, conveys little real meaning when it includes as its two chief forms an anæmia so simple and easily curable as chlorosis on the one hand, and so severe and fatal as Addisonian anæmia on the other.

Normoblastic and Megaloblastic Anæmias.—For reasons given the most recent classification of anæmias, suggested (on purely hæmatological grounds) by Ehrlich, 1892, namely, into "normoblastic" and "megaloblastic" anæmia respectively, is particularly misleading, historically, etiologically, clinically, diagnostically and prognostically, and should be forthwith abandoned. The former is characterized by the presence or preponderance of normal nucleated red cells (normoblasts) and by, it is stated, its simpler character and more favourable course; the latter by the presence of abnormally large degenerated nucleated red cells (megaloblasts), by its severer character, and, it is stated, by its more pernicious course. (*See* Scheme III.)

The net result of such a classification is, as has been shown, to change the historical character of the already loose combination of anæmias termed "progressive pernicious anæmia," and create an extension of and new criteria for "progressive pernicious anæmia" such as Biermer never contemplated, and in his last words on the subject (1886) directly repudiated. The *megaloblastic criteria* here laid down are wide enough to include at times the simple anæmia of lead poisoning, and of severe but easily curable tapeworm anæmia on the one hand, and to exclude many cases of severest Addisonian anæmia on the other; for, as is admitted by Ehrlich, "the discovery of megaloblasts often requires great patience." In my experience they may be absent from the blood altogether for long periods, during which other features, to which I attach real significance, show that the disease is still persisting. If this be the outcome of the megaloblastic criteria, no less perplexing is the result of the *normoblastic criteria*. For these group together such widely divergent forms of anæmia as those of loss of blood and chlorosis at the one end of the scale; of malignant disease and fevers in the middle; and of the forms of anæmia approaching in severity and almost in their fatal course that of Addisonian anæmia, forms which I have associated with sepsis, and have termed "septic anæmia."

This particular cytological road, first opened up by Ehrlich (1880-8), and definitely divided up by him (1892) into great avenues—entitled "normoblastic" and "megaloblastic" respectively—has for the last ten to fifteen years been the one selected by most observers by which to penetrate the anæmic forest.

Little wonder that roads so easy to traverse should have attracted so many observers coming to this subject since 1893, and should have led them to conclude that here at last were the paths

by which to penetrate into the anæmic forest more deeply than by any other. Like every young observer, I selected this path at the outset of my work (it had not then been laid out in its present broad avenues); and I spent three years (1885-8) in travelling along it, hoping it would lead me through. No one spent more time on endeavouring experimentally and otherwise to gauge the true significance of microcytes and poikilocytes and megalocytes, the parts played by loss of blood, defective blood-formation, increased blood-destruction (or "hæmolysis," the title I in my first paper in 1888 first gave this process); their significance in relation to the anæmic process, their distribution among the various blood organs.

My interest in this class of observation finally ceased about the end of 1887, when I found that I could produce the whole degree of anæmia and the whole series of corpuscular changes presented in pernicious anæmia experimentally in a few days—almost in a few hours—by large doses of blood-destroying agents. And it is interesting to note that the most recent observations of Bunting (1905) show that by similar agents megaloblastic degeneration can be rapidly induced in a few days. (*See* p. 64.)

The problem presented by the blood changes which already, in 1886 (*see* p. 33), I had concluded to be a chemical one, became more and more from that time an etiological one, as its first observers (Combe, 1822, and Addison, 1855), on clinical grounds, rightly surmised it to be.

As it happens, I was invited (but was unable to attend) to take part in the great discussion on anæmia at Wiesbaden in 1892, in which Ehrlich laid down his broad generalizations regarding normoblastic and megaloblastic anæmias, which, as already pointed out, have so profoundly influenced the work of younger observers since that period.

It has been a matter of deep interest to me, therefore, to watch the extraordinary fascination which this path of observation has had since 1892. Although acquainted with the literature, I was myself unable to gather from it in what direction this new road was leading, till, in 1899, Ehrlich and Lazarus published their joint work on *Anæmia* at the time I had in preparation my own work on *Pernicious Anæmia*.

The divergence between the two lines of work—the hæmatological, pursued by Ehrlich and his followers, and the experimental, pathological, clinical, and etiological, pursued by myself—was most startling and complete; so much so that it determined the

form which was finally given to the latter book—namely, essentially that of a reproduction in chronological order of my former published work.

For simultaneously with my later conclusions (1890-1900) that Addisonian anæmia deserved more and more to be recognized and *marked off* from other forms of apparently similar anæmia, not merely as a "remarkable anæmia," but as a "*remarkable infective disease*" with definite mode of onset, clinical features, course, and pathological lesions—the conclusion led up to by Ehrlich's hæmatological line of work, emphasized by Schauman, was that all sorts of anæmia required to be more and more *grouped together*.

"Pernicious anæmia was not a disease *sui generis*, but a mere group of symptoms met with in very different conditions of disease.—*The essential changes are blood changes.*"

And Addison's anæmia is dismissed curtly in a single sentence as having nothing distinctive about it, as failing to reveal anything in its mode of onset, clinical features, or *post mortem*, to throw any light upon it. (Map 2, p. 66.)

These results are thus described by Ehrlich and Lazarus (1899), and Schauman (1900). (*See* Scheme III.)

It will be seen from this what an extraordinary extension has thus been given to the title "pernicious anæmia"—what an addition is thereby made to the already large, ill-defined, and ill-conditioned family termed "Progressive Pernicious Anæmia"—by this creation of a new family group with a new name termed "Megaloblastic Anæmia," even although it is admitted this megaloblastic anæmia *does not correspond clinically with* Biermer's division of pernicious anæmia from other forms of anæmia.

I regard this extension as the most retrograde step taken in connexion with the pathology and etiology of Addison's anæmia since Biermer, in 1871, while giving a clinical and anatomical account in all respects applicable to Addison's anæmia, stated that all sorts of causes could produce it; and subsequently, in his last word on the subject (1886), himself repudiated this view by emphatically asserting that the cause of the *real pernicious anæmia* was up to that time (1886) quite unknown.

Infective and Non-infective Anæmias.—For reasons here detailed, the classification of anæmias which goes deepest into their *nature*, throws most light on their *clinical features*, and carries furthest in their *treatment*, is one that has regard to their "non-infective" or "infective" causation. (*See* p. 63, and Frontispiece.)

The essential changes are not the blood changes but the infective processes underlying these changes.

The infective processes here had in view *are not terminal processes.* For, as a matter of fact, their lesions are most marked in the earliest stages of the disease, and become less and less obvious as the disease progresses, owing to the profound anæmia which they cause. *Nor are they the result of the anæmia per se.* For the anæmia is profoundly modified by their removal, or may be arrested altogether. (*See* Charts, p. 148.)

On the contrary, these processes not only explain the more prominent and characteristic clinical and pathological features of the disease — its *glossitic, gastric, and intestinal lesions and disturbances*, the *intense hæmolysis* with its resulting *anæmia* and the *compensatory marrow changes.* They also account for other features no less constant and characteristic — its *fever*, and *the nervous symptoms and lesions* (peripheral paræsthesiæ, striking psychical and even mental disturbances, and the subacute combined degenerations of the cord), which, in varying severity—singly or combined —are in my experience presented by every case of the disease.

The character and pathogeny of these disturbances and lesions are fully elucidated, according to the writer's observations, by the lesions presented in the tongue. As can there be seen in severe cases (Plate IV), the lesions extend down and involve the nerves, causing a toxic neuritis. This is marked, *clinically*, by tenderness of the tongue—in many cases of the most intense character ; and it is followed, *pathologically*, by two sets of changes : (1) Intense *neurotrophic changes* in the epithelial covering and in the muscle of the tongue (Plate V)—shown also during life by the *glossiness* of the tongue surface, and the *diminished size* of the tongue ; and (2) *secondary degenerative changes* extending along the sensory nerves to the cord, and causing the various peripheral sensory disturbances and the subacute degenerations above described.

Similar changes, doubtless, accompany the lesions in the stomach and intestine, and cause similar effects, notably the unusual degree of gastric atrophy which attends the disease. (Fig. 20, Plate X.) For, in many cases, the sensory disturbances—evidenced by acute gastric discomfort, repeated vomiting, sharp attacks of tearing, griping pain in the intestine followed by diarrhœa—are even more marked in the stomach and intestine than in the tongue, and are accompanied by peripheral paræsthesiæ in the legs and arms.

Moreover, *the site of the chief lesions can, according to my observations, be approximately determined by the distribution of these peripheral nervous disturbances.* Those most marked in the legs or accompanied by symptoms (ataxia, loss of reflexes, paralysis) of combined degeneration of the cord, denote that the lesions are in the intestinal tract ; while those most marked in the upper arms or in the brain (psychical and mental changes) most commonly denote glossitic or gastric lesions. But these groups constantly overlap, since the lesions may concurrently affect various portions of the alimentary tract, by spreading from one portion to another.

Lastly, the infective processes of the disease satisfactorily explain the feature to which attention has been drawn (p. 145), viz., *its extraordinary powers of recovery.* For just as its mode of onset is by no means the slow or insidious one which is generally described, but is often very acute and sudden at a time when it is unrecognized (*see* Chart 2, p. 147)—so, also, its powers of recovery are far greater and more rapidly manifested than is generally supposed. (*See* Charts, p. 148.) And this recovery is frequently ushered in by a *process of crisis* more remarkable, having regard to the blood condition, than anything observed in any other disease. The patient *in extremis*, unconscious or semi-conscious, with high fever of 103° or 104° F., rejecting all food and sick independently of food, with repeated diarrhœa, and with a degree of anæmia declared to be "incompatible with life"—sometimes, also, œdematous all over, wakes up suddenly, takes a sudden turn for the better, and in a short period of a month or two, sometimes even in a few weeks (*see* Chart 3, p. 148)—is going about well, with a blood count of 70 or 80 per cent., and declaring he has never felt so well in his life. Even if a relapse follows, as it usually does (Charts, pp. 147, 148), these facts denote—not a slow process of blood repair, such as we are accustomed to see in simple non-infective anæmias, *e.g.*, chlorosis, but a remarkable *sudden arrest* followed by a period of complete or relative *immunity* such as only an infective disease can produce.

In other words, the whole phenomena of the disease—its mode of onset, its clinical features and *their constant association*, its periodicity, and its course—far more uniform than in any anæmic condition known to me—are characteristically those of a *specific infective disease*, and not those of an *anæmic condition.*

Addisonian Anæmia.

So far as Addisonian anæmia is concerned, the whole facts of the disease place this great malady among the group of *Infective Diseases* as firmly and securely as the pathological lesions, clinical features, and clinical course of scarlet fever place it amongst recognized infective diseases ; or the features and clinical course of typhoid fever (even prior to the actual discovery of its bacillus) separated it from other apparently allied fevers such as typhus, and placed it in the group of specific infective disease.

Editorial comment by an unknown writer (1874), as has been seen (pp. 86 and 89), played no unimportant part in erroneously introducing Biermer's work to English readers as "a new disease" thereby helping to create the sorry confusion about the identity of Addison's anæmia and "progressive pernicious anæmia" which has existed from that time till now. Editorial comment of another character may, therefore, be fittingly adduced as the corrective ; and such comment—by writers unknown to him—the author's work has had the good fortune to receive, from its outset (1888, *see* p. 57) to its termination (1903, *see* p. 63).

"The author has arrived at very definite and clear conclusions regarding the real nature of pernicious anæmia. . . . . We must refer our readers to the text of his paper for his close and searching criticism of recent literature on pernicious anæmia, merely remarking that the criticism appears to us to be sound. . . . Addison's anæmia is a definite entity, specific, infective, hæmolytic, presenting characteristic local lesions (especially a peculiar form of glossitis). . . . There is no gainsaying the advantage of arriving at so definite a conclusion, aud we must hasten to recast our nosology accordingly. *For the practical outcome of such considerations is the total reversal of the situation as it was when Biermer wrote* (1871) *on 'progressive pernicious anæmia.'* . . . . Now we learn that the condition entitled to chief consideration is just that which was neglected by those observers, and that it alone possesses a single and well-defined etiology. . . . We doubt not that by following up his line of enquiry much will be gained, not only in the direction of clearness of conception, but in the treatment of this grave disease."

The Practical Outcome.

The labour given to the study during the past twenty years has not only been repaid by the variety of problems successively presented—it has had an important practical outcome, the benefits of which extend far beyond the limits of this particular condition. For as the direct outcome of my study of the etiology of this disease, I have been led to recognize and attach an entirely fresh significance and importance to one of the commonest and most overlooked forms of infection in the body—that which I have entitled "*Oral Sepsis*"; and to bring this into etiological relation not only with this and other severe forms of anæmia, but with a wide range of septic infections met with in medicine—conditions which I have designated "*Medical Sepsis.*"

The daily experience of many—both patients and doctors—and the literature of the last seven years show the enormous practical benefits which have been derived from this "sequel and outcome" (as one observer has rightly termed them—Grawitz, 1901) of the experimental investigations which I have undertaken in connexion with this disease. (*See* p. 46.)

My experience satisfies me that this outcome cuts as deeply into the pathology and treatment of severest forms of anæmia and medical sepsis as the adoption of antisepsis has cut deeply into the pathology and treatment of surgical sepsis; that, irrespective of any controversy which it has created, it is destined to influence conception and practice with regard to blood diseases, as profoundly as the assertion of the "pythogenic origin" of typhoid fever by Murchison first—long prior to the discovery of the typhoid bacillus—formed the first great basis of all of the measures now taken for the prevention of all sorts of other infections communicable through drain sources.

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The attention of German observers may be drawn to this paper. It deals —as do all the other papers of this observer on this subject—with what he designates "*this remarkable and peculiar disease, termed*," as he elsewhere states (1902), "*by the not quite appropriate name of pernicious anæmia*"—not with "nothing more than a well-characterized group of symptoms with very different causes," which Professor Eichhorst in 1878 (*see antea*, p. 96) emphatically asserted to be "*the progressive pernicious anæmia* of Biermer."

If the extreme confusion *created by this latter name* be recognized by German observers such as Professor Ewald and Professor Strumpell (*see* p. 50), as it undoubtedly is by all English and American observers, the author would fain hope that all observers alike would agree, in the interests of Clinical Medicine and Medical Science, to abandon that name altogether in connection with any anæmia.

No single name except that of Addisonian accurately connotes in all its relations without any dubiety or ambiguity the *remarkable and peculiar infective anæmic disease* here described.

If, for the future, observers would record their cases of "severe" anæmia, of whose etiological nature they may be doubtful, under that title or that of "severest" used in this work, and with that title would record *all the facts of the case*—not merely those relating to the blood, but also those connected with their possible etiology—*e.g.*, infective glossitic, hæmolytic, febrile, and nervous ("*Addisonian Infective Anæmia*"), or septic ("*Septic Anæmia*"), or loss of blood ("*Traumatic anæmia*"), &c., &c.—the existing confusion would speedily clear away.

The title "pernicious," as now employed, has no meaning whatever. It is a mere cloak for ignorance, and a cause of pernicious confusion.

The title "Biermer's Anæmia," or "Anæmias," used only by German observers, connotes even for them (*see* p. 93) something that is at once "real and unreal," "true and false."

The title "Biermer-Ehrlich Anæmias" degrades even that of "Biermer's Anæmia." It connotes nothing at all, except an hæmatological generalization which runs athwart all anæmias, both simple and severe, without any true regard to their clinical, etiological, pathological and prognostic characters.

INDEX.

THIS Index is arranged under the heads of the chief subject matters dealt with, viz., *Forms of Anæmia*, *History*, *Etiology*, *Clinical Features*, *Pathology*, *Diagnosis*, *Prognosis* and *Treatment*.

The importance attached by the Author to individual subjects is indicated by black and italicized type (*e.g.*, **"Conception,"** "*Scheme*"); his own conclusions by black figures (*e.g.*, **41**).

The chief subjects dealt with in this volume are: The *Nature of Severest Anæmias*, their *History*, *Etiology* and *Pathology*, as illustrated by the severest and most mysterious of all blood-diseases, viz., Addisonian Anæmia.

The Author's conclusions regarding the *Clinical Features*, *Diagnosis*, *Prognosis* and *Treatment* of this Anæmic Disease and allied Anæmic Conditions arise out of the etiological and pathological studies here described. A full index to these subject matters is here given, so far as they are dealt with in this volume. They will be amplified and fully dealt with in Volume II.

A. FORMS AND CLASSIFICATIONS OF ANÆMIA.

B. ADDISONIAN ANÆMIA.

I. NAME OF DISEASE.

The most important requirement, for observer and patient alike, is a name that connotes its *Identity*—not what is both "real" and "unreal," "true" and "false"; that connotes the *Nature* of the disease—without reference to its prognosis; that helps in early *Diagnosis* and *Treatment*—not retarding the one and interfering with the other; that has regard to *Clearness*, and does not perpetuate confusion (**98**).

II. HISTORY.

(**9**; **11-47**; *Schemes*, **28, 42, 44**; *Maps*, **65, 66.**)

III. ETIOLOGY.

Alleged Causes.

(*Schemes I and III*, 28, 44 ; **81**. *Map* **2, 66**.)

Infective Etiology.

(*Frontispiece. Scheme II*, **41, 70, 72, 82, 114-118.**)

IV. PATHOLOGY.

(**6**, *Scheme II*, **42, 99-179.**)

V. CLINICAL FEATURES.

(*Scheme II*, **41, 42**; *also Vol. II.*)

VI. DIAGNOSIS.

(*Scheme II*, **42, 74, 76, 117, 174, 179**; and *Vol. II.*)

VII. PROGNOSIS.

(7, *Charts*, **147, 148**; and *Vol. II.*)

VIII. TREATMENT.

(*Preface*, **174, 182, 179, 10**; and *Vol. II.*)

C. "SEPTIC ANÆMIC CONDITIONS."

Preface, **10, 56, 181.**

I. "SEPTIC ANÆMIA."

(*Frontispiece*, **43, 45, 63, 78, 82**; *Map* 1, **65**, and Vol. II.)

II. " BOTHRIOCEPHALUS ANÆMIA."

(*Frontispiece*, **177** ; and Vol. II.)