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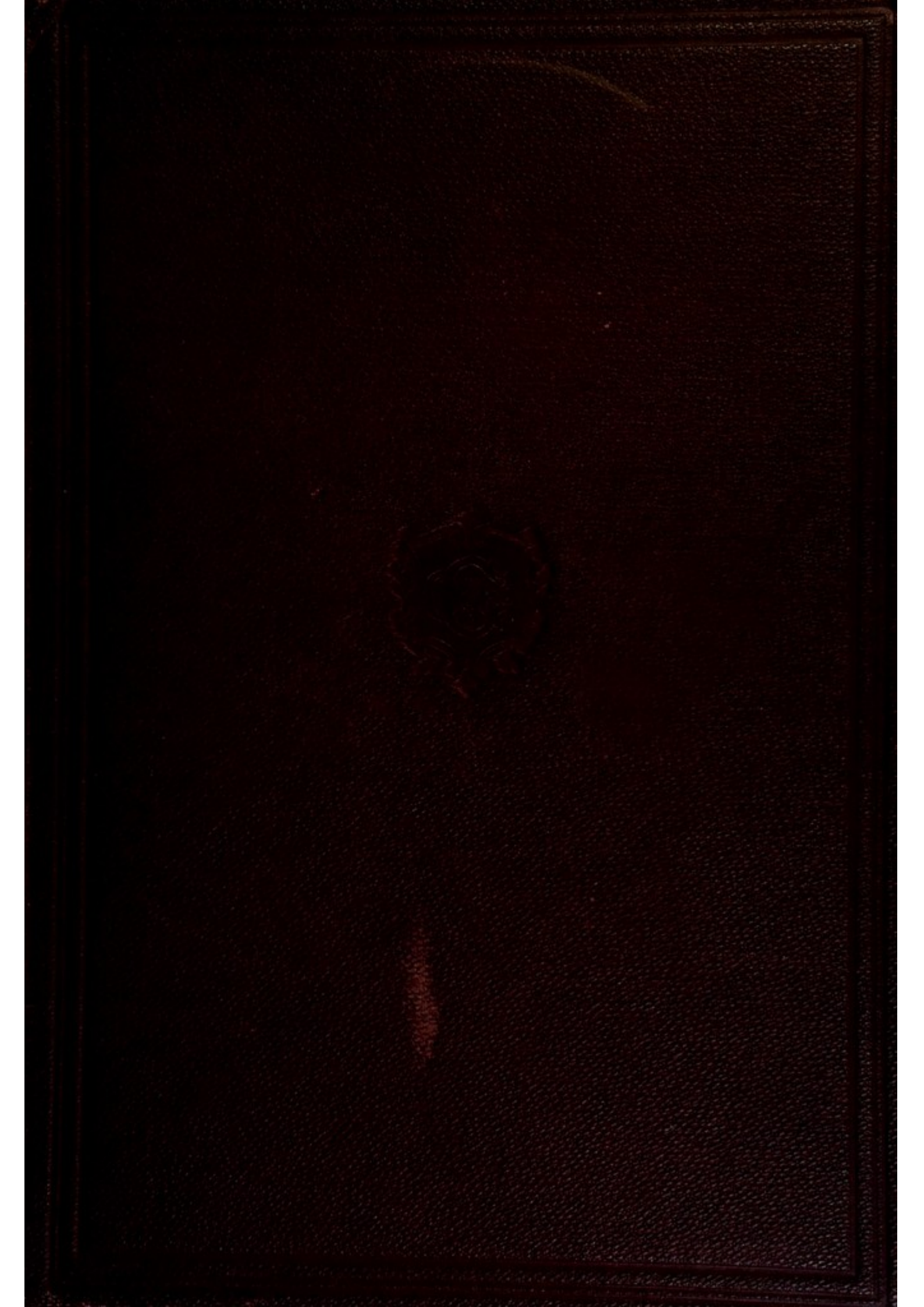
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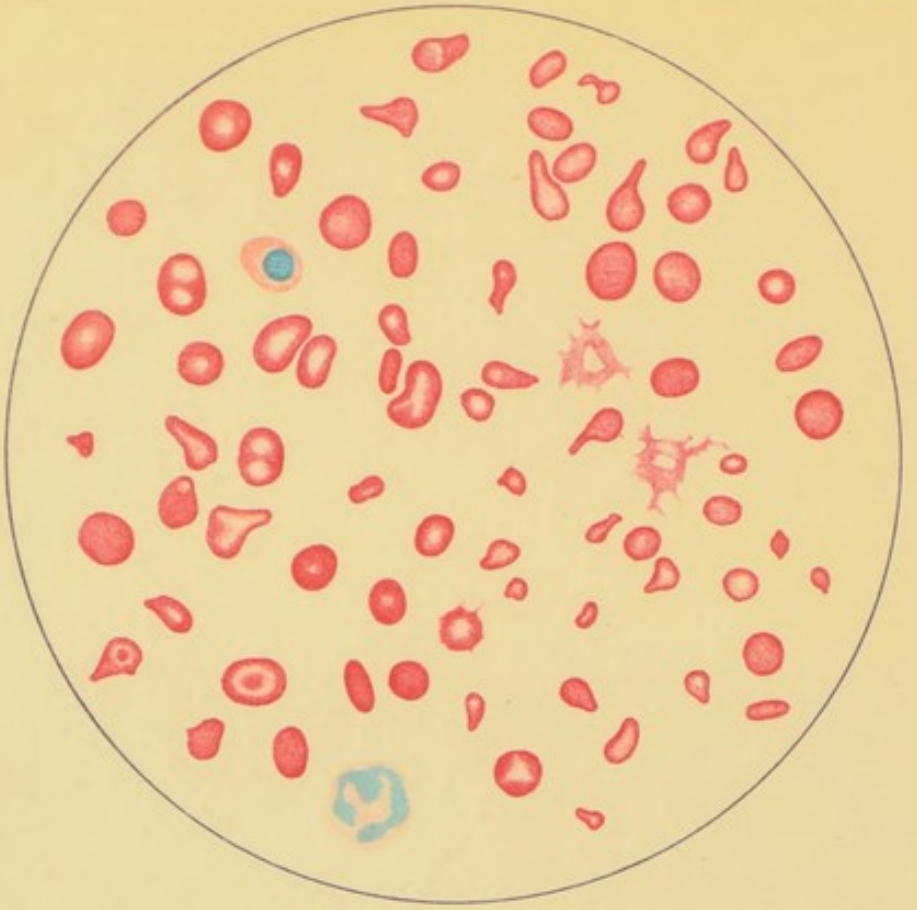
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Kidney in Pernicious Anæmia.

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PERNICIOUS ANÆMIA:

ITS PATHOLOGY, SEPTIC ORIGIN, SYMPTOMS, DIAGNOSIS, AND TREATMENT.

BASED UPON ORIGINAL INVESTIGATIONS

BY

WILLIAM HUNTER, M.D. EDIN.,
F.R.C.P. LOND., F.R.S.E., ETC.

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PHYSICIAN TO THE ELECTRICAL DEPARTMENT;
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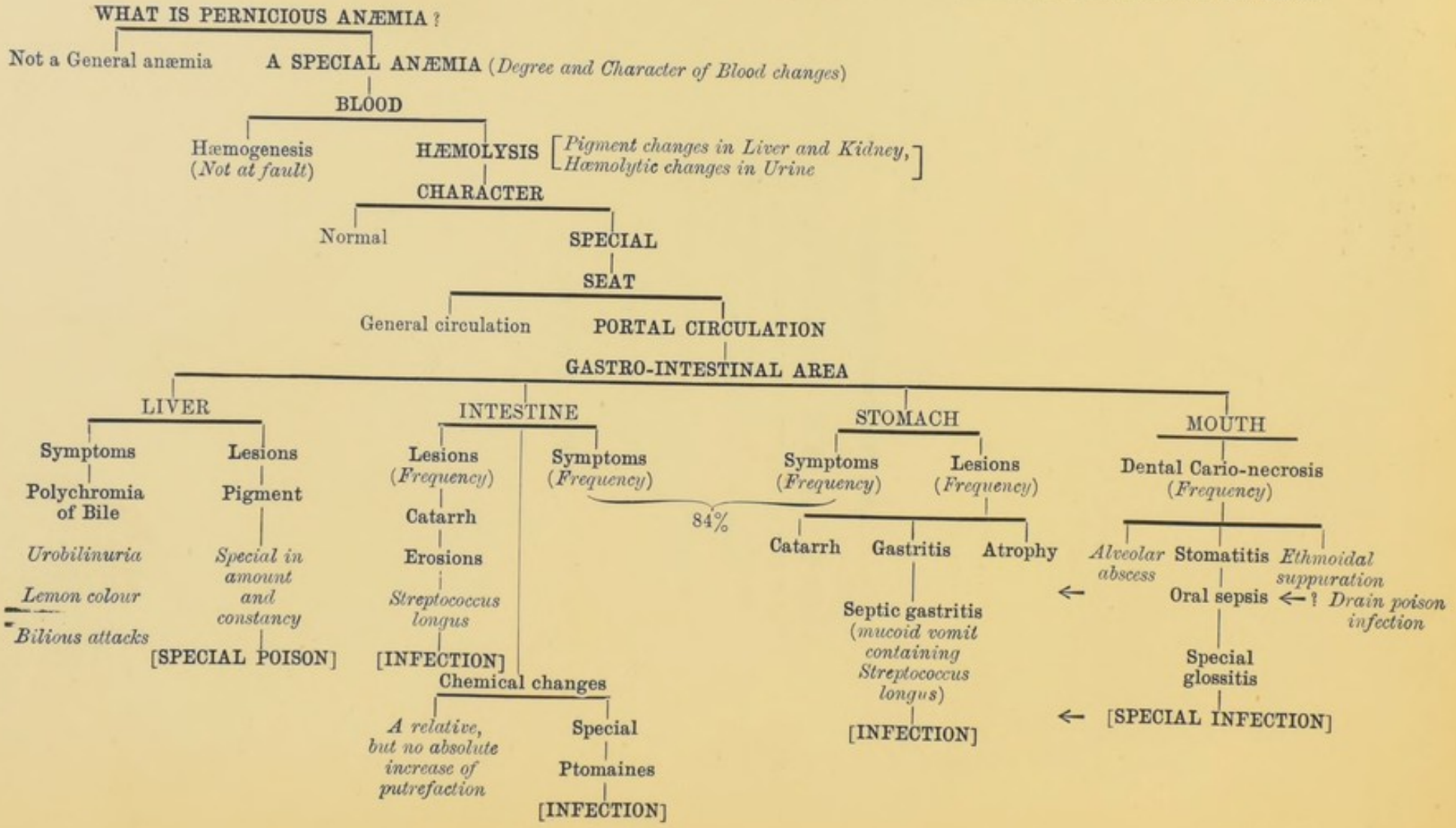
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President of the General Medical Council,

IN RECOGNITION OF MANY KINDNESSES,

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This Volume.

SCHEMATIC REPRESENTATION OF COURSE AND RESULTS OF AUTHOR'S PATHOLOGICAL INVESTIGATIONS REGARDING THE HÆMOLYTIC NATURE, GASTRO-INTESTINAL SITE, AND INFECTIVE ORIGIN OF PERNICIOUS ANÆMIA.



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PREFACE.

THE following account of Pernicious Anæmia is based upon the results of fifteen years' investigations regarding the nature of this disease—one first made known to English physicians under the title "Idiopathic Anæmia," originally given to it by Dr. Addison in 1855, and afterwards independently redescribed by Professor Biermer of Zurich in 1871 under the name, by which it has since been more commonly known, of "Pernicious Anæmia."

Few diseases have, from the very outset, been wrapt in mystery apparently so impenetrable as this form of Anæmia. Its very essence, as originally described by Addison, was that it occurred without any discoverable cause whatever; and this character of mystery, in spite of thirty years' subsequent studies, was held, in the view of the later observers best qualified to judge, to extend even to its clinical and pathological features. According to Professor Eichhorst (1878)—representing Continental observers—neither clinically nor anatomically did it possess any distinctive features; according to Dr. Pye-Smith, one of Addison's most distinguished pupils, (1883)—representing English observers—the essence of the disease was, that it was without any symptoms during life, and without any lesions after death, which could not be explained as directly due to the anæmia.

Such was the standpoint of knowledge regarding the disease at the time—1885—when the investigations here recorded were first commenced. The larger portion of them were carried out during the five years 1885–1890—the most of them during my tenure of the research appointment of John Lucas Walker Student of Pathology in the University of Cambridge; and the results were recorded in various papers between the years 1888–1890.

The investigations as a whole have presented certain special features; the chief, perhaps, being the remarkably varying character of the problems successively presented; and, second only to this, the value attached to the detailed study of individual cases of the disease. As regards the former, the investigations have been in succession: (1) *histological*—involving three years' studies regarding the origin and significance of blood pigment in various organs in health and disease; (2) *experimental*—involving experiments (one hundred and fifty in number), extending over five years, with the object of throwing light on

the hitherto obscure subject of the nature and seats of hæmolysis in health; (3) *chemical*—involving studies regarding the chemical processes within the gastro-intestinal tract in this particular disease; and (4) *clinical*—involving studies with regard to the character and significance of various symptoms of the disease, and especially their relation one to another.

At this point (1890) the investigations seemed for a time to be brought to a standstill. For the problem then presented was the most difficult of all, viz., (5) *etiological*—the nature and source of the infective agencies at work, pointed to by the previous observations. It was only by following out certain clues presented by individual cases—from the rarity of the disease necessarily few in number, that I was enabled after ten years to gain light on this all-important branch of the subject. Lastly, throughout the course of the investigation, the (6) *therapeutic* problem has ever been present to my mind.

The conclusions arrived at as the result of these various investigations relate not merely to the chief subject-matter of study—the nature of pernicious anæmia, but also to many matters of physiological and pathological interest investigated in connection therewith. For convenience, I have given references to the more important of these conclusions in the Index. The chief of them relate to the Physiology of Hæmolysis, and the Pathology of Jaundice associated with blood disorder. The studies relating to these two subjects I have here appended in full.

As regards Pernicious Anæmia, the conclusions reached are of a definite character, so much so, that if read alone, without relation to the studies on which they are based, one might perhaps, at first sight, doubt whether they could refer to the disease originally described, and subsequently characterised as the result of much later study, in the terms I have already referred to. The general scope and character of these conclusions and of the investigations on which they are based, I have, for convenience of reference, represented graphically in the accompanying scheme.

As regards its *Nature*—they shew the disease to be not merely a special form of anæmia, but a definite and—in regard to mode of onset and site of infection—a well characterised, chronic, infective disease, localised to the alimentary tract—one in which long-lasting *Sepsis*, oral and gastric, plays an essential and important antecedent and concurrent part. As regards its *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; and there are at least three other groups, hæmolytic, gastro-intestinal, and toxic—no less striking, in their grouping no less characteristic, and in regard to the site of infection, far more instructive than the actual anæmia itself—caused not by the

anæmia itself but by the infective agencies underlying the disease. As regards *Diagnosis*—the disease can, even in its early stages, if not easily, yet with certainty, be diagnosed both during life and after death; *during life*, by having regard to: (1) its mode of onset with special reference to its oral and gastric symptoms; (2) the degree of blood change, out of all proportion to that caused by organic or wasting disease even when severe; (3) the characteristic groups of symptoms I have described; and *after death*, by the no less characteristic changes in the liver, bile, and kidneys. Lastly, as regards *Treatment*, the conclusions suggest new lines in regard both to the prevention of the disease, and possibly also to its permanent arrest after it has commenced.

Moreover, these conclusions relate to the form of anæmia described by Addison, and to that alone. For as regards *Etiology*—the foundation of our knowledge was, in my judgment, laid deep and broad by Addison in his original description: namely, the disease occurs apart from the usual causes or concomitants of the anæmic state. The different conclusion of Biermer, 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 (its so-called 'secondary' forms)—has, in my experience, no firm basis. The disease 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—even during life, and still more easily after death—by the absence of the characteristic grouping of clinical features and of the pigment changes I have described. I therefore do not recognise any primary or secondary forms of this disease, any more than I recognise primary or secondary forms of typhoid fever or tuberculosis. On the contrary, it has a special (infective) etiology underlying it; and as an infective disease it is quite possible for it to occur—albeit but rarely, since I have not met with any such case—in those who may already be the subject of other diseases. By its characteristic clinical and pathological features, it would be as easy to diagnose its existence in such a case, as it would be in the case of any other infective disease, *e.g.*, typhoid fever in the course of phthisis.

Subsequent experience of the disease will doubtless necessitate modification of the character of some of these conclusions with regard to individual details; but I do not anticipate that this will apply in any essential particulars to the view of the disease here presented. For the basis of all my conclusions as to the special nature of the disease, I would point out, is not any clinical views regarding the possible importance of this or that group of symptoms, but the firmer one of extended pathological observations regarding the *hæmolytic nature* of the disease, the *special character of the hæmolysis*, and its *gastro-intestinal site*; supported clinically by all subsequent observations re-

garding the chief clinical features of the disease. In no case have the conclusions been lightly formed—as may perhaps be best judged from the length of time devoted to each portion of the investigation. Moreover, the fact that those portions of them relating to the pathology of the disease have stood the test of twelve years' later experience—so much so, that I have here reproduced them in their original form, as expressing my present opinions regarding the disease, any additions or modifications being indicated by enclosure within brackets—holds out the hope, that the further conclusions based upon them may likewise stand the test of further experience. Indeed, since my later conclusions regarding the Septic origin of the disease, and especially as regards the significance of its lesions of the tongue, were recorded (1900), I have had opportunities of confirming them in a more and more striking manner in every subsequent case of the disease (ten in number) I have seen. Two of these cases (cases 10 and 11) I have recorded in full, as typical in my experience of the antecedent history, mode of onset, and clinical features of the disease.

Wherever the views and opinions of other observers are described, the words employed are, in all cases, whether expressly stated or not, those of the authors themselves.

In conclusion I desire to express my warm thanks to those to whom I have been indebted in the course of these investigations: to Dr. Byrom Bramwell of Edinburgh, who early in my studies most kindly placed at my disposal valuable pathological material from six of his cases; to the Physicians of Charing Cross Hospital—Dr. Green, Dr. Mitchell Bruce and Dr. Abercrombie—for having at all times freely placed at my disposal for study, as Pathologist of the Hospital, the cases of the disease coming under their care; to Mr. Percy Richards, F.C.S., of the Chemical Laboratory, Charing Cross Hospital, for carrying out, with special care, the analysis of organs for iron in my later cases; and to Dr. Eyre, Bacteriologist of the Hospital, for bacteriological reports in two cases of the disease.

To my friend Mr. Stephen Paget I am greatly indebted for much valuable criticism and suggestion in the revision of proof sheets in various sections of this work. To my Publishers I also desire to express my thanks for the care they have bestowed in the reproduction of the various figures and drawings, and especially the charts of temperature in which I have shown the relation of various clinical features to one another; as well as for continuous courtesy and consideration during the passage of this work through the press.

WILLIAM HUNTER.

103 Harley Street,
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PERNICIOUS ANÆMIA.

PART I.—HISTORICAL.

CHAPTER I.

In the introduction to his well-known work, "*On the Constitutional and Local Effects of Disease of the Suprarenal Capsules*," Dr. Addison of Guy's Hospital, London, wrote (1855):

"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 a manner that the patient can hardly fix a date to his earliest feeling of that languor 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."

In these terms Dr. Addison described what was really a new disease, one known to him from 1849 onwards. Under the title he gave it, "Idiopathic Anæmia," the condition from that time forward became known to English observers; and cases were described by Dr. WILKS (1857), Dr. BRISTOWE (1858), Dr. HABERSHON (1863), and others. Even before Addison's formal description in 1855, a typical case of the disease had been described by Dr. BARCLAY under the title of "Death from Anæmia" (1851). It was also recognized by Continental observers; by LEBERT (1858), who described it under the title of "Essential Anæmia"; by CAZENAVE (1860), under the same title; by WAGNER (1864); and by TROUSSEAU (1868).

Addison's account was not however generally known; hence when, in 1871, the same condition was re-described by a Swiss observer, Professor BIERMER of Zurich, under another title, "Progressive Pernicious Anæmia," claim was laid to the discovery of a new disease. Biermer's communication took the form of an address on a variety 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 serous membranes. He had observed the disease 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 Zurich 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 fifteen, the oldest fifty-two. 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, etc.

(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; it was for that condition that the patient was sent into hospital. Usually it was slight, and apparently causeless; hence in the clinic it was often, for shortness sake, 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 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 the ventricular wall and septum was often similarly affected. It was exceptional, however, for the fatty degeneration 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 on 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, and Kidneys shewed nothing special.

The disease thus described under the title of *Progressive pernicious anæmia* was obviously the same condition as the *Idiopathic Anæmia* of Addison, the *Essential Anæmia* of Lebert and others. It was no new disease, as Biermer and others at first thought. This fact, however, detracted in no way from the originality and merit of Biermer's observations. Addison's account was evidently not known to him; he described the condition as he had met with it in his experience: and, above all, while previous contributions to our knowledge of the disease had been few and isolated, Biermer's description excited general attention, and stimulated observation on every hand. This was, and must remain, the chief merit of his observations. Apart from that, they supplemented Addison's masterly description in two essential points; with regard namely to the occurrence of retinal hæmorrhages during life, and fever. In another and more important point they were at variance with Addison's account. The latter described as the chief feature of the disease,

that it occurred without any discoverable cause whatever, and apart from the usual causes or concomitants of the anæmic state. Biermer on the other hand described it as specially prevalent amongst the poorer classes; *i.e.* in the very class of people amongst whom the ordinary causes of anæmia were most to be found. The influence of this teaching of Biermer, as opposed to the original teaching of Addison, continued to be felt in all later work.

During the next few years following Biermer's account, the disease received more and more attention ; and important contributions were made, especially by IMMERMANN of Basle (1874 and 1875), and Professor QUINCKE (1877); also by LEBERT (1876), SCHEBY-BUCH (1876), PEPPER (1875), LÉPINE (1877), OSLER and GARDNER (1877), COHNHEIM (1876), BYROM BRAMWELL (1877), and STEPHEN MACKENZIE (1878).

Professor Immermann's studies were of special value. He drew special attention to the fever, the probable cause of which he considered to be the great diminution in the number of red cells. He also directed attention to the striking resemblance between the disease and the so-called "tropical chlorosis" produced by the intestinal parasite, *Ankylostomum duodenale.* He distinguished two forms of pernicious anæmia—one *primary*, due to blood impoverishment, arising in individuals formerly healthy, and, apparently, quite spontaneously, apart from disease or from weakening factors ; progressing to the extremest degree, and then ending fatally ; with nothing discoverable, *post-mortem*, that could not be ascribed to the anæmia present. These cases were not very common. The other group of cases, *secondary*, arose originally from known causes, or at least with their help. They began as common or secondary anæmia, and then took on a peculiarly severe character, which they continued to maintain, even although in the meantime the apparent original cause had ceased to exist. The etiology of the disease he considered to be so far quite obscure. If the causes were such as Biermer described, the wonder was, that more people did not suffer from the disease. It was quite inexplicable to him, why social misery, pregnancies, diarrhœa, epistaxis, and the like, should cause the disease relatively often in Zurich, as Biermer described ; while in neighbouring Basle the same conditions hardly ever produced

the disease. He had only met with five cases of the disease among 7000 patients, and none of these had been in poor circumstances. The causal factors described by Biermer had therefore, in his view, only an accessory, not a cardinal importance.

Professor Quincke's contributions added much to our knowledge regarding the symptoms, the blood changes, and the pathological anatomy. He described ten cases. In half his cases, he found great differences in the size of the red corpuscles, and, in three cases, a remarkable variation also in their shapes—changes since included under the term, he gave, *poikilocytosis*. In some, there were no fatty changes in the heart muscle. He found no changes in the bone marrow, such as had been described by Pepper and Cohnheim; but he noted an increase of iron in the liver from the presence of pigment—in two cases, in the kidneys and pancreas also—an observation which subsequently proved to be of importance, although at the time it was considered as not possessing any special significance. He regarded pernicious anæmia as merely an extreme condition, differing from other forms of anæmia only in its intensity; it might arise in many different ways, and be the result of very various morbid conditions; loss of blood, long-continued discharges, defective nutrition might all, provided they were of sufficient intensity or duration, be factors in its production. It might have, for purposes of classification, a *clinical* existence, its group of symptoms being fairly uniform and distinctive; but it was not a separate *pathological* entity, seeing that it could be induced in many different ways, and be the result of very different morbid conditions. Some forms, being found in association with definite structural lesions, such as malignant disease, were to be regarded as *secondary* to these lesions; other forms in which these lesions were absent, were *primary* in their nature; while others again, and these perhaps the most frequent in their occurrence, belonged to neither category, and could only be described as *intermediate*.

In 1877 Dr. Byrom Bramwell published an account of seven cases—this account being specially interesting from the remarkable success of treatment by arsenic in three of the cases. He agreed with Quincke, that we had probably in pernicious anæmia not to do with a single diseased condition; but that,

like anæmia in general, it was the product of extremely various morbid processes, and represented the very last stage of the anæmic process.

Lépine, also (1877), as the result of a careful review of all the cases (fifty) published, arrived at much the same conclusion. Under the term essential anæmia, he thought, should be included not only primary cases, but also cases depending upon recognized, and more or less adequate causes, such as insufficient food, pregnancy, dyspepsia, and diarrhœa; as also those, in which there was a decided affection of the spleen, lymph glands, or marrow.

Dr. Stephen Mackenzie described three cases, and summarized in a precise way the chief clinical and pathological features of the disease, in a lecture in 1878. He, also, thought it probable, that in idiopathic anæmia we had not to do with any one morbid state dependent upon a single anatomical condition. Rather, we had, with Immermann, to regard the term idiopathic or progressive pernicious anæmia as "a sort of provisional shelter for a multitude of cases possibly of various origins." It was still undecided, whether the deficiency of coloured corpuscles was due to defective formation (anhæmatosis), or to increased destruction of the corpuscles (hæmophthisis).

Dr. W. Pepper (1875) suggested as an alternative title for the disease the term "anhæmatosis." He was the first to describe changes in the red bone marrow—confirmed later by Cohnheim, an observation he regarded as bringing pernicious anæmia into relation with the myelogenous variety of leukæmia.

In 1877 appeared the first monograph on the disease—by Dr. HERMANN MÜLLER of Zurich. It contained an account of sixty-two cases, observed in the Zurich Hospital—most of them (forty-four) from the wards of Professor Biermer, with a detailed analysis of their chief clinical and pathological features. The general results of his studies were in agreement with those of Biermer, more especially with regard to the etiology of the disease. Like the latter, he emphasized the prevalence of the disease amongst the poorer classes, and especially among women; unfavourable hygienic surroundings played an important part in its production. And yet, as he noted, these could not be the only factors, for only one of the patients had actually

suffered from hunger before his illness. Most of them had previously enjoyed good health. On the other hand, according to him, not a single case of the disease had ever been observed in one of good position in life, a fact which distinguished the disease etiologically from leukæmia, to which otherwise pernicious anæmia stood in the closest relation. Pernicious anæmia was no disease of the town, as was often said of chlorosis; it was no disease common to all, such as leukæmia.

The following year appeared a second, and even more important treatise on the disease, by Professor EICHHORST of Jena, based upon a minute analysis, and study, of seven cases observed by himself, and eighty-four cases (including those of Müller) collected from the literature of the subject. Eichhorst admitted to the full the claim of Addison to the discovery of the disease; while at the same time claiming for Biermer's studies the merit, that they brought together under one title a number of different forms of anæmia possessing certain characteristic features in common. The chief anatomical characteristic of the disease he held to be, that in addition to fatty changes, small hæmorrhages, and (occasionally) slight congestion of spleen, no other changes should be found in the organs. If this position were not taken up, then one would be entitled to regard as pernicious anæmia every disease which presented anæmia, and ended fatally. In this relation, he criticized adversely certain cases described by Quincke; and even Biermer was not held free from blame in the matter, for including within his list of cases, some which showed follicular ulcers of the colon. As regards etiology, he considered Biermer's claim to be right, "that a perfectly spontaneous origin without a clear etiology was the exception."

He summed up his conclusions as follows:—The name *progressive pernicious anæmia* denoted no one condition, no special disease. There were different forms of the disease differing in etiology and in pathology. As regards *Etiology*, one had to distinguish betwixt *primary*, *essential*, *idiopathic* forms; and *secondary*, *deuteropathic*, or *symptomatic* forms, — caused by (*a*) pregnancy and childbirth; (*b*) disturbances of digestion; (*c*) hæmorrhages and discharges; and (*d*) unhealthy surroundings.

(In his ninety-one cases, the proportions of these were, twenty-four primary, and sixty-seven secondary.)

As regards *Pathology*, one had to divide the disease into those forms depending on disease of the blood-forming apparatus, and those in which there was an abnormal destruction of blood. This applied to both the primary and secondary varieties. The above-mentioned factors did not operate singly, but they mutually affected each other injuriously; and it was by this duality of cause that the nature of the disease, as regards progressiveness and perniciousness, was explained. The *clinical picture* presented by the disease shewed no special features; and one was therefore not justified in diagnosing it from the clinical features alone. These latter were only results of the anæmia, or of a condition like it; and could therefore be met with in other forms of anæmia. Nor could one diagnose a pernicious anæmia from the *anatomical changes*; none of these were peculiar to the disease, they were merely results of the anæmia. The diagnosis could only be made on a combination of the clinical and pathological features. Only one form of the disease could be recognized during life, namely, that in which certain small spherical red corpuscles were constantly found in the blood; these were to be regarded as red corpuscles, atrophied and arrested in development. This form of the disease appeared to be traceable to disease of the blood-forming apparatus. All other changes in the red corpuscles described by observers—variations in size and shape, amœboid movements, etc.—were only the results of anæmia in general, not of this particular form of anæmia. The proof, that certain forms of the disease might depend primarily upon disease of the bone marrow, was not yet forthcoming; since one could regard these marrow-changes (which after all were not constant) as results of the anæmia. And, similarly, there was no sufficient proof, that one particular form of the disease might arise primarily from nervous disturbances.

In 1881, Dr. SIDNEY COUPLAND gave a full account of the disease in the second of the Goulstonian Lectures on Anæmia. He grouped chlorosis with pernicious anæmia as forms of idiopathic anæmia. He distinguished two great classes of anæmia, the *symptomatic* and the *idiopathic*; broadly speaking,

the former corresponded to the secondary, the latter to the primary forms of other observers.

Of symptomatic anæmia he distinguished two varieties, the *simple* in which the anæmia was slight, and the *pernicious* in which it was profound, as in wasting diseases generally. Of idiopathic anæmia he also distinguished two varieties, the *simple*, *e.g.* chlorosis, in which the anæmia though distinct, and constituting in itself almost the whole of the disorder, was by no means dangerous to life; and the *pernicious*, exemplified by those forms of anæmia now under consideration, which from their clinical characters, and their tendencies, deserved the titles of 'pernicious' and 'progressive.' This classification had, according to Dr. Coupland, the merit of distinguishing between the two great varieties of pernicious anæmia which he believed to exist—varieties "destined like the simpler forms to be merged again into one when etiology was perfected." The symptoms of pernicious anæmia proper were those of simple anæmia, aggravated and intensified, its effects those of simple anæmia carried to an extreme degree.

In 1883 Dr. PYE-SMITH gave an admirably full account of the condition in the Guy's Hospital Reports, based upon a study and analysis of 103 selected cases. He vindicated in the fullest manner, as he had already previously done (1875), the claim of Addison, as the observer to whom belonged the credit of giving the first formal description of the condition. He recognized no secondary forms of the disease, as others had done. Addison's anæmia "stood by itself; idiopathic, autochthonous, primary, *i.e.* it did not depend on known loss of the constituents of the blood, nor on diminished income, nor on increased destruction of formed elements."

From a clinical point of view, he distinguished three classes of anæmia, namely:

(1) *Secondary or Symptomatic anæmia, e.g.* (*a*) anæmia of hæmorrhage (whether from accident or from disease of blood vessels); (*b*) anæmia from suppuration or discharges; (*c*) anæmia due to deficiency of blood from diminished income (starvation, dyspepsia, malignant disease, rheumatism, fever, phthisis, syphilis, and malaria, and *chlorosis*). All these forms agreed, according to him, not only in being symptomatic, but also

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in their comparatively slight degree, the absence of leucocytosis, or of poikilocytosis; in the absence (with very rare exceptions) of pyrexia not due to the primary disease; in the absence of hæmorrhages in internal organs resulting from the anæmia; and in amenability to treatment, and especially to treatment by iron.

(2) *Anæmia associated with disease of the cytogenic organs*, whether or not leukæmic, *e.g.* leukæmia, lymphatic anæmia. This group, (from which it will be noted chlorosis was excluded), differed from the preceding group of secondary anæmic states as well as from chlorosis, and resembled the idiopathic form described by Addison in the following particulars: (*a*) the frequency of hæmorrhages,—usually larger in amount in the former, and more numerous in the latter; (*b*) the very common irregular pyrexia; (*c*) the severity and ingravescence; (*d*) the resistance to preparations of iron, and more or less marked influence by arsenic; (*e*) the occasional remittance of symptoms; and (*f*) the almost invariably fatal termination.

(3) *Idiopathic*, *primary*, or *essential anæmia*, without any symptoms during life, and without any lesions after death, which could not be explained as directly due to anæmia. The absence of leukæmia, the almost constant structural changes in the red discs, and the absence of notable overgrowth of spleen, lymph glands, or red marrow distinguished them from the second group; while their severity and malignancy, the ecchymoses in the retina and elsewhere, the pyrexia, and the almost uniformly fatal result, distinguished them from the first.

With regard to their pathology, such cases shewed with equal constancy fatty degeneration of heart, numerous but small internal hæmorrhages, and slight passive exudations; but no lesion which could not be ascribed to the primary anæmia. The true note of the malady was, not its severity, nor even its fatality, but its being *primary* (not the result of hæmorrhage or of organic disease), and *simple* (not part of a general disease). With regard to the name of the disease, the choice lay betwixt the original *Idiopathic Anæmia* given by Addison, *Essential Anæmia* used by Lebert and many French writers, and *Progressive pernicious Anæmia* given by Biermer. Since the first was the name first given, there was no reason to use any other, till we could replace it by the result of greatly increased knowledge.

In the same year (1883), a very valuable monograph on the disease was published by Professor LAACHE of Christiania; based on observation of eleven cases; containing numerous studies relating more especially to the number of the red corpuscles and their richness in hæmoglobin, both in this, and other forms of anæmia. He found, that the diminution in the number of corpuscles was even greater than supposed; but much more important and characteristic than this, in his opinion, was the high hæmoglobin value of the individual corpuscles. The presence of *large, deeply-coloured* corpuscles he considered to be the chief characteristic presented by the blood, the microcytes of Eichhorst, and the poikilocytes of Quincke, being in comparison of little importance.

To these various observations were added certain others, which served to influence to no slight degree the views existing regarding the nature of the disease.

As early as 1877, and subsequently in a monograph "On Atrophy of the Stomach" (1880), Dr. SAMUEL FENWICK described cases of atrophy of the stomach, which presented symptoms identical with Addison's description of Idiopathic Anæmia. He pointed out, that general atrophy of the gastric glands was accompanied by intense anæmia, and that certainly some cases of pernicious anæmia must be referred to it. He did not think, that this explanation could be applied to all cases of the disease; some might be due, he suggested, to other morbid conditions of the digestive canal, more especially to chronic tubular gastritis. The symptoms were not the immediate result of the atrophy of the stomach, but arose from the deficiency of blood produced by it.

The view, thus apparently the prevalent one, that pernicious anæmia was merely an extreme condition and not a special disease, received support from another side. The anæmia of the workers in the St. Gothard's Tunnel, which, like 'tropical chlorosis,' as noted by Immermann, presented apparently all the features of pernicious anæmia, was shewn by BAUMLER (1881), and SAHLI (1883), to be associated with the presence of the intestinal parasite, *Ankylostomum duodenale*; the anæmia generally disappearing rapidly on their removal. And subsequently a similar relation was shewn by REYHER (1884), and RUNEBERG (1888),

to exist between a form of anæmia presenting the features of pernicious anæmia, and the presence of another intestinal parasite—*Bothriocephalus latus*.

Up to this time (1888), as will be seen from the foregoing account, the only point, about which observers seemed agreed, was that anæmia sometimes reached an exceptional degree of severity, entitling it to be recognized as at least a clinical entity, and to be distinguished by some special name—*primary*, *idiopathic*, *essential*, or *pernicious*, as the case might be. This view had received strong support, from numerous observations, shewing, that, corresponding to the general appearance, the actual blood changes were of a more severe character than those met with in ordinary forms of anæmia. But beyond this point, there was no general agreement.

As regards *Etiology*, a wide departure had been made, as the result of Biermer's teaching, from the original teaching of Addison. The latter considered the characteristic feature of the condition to be, that it occurred "without any recognizable cause whatever"—without the operation of any of the ordinary causes of anæmia. The great majority of observers,[1] following Biermer, held, on the contrary, that all the ordinary causes of anæmia were operative in producing it, and that there was nothing distinctive about these except their severity. The disease might originate in very various ways; be the product of extremely various morbid processes; the chief factors in its production were insufficient nourishment, unhealthy surroundings, hæmorrhages, and wasting discharges; the first of these factors being so important, that in the opinion of Eichhorst the disease was never met in the well-to-do classes. In short, the title *idiopathic* or *pernicious anæmia* was "a sort of provisional shelter for a multitude of cases possibly of various origins" (Immermann).

As regards *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, admitting

[1] Immermann, Quincke, Mackenzie, Bramwell, Fenwick, Eichhorst, Coupland.

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 intestinal parasites.

As regards its *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; it might, on the other hand, be the product of very various morbid processes, *e.g.* malignant disease, loss of blood, atrophy of the stomach, intestinal parasites. In short, the disease could not be diagnosed from the anatomical changes alone (Eichhorst). 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 shewed "no lesion which could not be ascribed to the primary anæmia." He recognized no secondary forms. The suggestion thus was, that the fact of any lesion being discovered excluded the case from being one of pernicious anæmia. This was, however, I would point out, not in accordance with Addison's own teaching. Addison had not asserted, that no lesion other than the anæmia should be present; but only, that he had "failed to discover any organic lesion that could properly or reasonably be assigned as an adequate cause of such serious consequences"—a conclusion of a very different character. So far, indeed, from laying it down as a criterion of the disease, that no lesion should be found other than that ascribable to the primary anæmia, he himself, and, following him, Sir Samuel Wilks, had felt disposed to attach a causal importance to the only lesion they could discover, *i.e.* the fatty degeneration observed in the heart, semilunar ganglia, and solar plexus. Addison had expressed his belief, that these morbid changes might be "essentially concerned in giving rise to this very remarkable disease"—a point that future observations would have to decide.

Lastly, as regards the *Nature of the Anæmia*, no definite conclusion had been come to; it might be due either to defective blood formation, or excessive waste of blood, or to both factors combined, according to the nature of the determining cause. The chief changes, viz., the great reduction in the number of red cells, their irregularity in size and form, the presence of nucleated forms, the great deficiency of hæmoglobin, taken along with the changes in the bone marrow described by Cohnheim—all these pointed strongly, in the opinion of most, to defective blood formation as the real nature of the disease.

On the other hand, the high colour of urine observed in certain cases, as noted by Eichhorst, Quincke, Pye-Smith, and Bristowe, suggested that, in certain cases at least, there might be an increased waste of blood—a 'hæmophthisis'; such cases, according to Quincke, coming under the category of *secondary* forms of the disease, while those dependent on deficient blood formation were to be regarded as *primary*.

To the individual blood changes themselves, a very varying importance was attached by the individual observers: Quincke attaching most to the deformity of the red cells (poikilocytosis) described by him; Eichhorst to the presence of his small yellow spherical corpuscles ('Eichhorst's corpuscles'); Laache to the relatively high hæmoglobin ratio; Ehrlich to the presence of nucleated corpuscles.

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CHAPTER II.

INTRODUCTORY—WHAT IS PERNICIOUS ANÆMIA?

[THE investigations recorded in this treatise were commenced in 1885, with the object of throwing light on the pathology of that "very remarkable form of general anæmia occurring without any discoverable cause whatever" (Addison), commonly known as *pernicious* or *progressive pernicious anæmia*. The results recorded in this and succeeding Chapters (II.–IX.) were originally published in 1888 under the titles, "Is Pernicious Anæmia a Special Disease?"[1] and "An Investigation into the Pathology of Pernicious Anæmia."[2]]

What is 'Pernicious Anæmia'? May any anæmia become *progressive* and *pernicious*, provided it grow steadily worse, prove unamenable to treatment, and terminate fatally? In other words—Is it merely an extreme condition?

Or is it, on the other hand, a special form of anæmia? Are its clinical and pathological 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*?

From the account already given and the extracts appended below, it is clear that the majority of observers are of the first view. They hold that there is nothing characteristic about it, either clinically or pathologically; that it may originate in many different ways and be the product of very various morbid processes; that its symptoms are those of simple anæmia aggravated and intensified; its effects, those of simple anæmia carried to an extreme degree; that the title denotes no single disease, but that there are different forms of pernicious anæmia,

[1] *Practitioner*, August 1888.

[2] *The Lancet*, September 22, 29, October 6, 1888.

differing in etiology and in nature: some primary, essential, idiopathic; others secondary, deuteropathic, symptomatic; some depending on defective blood formation, others on abnormal destruction.

"The disease may originate in many different ways, and be the product of extremely various morbid processes,—loss of blood, continuous discharges, insufficient nourishment, all being possible factors in its development, provided they last sufficiently long and are of sufficient intensity." (Quincke.[1])

"It is a clinical entity (not a pathological); although a picture of the disease in every way complete may be presented by cases of cancer of stomach, or cirrhosis of the stomach, as in Nothnagel's case. Such cases come under the category of *secondary* forms of the disease, while those dependent on deficient blood formation are to be regarded as *primary*. In addition, cases undoubtedly occur which have to be considered as *intermediate* forms of the disease, in which microcytes and poikilocytes occur in small number, but which are not so severe as ordinary cases." (Quincke.[2])

A similar conclusion was arrived at as the result of a careful review of all the cases (fifty in number) published up to 1877. (Lépine.[3])

"It is probable, as several writers have observed, that in idiopathic anæmia we have not to do with one morbid state dependent upon a single anatomical condition. As Immermann says, we must regard the term idiopathic or progressive pernicious anæmia as 'a sort of provisional shelter for a multitude of cases, possibly of various origins.' It is as yet undecided whether the deficiency of coloured corpuscles is due to defective formation (anhæmatosis), or to increased destruction of the corpuscles (hæmophthisis)." (Stephen Mackenzie.[4])

"Probably, as Professor Quincke says, we have not to do with a single diseased condition; but pernicious anæmia, just like anæmia in general, is the product of extremely various morbid processes, and represents the very last stage of the anæmic process." (Byrom Bramwell.[5])

"In pernicious anæmia and leukæmia we have to do with two processes not essentially different; the latter possesses the power of becoming the former." (Litten.[6])

[1] *D. Archiv f. klin. Med.*, xx., 1877.
[2] (A later modified view), *D. Archiv f. klin. Med.*, xxv. 579.
[3] *Rev. mensuelle de Méd. et de Chirurg.*, 1877, pp. 59 and 124.
[4] *Lancet*, ii., 1878.
[5] *Med. Times and Gaz.*, ii., 1877.
[6] *Berlin. klin. Woch.*, 1877, No. 19.

"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'—essential or non-essential, protopathic or deuteropathic, idiopathic or symptomatic—apart altogether from the way it has arisen. Since it in general presents a certain set of symptoms, one is justified in speaking of it as a 'clinical entity,' rather than as a 'pathological entity.' If the etiology of the essential anæmias should ever be made clear, *which at present* (1878) *it unfortunately is not*, 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. Personally, I can for comfort's sake only wish that not the first, but the latter will be the case, and the sooner the better." (Immermann.)

"Pernicious anaemia is not a special form of anaemia, but one which may result from very different causes." (Eisenlohr.[1])

"Like beri-beri, scorbutus, chlorosis, etc., it belongs to a class of constitutional diseases brought about by disturbances of nutrition." (Wernich.[2])

"All the symptoms common to the disease may be regarded as due to want of hæmoglobin, whether induced by disturbances of nutrition at time of puberty, *e.g.* chlorosis, or by loss of blood whether direct or indirect (*e.g.* caused by ankylostomum duodenale); and in all cases it ends in pernicious anæmia if it last long enough. Symptoms characteristic of pernicious anæmia are not to be found, nor any anatomical changes which can be regarded as the cause of the disease. The boundary line between the simplest form of anæmia and the most severe is purely arbitrary; between the two there are an uninterrupted series of intermediate forms, and hence no justification exists for entitling a special variety of it *pernicious*. In other words, neither as regards symptomatology nor etiology can it be regarded as an independent disease." (Runeberg.[3])

"There are two great varieties of pernicious anæmia—the *symptomatic* (secondary), and the *idiopathic* (primary),—varieties 'destined to be merged again into one when etiology shall be perfected.' The symptoms of pernicious anæmia proper are those of simple anæmia aggravated and intensified; its effects, those of simple anæmia carried to an extreme degree." (Sidney Coupland.[4])

"The anæmia that so rivets the attention is only a symptom, and may arise from an imperfect performance of the functions of any of the

[1] *D. Archiv f. klin. Med.*, xx., 1877, p. 495.
[2] *Ibid.*, xxi., 1878, p. 115.
[3] *Ibid.*, xxviii., 1881, p. 500.
[4] *Lancet*, i., 1881, p. 571.

organs engaged in the formation of the blood. General atrophy of the gastric glands is accompanied by intense anæmia, and some of the cases of pernicious anæmia must be referred to it. Others may be due to other morbid conditions of the digestive canal, more especially to chronic tubular gastritis—a morbid change that is analogous to the smooth white kidney in chronic Bright's disease. During life the more prominent symptoms can be most easily explained by the supposition that the various tissues are starved of their usual supply of nourishment—the gradually increasing anæmia being the direct result of the disorganization that has taken place in the glandular apparatus of the stomach. Most of the symptoms are not the immediate results of the atrophy of the stomach, but arise from deficiency of blood produced by it." (Samuel Fenwick.[1])

"The name progressive pernicious anæmia denotes no single picture, no single disease. There are different forms of progressive pernicious anæmia, differing in etiology and in nature—some primary, essential, idiopathic; others secondary, deuteropathic, symptomatic; some forms depending on disease of the blood-forming apparatus; others in which there is an abnormal destruction of blood. The clinical picture presents no special (pathognomonic) features, and one is not justified in diagnosing the disease from the clinical features alone. They are only the consequences of the anæmia. Nor can one from the anatomical changes diagnose a pernicious anæmia, since none of them are peculiar to the disease, but only results of the anæmia." (Eichhorst.[2])

On the other hand, there appears to be but little support for the alternative view that the disease is to be considered as a form of anæmia by itself—"idiopathic, occurring without any discoverable cause whatever" (Addison); "without any symptoms during life, and without any lesions after death which cannot be explained as directly due to anæmia; not depending on known loss of blood constituents, nor on diminished income, nor even on increased destruction of formed elements — essential, primary." (Pye-Smith.)

The extracts bearing on this point have been already given in the previous chapter, as was also the case with several of the foregoing, but are here repeated for the sake of completeness.

"A very remarkable form of general anæmia, occurring without any discoverable cause whatever—cases in which there had been no

[1] *On Atrophy of the Stomach*, Lond., 1880.
[2] *Die progressive perniciöze Anämie*, Leipzig, 1878.

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 of '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."

"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."

"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; in the case last examined the heart had undergone such a change; also the semilunar ganglia and the solar plexus."

"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 observations will probably decide." (Addison.)

"Anæmia, idiopathic, primary, essential, without any symptoms during life, and without any lesions after death which cannot be explained as directly due to anæmia. . . . For the present, it seems in every way desirable to separate chlorosis from idiopathic anæmia in our notions, as they certainly are separated in our practice. Neither the one nor the other can be definitely put aside as a completely known 'disease,' because in both cases we are ignorant of the efficient cause, and in neither are we able to point to any definite anatomical lesion as decisive in our diagnosis. So far from extending the title of 'pernicious anæmia' to all cases in which, whatever the cause, there is great and progressive diminution of the red corpuscles, I would for the present exclude, not only cases of chlorosis, but those which directly follow menorrhagia or puerperal flooding, and those which appear to result from long and severe dyspepsia, chronic diarrhœa, or any other recognized cause of anæmia. In such cases the anæmic condition may be regarded as more or less secondary, and they may properly be grouped with other forms of secondary or symptomatic anæmia."

"It is idiopathic, autochthonous, primary—that is to say, it does not depend on known loss of the constituents of the blood, nor on diminished income, nor on increased destruction of formed elements." (Pye-Smith.[1])

"Two theories have recently been proposed, according to each of which there is a local starting-point for the disease. Cohnheim and some other German pathologists have found that in certain

[1] *Guy's Hospital Reports*, xxvi., 1883, p. 219.

cases the medulla of the bones, even when it should normally be yellow, has a deep red or purple colour, and that is due to the presence of large numbers of cells, including many which are globular and nucleated, but which yet have a red colour. It has therefore been suggested that perhaps pernicious anæmia bears the same relation to a 'myelogenous leukæmia' as the so-called 'splenic anæmia' to ordinary 'splenic leukæmia.' But in some instances Eichhorst and others have found the bones perfectly healthy. And for my own part I shall prefer to adopt Immermann's hypothesis, according to which the medullary changes, when they are present, are a result of the disease rather than the cause of it, and perhaps indicate 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 spleen and lymph glands to maintain the blood in a normal condition.

"The other theory was propounded by Dr. Fenwick in the *Lancet* in 1877. He thinks that atrophy of the gastric glands may be the primary lesion.

"It is an obvious objection that one would, *a priori*, expect wasting of the glands of the stomach to produce emaciation of the body to at least as marked an extent as anæmia. As a matter of fact, however, in Dr. Fenwick's cases a large amount of fat was actually present at the time of death, both beneath the skin and around the viscera.

"It certainly seems, therefore, that the attention of pathologists should in future be directed to this question, so that his view may either be confirmed or overthrown." (Fagge.[1])

Lastly, in this relation the gradual development both of interest and of knowledge regarding the disease may be well brought out by the references to the subject made by Dr. Bristowe—one of the earliest observers of the disease—in successive editions of his *Theory and Practice of Medicine.*

In the first edition (1876), under the title of 'Anæmia,' the only subject treated of is *chlorosis.* In the third edition (1880), also in the fifth edition (1884), under the title 'Idiopathic Anæmia,' two conditions are included, *chlorosis* and *pernicious anæmia*, and the description of the latter is in identical terms, viz., "Idiopathic anæmia is a form of anæmia coming on independently of any organic lesion or specific dyscrasia. Two varieties are recognized, the one occurring in young women, which is usually amenable to treatment, and is known as chlorosis; the other arising under other conditions, almost always fatal, and described by different observers under the names of 'idiopathic anæmia,' 'essential anæmia,' 'progressive pernicious anæmia.' Its causes are, if possible, even more obscure than those of chlorosis; occasionally it seems to be

[1] *Principles and Practice of Medicine*, vol. ii. p. 594, 1886.

induced by pregnancy. It is characterized mainly by occurring as a general rule in those who from age or sex are not liable to chlorosis; and by its almost invariably fatal result, usually in from six to twelve months. During life cases are liable, at any rate for a time, to be mistaken for cases of visceral cancer, undetected hæmorrhages from the bowels, Addison's disease without melasma, or leucocythæmia; with the last two, and with purpura, pernicious anæmia has manifest and close relations. Its pathology is not at all understood. In addition to fatty degeneration, hæmorrhages and dropsies, and an affection of the marrow of bones are occasionally observed."

To decide on the proper answer to the questions thus raised is not an easy task. Its difficulty may be gauged by the fact that, writing in 1888, Dr. Bristowe affirmed the state of our knowledge to be:—"It is impossible at the present time to lay down any trustworthy distinction between the chlorosis of young girls and pernicious anæmia, except such as depend on the age and sex of the patient, and on the effects of treatment"; while at the same time he expressed his belief that some fundamental difference between the two conditions must exist.

This fundamental difference it has been the object of the following pathological researches to discover.

Nomenclature.

From the clinical standpoint Biermer's name for the disease —progressive pernicious anæmia—is, it must be confessed, a somewhat unfortunate one, and is probably accountable for much of the confusion which exists on the subject. The terms *progressive* and *pernicious* are apparently used in different senses by different observers. Any anæmia, whatever be its true nature, is by some described as *pernicious*, if only it is sufficiently profound; and it is described as *progressive* merely on the ground that the patient does not recover. Whatever view, however, we hold as to the nature of the disease, there can be little doubt that though in the majority of cases it tends ultimately towards death, it is by no means uniformly fatal.[1] A sufficient number of instances have been recorded in which not only marked improvement, but even recovery has taken place.[2]

[1] Pye-Smith, *Guy's Hospital Reports*, xxvi., 1883, 219; Padley, *Lancet*, ii., 1883, 811.

[2] [In my experience the recovery, however marked, is usually only temporary.]

From the point of view of pathology, confusion has moreover arisen from the vague way in which the term *anæmia* is employed. Anæmia is constantly used as almost synonymous with *pallor*, and is hence applied indiscriminately to the most diverse conditions affecting the blood, whether the disorder be slight and involving little disturbance of health, or that associated with the severest forms of wasting or malignant diseases, or, lastly, that characteristic of the most pernicious form of 'pernicious anæmia.'

The underlying assumption in all these instances appears to be that the changes in the blood on which the *pallor* depends are always the same in kind, varying only in degree in different cases. This assumption is, I believe, groundless, and if it be cleared away, much of the prevailing confusion as to the pathology of 'anæmia' in general, and of 'pernicious anæmia' in particular, will disappear with it.

Literally speaking, the word *anæmia* may designate any condition in which some degree of pallor or 'bloodlessness' exists. But we must distinguish between: (1) anæmia that is only symptomatic of disease elsewhere than in the blood; and (2) anæmia in which the changes in the blood are the chief or characteristic feature. In the former the changes in the blood are not more marked than corresponding changes in other tissues not the seat of the primary disease. In the latter the blood-changes are the most marked changes found in the disease, if they are not actually the disease itself. In all wasting diseases, such as malignant disease, phthisis, chronic suppuration, etc., there is undoubtedly a degree of bloodlessness, of anæmia in the broad sense; for there is less blood in the body, and that of poorer quality than in health. But other tissues of the body are likewise wasted, the muscles, the adipose tissue, and so on; and the wasting of the blood simply corresponds to this general loss of substance in the parts not specially affected by the primary disease. The general disturbance of nutrition affects the blood and the other tissues simultaneously, and in the majority of cases proportionately. As regards the muscles indeed, on whose condition the appearance of the patient so much depends, we may find that the changes in them are qualitatively and quantitatively more marked than the changes in the blood; and this occurs even in patients whose anæmia, as judged by the pallor only, is

apparently profound enough to be called *pernicious*, or if the case ends fatally, *progressive* and *pernicious*. But if the marked pallor is alone sufficient to identify such a case as one of pernicious anæmia, to be consistent we should also class it as one of 'progressive muscular atrophy,' the changes in the muscles being even more marked than those in the blood. We are prevented from so describing it simply by the knowledge that 'progressive muscular atrophy' is not the result of general malnutrition, however profound, but is due to changes in the nutritional centres of the muscles, which lie in the anterior horns of grey matter in the cord. We have hitherto had no such definite knowledge of the pathological changes which underlie pernicious anæmia; and hence the term has come to be applied to forms of bloodlessness having, I find, as little in common with each other as the muscular wasting of phthisis or œsophageal cancer has with true progressive muscular atrophy.

Classification.

That some essential difference exists between certain forms of anæmia has of course long been known, and various provisional classifications have accordingly been proposed from time to time. Thus, as has been hinted above, anæmia has been spoken of as *primary* or *secondary*, according as the blood-changes constitute the chief or the sole character of the disease, or are consequent on the existence of demonstrable disease elsewhere. Chlorosis is, in the view of most, an example of the former; the anæmia of Bright's disease or of cancer of the latter. For ordinary purposes of clinical description such a division may be useful: and it serves to distinguish broadly two apparently distinct types of anæmia. But such terms as 'primary,' and 'secondary,' are at best vague and inapt, and they have no pathological significance. In no case can a condition of anæmia be really primary; in every case it must be secondary to changes in some organ or organs, whether these changes are manifest as in the wasting diseases, or obscure and difficult of recognition as in chlorosis. And even from the clinical point of view the distinction is useless, when the question is to determine the separate existence of such a form as per-

nicious anæmia, or to give grounds for referring a given case to its true position. To one observer the anæmia in a given case will appear primary, since he finds no morbid condition sufficient to account for it; to another it will appear secondary, if malignant disease is suspected during life or discovered after death.

The classification proposed by Dr. Sidney Coupland in the Goulstonian Lectures[1] of 1881, is on this ground open to criticism. He distinguishes two great classes of anæmia, the *symptomatic* and the *idiopathic*. Broadly speaking, the former would correspond to the secondary, the latter to the primary forms just mentioned. Of symptomatic anæmia he distinguishes two varieties—the *simple*, in which the anæmia is slight; and the *pernicious*, in which it is profound, as in wasting diseases generally. Of idiopathic anæmia he also distinguishes two varieties —the *simple*, including such conditions as chlorosis, in which the anæmia, though distinct, and constituting in itself almost the whole of the disorder, is by no means dangerous to life; and the *pernicious*, including those forms of disease now under consideration, which from their clinical characters and their tendencies deserve the titles of 'pernicious' and 'progressive.'

This classification has, according to Dr. Coupland, the merit of distinguishing between the two great varieties of pernicious anæmia which he believes to exist—varieties "destined like the simpler forms to be merged again into one when etiology shall be perfected." This forecast is based on the assumption that the anæmic process is identical in the two varieties, the forms it takes differing one from another only in their intensity—"the symptoms of pernicious anæmia proper being those of simple anæmia aggravated and intensified; its effects those of simple anæmia carried to an extreme degree." This classification I regard as faulty in that it recognizes two varieties of anæmia each entitled to be called 'pernicious.' These varieties have, I find, really little in common as regards their pathology, and are capable of being distinguished clinically. The classification in fact tends only to perpetuate the prevailing confusion as to the clinical and pathological existence of the disease as a distinct form of anæmia.

I would endeavour to clear up in some measure this confusion

[1] *Lancet*, i., 1881, 571.

by defining, as clearly as our knowledge permits, the meaning of the terms *idiopathic* and *symptomatic* as applied to anæmia. The term *symptomatic* is doubtless open to the objections urged against the terms *primary* and *secondary*—anæmia, whatever its nature or its intensity, must always indicate the existence of pathological changes somewhere, and is so far always 'symptomatic,' whether for example it be the anæmia of chlorosis or that attending malignant disease. But, nevertheless, the division into symptomatic or idiopathic varieties, broadly speaking, is not without advantage from a clinical standpoint, and I propose for the present to retain it.[1]

I begin, for clearness' sake, with the definition of the term *idiopathic*; for any form of anæmia not coming under this head may then be regarded as *symptomatic*. The term *anæmia* I use in the widest sense to include every condition, whether local or general, in which the blood is either qualitatively or quantitatively impaired. *Idiopathic anæmia* is therefore a condition resulting from diminished production or increased destruction of blood, these disorders of hæmogenesis or hæmolysis being in excess of any corresponding changes in other tissues of the body.[2]

Before we can describe a given case of anæmia as truly idiopathic it must comply with the following conditions:—

(1) The changes in the blood must not only *apparently* (as judged by pallor) but *actually* (as judged by examination) constitute the most marked feature of the disease.

(2) The other chief symptoms of the disease must in great part at least be referable to the altered condition of the blood.

(3) With regard to *post-mortem* appearances, the changes in the blood, whether alone or in association with changes in the blood-forming (hæmogenic), or blood-destroying (hæmolytic), organs, must constitute the characteristic morbid feature of the disease.

[1] [It is only in this limited *clinical* sense that the term 'idiopathic' is here employed at all, not in any *pathological* or *etiological* sense. In relation to etiology, the use of the term 'idiopathic'—*e.g.* meningitis, peritonitis—cannot be too much deprecated. It is a mere cloak for ignorance.]

[2] [The anæmia of loss of blood I have for a long time been accustomed to keep in a class by itself, and to entitle simply 'traumatic anæmia.' In reality, regarded purely *clinically* (apart from cause), it is the most perfect example of idiopathic anæmia that exists. That is to say, all its effects are solely due to the anæmia prevailing.]

The diagnosis of idiopathic anæmia *during life* will therefore rest upon—

(1) The detection of certain definite changes in the blood, the changes being more marked than the concomitant change in any other tissue;

(2) The existence of a definite causal relation between these changes in the blood on the one hand, and the clinical features on the other; and

(3) *Post-mortem*, the demonstration that the special morbid phenomena present must be referred to disorder of the great processes, hæmogenic and hæmolytic, on which the condition of the blood depends, and to these alone.

These propositions may be illustrated by reference to the anæmia of phthisis as compared with that of chlorosis. In phthisis, the blood-changes, however profound the pallor, do not by any means constitute the most marked clinical feature of the disease; while the other symptoms, the night-sweats, the fever, the cough, the expectoration, cannot be explained by reference to those blood-changes, nor are they dependent on hæmogenic or hæmolytic disorder. The condition of the blood, in fact, throws no light either on the nature of the disease or on its seat. The anæmia of phthisis is therefore rightly classed as symptomatic.

In chlorosis, however, the blood-changes, especially the great diminution in hæmoglobin in comparison with the slight diminution in the number of red corpuscles, constitute the chief clinical feature (as in this case also the chief pathological feature) of the disease; they suffice in themselves to account for the remaining clinical characteristics—pallor, debility, giddiness, breathlessness, palpitation; and, lastly, the blood-changes themselves appear to depend on disordered blood-formation or hæmogenesis. It is unnecessary here to stop to discuss at length the nature of the dependence of the blood-change on the constipation and gastro-intestinal disturbance generally associated with chlorosis. A single reference may suffice. Bunge[1] has satisfactorily shewn how the excess of decomposition-products in the intestine, naturally accompanying the characteristic constipation, will by breaking up the organic iron compounds of the food, tend to prevent the due absorption of iron in the only assimilable form, and so lead

[1] "Ueber die Assimilation des Eisens," *Zeitschr. f. Physiol. Chemie*, 1885, 49.

to impaired blood-production. Chlorosis may therefore be considered an idiopathic anæmia, hæmogenic in its origin, due probably to a deficient supply of assimilable iron at a time when the recent onset of menstruation has removed a certain proportion of the already small supply of that element in the body.

Let me now apply these considerations to the case of pernicious anæmia. Here the blood-changes certainly constitute the most marked clinical feature of the disease. They appear in themselves to account for, at any rate, most of its other features—the extraordinary pallor, the debility, breathlessness, and palpitation, the fatty degeneration of the vessels with the attendant hæmorrhages, and all this without any characteristic emaciation. At this point, however, a distinction appears to arise between pernicious anæmia and *e.g.* chlorosis, considered as forms of idiopathic anæmia. What relationship exists between the blood-changes and the remaining characteristic features of the former disease—viz., the peculiar lemon-coloured, sometimes icteric, tint so frequently observed, the occasional attacks of jaundice, the gastro-intestinal troubles, such as dyspepsia, vomiting, constipation or diarrhœa, the recurrent pyrexia usually followed by aggravation of all the previous symptoms, and the persistent tendency of the disease toward a fatal issue—in other words its perniciousness? Why, moreover, should most if not all of the features regarded as more or less characteristic of pernicious anæmia be sometimes associated with, and *apparently* due to, definite organic disease, such as cancer of the stomach; while in other instances, and indeed more commonly, the same symptoms, with a degree of anæmia far in excess of that ever observed in malignant disease, occur in the absence of any such organic disease, or any other obvious lesion?

Result of Studies.—This gap in our knowledge it has been the aim of these investigations to fill up.

It has been their primary object to learn, with special reference to pernicious anæmia, whether any fundamental differences exist between this and other recognized forms of anæmia, and if so, in what these differences consist.

Such differences I find to exist. When we come to compare the *blood changes* and *combination of clinical features* in pernicious anæmia with those found in other forms of anæmia apparently

resembling it, I find that these alone are, either in character or degree, sufficiently distinctive to mark off the disease as a special form of anæmia.

Still more distinctive are the pathological changes which determine these specific features. The pathological changes in pernicious anæmia are, I find, no mere exaggeration of those met with in other forms of anæmia. On the contrary, they are in a high degree distinctive.

The disease is thus not only a clinical, but also a pathological entity; no mere aggravation of an ordinary anæmia, but a special and distinct variety. From no form of anæmia is it, in my judgment, more easily distinguishable *pathologically* than from the very forms which *clinically* it appears most closely to resemble, viz., the anæmia of malignant disease, of wasting discharges, and of loss of blood.

The pathological observations which establish those conclusions have been of two kinds—*anatomical* and *experimental.*

I have sought to learn, in the first instance, what anatomical changes are constantly found associated with this form of anæmia; and I have then endeavoured in various ways to produce similar changes experimentally in animals. These investigations will be described in the following pages in the order indicated above.

PART II.—MORBID ANATOMY.

CHAPTER III.

GENERAL MORBID ANATOMY.

THE anatomical changes hitherto found in pernicious anæmia have been somewhat varied and numerous.

SUMMARY OF ANATOMICAL CONDITIONS.

The following is the list of the chief conditions summarized from the accounts given by Eichhorst (1878), and Dr. Pye-Smith (1883).

1. *Skin, Mucous Membranes and Serous Membranes.*—Pallor, usually of a waxy lemon tint; œdema of subcutaneous tissue; no special emaciation; subcutaneous fat of a deep yellow colour; punctiform hæmorrhages in the mucous membranes (of trachea, larynx, root of tongue, inner aspect of epiglottis, intestine, pelvis of kidney, bladder (and even of gall bladder), pericardium, endocardium, subdural arachnoid, pleura, mesentery, peritoneum).

2. *Muscles.*—Very pale, sometimes dry and reddish-brown; punctiform hæmorrhages (rare); no special change microscopically in muscles of trunk; but fatty degeneration in intercostal muscles and in diaphragm.

3. *Nervous System.* — Capillary hæmorrhages; subdural hæmorrhages, with formation of membranes; punctiform hæmorrhages in pia mater.

4. *Organs of Sense.*—Hæmorrhages into retina.

5. *Cardio-Vascular System.*—Pericardial effusion; punctiform hæmorrhages in pericardium, endocardium, rarely myocardium;

marked fatty degeneration of myocardium, especially of left ventricle (almost constant).

6. *Lungs.*—Subpleural punctiform hæmorrhages; hydrothorax.

7. *Mouth and Œsophagus.*—Pallor; punctiform hæmorrhages (rare).

8. *Stomach.* — Mucosa very pale; punctiform ecchymoses; sometimes œdema (Stricker and Quincke), referable to the hydræmia (Eichhorst); occasional fatty degeneration of cells of tubules (the result of the anæmia, according to Ponfick, Eichhorst and Habershon); occasionally deeper changes, *e.g.*, cellular infiltration with hæmorrhages (Schumann); atrophy of glands (Quincke, Fenwick).

9. *Intestine.*—Similar changes (usually less marked) to those in stomach, viz., pallor, hæmorrhages, and œdema; the latter more frequently observed than in the mucosa of stomach (two out of five cases—Eichhorst); not general, but here and there; sometimes in colon (Eichhorst), upper part of jejunum, lower part of ileum, and whole of colon (Eichhorst); occasionally slight degrees of hyperæmia; swelling of solitary follicles and Peyer's patches (Pepper, Quincke, Müller, and Eichhorst).

10. *Mesenteric Glands.*—Hyperplasia, and slight congestion.

11. *Liver.*—Fatty degeneration (Wilks) very common; absent, on the other hand, in all Eichhorst's cases; size normal; parenchyma firm in consistence, lobules distinct. *Chemical constitution:* Leucin and tyrosin (one case Lebert, also in lungs, spleen, and pancreas); greyish-black colour due to iron—one case (Grohé); two cases, iron percentage 2·1 and 0·6 (Quincke); one case, percentage 0·5187 (Rosenstein). "In all of them there is the suspicion that this increase is an artificial one due to overloading of the liver with iron preparations" (Eichhorst).

12. *Gall Bladder.*—In all cases filled with bile, of an intense golden colour, darker than usual (Eichhorst).

13. *Pancreas.*—Punctiform hæmorrhages (Eichhorst, Quincke); unusually large, firm, vascular, otherwise normal (Broadbent); leucin and tyrosin (Lebert); marked fatty degeneration of cells (Huguenin); increase of iron (Grohé).

14. *Kidneys.*—Pallor; sometimes a yellow or a greyish-yellow colour; more or less fatty degeneration of the epithelium of the tubules (Eichhorst and others), common, but not constant, the

result of the anæmia (Eichhorst). *Chemical changes* (but few observations): leucin and tyrosin (Lebert); excess of iron in one case 0·32 per cent. (Quincke); on the other hand, in one case 0·0422 (Rosenstein); probably due to administration of iron—(Eichhorst).

Blood Organs.—Perfectly normal in the majority of cases (Quincke, Lépine, Bradbury, Burger and many others).

15. *Bone Marrow.*—In all his observations, perfectly normal both to naked eye and microscopic examination (Eichhorst); all changes described by others (Cohnheim, Osler and Gardner) are secondary to the anæmia, not the cause of it (Eichhorst); marrow in all cases intensely red; absence of fat; presence of (1) colourless cells, (2) great numbers of red cells, especially of spherical red cells of different sizes, also nucleated red cells (Cohnheim, Pepper, Osler and Gardner). These latter cases "must be separated from those of idiopathic anæmia" (Pye-Smith).

16. *Spleen.*—Size varies, at first normal; later on, moderate enlargement—the result of the disease (Eichhorst); spleen pulp firm in consistence (Eichhorst and many others); small infarcts (several authors). *Microscopically:* No changes; the occasional enlargement a simple hyperplasia (Eichhorst). *Chemically:* Leucin and tyrosin (Lebert); increase of iron (Grohé); 0·2275 per cent. (Rosenstein); the result of therapeutic administration (Eichhorst).

17. *Lymph Glands.*—No enlargement of general lymphatic glands; mesenteric glands often shew changes; atrophy, one case (Krieg); reddish colour (Müller); intumescence (Ferrand, Quincke, Schumann); swelling in three out of five cases, "secondary to the anæmia." (Eichhorst.)

A consideration of these changes has hitherto failed, and seems at first sight little fitted, to throw much light on the true pathology of the disease. As the result of my studies, I divide them into three groups:—

1. Those which may in whole or in part be regarded as the result of the general anæmia, including especially *pallor* and *fatty degeneration* in various organs of the body.

2. Those *occasionally* found associated with the clinical features of pernicious anæmia, and which *appear in some cases* to

be its cause, including especially *malignant disease* and various *gastro-intestinal lesions.*

3. Those found in the blood itself or in those organs concerned either in blood formation or blood destruction.

I.—Anatomical Changes, the result of the General Anæmia.

These include,

(1) *Pallor*, so generally observed in all the tissues of the body, with, in my experience, only two exceptions—the spleen and the bone marrow, both of which frequently present a deep plum colour.

(2) *Fatty degeneration* so frequently met with in varying degree in certain tissues of the body, more especially the heart muscles, the liver and kidneys, and in the smaller arteries and capillaries.

(3) *Extravasations* met with, especially in the retina and elsewhere.

Fatty degeneration of the heart, originally drawn attention to by Addison, is a condition so often met with that it has been regarded by various observers, amongst others by so great an authority as Dr. Wilks, as the chief pathological lesion to be found in this disease. Pernicious anæmia, according to this view, is ordinary anæmia intensified by the occurrence of this change in the heart.

There is no doubt that more or less marked fatty degeneration of the heart muscles is found in the great majority of cases of pernicious anæmia, and is a marked feature, "the most constant anatomical condition in the disease—its absence throws doubt on the genuine character of the case" (Pye-Smith, p. 62). Dr. Coupland found that in no fewer than sixty-four out of seventy-six cases this condition of the heart was expressly stated to have been present; in six no mention of it was made, and in six the heart was described as healthy.

Apart altogether from the likelihood—so strong as to amount to certainty—that this change in the heart is the result of general anæmia, it is certain that it is not distinctive, and that no essential importance can be attached to it. Fatty degeneration of the heart is met with in many other conditions of disease; it

has been described as occurring to a very marked degree in a case of anæmia resulting from metrorrhagia[1] (I have met with a similar case); and can be produced artificially by bleeding animals.[2]

Extravasations are common in the retina, and not unfrequent elsewhere. Next to the retina, they are perhaps most common in the subdural arachnoid and on the surface of the brain. In the latter situation they may be so numerous as to lead (in a case that came under my own observation) to the formation of sero-gelatinous cysts. Other sites in which ecchymoses may be found are the serous membranes, the endocardium, the mucous membrane of the stomach, the lungs, œsophagus, larynx, and trachea; the bladder, pancreas, and gall bladder; also the interstitial tissues of the muscles and those of the orbit. The hæmorrhages are usually minute in size. Epistaxis is sometimes a troublesome and frequent symptom.

[The view regarding these hæmorrhages taken by Professor Stockman (1895) is that they are the actual *cause* of the anæmia. Pernicious anæmia, according to Professor Stockman, is simply ordinary anæmia aggravated by repeated capillary hæmorrhages. I have not, however, found that capillary hæmorrhages occur with such frequency or magnitude as to cause so marked a degree of anæmia. Moreover, they may in my experience be entirely absent even in severe cases.]

II.—Anatomical Changes occasionally found associated with Pernicious Anæmia.[3]

In certain cases the features of pernicious anæmia are presented by patients who (either during life or after death) are found to be the subjects of definite organic disease such as cancer. The nature of this association has proved one of the most difficult points to elucidate in the study of the disease. The

[1] Neumann, *Zeitschrift f. klin. Med.*, Bd. iii., 1881, p. 414.

[2] Perls, *Virch. Archiv*, 1874.

[3] [This section has for me a special interest. In the order in which it is here considered, it appears to form a natural preliminary to the studies which hereafter follow. As a matter of fact, it forms one of the last series of conclusions I was led up to. That is to say, the subject here dealt with was not considered by me till the end of my investigations, just prior to publication (1888). Up to that time all I knew was, that in the opinion of most (*v. antea*) pernicious anæmia might be, and often was, the result of "most various morbid processes," "the last stage of the anæmic process," how-

mere existence of organic disease in such a case has been held on the one hand to prove that the case was not one of pernicious anæmia, however much it resembled that condition clinically. On the other hand, assuming it to have been pernicious anæmia, the concurrent presence of another disease has been held to prove that pernicious anæmia is not a special disease, but only a profound form of ordinary anæmia.

(1) **Relation to Malignant Disease.**—That the clinical features of pernicious anæmia *appear* to be in certain cases associated with malignant disease, especially cancer, there cannot be a doubt. At the same time, the frequency of this association has been greatly over-estimated, mainly owing to the indiscriminate use of the term *pernicious* to designate any anæmia or any pallor sufficiently profound, irrespective of actual changes in the blood; for, as will presently be seen, the blood changes associated with the pallor of malignant disease are totally different from those of pernicious anæmia.

Apart from these doubtful cases, however, a certain number have been recorded, *seeming to prove* that all the characteristic features of pernicious anæmia may be presented by patients the subjects of malignant disease. The actual number of such cases recorded is, however, remarkably small, considering the widespread impression to the contrary—doubtless for the reason above noted that the discovery of malignant disease *post-mortem* has been held *ipso facto* to cast doubt on the diagnosis of pernicious anæmia. Thus among the 103 cases from the literature between 1855 and 1883 collected by Dr. Pye-Smith there is no mention of malignant disease as a *post-mortem* condition.

The only cases I have been able to find are the following:—

Quincke[1] considered that all the symptoms of pernicious anæmia

ever caused. When my studies here detailed led me back to the *portal area* as the seat of the hæmolysis which I found to characterise the disease, and *consequently* back to the *gastro-intestinal* area, I had to ascertain how this conclusion could fit in with the views above expressed, according to which all sorts of morbid conditions, *irrespective of site*, could occasion the disease. On coming to deal with this section of my subject, I found to my surprise that *all the various morbid processes actually described, including even malignant disease, were exclusively in association with the gastro-intestinal area*, a fact here brought out for the first time in the history of the subject.]

[1] "Weitere Beobachtungen über Perniciöse Anæmie" (*D. Archiv f. klin. Med.*, xxv. p. 579).

might be presented by cases of carcinoma ventriculi; one case of this kind having come under his notice.

Eisenlohr[1] records two cases of pernicious anæmia, one of them occurring in a woman aged forty-three suffering from carcinoma of stomach of two years' duration. The symptoms then gave place to those of pernicious anæmia, the red corpuscles shewing same alterations as in first case, becoming very watery and almost yellowish-red in colour. Retinal hæmorrhages were absent. *Post-mortem* the conditions found were, anæmia of all the organs; fatty degeneration of liver and kidneys; numerous nucleated red corpuscles in bone marrow, although not so numerous as in first case. He agreed with Quincke that pernicious anæmia was not a special form of anæmia, but one which might result from many different causes.

Litten[2] records the case of a man (formerly healthy) who was seized with weakness, want of appetite and vomiting, and who on admission presented the complete symptoms of a case of pernicious anæmia (without, however, any microcytes in the blood). After a three weeks' illness he developed a pronounced leukæmic condition of blood, which increased rapidly till his death four days later. Neither spleen nor glands were enlarged, nor were the bones tender. *Post-mortem.*—General anæmia; fatty degeneration of heart; slight swelling of follicles of spleen; and leukæmic nodules in kidney. Bone marrow in diaphyses of long bones of dust-grey colour, with several larger purulent, and smaller gelatinous portions. In sternum, ribs, vertebrae, and pelvis nothing abnormal. In the affected bone marrow, no nucleated red corpuscles. The fatty heart, Litten thought, was to be ascribed to the anæmia, since in pure cases of leukæmia it did not occur with such intensity. In pernicious anæmia and leukæmia he saw two processes not essentially different, the latter possessing the power of becoming the former. In the present case he thought the hyperplasia of bone marrow resulting from the pernicious anæmia was the occasion of the leukæmia.

Grawitz[3] has described three cases of what he regards as malignant osteomyelitis which presented the features of pernicious anæmia during life.

Case 1 is the foregoing case of Litten's. The bone marrow changes he regarded as the result of a malignant osteomyelitis which had led

[1] "Blut und Knochenmark bei progressiver perniciöser Anæmie und bei Magencarcinom" (*D. Archiv f. klin. Med.*, xx., 1877, p. 495).

[2] "Ueber Einen in medullare Leukæmie übergehenden Fall von perniciöser Anæmie nebst Bemerkungen über die letzere Krankheit" (*Berl. klin. Wochen.*, 1877, No. 19).

[3] "Maligne Osteomyelitis und sarcomatöse Erkrankungen des Knochensystems als Befunde bei Fällen von perniciöser Anæmie" (*Virch. Archiv*, lxxvi. p. 353, 1880).

to death under the clinical features of pernicious anæmia, while the leukæmia was a secondary production.

Case 2 was that of a man aged thirty-one, taken ill after typhoid fever with all the symptoms of pernicious anæmia. *Post-mortem.*—Fatty heart; no hæmorrhages into retina or brain; a general affection of bone marrow—conversion of yellow into red marrow; but in addition a multiple tumour growth in base of skull, in bodies of the vertebræ, the ribs, and the sternum; also in the long bones, with distinct metastases in the liver and in the peritoneum. The tumours were round-celled sarcomata, whose tissue was with difficulty distinguishable from the red bone marrow. Grawitz thought that an increase of lymphoid growth in consequence of the anæmic dyscrasia had occasioned the formation of metastatic tumours.

Case 3, which likewise presented the features of typical pernicious anæmia (although without fever), he also regarded as one of malignant osteomyelitis. *Post-mortem.*—In most of the long bones there was a widespread conversion of bone marrow into a soft purulent-like cellular growth, with, at the same time, a thickening of the cortical portions of the bones; at parts the periosteum had formed small sarcoma-like growths.

Ehrlich [1] describes a case similar to the preceding one of Grawitz. A man with all the appearances of severe anæmia, with irregular fever and splenic tumour, suddenly died of heart failure. There was found, *post-mortem*, malignant osteomyelitis of all the long bones; enlargement of spleen; multiple sarcoma and fatty degeneration of heart. He considered the sarcoma to have followed on the anæmia.

These cases, it will be seen, are not entirely free from question as to the character of the anæmia present.

From a pathological point of view, however, even one case, such as the foregoing, would be of sufficient interest to raise the question:

What is the nature of this connection?

That malignant disease is not usually characterised by the clinical features *and blood changes* of this variety of anæmia is, I consider, certain (*vide p.* 61). Hence, when exceptionally the two are found in association, the question arises—Have the special clinical features, *including the blood changes*, met with in pernicious anæmia been stamped on those proper to malignant disease without further anatomical morbid change than that constituted by the malignant disease itself? Or have other

[1] "Beobachtungen über einen Fall von perniciöser progressiver Anaemie mit Sarcombildung (*Centralbl. f. d. med. Wissensch.*, 1880, p. 484).

anatomical changes special to pernicious anæmia been superadded to those independently existing?

The cases recorded by Litten, Grawitz, and Ehrlich may be excluded from consideration in this relation. In all of them these observers were agreed in referring the new growths to the anæmia rather than conversely.

The other cases of this nature recorded have been cases of malignant disease of the stomach. Nevertheless, I have to point out that malignant disease of the stomach is constantly met with, running its course to the fatal termination without the blood presenting any changes, and without any clinical features, other than those of ordinary wasting diseases. Even then the resemblances are only superficial. They relate to degree of pallor, or lemon tint of skin only. The blood changes are totally different in the two conditions.[1]

It is equally without doubt that all the features of pernicious anæmia in their fullest intensity may be presented by cases in which no definite organic changes, whether of malignant or of other nature, are to be found.

Hence I conclude, on general grounds alone, that when the two conditions—malignant disease and pernicious anæmia—are found associated, the connection is to be regarded, if not precisely as accidental, at least as not essential; that the malignant disease *per se* does not constitute the essential anatomical change underlying the pernicious anæmia associated with it, however much *in certain situations* it may *at times* be associated with effects resembling pernicious anæmia. Not otherwise can one explain why malignant disease, even in the stomach, is not more often found associated with the features and blood changes of pernicious anæmia.

(2) **Relation to Gastro-intestinal Lesions.**—In the case of another group of anatomical changes, it is not so easy to decide what the precise relation between them and the anæmia is. This applies to the very various gastro-intestinal lesions sometimes met with in patients dying of this disease.

The comparative frequency with which I find gastro-intestinal changes are recorded in connection with the disease appears at first sight to lend colour to the view held by most observers, that

[1] *Vide postea*, p. 61.

pernicious anæmia cannot be regarded as a special disease, but is merely the outcome of a profound disturbance of nutrition such as is met with in greater intensity in gastric disease than in any other. This view is apparently borne out by the fact that often no recognisable lesions other than those of the gastro-intestinal tract have been detected *post-mortem*. The lesions and changes so recorded are as various as they are numerous, and include—

Atrophy and fatty degeneration of the gastric glands;[1]

Cirrhotic changes in the stomach, with disappearance of the gastric glands;[2]

Interstitial inflammation of the gastric mucosa, with partial or total atrophy of the gastric glands;[3]

Ulcers of the stomach and duodenum;[4]

Duodenitis;[5]

Degenerative changes in the sympathetic ganglia of the abdomen;[6]

Similar *changes in the nerves of Meissner's and Auerbach's plexus* in the intestinal wall;[7]

Diphtheritic colitis, (Quincke); *slight intestinal ulceration*, (Bramwell); *fatty degeneration of gastric and intestinal tubules*, (Burger);[8] *ulcers of colon*, (Biermer).

The presence of intestinal worms.[9]

In no other portion of the system have the morbid changes found in association with pernicious anæmia been so various or so numerous. But the very number and variety of these lesions make it difficult on general grounds alone to assign essential importance to any one of them as the chief pathological factor in pernicious anæmia. Some of them, on the one hand, such as atrophy and degeneration of various parts of the intestinal wall, may be as much the result as the cause of the disease; while, on the other hand, similar or even more marked changes in the

[1] Fenwick, *Lancet*, ii., 1877, p. 77; *Atrophy of the Stomach*, London, 1880.

[2] Nothnagel, *Deutsches Arch. f. klin. Med.*, xxiv. p. 353.

[3] W. Nolen, *Centralb. f. d. med. Wiss.*, 1882, p. 767.

[4] Zahn, *Jahresb. üb. d. gesammte Med.*, 1882, ii. p. 218; Litten, *Berl. klin. Woch.*, 1880, p. 693.

[5] Homolle, *Centralb. f. d. med. Wiss.*, 1879, p. 815.

[6] Banti, *Jahresb. üb. d. gesammte Med.*, 1881, ii. p. 239.

[7] Sasaki, *Virch. Arch.*, xcvi. p. 287.

[8] Quoted by Pye-Smith (103 collected cases), *Guy's Hospital Rep.*, *op. cit.*

[9] Bäumler, *Centralb. f. d. med. Wiss.*, 1881, p. 560; Sahli, *Deutsches Arch. f. klin. Med.*, 1883, xxxii. p. 421.

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gastro-intestinal tract are frequently found without the features of pernicious anæmia.

As in the case of malignant disease, so here, the question to determine is how far these lesions are to be regarded as the essential morbid anatomical change underlying the anæmia *sometimes* associated with them. What importance is to be attached to them in those cases in which they are present?

To obtain an answer to this question, it is necessary to consider the various changes individually.

(1) *Changes in Gastric Mucosa.*

It will be noted how frequently changes in the gastric mucosa —thickening, interstitial inflammation, and atrophy of the gastric glands—have been described. To these points particular attention has been drawn by Dr. Fenwick,[1] who has shewn that general atrophy of the gastric glands is accompanied by intense anæmia, and that some of the cases of pernicious anæmia must be referred to this cause, while others may be due to morbid conditions of the digestive canal, more especially to chronic tubular gastritis. According to him, the symptoms of atrophy of stomach are identical with Dr. Addison's description of 'Idiopathic anæmia'; although, all cases of pernicious anæmia, he admits, cannot be ascribed to gastric atrophy.

Dr. Fenwick records seven cases of this kind, in all of which there existed, along with extreme anæmia, well-marked and extensive atrophy of the secreting tubes of the stomach—in one case to such an extent that a part of the mucous membrane when tested proved incapable of furnishing an artificial digestive fluid. Hence he concludes "that the gradually increasing anæmia is the direct result of the disorganization that has taken place in the glandular apparatus of that important organ."

Pain after eating was not complained of, and the vomiting was only occasional, so that there was no evidence of a chronic inflammatory condition of the stomach,—thus shewing that the destruction was the result rather of a slow degenerative process than of an inflammatory one.

The prominent pathological condition observed during life was one of intense anæmia without wasting, and all the more

[1] *The Lancet*, vol. ii., 1877, pp. 1, 39, 77; *Atrophy of the Stomach*, London, 1880.

prominent symptoms accompanying it could be most easily explained by the supposition that the various tissues were starved of their usual supply of nourishment. It was clear that some of the cases Dr. Addison had in view when he wrote 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.

The anæmia that accompanies atrophy of the stomach was the result of imperfect secretion of the gastric juice consequent upon it. He was induced to regard the fatty state of the gastric tubules—so frequently noted by authors in those dying of pernicious anæmia—as often the cause, instead of being merely the consequence, of the malady.

Nolen has also directed special attention to this condition. In two cases he found the stomach small, walls thin, the epithelium and glandular cells degenerated, and, in some places, no glands at all. He considered the glandular condition the essential cause of the anæmia—which he therefore thought should be called *secondary*.

Nothnagel[1] found the stomach in one case extremely small, with walls thickened, and cutting, at parts, like cartilage. In the region of the cardia there was loss of glands.

[Mucous membrane intensely anæmic, apparently thinned, and with very smooth surface. Microscopically (by Professor Weichselbaum), mucous membrane appears considerably diminished; the intertubular connective tissue increased, and markedly infiltrated with small cells, especially in the deeper parts; peptic glands displaced, and shortened by this infiltration. The condition, one of chronic gastritis, with small-celled infiltration, and atrophy of the mucous membrane. (Mader.)[2]

Stomach contained a quantity of brownish mucus, and there were a few small ecchymoses in the mucous membrane, and evidences of acute or chronic gastric gastritis. (Holt.)[3]

Mucous membrane pale, with several punctiform hæmorrhages. Mucosa of stomach and intestine to the naked eye unchanged. Microscopically, mucosa and submucosa of the

[1] "Cirrhotische Verkleinerung des Magens und Schwund der Labdrüsen unter dem klinischen Bilde der perniciöser Anæmie." *D. Archiv f. klin. Med.*, xxiv. 353.

[2] [Mader, *Ber. d. k. k. Krankenanstalt*, Wien, 1890, p. 265.]

[3] [L. E. Holt, *Med. Rec.*, N.Y., 1891, xxxix. p. 410.]

stomach and duodenum shewed a small-celled infiltration around the glands, which were not otherwise atrophied. (Nonne.)[1]]

What significance is to be especially attached to these conditions, especially that of atrophy of the gastric glands?

The answer to the question is, I think, best supplied by the observations of Dr. Fenwick himself. He states that he was "struck with the frequency with which atrophy of the gastric glands presented itself in those dying of cancer." He found some degree of atrophy in every case of cancer of the stomach, and in eleven out of fifteen cases of cancer of the breast.

If atrophy of the gastric glands is to be regarded as the essential anatomical change in pernicious anæmia in those cases in which it is found, one might reasonably expect to find pernicious anæmia frequently associated with cancer of the breast, and almost invariably with cancer of the stomach. Curiously enough, however, I have failed to find a single case recorded in which cancer of the breast has presented the features of pernicious anæmia; and as regards cancer of the stomach, we shall see that it is the exception and not the rule for it to be marked by blood changes and clinical features characteristic of pernicious anæmia.

In this case, therefore, as in the case of malignant disease, I am compelled to conclude that, however important atrophy of the gastric glands and other changes in the gastric mucosa may be as etiological factors,—and what part they probably play I shall afterwards have occasion to refer to[2] (see chap. xix.), —they cannot be regarded as the essential anatomical lesions underlying this form of anæmia, in the few cases in which they are associated with it.

(2) *Other Gastric and Duodenal Conditions.*

Zahn (1882) records the case of a man, aged forty-six, who had suffered for years from gastric pain, frequent vomiting, and repeated hæmatemesis, and who finally died with the symptoms of pernicious anæmia.

Post-mortem a circular ulcer was found at lower end ot œsophagus and another in duodenum. The blood shewed

[1] [Nonne, *Archiv f. Psychiat.*, Berl., 1893, xxv. pp. 421–449.]

[2] See ETIOLOGY, chap. xvii.–xix., also CASES.

numerous nucleated red corpuscles, as also the bone marrow; there were fewer in the spleen.

Litten[1] also describes a case of perforating ulcer of the stomach with bleeding, which, during life, presented the features of pernicious anæmia.

Homolle[2] records the case of a man, aged forty-eight, who was seized with profuse diarrhœa, without blood, and fell rapidly into a condition of profound weakness and anæmia (red corpuscles, 536,000 per c.mm.), from which he died in two and a half months. The only lesion found was marked hyperæmia and swelling of the mucous membrane of duodenum. No Ankylostoma were found.

It is probable that the first two of these were cases of anæmia from long-standing hæmorrhage. The condition of duodenum found in the third case is interesting in a relation which will subsequently be noted (see APPENDIX, "Jaundice").

(3) *Degenerative Changes in the Nervous apparatus* of the intestinal wall and of the abdomen have been described, among others, by Sasaki[3] and Banti,[4] and regarded by these observers as independent lesions and as the causes of the anæmia. In a case of pernicious anæmia, Sasaki found marked alterations in the nerves throughout the whole intestinal tract, consisting in atrophy of the ganglion nerve cells and nerve fibres of Meissner's plexus. In another case he found fatty degeneration of the whole of Auerbach's plexus along with fatty degeneration of the muscular fibres. Banti likewise found changes in the sympathetic ganglia both of neck and abdomen, which he also regarded as the cause of the anæmia, acting through the liver and spleen.

The view naturally suggests itself that these changes may possibly be as much the result as the cause of the anæmia; and this is fully supported by the observations of Scheimpflug,[5] made with special reference to these observations of Sasaki.

Scheimpflug finds that in a large number of cases the

[1] *Berl. klin. Woch.*, 1880, p. 693.

[2] "Anémie cachectique progressive (Anémie pernicieuse), Duodénite," *op. cit.*, 1879.

[3] "Ueber Veränderungen in den Nervösen Apparaten der Darmwand bei perniciöser Anaemie," *Virch. Archiv*, Bd. xcvi. p. 287.

[4] *Jahresb. u. d. ges. Med.*, Bd. ii., 1881, p. 239.

[5] *Zeitschrift f. klin. Med.*, Bd. ix., 1885, p. 58.

nervous structures of the intestinal wall present changes which may be regarded as the result of inflammatory, degenerative, or other pathological processes. He made a number of observations on the appearance presented by the plexus of Auerbach and of Meissner in various conditions. The result was that in many various conditions each plexus shewed more or less fatty degeneration. As regards the general frequency of pathological changes in the nervous structures of the intestinal wall, he found such changes by no means uncommon; and that not only in wasting diseases, but also in certain acute infectious diseases, changes in the nervous apparatus of the intestinal wall—cloudiness, swelling, atrophy, fatty degeneration, etc. — frequently occurred.

In the face of these observations, it is difficult to agree with Sasaki in regarding these degenerative changes as absolutely independent lesions, and as the essential morbid anatomical condition underlying the disease.

(4) *Presence of Intestinal Worms.*—The connection between this condition and anæmia similar in its nature to pernicious anæmia, has recently excited much interest and attention both in this country and on the Continent.

The anæmia of the workers in the St. Gothard Tunnel presented apparently all the features of true pernicious anæmia, and was associated with the presence of the *Ankylostomum duodenale*, sometimes in large numbers in the intestinal tract; it usually disappeared rapidly on their removal. The symptoms were those of gradually increasing weakness and pallor without obvious cause. Accompanying the anæmia were sometimes colicky pains or other signs of digestive disturbance, diarrhœa and occasional vomiting. The red corpuscles were greatly reduced, *e.g.* 850,000 per c.mm.

The following case recorded by Sahli [1] gives the main features of the condition. Illness began with frequent vomiting and diarrhœa, with stools at first black, afterwards of normal colour. The patient finally came to present exactly the appearance of a case of pernicious anæmia, face and mucous membranes being waxy pale, and weakness very great. Appetite remained good,

[1] "Beiträge zur klinischen Geschichte der Anaemie der Gotthard Tunnelarbeiter" (*D. Archiv f. klin. Med.*, xxxii. p. 421, 1883).

in fact even better than usual, bowels regular, stools of normal colour, urine pale and clear, subcutaneous fat well developed, no bleedings, no retinal hæmorrhages.

Red corpuscles were reduced to 850,000 per c.mm., but shewed little change either in form, size, or colour. Some of them were very pale, while others of small size presented a deep colour

On examination, eggs of the *Ankylostomum duodenale* were found in large numbers in the stools, and on administration of extract of male fern large numbers of Ankylostoma were evacuated. From this time onward the patient seemed to have no more worms, and the effect on the anæmia was very marked. In the course of three weeks the red corpuscles rose from 850,000 to 2,720,000 per c.mm., and two weeks later under the administration of iron to 4,200,000. At the same time all the subjective symptoms disappeared.

More recently a number of cases have been recorded by Reyher and Runeberg, in which the connection between anæmia of this kind and the presence of *Bothriocephalus latus* has been apparently equally close and equally marked.

In neither instance has the nature of the relation between the condition of anæmia and the presence of the worms been, in my opinion, satisfactorily explained. In the anæmia associated with the *Ankylostomum duodenale* the condition has been ascribed, probably with some truth,[1] to the loss of blood abstracted by the parasite itself. For in patients dying of the disease, the Ankylostoma are found of a black colour from the presence of blood in their intestinal tract. This explanation, however, cannot apply to all cases; for curiously enough the anæmia is not always proportionate to the number of worms present. Thus in one case in which there were numerous worms in the stools, Sahli found hardly any anæmia (red corpuscles, 4,000,000 per c.mm.). In other cases anæmia is almost absent, even when large numbers of the eggs of Ankylostoma are similarly to be found in the stools.[2] Hence, the part played by the worms in producing the anæmia cannot

[1] [This surmise proves to have been the correct one, *v. postea*, chap. ix.]

[2] Sahli, *Deutsch. Archiv f. klin. Med.*, Bd. xxxii., 1883, p. 422.

be considered as simple as the above view would seem to indicate. As Sahli clearly shews, the degree of anæmia is certainly not dependent *solely* on the number of worms present, nor yet on the disturbances in digestion occasioned by their presence, since digestive disturbances may be entirely absent. Sahli himself regards the anæmia as totally distinct from pernicious anæmia—a conclusion borne out by evidence subsequently to be adduced.[1]

In the case of the *Bothriocephalus latus*, it is not even pretended that the anæmia is occasioned by any loss of blood. *Some pathological factor other than the presence of worms must be here at work.*[2] Runeberg's observations[3] clearly shew that not only may worms be present, sometimes in considerable number, without any of the features of pernicious anæmia; but that—and this fact is still more important—even in Finland, where this parasite abounds, cases of pernicious anæmia are met with in patients not infested by the parasite, and that these cases prove especially intractable.[4] This observation agrees with our experience of the disease in our own country, where undoubtedly it constantly occurs, independently altogether of the presence or otherwise of worms.

For these and like reasons, I am forced to conclude that, as with malignant disease so with intestinal worms, their presence alone cannot be held as sufficiently accounting for the pernicious anæmia *occasionally* associated with them.

General Conclusion.—The result of our enquiry so far therefore is, that even if pernicious anæmia were merely regarded as an extreme manifestation of ordinary anæmic processes, or as the result of a profound disturbance of nutrition occasioned by, *e.g.* malignant disease, gastric atrophy, or other intestinal conditions, we should still be unable to explain its *absence* under apparently favourable conditions, and its *presence* under others which would seem unfavourable to it.

None of the conditions just considered, whether malignant disease or other gastro-intestinal lesions, can, in my judgment, be

[1] [*V. postea*, chap. ix.]
[2] [That factor is increased hæmolysis, *v. postea*, chap. ix.]
[3] *Deutsch. Archiv f. klin. Med.*, Bd. xxxii., 1888, p. 428.
[4] See also Reyher, *Deutsch. Archiv f. klin. Med.*, 1884.

regarded as the *essential anatomical causes*, even in the few cases (a minority) in which they are present, or as accounting for the peculiar features and extreme degree of blood change characteristic of this as distinguished from other forms of anæmia.

With regard to all the conditions above mentioned, it is necessary to assume that there have been superadded to them certain more deeply-seated conditions which are essential to pernicious anæmia, and upon which its characteristic features depend.

This conclusion is based chiefly on two considerations:

(1) That similar anatomical changes, sometimes even more marked, are constantly to be met with in cases presenting none of the features of pernicious anæmia.

(2) That cases of pernicious anæmia are constantly met with, in which no such anatomical changes are to be found.

Pernicious anæmia cannot therefore, in my judgment, be regarded simply as *secondary* to definite organic disease, or to the anatomical changes with which it is in a few cases associated.

CHAPTER IV.

SPECIAL MORBID ANATOMY.

Previous Observations.

I.—CHANGES IN THE BLOOD.

THE changes in the blood in pernicious anæmia affect all its characters, but the most notable are those affecting the number and variety of the red corpuscles, and their richness in hæmoglobin. As regards these corpuscles, the changes are of threefold nature.

1. *Oligocythæmia* far more marked than that ever met with in ordinary forms of anæmia, more marked even than that resulting from loss of blood, of which it is often quite independent.

2. *Poikilocytosis.*—An extraordinary variation in the size and shape of the red corpuscles, aptly described by Quincke under this comprehensive term. Many of the red corpuscles are double the size of ordinary hæmocytes—the so-called 'macrocytes' or 'megalocytes'; while others are small, and of the most varying form—pear-shaped, spindle-shaped, etc. These changes are common to all severe forms of anæmia, and express the degree and not the nature of such anæmia. They are especially common in pernicious anæmia, but are also to be found in the anæmia resulting from loss of blood, if the latter be of sufficient degree. Hence they cannot be regarded as peculiar to pernicious anæmia.

3. The presence of small deeply-coloured spherical elements —the so-called 'Eichhorst's corpuscles,' absent from normal blood, and regarded by Eichhorst as the one pathognomonic feature of the disease.

4. *Nucleated red corpuscles.*—The presence of these in the blood has been described by a number of observers (Bramwell, Ehrlich).[1] They are not always to be found. In no case were they ever found by Quincke[2] in his many observations. On the other hand, Ehrlich[3] found them in the blood in all varieties of severe anæmia; and Neumann[4] found them in the blood in a fatal case of anæmia, resulting from long standing and profuse metrorrhagia.

5. *Leucocytes.*—The great majority of cases agree in shewing that there is no increase in the number of white corpuscles in this disease. In some they appear rather to be reduced. Nor is there any special change in the character of the *leucocytes*, or any increase in the number of *granular elements* and *blood-plates* —in striking contrast, therefore, with the condition of the blood in many forms of wasting disease, such as phthisis, in which there is usually a very considerable increase in the number of these elements.

6. *Hæmoglobin.*—The hæmoglobin is always greatly reduced —according to Leichtenstern[5] as low as $\frac{1}{6}$ of the normal; according to Hayem[6] even lower, viz., $\frac{1}{8}$–$\frac{1}{10}$. The interesting point, however, is that the reduction in hæmoglobin is not so great as the reduction in the number of red corpuscles; so that the hæmoglobin value of the individual corpuscle, instead of being reduced (as it is in chlorosis), is generally greater than the normal. (Laache.[7])

In connection with the relative richness of the corpuscles in hæmoglobin there have been noted, further, two other facts, namely:

(*a*) The readiness with which, in this condition, the hæmoglobin of the corpuscles separates from the stroma, and diffuses out, or becomes collected towards one part of the corpuscle,[8] the latter appearance often resembling that of a nucleated corpuscle, and often (though erroneously) regarded as such.

[1] *Berl. klin. Woch.*, 1880, p. 405.
[2] *D. Archiv f. klin. Med.*, Bd. xxv. p. 577.
[3] *Berl. klin. Woch.*, 1880, p. 405.
[4] *Zeitschr. f. klin. Med.*, Bd. iii., 1881, p. 414.
[5] *Hæmoglobinulingehalt des Blutes*, Leipzig, 1878, p. 104.
[6] *L'Union Méd.*, No. 75, 1877.
[7] *Op. cit.*
[8] Mackern and Davy, *The Lancet*, vol. i., 1877, p. 642.

(*b*) The readiness with which crystals of hæmoglobin may be obtained from the blood,[1] a peculiarity shared by the blood in septic disease—a change which normal blood only shews after it has been allowed to putrefy.

The changes in the blood just enumerated are, without doubt, the most marked and most constant anatomical changes occurring in cases of pernicious anæmia. One naturally turns, therefore, to the organs concerned either in blood formation or blood destruction to discover their cause. It must be on some disorder of one or other of these two great processes that the condition of the blood depends. It is in these organs, therefore, that we must look for any characteristic anatomical changes that may underlie the disease. The changes which occur will now be considered *seriatim* in connection with the various organs most concerned in these two processes, viz., the bone marrow, the lymphatic glands, the spleen, and the liver.

II.—CHANGES IN THE BONE MARROW.

In the bone marrow the changes found have been both macroscopic and microscopic. The red marrow is increased in amount at the expense of the yellow marrow of the shafts of the long bones, and presents in the great majority of cases a striking change in its appearance, assuming a peculiar rosy-red or violet-red colour (Pepper, Cohnheim).

These changes have directed attention to it as the possible seat of the disturbances in this disease. The histological changes are of a twofold nature, the abnormal presence of large numbers of *nucleated red corpuscles* apparently pointing to some profound disorder of hæmogenesis (blood formation); and that of large numbers of *corpuscle-carrying cells*, enclosing old red corpuscles or their pigment remains—apparently pointing to some disorder of hæmolysis (blood destruction). When first described, both these changes were thought to be peculiar to pernicious anæmia. Both have, however, since been shewn to be common to this and other severe forms of anæmia (*e.g.* leukæmia).

[1] Copeman, *St. Thomas's Hospital Reports*, 1887.

III.—CHANGES IN THE LYMPH GLANDS.

Few or no changes have been described in connection with the lymphatic glands. The absence of any enlargement or other marked change is a notable feature (Addison) distinguishing this form of anæmia at once from leucocythæmia and other forms of glandular anæmia, and this observation has been confirmed by all subsequent observers.

In some cases, however (Eichhorst[1]), the mesenteric glands have presented some appearance of redness and swelling.[2] Another case is described by Weigert,[3] in which, along with dilatation of the lymphatics of the neck, and of the mesenteric portal, omental, and retro-peritoneal lymphatics, there was also some swelling of the mesenteric glands, their sinuses being filled with lymph containing many red corpuscles. This case Weigert was inclined to regard as one of supplementary blood formation on the part of the glands; but it stands alone, and no great value can therefore be attached to it. No abnormal microscopical changes have been noted; and as regards the importance to be attached to the appearance of redness and swelling, it is only necessary to state that precisely similar changes were found by Neumann in the case of anæmia resulting from severe metrorrhagia already referred to. In this case likewise, with the exception of a very few nucleated red corpuscles, no changes were found microscopically.

IV.—CHANGES IN THE SPLEEN.

As regards the spleen, the changes hitherto described have, as in the case of the bone marrow, been partly visible to the naked eye, and partly microscopic. The changes, however, have not by any means been so constant or so marked as in the case of the bone marrow.

Size.—In a certain number of cases the spleen has been found enlarged, this condition being even recognizable during life.[4]

[1] *Die progressive perniciöse Anæmie*, Leipzig, 1898, p. 288.
[2] *V. postea*, p. 70.
[3] *Virch. Archiv*, Bd. lxxix., 1880, p. 387.
[4] Bristowe, *Brit. Med. Journ.*, vol. i., 1888, p. 1149.

Thus, in a case recorded by Dickinson,[1] it weighed 'at a guess' 10 oz. In two cases described by Dr. Finlay[2] it weighed 19½ and 16 oz. In the great majority of cases, however, the spleen is described as normal, or no mention is made of it. Thus it is described as not enlarged;[3] of natural size;[4] 4 oz.;[2] 3½ oz.[5]

The normal weight may be taken at 225 grammes. Instances of the following variations are given by different observers.

330 grammes, . .	Wilks.	300 grammes, . .	Eichhorst.
360 ,, . .	Ferrand.	500 ,, . .	Wilks.
200 ,, . .	Lepine.	445 ,, . .	Rosenstein.

Twenty-six cases have thus been commented upon by Dr. Pye-Smith—

11 oz. (311 grammes).	'Slightly swollen.'
'Somewhat large.'	'Small.'
'Normal.'	10½ oz. (300 grammes).
11 oz. ('normal').	'Scarcely enlarged.'
'Enlarged.'	'Enlarged.'
'Shrunken.'	'Healthy.'
7 oz. (200 grammes).	12 oz. (340 grammes).
'Normal.'	8½ oz. (241 grammes).
'Somewhat enlarged.'	7 oz. (200 grammes).
'Slightly enlarged.'	7 oz. (,,).
'Somewhat enlarged.'	8 oz. (277·9 grammes).
'Slightly swollen.'	8 oz. (,,).
16 oz. (453·5 grammes).	10 oz. (283 grammes).

Other Features.—Its other characters have equally varied. It has been described as soft and diffluent;[1] pale and soft;[6] and soft;[3] and, on the other hand, firm and red; or firm in consistence and of deep purple colour.

Microscopically, no changes at all have been described in the great majority of cases. In some cases, a few nucleated red corpuscles have been found. The changes generally are those of simple hyperplasia. (Eichhorst.)

[1] Dickinson, *Brit. Med. Journ.*, vol. i., 1878, p. 531.
[2] Finlay, *Brit. Med. Journ.*, vol. ii., 1885, p. 864.
[3] Carrington, *The Lancet*, vol. i., 1883, p. 193. Bradbury, *Brit. Med. Journ.*, 1876.
[4] S. Mackenzie, *The Lancet*, vol. i., 1878, p. 13.
[5] Smith, *The Lancet*, vol. ii., 1881, p. 133.
[6] Coupland, *The Lancet*, 1881, p. 569.

Micro-chemically, the spleen has been found in certain cases to contain a certain amount of pigment rich in iron (Grohé); in one case 0·227 per cent.[1] (Rosenstein.)

V.—THE LIVER.

Fatty Degeneration.—More or less marked *fatty degeneration*, found especially in the centre of the lobules, is the only change in this organ to which attention has been hitherto directed by observers in this country. (Wilks, Coupland.)

Excess of Iron.—In the earlier cases published by Quincke[2] in 1876, the interesting observation was made that in three instances the liver contained a great *excess of iron*, as determined both on microscopic examination and chemical analysis. The value of the observation was diminished in his opinion by the circumstance that in two of the three cases, the kidney and pancreas also contained an excess of iron; and, further, by the possibility of the condition being due to the administration of that drug during life.

In the year following this observation of Quincke, Rosenstein[3] found a great excess of iron in the liver, in a case in which no changes were to be found in any other organ of the body. The same doubt, however, attached in this observer's mind to the significance of this discovery, his patient having likewise been under treatment with iron for some time before death.

At first, therefore, little or no importance was attached to these observations, either by Continental or by home observers.

It had "no pathogenetic significance whatever, and depended probably on the free administration of iron as a medicine." (Müller.)

"In all of them there was the suspicion that the increase was an artificial one due to overloading of the liver with iron preparations." (Eichhorst.)

"Quincke found the liver, pancreas, and other organs stained of a dark colour and rich in iron, probably from the medicine

[1] Quincke, *Deutsch. Archiv f. klin. Med.*, Bd. xxvii. p. 199; Peters, *Ibid.*, Bd. xxxii. p. 182.

[2] *Med. Times*, vol. ii., 1876, pp. 374, 428.

[3] *Berl. klin. Woch.*, 1877, p. 113.

given, but perhaps also from destruction of hæmoglobin." (Pye-Smith.)

Stephen Mackenzie[1] and Coupland[2] in their able lectures expressed themselves with caution regarding them. They both considered that the condition of the liver noted was probably connected with the administration of the drug medicinally. In one case, indeed, the former found an excess of pigment in the liver, the result of what he considered local extravasations in that organ, and he expressed the opinion that in Quincke's cases the excess of iron was perhaps due to a similar cause.

Quincke's later observations appeared to confirm this view as to the want of diagnostic significance of this pigment. The presence of iron pigment in the liver and other organs—a condition to which he gives the name '*Siderosis*'—was, he found, by no means an uncommon one. It was interesting as denoting some excess of blood destruction, but in no way distinctive of any one disease. The different forms of pathological siderosis arose through quantitative disturbance of the destructive process, however produced. Accumulation of iron-containing derivatives of the corpuscles in spleen, bone marrow, and in liver capillaries, took place—(1) when the destruction of red corpuscles was increased, (2) when the formation of new red corpuscles out of the old was retarded.

At his request his pupil Peters (1883) examined the organs in 77 cases in this relation, with the following results:

1. In 17 cases, no reaction of iron in any of the organs.
2. In 27 cases, iron reaction in bone marrow and spleen.
3. In 33 cases, iron reaction in bone marrow, spleen, and liver.

Group 1 included cases of every age, dying partly of acute disease, *e.g.* croupous pneumonia, scarlet fever; partly of chronic diseases, *e.g.* cancer and tuberculosis.

Group 2 included cases of wasting disease of every age; most of them due to phthisis. The iron reaction in this case was always very slight, and was confined to the spleen and marrow, *none in the liver.*

Group 3 included 33 cases of different diseases—4 of granular atrophy of the kidney, 5 of chronic lung disease, with amyloid

[1] *The Lancet*, vol. ii., 1878, p. 836.
[2] *Ibid.*, vol. i., 1881, p. 531 *et seq.*

degeneration, 12 of intestinal catarrh (in children), 4 cases of different anatomical nature, in which the liver showed congestive changes. The remaining cases were partly cases of subacute course (typhoid, spinal meningitis, gangrene of lung), partly diseases of the blood (pernicious anæmia, purpura hæmorrhagica), and finally 2 acute cases.

He summed up his results as follows:

I. "Siderosis" of the spleen and bone marrow was met with (1) in most old individuals, (2) in people of every age dying of a chronic disease. In both cases the result was due to imperfect formation of red corpuscles out of the old material, as a result of the advancing marasmus.

II. "Siderosis" of the liver, spleen, and bone marrow, was found (1) in certain acute diseases; (2) in certain subacute diseases; (3) in diseases running a chronic course. The slight "siderosis" of the liver in subacute cases was to be ascribed to diminished secretory activity of the liver—the supply of iron being normal. The marked "siderosis" of acute cases was due to considerably increased destruction of red corpuscles; and as regards the "siderosis" of chronic cases, this probably arose from increased destruction of red, and a diminished excretion of iron out of the liver cells.

The "siderosis" of pernicious anæmia was thus regarded as a condition common to it, and to other chronic, as well as subacute and acute, diseases; and in no respect as at all special to it. The "siderosis" of pernicious anæmia was indeed exceeded by that Quincke found in certain other diseases—diabetes, typhoid.[1] Quincke,[2] summing up these and his other extensive observations, regarded them of importance in relation to pernicious anæmia, only in so far as the presence or absence of pigment in any case might enable us to distinguish whether the anæmia *in that particular case* had arisen from a destruction of blood—a *hæmophthisis*, or from a poverty of building material in the body.

[1] *Postea*, chap. vii., table 2.

[2] *D. Archiv. f. klin. Med.*, xxxiii. p. 41, 1883.

CHAPTER V.

CHANGES IN BLOOD AND BLOOD-FORMING ORGANS.

Author's Observations.

I.—Changes in the Blood.

Oligocythæmia.—The diminution in the number of corpuscles is sometimes extraordinary, and certainly constitutes one of the most marked of the changes in the blood. The degree of oligocythæmia varies much in different cases. From the first, however, the number of corpuscles is reduced from the normal 5,000,000 per cubic millimetre (c.mm.) to 2,500,000 (50 per cent.), or less; in not a few it falls to 1,000,000 (20 per cent.), or even to 500,000 per c.mm. (10 per cent.).

Sorensen[1] thought the latter number the lowest compatible with life, or at least with subsequent recovery. But Quincke records the case of a patient whose proportion fell to 143,000 per c.mm., and who, notwithstanding, recovered.

My own experience has been, that it is not uncommon to find the proportion so low as 700,000 or 800,000, even when the patient first presents himself; and this without any urgent symptoms, other than the extreme debility.

Comparison with other Forms of Anæmia.—The marked character of the oligocythæmia will best appear, if we compare it with that found in three anæmic conditions in which, if we were to judge by the *pallor alone*, the 'anæmia' might sometimes be thought as intense as in pernicious anæmia, viz., chlorosis, the anæmia of wasting disease, and the anæmia from loss of blood.

[1] Virchow and Hirschwald's *Jahresb.*, 1878, i. p. 241.

(1) In *Chlorosis* the diminution in the number of corpuscles is by no means proportionate to the degree of pallor.

Observer.	No. of Cases.	Average No. of Red Corpuscles.
Sorensen, . . .	7	3,790,000.
Coupland, . . .	7	3,000,000.
Hayem, . . .	18	3,520,000.
Laache, . . .	24	3,632,000.
[Schmaltz,[1] . . .	13	3,600,000.]
[Graeber,[2] . . .	28	4,482,000.]

My own observations agree, in the main, with these results, the average obtained being about 3,750,000. [An examination of 247 cases from the literature of the subject leads Reinert to the conclusion, that the number of cases of chlorosis in which the number of corpuscles is within normal limits is not much less than the number in which it is diminished.]

The number may fall lower than this, especially if the case be in any way complicated, as it not unfrequently is, by hæmorrhage, *e.g.* from a gastric ulcer; but, on the whole, there is no feature of chlorosis more remarkable, than the extraordinary disparity between the actual diminution in the number of corpuscles and the profound degree of pallor.

The change in the blood in chlorosis is, as is now clear, not so much an oligocythæmia, as a poorness in hæmoglobin, the latter being far lower than can be explained only by the diminution in the number of corpuscles. In few cases of chlorosis does the number of corpuscles fall below 60 or 70 per cent. per unit volume; while in pernicious anæmia a diminution to 30, 20, and even 10 per cent. of the normal is not only possible, but is not infrequently met with, and that, too, early in the disease.

(2) *In Wasting Diseases* an equally striking contrast with pernicious anæmia is presented; a contrast all the more remarkable, inasmuch as the anæmia in these cases, judged by the degree of pallor, is often so profound as apparently to entitle it to be termed pernicious. This variety of anæmia constitutes, in fact, that termed by Dr. Coupland the pernicious variety of symptomatic anæmia.

[1] ["*Die Pathologie des Blutes*," Leipzig, 1896, p. 150.]

[2] [Grawitz, "*Klinische Pathologie des Blutes*," Berlin, 1896, p. 77.]

(*a*) Thus, in *Phthisis*, there is no marked or constant diminution per unit volume; a fact agreed to by all observers.

Observer.	No. of Cases.	No. of Corpuscles.
Laache, . . .	14	4,457,000.
Sorensen, . .	11	4,350,000.
[Oppenheimer,[1] .	8	5,000,000 to 4,400,000.]

(*b*) In *Malignant Disease* the change is but little more marked. In six cases of carcinoma, Sorensen found the average to be 3,660,000. Laache, in eight cases, found an average of 3,500,000 per c.mm. In cancer of œsophagus, which often presents the features of a pernicious anæmia, the red corpuscles may be actually increased per c.mm. [In one case of cancer of stomach, Reinert found 4,732,000; in another 6,200,000.[2]]

(*c*) In *Bright's Disease*, Laache (nine cases) found an average of 4,006,000 corpuscles per c.mm.; Sorensen (eight cases), an average of 4,740,000; [Reinert, two cases, an average of 3,845,000].

Lastly (*d*) in *Inanition*, the result of starvation, the changes in the blood are relatively less marked than those in most other tissues of the body. So far from being diminished, the number of corpuscles per c.mm. of blood is often actually increased.[3]

The result of this comparison goes, therefore, to shew, that *the oligocythæmia in pernicious anæmia is far in excess of that found in the anæmia accompanying wasting, and malignant disease.* This difference is not merely one of slight degree, but seems to be radical and peculiar to pernicious anæmia; for the oligocythæmia, which, in the anæmia of wasting disease, *in its most marked forms*, is rarely as low as 50 per cent., and is usually not even so marked as that, constantly in pernicious anæmia, *even in the early stages*, is as low as 20 per cent., or even lower.

(3) *Traumatic Anæmia.*—The resemblances betwixt the anæmia of chlorosis and of wasting disease on the one side, and of pernicious anæmia on the other, are thus limited to the degree of pallor they severally present; and do not necessarily

[1] [*D. med. Woch.*, 1889, Nos. 42, 43, 44.]

[2] Boekmann, *D. Archiv f. klin. Med.*, xxix. p. 490.

[3] With special reference to these changes in the blood, see also Stephen Mackenzie, *Lancet*, ii., 1878, p. 834. [Reinert, *Die Zählung den Blut Körperchen*, Leipzig, 1891. Grawitz, *Klinische Pathologie des Blutes*, Berlin, 1896.]

extend to the blood changes, (oligocythæmia), presented in the separate instances. As regards the degree of oligocythæmia, a much closer resemblance exists betwixt pernicious anæmia and the anæmia resulting from loss of blood. Loss of blood is a factor which, moreover, complicates many cases of pernicious anæmia; and has been held by some to be the chief factor in causing its high degree of blood change.[1]

There can be no doubt that repeated hæmorrhages, especially when occurring in a patient already debilitated by disease, will do more than any other adventitious condition to bring about profound anæmia, pallor, and debility, closely resembling those found in pernicious anæmia. The difficulty of determining what part is played by loss of blood in the production of the anæmia we term *pernicious* is all the greater, inasmuch as the two conditions are often found associated, and each is apt to aggravate the other—the loss of blood intensifying the oligocythæmia, and this condition of the blood, in turn, favouring the occurrence of further hæmorrhages.

Cases of this sort are not uncommon, the diagnosis remaining uncertain to the end; and, during life, it remains a question whether the patient died simply from the effects of repeated hæmorrhage, or whether the condition was really one of pernicious anæmia from the beginning, the fatal issue being merely hastened by the hæmorrhages.

Hence, in determining whether pernicious anæmia has any independent existence as a distinct clinical and pathological entity, or is not rather an extreme condition of ordinary anæmia, it is of the first importance—as a first part of the general inquiry, how far the features of the disease, *in their entirety*, can be produced by repeated and copious hæmorrhage—to determine how far the blood changes in the two conditions correspond.

Opportunities for observing the effects of loss of blood in man are often met with—in the hæmatemesis of gastric ulcer, the epistaxis of Bright's disease, the hæmorrhage of malignant disease, or the metrorrhagia of malignant or fibromatous disease.

[1 According to Professor Stockman (1895), hæmorrhages are responsible not only for the degree of anæmia, but for the whole of the other distinctive features that the disease presents; it is nothing more than very severe anæmia aggravated and complicated by hæmorrhages, many of its special features being the result of absorption of the extravasated blood. This view will be found considered in chap. xii.]

A condition of the profoundest anæmia may in this way result, closely resembling, in degree of pallor, the condition we term pernicious. This is true in part of the oligocythæmia, and, as will be afterwards seen, of the changes in form and size of the red corpuscles usually associated with it.

On the other hand, it is not true of certain other characteristic blood changes, notably the high hæmoglobin ratio of the individual corpuscles; and my studies satisfy me that, in regard even to the oligocythæmia, it is not true of the *extreme* degree of oligocythæmia met with in pernicious anæmia.

The observations of Laache shew that the degree of oligocythæmia producible by hæmorrhage, great though it is, is not so high as one might at first imagine.

Thus in five cases of *bleeding in individuals formerly healthy*, he found the corpuscles reduced to

2,781,000 (55 per cent.), 1,719,000 (34 per cent.),
1,671,000 (33 per cent.), 1,598,000 (32 per cent.),
1,415,000 (28 per cent.).

In five cases of *bleeding in individuals already diseased*—under conditions, therefore, most favourable to the production of the highest degree of oligocythæmia, he found

3,440,000 (68 per cent.), 2,696,000 (54 per cent.),
2,513,000 (50 per cent.), 2,135,000 (42 per cent.),
1,281,000 (25 per cent.).

In *purpura hæmorrhagica* he found

2,091,000 (41 per cent.), 2,342,000 (46 per cent.), and
2,680,000 (53 per cent.).

In a case of *scurvy* he found 4,050,000 (80 per cent.).

In a case of *hæmophilia*, 5,302,000 (106 per cent.).

In a case of *hæmoglobinuria*, 2,269,000 (45 per cent.).

If we compare these figures with those constantly met in pernicious anæmia [1]—*e.g.*, 700,000 (14 per cent.), 800,000 (16 per cent.), 1,000,000 (20 per cent.), and that too at the very outset of the disease—we must admit that *this result points to the conclusion, that mere loss of blood, unattended by any other factor, is not capable of explaining the high degree of oligocythæmia in pernicious anæmia—a feature, be it noted, often characteristically present even when no hæmorrhage has occurred.* Of the occurrence

[1] See CASES, *postea*.

of such an extreme degree of oligocythæmia, apart altogether from loss of blood, there can be no doubt; indeed, many such cases have come under my own notice. The rapidity of its progress, and its intensity, are moreover such as cannot be accounted for by any assumed failure of nutrition however profound, or any defect in the blood-forming functions however marked.

This experience accords with the results obtained by experiment. Hayem found it impossible (in dogs) to reduce by bleeding the number of corpuscles below 1,000,000 per c.mm.

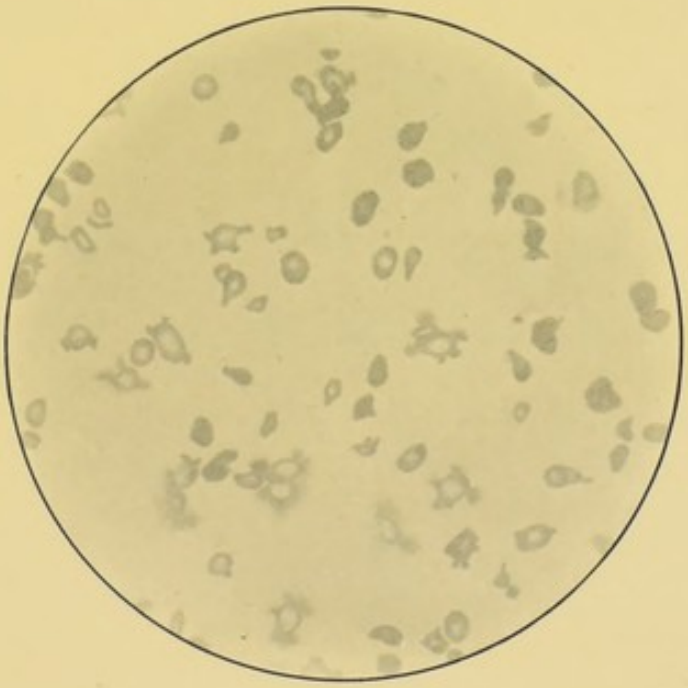
On the *three grounds* therefore: of the results of these experiments on animals; of the comparatively slight degree of oligocythæmia produced by hæmorrhage pure and simple; and lastly, of the occurrence of intense oligocythæmia in pernicious anæmia apart altogether from hæmorrhage, I am compelled to conclude that the diminution in the number of corpuscles in pernicious anæmia is not *ab initio* the result of hæmorrhage; though it may be, and undoubtedly is, aggravated by its subsequent occurrence.

While this is so, however, I am ready to admit that if, in a given case, the distinction to be drawn *during life* between anæmia resulting from loss of blood, and pernicious anæmia, had to rest solely on the *relative degree of oligocythæmia* possible in the two conditions, a great, if not insuperable, difficulty might attend the diagnosis. I refer here particularly to cases where the oligocythæmia is by no means so marked as, in itself, to be distinctive; and in which previous loss of blood has occurred, perhaps in itself sufficient to account for it. Such cases, so far as their degree of oligocythæmia is concerned, would afford fair ground for the view that pernicious anæmia is merely an extreme manifestation of the anæmic process, specially aggravated by loss of blood. While this is admitted, however, I find that the extraordinary degree of oligocythæmia is really one of those features which point very strongly to pernicious anæmia being a form of anæmia quite distinct in its origin from that resulting from loss of blood.[1] The oligocythæmia of pernicious anæmia is, however, as we shall see,

[1] I find, namely, that the highest degrees of oligocythæmia are easily and rapidly producible by hæmolytic agents; while it is impossible to produce such degrees by abstracting blood.]

PLATE I.

To face page 65.



BLOOD IN PERNICIOUS ANÆMIA

Showing extreme poikilocytosis; many of the red corpuscles throwing off "buds"—their stroma oozing out. From Case ix. a week before death. Extreme urobilinuria accompanied the above changes in the blood.

distinguishable from that of loss of blood in a still more important particular, viz., the relative richness in hæmoglobin.

Poikilocytosis.—To the various changes in the shape and size of the red corpuscles, aptly described by Quincke under the generic term *poikilocytosis*, to which so much attention has been given by various observers, I attach but little value. They are not characteristic in my experience of any one form of anæmia, but depend largely on the degree of hydræmia present. In pernicious anæmia, indeed, these changes are far more marked than in any other form; but that is dependent more upon the greater degree of anæmia present in such cases than upon any other factor.

It was a matter of special interest to me to determine how far the changes mentioned were common to the anæmia resulting from loss of blood, and to that resulting from increased hæmolysis, produced by destructive agents, such as pyrogallic acid, injected into the blood. I found that they could not be so readily produced by loss of blood as by the action of destructive agents; but that was solely due to the fact that it was *very much easier* to produce a profound anæmia by the latter than by the former method. The changes in the corpuscles were, however, in each case the same in kind, however much they might differ in degree.[1]

The poikilocytosis, therefore, the variation in the size and shape of the red corpuscles—so commonly met with in pernicious anæmia, testifies more to the degree of anæmia present than to its character; except in so far that, in the absence of hæmorrhage, it indicates the existence of a degree of hydræmia and oligocythæmia, such as, in my experience, one only meets with as the result of an increased hæmolysis.

Eichhorst's Corpuscles.—Much attention has also been directed to the presence of so-called *microcytes*—that is, of small, spherical, deeply-coloured corpuscles resembling minute red blood-

[1] [This is true with one exception, which I would specially note. The remarkable change in the red corpuscles—an oozing of their stroma—figured in the Frontispiece, and photographed in Plate I., is, in my experience, never found in traumatic anæmia. It is a change I regard as in a special degree of *hæmolytic* origin. It is never found in pernicious anæmia unless during an active exacerbation of the disease combined with other evidences of increased hæmolysis.]

corpuscles—as being more or less characteristic. First described by Quincke, they were afterwards more minutely described by Eichhorst,[1] who claimed that they were pathognomonic. Hence has arisen the title 'Eichhorst's corpuscles,' sometimes given to them. The term *microcyte* is applicable to so many bodies discoverable in the blood that the use of it in any restricted sense only tends to confusion. These elements are certainly present in the great majority of cases of pernicious anæmia, at some time or other during the course of the disease; although they vary[2] remarkably in their number, not only in different cases, but in the same case at different periods. They are remarkable for their smallness, their diameter in some cases scarcely exceeding the fourth part of that of a red corpuscle; for their perfectly spherical form, whatever the shapes of the other corpuscles in the blood may be; and lastly, for their deep yellow colour, in this respect sometimes resembling droplets of oil rather than corpuscles.

They are distinguishable by their uniform spherical shape and depth of colour from the various coloured microcytes so constantly seen in the blood in various conditions of profound anæmia, especially that due to loss of blood. The latter present the most various shapes—drawn out, pointed, oval, etc.; and their depth of colour varies for the most part according to their size, in no case, however, exceeding that of the surrounding red corpuscles.

As regards their nature, opinion has, as usual, been much divided, Eichhorst regarding them as stages in the evolution of the red corpuscles, and therefore as an evidence that blood formation is at fault; others, again, regarding them as products of blood destruction resulting from the breaking down of the red corpuscles. In favour of the former view is the fact that they have been described by two observers (Litten[3] and Lépine[4]) as occurring in anæmia resulting from loss of blood; on the other hand, they were found by another observer (Eisenlohr[5]) to be

[1] *Centralbl. f. d. med. Wiss.*, 1876, p. 466.

[2] Eisenlohr, *loc. cit.*, 1877, p. 496; Grainger Stewart, *Brit. Med. Journ.*, i., 1876, 40; Wagner, *Berlin klin. Woch.*, 1879; Lépine and Germont, *Gaz. Méd. de Paris*, 1877, No. 18.

[3] *Berlin. klin. Wochen.*, 1877, No. 1, No. 19.

[4] *Union Méd.*, 1877.

[5] *Loc. cit.*, p. 582.

absent under precisely similar conditions. The question is only of interest, in so far as it concerns the importance to be attached to their presence in pernicious anæmia, in which disease they certainly are met with more commonly than in any other. Since when present, they vary much in number, and may even disappear for a time altogether, their absence in any case can hardly be regarded as excluding the diagnosis of pernicious anæmia. And as it is apparently possible for them to be present in other diseases (Afanassiew[1] found them in a case of typhoid fever), I conclude, that although 'yellow spherical microcytes' are not pathognomonic of pernicious anæmia, their presence in any case of doubtful nature, associated with marked oligocythæmia, affords a valuable indication as to the origin of the anæmia we are dealing with. My experiments shew that similar bodies can be produced artificially by action of destructive agents; that they mark the anæmia as due to excessive destruction of blood and not to deficient formation,—that they denote the anæmia to be hæmolytic, not hæmogenic, in its origin.

Relative Richness in Hæmoglobin.—Another feature presented by the blood in some forms of anæmia is of special interest. I refer to the *comparative richness of the blood in hæmoglobin*, having regard to the number of corpuscles present. The percentage diminution in the number of corpuscles is often considerably greater than that of the hæmoglobin. The very opposite of the condition in chlorosis here obtains. Instead of 70 to 80 per cent. of corpuscles, with some 20 or 25 per cent. of hæmoglobin, a relation not infrequent in chlorosis, it is not uncommon to find in pernicious anæmia 30 or 40 per cent. of hæmoglobin associated with some 20 or 30 per cent. of corpuscles. Thus in one case Coupland[2] found the corpuscles diminished to 10·6 per cent. of the normal number, while the hæmoglobin was reduced only to 30 per cent. Quincke[3] found that while in general the corpuscles were reduced 10 or 12 per cent. of the normal, the hæmoglobin was 20 or 40 per cent. One observer, Laache,[4] has attached so much importance to this relation, as to regard it as

[1] *D. Archiv f. klin. Med.*, xxxv., 1884, p. 233.
[2] *Lancet*, i., 1881, p. 571.
[3] Quincke, *D. Arch. f. klin. Med.*, xxv. p. 577.
[4] Laache, *Die Anæmie*, 1883, Christiania, p. 224.

pathognomonic of pernicious anæmia. The individual corpuscles are thus larger and richer in hæmoglobin than normal blood-corpuscles.

[The following are some of the figures obtained in my cases.]

Case.	Percentage of Corpuscles.	Percentage of Hæmoglobin.	Case.	Percentage of Corpuscles.	Percentage of Hæmoglobin.
1	54	56	10	22	25
,,	34	30	,,	25	34
2	36	38	,,	24	30
3	37	54	,,	25	22
4	15	18	,,	26	30
,,	25	40	,,	27	40
5	24	40	,,	31	42
6	27	34	,,	28	35
8	32	28	,,	30	35
,,	25	24	,,	31	35
,,	32	40	,,	52	50
9	18	22	,,	65	75
,,	14	15	,,	55	70
10	20	40	,,	66	72

In what proportion of cases this feature is to be found remains a subject for future determination; but its presence in a certain number of cases is one of the characteristic features peculiar to pernicious anæmia which has always seemed to me urgently to call for explanation. Laache regarded it as a sort of compensatory hypertrophy on the part of the corpuscles.

To this condition of the blood I attach no little value, both clinically and pathologically.[1] Its pathological significance will be seen later. As regards its clinical significance, its presence in a case serves, in my opinion, to distinguish between anæmia resulting from loss of blood and pernicious anæmia. The results of all my observations on animals after bleeding (and the same conclusion applies to man), go to shew, that, after hæmorrhage, the hæmoglobin is proportionately more reduced than is the number of corpuscles,—the very reverse of what is found in pernicious anæmia. Moreover, it takes a longer time to be restored to the normal than do the number of corpuscles.

[1] See CASES, *postea*.

Summary.

The foregoing, then, are the chief anatomical changes found in the blood in pernicious anæmia. It will be noted that, with the *single exception of the relative richness in hæmoglobin*, scarcely one of them, unless perhaps as to degree, can be regarded as peculiar to this anæmia. The other changes—such as the oligocythæmia, poikilocytosis, presence of yellow microcytes, the occasional presence of nucleated red corpuscles, and the absence of increase in the number of white corpuscles, or in the colourless granular elements of the blood—are neither absolutely constant nor distinctive. It is only when they co-exist in a certain high degree and in certain associations, that they can be regarded as sufficiently distinctive, clinically, to diagnose that form of anæmia which we term *par excellence* pernicious.

II.—Changes in the Bone Marrow.

Nucleated red corpuscles are undoubtedly to be found in the bone marrow in large numbers in the great majority of cases of pernicious anæmia. Their presence, however, is neither constant nor distinctive. On the one hand, they have been described as absent altogether in certain cases, and in others as occurring in small numbers only. In a well-marked case of this disease, which I recently examined, nucleated red corpuscles were exceedingly few in number, and had to be sought for. On the other hand, they have been found in the bone marrow in other conditions, especially in cases of anæmia resulting from severe and long-continued hæmorrhages, as in a case of metrorrhagia described by Neumann.[1] Similar changes in the bone marrow have also been produced experimentally in dogs by Litten and Orth,[2] and by Bizzozero and Salvioli,[3] by repeatedly withdrawing blood, and thus bringing about conditions of severe anæmia.

The presence of nucleated red corpuscles cannot therefore be regarded as pathologically distinctive of pernicious anæmia; still less does it serve to explain the characteristic clinical features which the disease, in my experience, *invariably* presents.

[1] *Op. cit.*
[2] *Berl. klin. Woch.*, 1877, No. 51.
[3] *Centralbl. f. d. med. Wiss.*, 1879.

The same remark applies to the presence of *corpuscle-carrying cells*. These were, at first, regarded as indicative of some excessive destruction of red corpuscles, peculiar to pernicious anæmia; but they were soon shown to be common to this and many other conditions. Thus Osler, in observations on seventy-five cases of disease other than pernicious anæmia, found these bodies so frequently that he could not decisively connect their presence with any one disease. They were specially numerous in phthisis, pneumonia, typhoid fever, and ulcerative endocarditis.

My own observations entirely confirm those of Osler. On the one hand, I have not found their presence in excess a constant feature of pernicious anæmia. Thus, in one case, in an elderly man, they were extraordinarily numerous, individual cells containing as many as ten or twelve old red corpuscles; while in another, in a young man, they were exceedingly few in number. On the other hand, I have found them very numerous in many other conditions, especially cases of wasting disease in elderly people.

The nucleated red corpuscles usually present a high degree of coloration—this appearance indicating a great richness of the corpuscles in hæmoglobin, similar to that already described in the red corpuscles of the blood. Further, in most cases, as determined by micro-chemical tests such as the application of sulphide of ammonium, the bone-marrow tissue contained a considerable excess of iron, partly diffuse, partly in granular form. This excess, however, is not constant, nor is the reaction of iron given by the tissue at all proportionate to the amount of granular pigment or to the number of effete red corpuscles it sometimes contains.

III.—Changes in the Lymph Glands.

[The only changes I have found here have been, in certain cases, a swelling and congestion of the gastric and mesenteric glands. These I regard as results of the local lesions in the stomach and intestine (see p. 198).]

IV.—Changes in the Spleen.

Size.—In three cases—for the opportunity of examining which I am indebted to the great and friendly kindness of Dr.

Byrom Bramwell—the weights were 19 ozs., 11 ozs., and 10 ozs. respectively. In another case, on which I made a necropsy recently for Mr. Wherry of Cambridge, the spleen weighed 13 ozs. In all these cases, therefore, the enlargement has been very marked. The above, however, only constitute a very small proportion of the cases recorded. In the great majority of cases the spleen is either described as normal, or no mention is made of its condition at all.

Other Features.—In nearly all the cases which have come under my notice the spleen has been soft and pulpy in consistence, like the spleen of fever, and has presented an extremely *deep violet or purplish colour*, contrasting in this respect very markedly with the pallor presented by all the other organs of the body.

Iron.—In seven cases of pernicious anæmia which I have had the opportunity of examining, the amount of iron contained in the spleen, as determined by micro-chemical examination, has in no case been in excess of that met with in certain other conditions, as, for example, certain cases of cirrhotic Bright's disease. In three cases, no reaction of iron was obtained at all, in contrast to that usually met with in normal conditions.

Summary.

So far then as the bone marrow, lymphatic glands, or spleen —the chief seats of *blood formation*—are concerned, I have not found the changes either sufficiently constant, or sufficiently distinctive to throw any light on the nature of the disease.

CHAPTER VI.

CHANGES IN THE LIVER.

Results of Micro-Chemical Studies.

We have seen that the changes in the spleen, red bone marrow, and lymphatic glands are not sufficiently prominent or constant to be regarded as the essential anatomical changes in this disease. The case is, I find, very different when we come to consider the changes denoting disturbances of blood-destruction.

The observations of Quincke and his pupil, Peters, had shewn that an excess of iron in the liver was a more or less marked feature of *certain cases*, denoting a "hæmophthisis" to be a special feature of such cases. It was not, however, in any way distinctive; a similar, or even greater excess, being found in other conditions: *e.g.*, diabetes and typhoid fever.

Results of Micro-Chemical Observations.—My own observations in nine cases of pernicious anæmia enable me fully to confirm these observations of Quincke as to the presence of this excess, and as to its independence of the administration of iron medicinally. In all cases, without exception, I have found a great excess of pigment in the liver, differing entirely in its distribution and its character from that sometimes found in that organ as the result of extravasation, or as the result of chronic venous congestion. My observations, however, lead me to attach to this change in the liver a *distinctive* importance, in regard both to its *pathological* and its *diagnostic* significance. The presence of this pigment is the most constant morbid change in this disease; it is no less constantly absent in the anæmia of wasting disease, and of hæmorrhage.

My observations shew, with regard to the pigment changes in the liver, that they are in a high degree distinctive, and are such as to mark off pernicious anæmia from the other varieties of anæmia most liable to be confounded with it clinically: namely, the anæmia of malignant disease, of wasting diseases from discharges and the like, and of loss of blood;—and from none of these forms more sharply than from the latter, the one whose degree of oligocythæmia, as we have seen, approaches it most closely.

These distinctive changes consist for the most part of deposit of blood pigment within the liver—also within the kidney—of a *character*, *amount*, and *constancy*, such as to denote an excessive destruction of blood as one of the most characteristic features of the disease. Similar changes I find no less constantly absent in traumatic anæmia, and the anæmia of wasting, or malignant disease.

Origin of Interest in the Subject.—It may be noted incidentally, how my interest in pernicious anæmia first arose. It arose from studies regarding blood pigment—its origin from hæmoglobin; its distribution in certain organs, notably the liver and spleen, more particularly the former; and especially its dependence upon and relation to the presence of extravasated blood in various parts of the body. While engaged in these studies,[1] (1885) I had occasion to examine the liver from a case of pernicious anæmia. The excess of pigment in this case was so great—so very much greater than in any other case I had ever observed, that it particularly arrested my attention, more especially as it was unaccompanied by any excess at all within the spleen. A detailed study of the liver, in this case, revealed important differences, both as to character and distribution, between this pigment, and that derived from blood extravasated into the liver, (as in portal cirrhosis). Moreover, my experiments shewed me, that the condition could not be produced by absorption of blood from elsewhere. Hence, I concluded that it denoted an excessive destruction of blood; moreover, that the liver was specially concerned in this destruction.

[1] W. Hunter. "Intraperitoneal Transfusion of Blood, and the Fate of Absorbed Blood: An experimental Research." *Journal of Anatomy and Physiology*, xxi., 1887.

"The three great seats of blood destruction are the *Liver*, the *Spleen*, and the *Bone marrow*. The evidence of a blood-destroying function on the part of the liver under normal circumstances is mainly functional in its nature—namely, formation of bile pigments, perhaps also of urea; under abnormal circumstances, however, it is also histological and chemical, namely, accumulation of pigment within the liver cells, and greater richness of the liver in free iron."

"In health an accurate balance is maintained between the amount of blood destruction going on in the liver and spleen respectively. Any disturbance of this relation on the part of the liver is liable to be followed by much more serious consequences, (*e.g.* Pernicious Anæmia) than any disturbance on the part of the spleen; the reason being, that the destructive process within the liver is of a much more active character than that within the spleen. Pernicious anæmia is not a disease, but only the result of disease, being due to increased—morbid activity—on the part of one of the blood-destroying organs—the liver."[1] (1886).

From this time forward my studies, formerly directed to the mode of origin and source of blood pigment in general, became directed more particularly to the remarkable distribution of pigment in pernicious anæmia, focussing as this appeared to do all the problems connected with blood pigment in particular, and blood destruction—its nature and seats—in general. Examination of material from six cases of pernicious anæmia kindly furnished me (1887) by Dr. Byrom Bramwell, and from three other cases, satisfied me that the excess of pigment was *constant*; and comparative studies of the liver in various diseases characterized by more or less profound anæmia—*e.g.* typhoid fever, chronic Bright's disease, tubercular and syphilitic disease, phthisis, empyema, chronic suppurations, malignant disease; also Addison's disease, diabetes, leucocythæmia; also diseases of the liver itself, *e.g.* acute yellow atrophy, toxic poisoning, portal cirrhosis, chronic venous congestion ('nutmeg liver'), fatty degeneration; —satisfied me that, in its degree, it was *characteristic*.

[1] Wm. Hunter. "The Physiology and Pathology of Transfusion: and the Fate of Extravasated Blood." Gold Medal Thesis, University of Edinburgh, 1886.

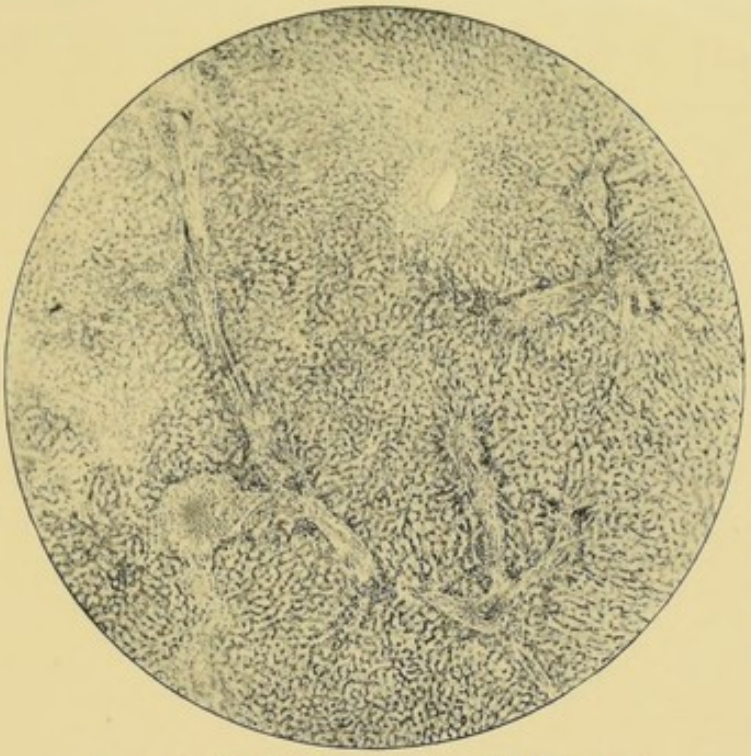


FIG. 1.—LIVER IN PERNICIOUS ANÆMIA. × 25.

Showing the extraordinary excess of blood pigment; its uniform distribution amongst the lobules; its special abundance in the outer two-thirds of the lobule; and its situation within the hepatic cells. Unstained. Treated with ferrocyanide of potassium and hydrochloric acid. (Prussian blue reaction.) The darker portions represent blood pigment.



FIG. 2.—LIVER IN PERNICIOUS ANÆMIA. × 25.

Showing the great excess of blood pigment; its uniform distribution amongst the lobules; its special abundance in the periphery of the lobules; and the fatty degeneration of the centres of the lobules.

The condition was thus not a mere wasting of the corpuscles ("*hæmophthisis*") common to this and other forms of anæmia, as Quincke appeared to suggest; nor could it, in the light of the studies of certain observers (1883-1884), regarding the effect on the liver of iron administered by the mouth, be reasonably ascribed to deposit of iron from that source. Moreover my own special studies shewed that it could not be ascribed to absorption of extravasated blood either in the liver, or elsewhere. Hence the conclusion above formulated, that the excess denoted an actual destruction of blood as *the most constant*, and —in regard to all the forms of anæmia (*secondary*, *symptomatic*) liable to be mistaken for it during life, *e.g.* the anæmia of malignant disease, loss of blood, etc.,—an *absolutely distinctive* feature of pernicious anæmia. Hence this excess of pigment seemed, at the very outset of my observations, to deserve special attention. The result of these observations with regard to the significance of this condition of the liver I shall now give.

Excess of Blood Pigment.

Amount.—This varies in different cases. In all cases it is large: in some, quite extraordinarily abundant. The thinnest sections of the liver, prepared for histological purposes, on being placed first in a solution of ferrocyanide of potassium, and then in a *dilute* solution of hydrochloric acid (2 per cent.), yield *at once* the marked blue reaction of free iron (Prussian blue), or *blackened* if placed in sulphide of ammonium solution. Sections of the liver from cases of malignant disease, loss of blood, and wasting diseases generally, similarly treated, yield either no reaction, or at most the faintest blue; and that only after lying in the acid for some time. In the case of pernicious anæmia, the liver section reveals, on microscopic examination, all the individual particles of pigment stained a deep blue colour. In the other sections, the faint blue coloration recognizable by the naked eye is hardly distinguishable on microscopic examination; it appears to be due rather to the disintegrating action of the acid on the iron normally present in the hepatic tissue, than to any pigment particles present. Hence in no case, when comparing conditions in the two cases, should

the acid used be strong, or the exposure to its action be long.

For a similar reason, in no case should comparisons be made betwixt the degree of colour reaction given by larger pieces of liver, placed in the appropriate solutions. A piece of liver allowed to lie in the test solution will always give a degree of colour reaction, either black or blue, as the case may be—due to the normal presence of iron in the liver tissue, especially when the reagent is a strong acid. And this colour reaction, however slight it be, will appear to be stronger when seen in a bulk of tissue. This is an error frequently made, and it must be avoided if the relative abundance of pigment in the liver in these cases is to be properly appreciated by micro-chemical tests.

Distribution.—The distribution of the pigment is uniform throughout the organ—*i.e.* in every lobule—and not irregularly distributed at different parts, as one finds it in cases of portal cirrhosis (figs. 1 and 2, Plate II.).

This peculiar *distribution* serves to distinguish this pigment accumulation in the liver from that found in cases of cirrhosis, where extravasations of blood are so often met with. The pigment is there found in irregular masses, made up of granules and globules of pigment of the most varying size, lying around the lobule in the perilobular connective tissue. The distribution of the pigment masses is simply determined by the site of the original extravasations (fig. 1, Plate IV.).

Relation to Lobule.—It is always most abundant in the outer part—generally the outer two-thirds of the lobule—; in which it contrasts with the condition found in the 'nutmeg liver,' where any pigment due to extravasation, that may be present, is confined to the central zone of the lobule.

This *situation* of the pigment in cases of pernicious anæmia serves at once to distinguish this condition of the liver from that found in chronic venous congestion. In this latter condition it is also common to find pigment in the liver; but it is found most abundant around the central vein of the lobule, and may be entirely confined to this situation, the liver cells at the periphery of the lobule being free from pigment. Moreover, an even more marked distinction exists—viz., that in chronic

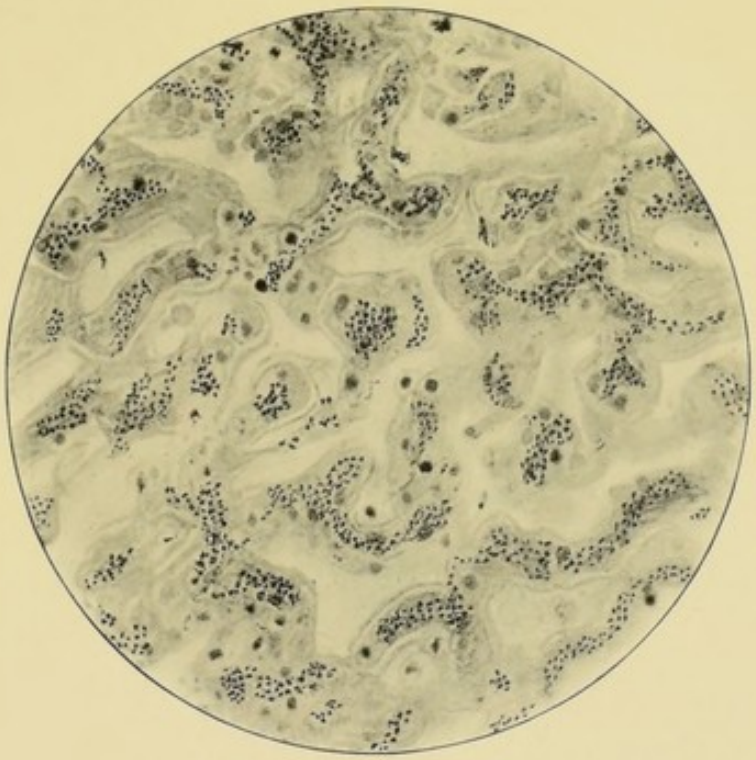


FIG. 1.—LIVER OF PERNICIOUS ANÆMIA. × 350.
Showing character and distribution of blood pigment—most abundant in the liver cells; very little in the capillaries.



FIG. 2.—LIVER OF PERNICIOUS ANÆMIA. × 300.
Showing the situation of the granules of pigment in relation to the bile capillaries.

venous congestion the pigment never gives any reaction of iron with the ordinary micro-chemical reagents.

Relation to the Liver Cells. — The pigment lies within the liver cells ; in some cases almost exclusively there, hardly a particle being found in the capillaries ; in all cases, most abundantly there. In some cases, it is also found in the capillaries, either within the leucocytes or within the endothelial cells lining the capillary walls. The pigment occupies the centre of the hepatic columns, and appears to be situated in the middle of the liver cells. On examination it is found to lie to one side of the liver cell, adjacent to the bile capillaries (figs. 1 and 2, Plate III.).

Character of the Pigment.—The pigment is in the form of yellow granules, varying somewhat in size in different cases, but in each instance fairly uniform in size (1–2 μ). It is rich in iron, and gives the iron reaction readily. This latter character serves as a further distinguishing feature betwixt it and the pigment found in chronic congestion of the liver. In the latter, the pigment gives no reaction of iron with micro-chemical reagents.

As the result of all these changes in well-marked cases the whole appearance of the liver lobules is transformed. The liver cells in the outer two-thirds of the lobule are usually filled with minute pigment granules, all giving the characteristic reaction of iron ; while the cells in the central third of the lobule usually show marked fatty degeneration and atrophy, and the yellow pigment granules often found within them fail to give any reaction of iron (figs. 1 and 2, Plate II.).

Micro-chemical Tests for Iron.—The presence of this pigment is, as already stated, most easily determined by placing a piece of the tissue in a fresh solution of *sulphide of ammonium.* The reagent at once darkens all pigment, whether in diffuse or granular form, in which iron is present in loose combination, most usually in the form of an albuminate. Iron as it is present, intimately bound up in the hæmoglobin molecule, is not affected by this reagent. Hence the colour reaction obtained is in no way affected by the richness of the organ or tissue in blood—a matter of the greatest importance where, as is often the case, the organ is congested. This test is the best for fresh tissues.

An equally valuable micro-chemical reagent is *ferrocyanide of potassium with hydrochloric acid*; this gives, with such pigment, a beautiful blue reaction (Prussian blue reaction). In using this reagent, two precautions are essential. (1) The solution of the ferrocyanide should be freshly prepared; (2) only *a dilute* solution, 2 per cent., of the acid should be employed, and the tissue should be exposed to action for half a minute or a minute. Prolonged contact with strong hydrochloric acid develops in time a blue reaction, even with ordinary tissues, owing to the iron they contain; still more with hæmoglobin.

With either of the above reagents, and with the precautions already indicated as to using thin sections, there is no difficulty in at once recognizing the extraordinary excess of pigment in the liver in cases of pernicious anæmia.

Significance of this Excess.—As already stated, my observations dispose me to attach quite a special significance to this condition.

(1) It cannot, I consider, be ascribed to the administration of iron during life. The observations of Kobert,[1] of Cahn,[2] and of Glavecke[3] all agree in shewing that the richness of the liver, in iron is in no way affected by the administration of that drug by the mouth, and only slightly by its subcutaneous injection. (Glavecke).

> After the injection of iron into the blood, the metal could be found abundantly in the epithelial cells of the convoluted tubules of the kidney, and in their lumen, as early as half an hour afterwards, never, however, in the glomeruli, and not in all the convoluted tubules. After the internal administration of the drug, no absorption of the metal took place. (Kobert.)

> Cahn found, with regard to manganese, that no absorption of this metal took place from the intestine.
>
> Kobert experimented on rabbits (twenty in number), administering doses of 0·12 to 1 gramme of iron salts (citrate of iron, chiefly). The greatest excretion took place through the kidneys; less

[1] *Archiv f. exper. Pathol. u. Pharmak.*, Bd. xvi., 1883, p. 390.

[2] *Ibid.*, "Resorptions- und Aus-scheidungsverhältnisse des Mangans im Organismus," Bd. xviii., 1884, p. 146.

[3] *Ibid.*, "Ueber Subcutane Eiseninjectionen," Bd. xvi., 1883, p. 469.

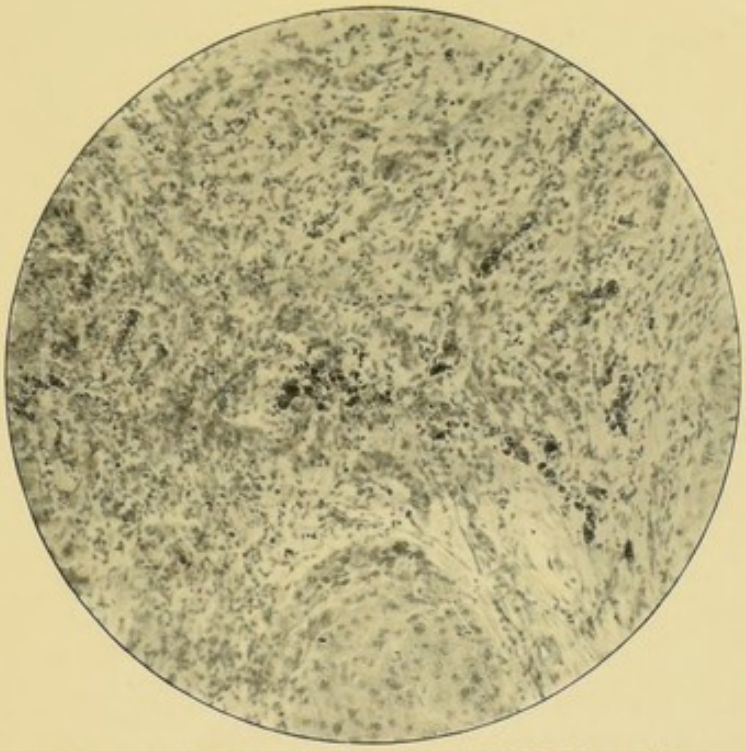


FIG. 1.—LIVER FROM A CASE OF CIRRHOSIS. × 150.

Showing at one part irregular pigment heaps as the result of local extravasations. The pigment is represented by the darker masses.



FIG. 2.—LIVER OF MALARIA (*Low Power View*).

Showing the irregular size and distribution of the pigment particles. The darker masses represent clumps of pigment within the capillaries.

See also Plate facing page 156.

through the liver; none at all through the pancreas, stomach, salivary glands, or intestine. In the kidney the secretion commenced half an hour after injection, reached its height in two to four hours, and ended by the twenty-fifth hour. Four to six hours after the injection, there was always an increase in the iron of the bile. In the *kidneys*, the glomeruli were always found free from iron. From one to nine hours after the injection the convoluted tubules contained iron, not only in the lumen, but in the form of fine granules within the cells themselves always lying close to the lumen, not—as Quincke found in pernicious anæmia—in the deeper part of the cells. After the ninth hour only a few convoluted tubules, especially those near the surface, contained iron lying in the lumen, sometimes in large masses, sometimes in the form of larger or smaller granules, lying close to the edge of the epithelial cells. The iron was excreted through the activity of the epithelial cells. *Liver.*—Till the ninth hour, all the cells were diffusely coloured, containing more or less fine granules. Later, only the cells of the peripheral parts of the lobule were diffusely coloured *without granules*; and still later, only a few irregularly scattered liver cells were diffusely stained.

He considered that the iron in solution was taken up by the liver cells and combined there with albumins to form albuminates of iron, which remained in the form of granules. This, however, was only temporary; the iron passed again into solution, and was excreted in the bile. The excretion did not take place in all cells, or to an equal extent in all. The injections had no influence on the amount of iron in the *spleen* and *bone marrow*.

The source of the pigment in the liver in pernicious anæmia can therefore only be the hæmoglobin of the blood.

(2) The question then arose, whether this excess of iron in the liver stood in any causal relation to the peculiar features of the anæmia, or was merely the result of some general weakness of the red corpuscles common to this and other forms of anæmia. I therefore made a large number of observations on the liver in various diseases, with a view to determine how far an excess of pigment in the liver was common to all forms of anæmia alike, varying merely in different cases according to the degree of anæmia present. If the richness of the liver in iron was merely an indication of some weakness on the part of the red corpuscles common to the corpuscles and other tissue elements of the body, it might be expected that in other conditions of anæmia—*e.g.*,

wasting diseases,—marked by failure in nutrition, a similar condition of the liver would be found.

With regard to this question how far the excess of pigment is merely the result of a general *weakness of corpuscles* common to this and other forms of anæmia, my observations supply a very definite answer. The conditions which should, in respect of abundance of pigment in the liver, most closely approach pernicious anæmia, would be such as malignant disease, or wasting disease, which *clinically* are regarded as resembling most closely pernicious anæmia. On the contrary, it is precisely these conditions which I find offer the greatest contrast to pernicious anæmia. My observations shew, and Peters' observations agree therewith in this particular, that *it is precisely in these conditions that the liver generally gives no reaction* of iron at all.

Even with regard to other conditions, in which the liver gives some iron reaction—*e.g.* chronic Bright's disease—there is, I consider, a very marked contrast between the two conditions. The reaction in such a disease is, in my experience, very slight, hardly to be compared with the condition in pernicious anæmia. On this ground, the grouping adopted by Peters tends to lead to error. For all his cases are grouped together, according as they give, or do not give, an iron reaction, irrespective of the *amount* or *distribution* or *general characters* of the pigment present. His observations appear to shew that some excess of iron in the liver, recognizable even on micro-chemical examination, is a condition by no means peculiar to pernicious anæmia, but is met with in a very considerable proportion of cases (44 per cent.). Thus cases of cirrhotic Bright's disease are grouped on the one hand with cases of pernicious anæmia, and on the other with cases of purpura hæmorrhagica. But the amount of pigment in the first of these diseases is, in my experience, so small as scarcely to give any appreciable reaction ; while in the latter the liver often contains a very large quantity of pigment, quite easily distinguishable by its distribution from pernicious anæmia.

In purpura hæmorrhagica the pigment is found in large irregular heaps, scattered irregularly throughout the liver. In pernicious anæmia the pigment is in the form of fine granules, lying for the most part within the liver cells and distributed

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uniformly throughout the liver, and confined for the most part to the outer two-thirds of each lobule.

The observations of Peters are therefore likely to lead to a wrong conclusion if they are regarded as indicating that in 44 per cent. of cases the liver contains any excess of iron at all comparable with that present in pernicious anæmia. It would be an analogous case to deny to the atrophy of progressive muscular atrophy any special significance, because *some* degree of atrophy is also characteristic of typhoid fever, phthisis, or diabetes.

Conclusion.

The excess of pigment in the liver in pernicious anæmia is thus, according to my observations, neither the result of congestion, nor simply a result of profound anæmia of like character to, only exceeding in degree, that found in ordinary anæmia. On the contrary, it is a feature so constant and so marked that it must be regarded as standing in direct causal relation to the peculiar features presented by the anæmia itself. In no disease *liable clinically to be mistaken for pernicious anæmia* does the richness of the liver in pigment and iron approach that *constantly present* in pernicious anæmia. And this is especially true of those forms of anæmia associated with wasting disease, regarded by Dr. Coupland and other observers as the symptomatic, deuteropathic, or secondary forms of pernicious anæmia. My observations shew, that *the liver in these cases shews no excess of pigment at all.* This difference is, I find, sufficient to enable one, on *post-mortem* examination, to distinguish between a true case of pernicious anæmia, and those forms of anæmia which resemble it *in degree of pallor* most closely during life, namely, the anæmia of malignant disease and of loss of blood.

CHAPTER VII.

CHANGES IN THE LIVER—(*continued*).

Results of Chemical Analysis.

It was of interest, in connection with these conclusions, based on the results of micro-chemical tests, to ascertain how far their accuracy was borne out by actual chemical analysis in these cases. It was conceivable that the differences, as revealed by micro-chemical tests, might be apparent rather than real: that they might be due to the fact that in the one case (pernicious anæmia) the iron was in a form (blood pigment) which could be detected by micro-chemical tests, while in other conditions the iron might be no less abundant, but more intimately bound up, so as not to give any micro-chemical reaction.

Micro-chemical tests, it was true, had this great advantage, that the presence of blood in the organ in no way affected the reaction. On the other hand, they had the disadvantage of not being sufficiently delicate to detect the presence of exceedingly minute quantities of iron, especially if these were organically bound up, as in protoplasm or in hæmoglobin.

To determine this point, I collected and made a study of all the analyses of the liver made with regard to the percentage of iron in the liver in various diseases, including pernicious anæmia. These are thirty-three in number, and have been arranged and summarized in the following Tables (I.–VIII.).

[Tables I.—VIII.

TABLE I.—*Analyses shewing Percentage of Iron in the Liver and Spleen in Health and various Diseases.* (1875–1888.)

No.	Various Diseases.	Percentage of Iron (per 100 parts dry substance).		Observer.
		Liver.	Spleen.	
1	Burn, with marked anæmia; spleen enlarged, . .	0·031	0·252	Stahel.[1]
2	Fracture of base of skull, .	0·167	0·217	,,
3	Fracture of sternum, and injuries, . . .	0·201	0·268	,,
4	Marasmus; nutmeg liver; congested spleen, . .	0·075	0·062	,,
5	Pneumonia; diphtheria, .	0·041	0·138	,,
6	Pneumonia; gangrene of lung, ...	0·048	0·163	,,
7	Pleurisy; bronchitis; nutmeg liver; congested spleen, . . .	0·038	0·125	,,
8	Hæmorrhage medulla oblong, . . .	0·044	0·084	,,
9	Leukæmia, . . .	0·102	0·329	,,
10	*Anæmia*, ...	**0·614**	**0·091**	,,
11	Mental disease, . .	0·081	...	Oidtmann.[2]
12	Syphilis neonati, . .	0·103	...	,,
13	Leukæmia, . . .	0·055	...	v. Bemmelen.[3]
14	,, ...	[0·396]	...	Graanboom.[4]
15	Pneumonia, . . .	0·099	...	,,
16	Burn, ...	0·039	...	,,

[1] *Virch. Archiv*, Bd. lxxxv., 1881, p. 26.
[2] Quoted by Zaleski, *Zeitschrift für physiol. Chemie*, Bd. x., 1886, p. 477.
[3] *Ibid.*, Bd. vii., 1883, p. 497.
[4] *Archiv für exper. Pathol. u. Pharmak.*, Bd. xv., 1882.

TABLE I.—*continued.*

No.	Various Diseases.	Percentage of Iron (per 100 parts dry substance).		Observer.
		Liver.	Spleen.	
17	Phthisis, ...	0·114	...	Graanboom.[1]
18	Nephritis, . . .	0·129	...	,,
19	Carcinoma uteri, . .	0·023	...	,,
20	*Pernicious anæmia*, . .	1·890	...	Quincke.[2]
21	,, ,, . .	0·539	...	,,
22	,, ,, . .	0·364	...	,,
23	,, ,, . .	2·1	...	,,
24	,, ,, . .	0·6	...	,,
25	Cachexia, . . .	0·294	...	,,
26	Typhus; hydroceph., .	0·581	...	,,
27	Diabetes mellitus, . .	(3·607)	...	,,
28	Human fœtus (8 months),	0·147	...	Zaleski.[3]
29	Diabetes mellitus, . .	0·068	...	,, [4]
30	Purpura hæmorrhagica, .	0·036	...	,,
31	*Pernicious anæmia*, . .	0·623	...	,,
32	Purpura hæmorrhagica, .	(1·24)	...	Hindenlang.[5]
33	*Pernicious anæmia*, . .	0·518	0·227	Rosenstein.[6]

[1] *Archiv für exper. Pathol. u. Pharmak.*, Bd. xv., 1882.

[2] *Deutsch. Archiv für klin. Med.*, Bd. xx., 1877, p. 1; Bd. xxv. p. 567; Bd. xxvii., 1880, p. 193; Bd. xxxiii., 1883, p. 22.

[3] *Zeitschrift für physiol. Chemie*, Bd. x., 1886, p. 474.

[4] *Virch. Archiv*, Bd. civ., 1886, p. 91.

[5] *Ibid.*, Bd. lxxix., 1880, p. 492.

[6] *Berl. klin. Wochensch.*, 1877, p. 113.

Summary.

TABLE II.—*Average Percentage of Iron in Liver in various Diseases other than Pernicious Anæmia.*[1]

Observer.	No. of Analyses.	Percentage of Iron.	Highest and lowest percentages.
Stahel, . . .	9	0·083	0·031 to 0·201
Oidtmann, . .	2	0·092	0·081 to 0·103
V. Bemmelen, .	1	0·055	...
Graanboom, . .	5	0·081	0·023 to 0·129
Zaleski, . . .	3	0·083	0·036 to 0·174
Total . .	20	0·078	0·023 to 0·201
Quincke, . .	3	1·494	0·294 to 3·607

[1] No. 32 has not been included in this list. From the account of the case, the pigment of the liver was due to extravasations such as are not infrequent in cirrhosis of the liver.

TABLE III.—*Percentage of Iron in the Liver in Pernicious Anæmia.*[1]

Observer.	No. of Analyses.	Percentage of Iron.	Other Diseases.	
			No. of Analyses.	Average Percentage.
Stahel, . .	1	0·614	9	0·083
Rosenstein, .	1	0·518	...	...
Zaleski, .	1	0·623	3	0·083
Total, .	3	0·585	12	0·083
Quincke, .	5	1·098	3	1·494

[1] No. 14, reported by Graanboom, is not included in this list, as it is not clear whether it should be in the group of anæmia or in that of general diseases.

TABLE IV.—*Percentage of Iron in the Liver in Wasting Diseases.*

OBSERVER.	Disease.	Percentage of Iron.
Stahel (No. 1),	Burn with marked Anæmia, .	0·031
„ („ 4),	Marasmus, ...	0·075
„ („ 16),	Burn, ...	0·039
Graanboom („ 17),	Phthisis, ...	0·114
„ („ 18),	Nephritis, ...	0·129
„ („ 19),	Carcinoma uteri, . . .	0·023
	Average,	0·068

TABLE V.—*Percentage of Iron in Nutmeg Liver.*

OBSERVER.	Percentage of Iron.
Stahel (Case 4), . . .	0·075
„ („ 7), . . .	0·038
Average,	0·056

TABLE VI.—*Percentage of Iron in the Liver in Leukæmia.*[1]

OBSERVER.	Percentage of Iron.
Stahel (Case 9), . . .	0·102
v. Bemmelen (Case 13), .	0·055
Average,	0·078

[1] See Footnote, Table III.

TABLE VII.—*Percentage of Iron in the Liver in Purpura Hæmorrhagica.*

OBSERVER.	Percentage of Iron.
Zaleski (No. 30), . .	0·036
Hindenlang („ 32), . .	1·240
Average,	0·638

TABLE VIII.—*Percentage of Iron in the Liver in Acute Diseases.*

OBSERVER.	Disease.	Percentage of Iron.
Stahel (No. 5),	Pneumonia; diphtheria, . .	0·041
„ („ 6),	Pneumonia; gangrene of lung,	0·048
„ („ 7),	Pleurisy; bronchitis, . .	0·038
Graanboom („ 15).	Pneumonia, ...	0·099
	Average,	0·056

Results.

General Diseases.—In the group of general diseases (Table III.) the analyses number twenty-five. Excluding two, whose nature is open to question (Nos. 19 and 26), the analyses are twenty-three in number, three by Quincke, and twenty by other observers.

In this latter group of twenty analyses, *the average percentage of iron in the liver was* **0·078** varying from 0·023 to 0·201. In seventeen of these, made by three observers—Stahel (9), Graanboom (5), and Zaleski (3)—the average percentages obtained are, remarkably enough, almost identical, namely, 0·083, 0·083, and 0·081.

The three analyses of Quincke, in marked contrast, give a much higher average, namely, 1·494; the lowest being 0·294, and the highest (diabetes mellitus) the amazing percentage of 3·607. This latter figure is so high, as to suggest some probable error, as has also been pointed out by Zaleski.

Pernicious Anæmia.—The analyses in cases of pernicious anæmia (Table III.) number only eight: five by Quincke, and three by Stahel, Rosenstein, and Zaleski.

The percentages in these three were **0·614, 0·518,** *and* **0·623**—*average* 0·585.

This percentage is in strong contrast with an average in other diseases obtained by these observers of 0·083, (Stahel), and 0·081, (Zaleski).

The five analyses of Quincke, on the other hand, are again, oddly enough, in marked contrast, in yielding a much higher

average, namely 1·098: this contrasting with an average for other diseases, obtained by this observer, of 1·494.

> The average of twenty analyses in twenty cases other than pernicious anæmia—0·078—thus contrasts with an average of 0·585 in three of pernicious anæmia. This represents a very large increase—more than sevenfold—in favour of pernicious anæmia.

Comparisons of this kind are of most value, when the analyses in both instances have been made by the same observer. The percentage richness of the organ in iron is to some degree determined by the richness of the organ in blood, at the time the chemical analysis is made. Hence the results obtained may vary considerably in the hands of different observers, according to the degree of care taken to remove all the blood from the organ, previous to the analysis being made. This is a matter of difficulty in the case of most organs, and can only be successfully accomplished by the method adopted by Zaleski of washing out the fresh organ through its vessels.

The necessity for precautions in this respect has probably not been equally present to the minds of all observers; and if one may judge from the results of his analyses, to Quincke least of all. In nearly every case, his analyses give a notably higher percentage than that obtained by other observers for all conditions. For purposes of comparison, therefore, I prefer to keep Quincke's analyses by themselves; and although this reduces very considerably the number of analyses available for comparison, two or three analyses of a trustworthy nature are of more weight than a number of possibly very unequal value.

Hence I am inclined to attach most importance to the analyses of Stahel and Zaleski. In twelve analyses made by these two observers the average percentage of iron in the liver in various diseases was precisely the same—viz., 0·083. In two cases of pernicious anæmia the percentage obtained was also much the same—viz., 0·614 and 0·623; and the analysis of Rosenstein gave a closely similar result—viz., 0·518 per cent. This represents a more than sevenfold increase in pernicious anæmia, and this result I am inclined to regard as more probably representing the average extent of increase in this disease than the one arrived at when Quincke's analyses are also included.

These observations I regard as establishing the following conclusions:

(1) That the amount of iron contained in the liver in pernicious anæmia is far in excess of that met with in any condition at all resembling it;

(2) That the presence of this excess can no longer, as hitherto, be regarded as an accidental condition—the result of some weakness of the corpuscles common to all forms of anæmia alike, and only varying in degree in different cases.

On the contrary, this condition of the liver appears to me clearly to indicate—and this I would regard as one of the most important results of my study of the morbid anatomy of this disease—that:

(1) A destruction of blood occurs in pernicious anæmia, far greater than that met with in any other form of anæmia presenting clinically any resemblance to it, or liable to be mistaken for it, notably the anæmia of wasting disease and loss of blood.

(2) The liver must be regarded as playing an important part, if not in the destruction itself, at least in the disposal of the remains of the pigment.

Distribution of the Pigment between Liver and Spleen.

Further evidence of the importance of the part taken by the liver in the disposal of the products of the blood destruction in pernicious anæmia is afforded by contrasting, as regards richness of iron, the condition of the liver with that of the spleen —the other organ of the body most closely concerned in the disposal of remains of pigment.

I find from Stahel's analyses, (Table I.) that in most diseases the relation between the liver and spleen, as regards richness in iron, remains the same as in health, viz., that the percentage richness of the spleen usually considerably exceeds that of the liver. His analyses (nine in number) give an average of **0·171** per cent. *for the Spleen*, as contrasted with **0·083** per cent. *for the Liver*. In one case only, was the percentage in the spleen slightly less; in most cases it was more than double, and in a few cases it was five or six times greater than in the liver.

I have already stated that, as determined by micro-chemical

examination, the spleen in my own cases of pernicious anæmia contained little excess of iron; and that, in three cases, it appeared to contain less iron than usual. Only two analyses have been made of the spleen in cases of pernicious anæmia; but the results so strikingly agree with those of qualitative micro-chemical examination, that I regard them as confirming the conclusion, that a marked disturbance, as regards richness of pigment, occurs in the relation of liver and spleen to each other, in cases of pernicious anæmia. Thus, in Rosenstein's case, the percentage of iron in the *Liver* was **0·518**, while that in the *Spleen* was only **0·227** per cent.—less, therefore, than one-half; and in Stahel's case, the *Liver* contained **0·614** per cent. of iron, while the *Spleen* contained only **0·091** per cent.—less than one sixth.

In pernicious anæmia, therefore, the relative richness of the liver and spleen in iron appears to be transposed, and that, too, in a very striking way.

It is necessary to bear in mind that these analyses express merely the percentage of iron per 100 parts of dried substance; and that, if the spleen were greatly enlarged, it is quite conceivable that a considerable excess of iron might be contained in the whole organ as compared with that normally present, without that excess in any way appearing in the results obtained by analysis. But no such gross enlargement is met with. Hence the results of these analyses must, I think, be regarded as strengthening the conclusion that the increase of iron in the liver in pernicious anæmia is significant, inasmuch as it is not only absolutely, but (as regards the spleen) still more relatively, great.

The result is not a little surprising. As we have seen, little or no importance has hitherto been attached to the presence of pigment in the liver in this condition. It has been held to indicate merely some general weakness and premature decay of the red corpuscles, the accumulation of the remains of their pigment taking place in organs, such as the liver, usually concerned in the disposal of such products. Or at most, its presence in certain cases has been taken as evidence that in that particular case of pernicious anæmia, blood destruction has been in excess. (Quincke).

According to such a view, one would naturally expect to find an increase in the amount of pigment in the spleen, at least in some degree proportionate to that found in the liver. For all observers are agreed, that the spleen plays an important part in storing up pigment particles circulating in the blood (Ponfick); and my own observations, after transfusion of blood, shew that the spleen is a special seat for the deposition of pigment, and contains, under these circumstances, more than the liver.

In pernicious anæmia, on the other hand, not only is there no proportional increase in the pigment of the spleen; but on the contrary, the sevenfold increase in the iron of the liver is unaccompanied by any increase at all in the amount contained in the spleen. So far as I am aware, this disturbance in the relation of the two organs to each other, as regards their richness in iron, has not before been drawn attention to. Taken in conjunction with the great increase in the amount of iron in the liver, it undoubtedly serves, to my mind, to accentuate considerably the importance to be attached to this peculiar condition of the liver as one of the most essential pathological changes, if not the most essential, to be found in this disease.[1]

[1] This conclusion is confirmed by the analyses, which will be found in Chap. IX.

CHAPTER VIII.

CHANGES IN THE KIDNEY.

Author's Observations.

To the anatomical changes already described, it remains to be added, that some *excess of pigment* is occasionally to be found in certain other organs in cases of pernicious anæmia. This is specially true of the kidney, (Quincke); only, however, in a certain number of cases.

Its presence seems to be inconstant.[1] When present, the pigment is in the form of small, yellow spherical granules or globules, lying for the most part within the cells of the convoluted tubules, rarely within the lumen of the tubule itself. It is not found in all the convoluted tubules. Both in its appearance and in its situation it differs entirely from the pigment of extravasation. It only gives a somewhat imperfect, though easily recognizable, reaction of iron with micro-chemical methods. The quantity present varies much in different cases: in some, in which a very large excess is contained in the liver, it may be absent altogether from the kidney. In no case have I found it lying within the glomeruli. Within the renal cells of the convoluted tubules, it presents the appearance of hæmoglobin of the blood in process of excretion (see Frontispiece).

Changes in the Kidney in Pernicious Anæmia.—The following description of a *typical* case of the disease may be taken as

[1] [It will be seen from my subsequent analyses given in Chap. IX. that this statement must be farther qualified. I have found it just as constant as, and proportionately even greater than the excess in the liver, the percentage of iron being on an average about twentyfold greater than that of the normal kidney.]

applying to all the other cases (twelve in number) which I have so far had the opportunity of examining, in which pigment has been present.

On placing sections first in a solution of ferrocyanide of potassium and afterwards in dilute hydrochloric acid, a well-marked blue reaction is developed in the cortex, most marked close to its periphery.

On microscopic examination this change is found to be due

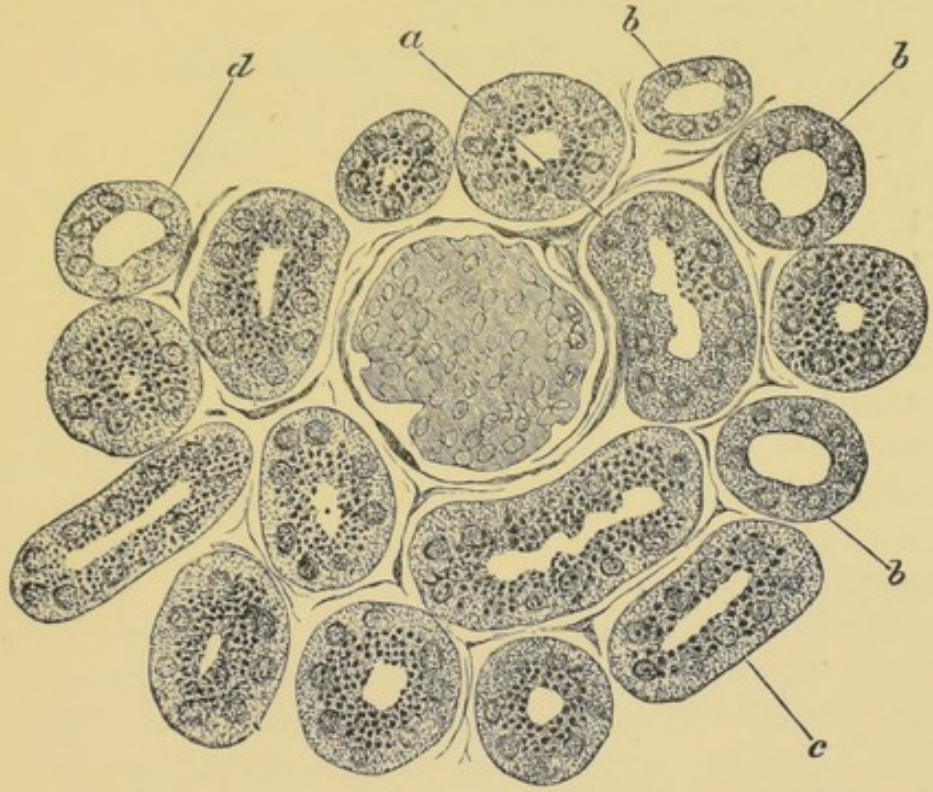


FIG. 1.—SECTION OF THE KIDNEY IN PERNICIOUS ANÆMIA: BLOOD-PIGMENT IN PROCESS OF EXCRETION THROUGH THE EPITHELIUM OF THE CONVOLUTED TUBULES.

a, Normal convoluted tubule, one cell shewing traces of pigment; *b*, ascending limb of Henle's loop; *c*, convoluted tubule, pigment lying within the epithelium; *d*, descending limb of Henle's loop.

to the presence of pigment lying within certain of the tubules, and giving the characteristic reaction of free iron. The pigment is in the form of fine granules, the individual granules being of spherical shape and fairly uniform in size, their diameter varying 1 to 2 μ.

The distribution of the pigment amongst the tubules is peculiar. It seems to be confined to the convoluted tubules, the deeper blue coloration of the cortex being due to the presence of

pigment in the tubules in this region. More careful examination shews that this is the case: all the pigment is to be found within the convoluted tubules, and is fairly equally distributed between their primary and secondary convolutions.

A small trace of pigment is also seen at certain portions of Henle's loops, those portions, namely, whose epithelium most closely resembles in character that of the convoluted tubules. With this exception, the loops of Henle are free from pigment granules. Their epithelium presents at most a faintly bluish and diffuse coloration. The same faintly bluish tint is to be observed in the epithelium of the angular tubules.

In the collecting tubes not a trace of pigment of any kind, either in diffuse or in granular form, is to be seen; and the same holds true of the glomeruli.

It is to be noted that the convoluted tubules do not all contain pigment. The amount varies much; while some are free, others contain very varying quantities. In all cases alike, the pigment lies within the cells of the tubules, not free within the lumen, unless, as sometimes is the case, the cells have become detached. In some of the convoluted tubules the pigment appears to fill up the lumen, an appearance seen, on closer examination, to be due to the circumstance that the pigment lies close to the unattached free border of the cells (see figure).

With the exception of the presence of this pigment, the kidney shews nothing abnormal. The cells, even those containing the pigment, often shew no signs of degeneration, their nuclei staining readily. In other cases, however, they are fattily degenerated. Some of them may be detached.

I conclude from the appearances, that hæmoglobin has been in process of excretion through the epithelium of the convoluted tubules, and that while in process of excretion it has assumed a granular form. In passing through the cells, the hæmoglobin has undergone disintegration, and become converted into blood-pigment. The bluish tint of the epithelium in certain parts of Henle's loops, denoting the presence of iron, I judge to be due rather to the absorption of some iron-containing constituent of the urine passing along the tubules, than to any excretion of iron by them. A similar blue appearance I have found presented by the kidney epithelium in ordinary hæmoglobinuria.

CHAPTER IX.

HÆMOLYTIC NATURE OF THE DISEASE.

Summary of Anatomical Observations.

THE anatomical changes found more or less constantly in patients dying of pernicious anæmia have now been described, and may here be summarized.

It will be seen that they are most constantly to be found in those organs of the body concerned either in blood formation or blood destruction—viz., the spleen, the bone marrow, and the liver; or in those organs concerned in excretion—viz., the liver and kidneys.

Of these changes, *the most marked are those which point to some disorder of blood destruction as the most constant pathological feature of this form of anæmia.*

In their order of frequency these changes are to be found (*a*) constantly in the liver, (*b*) more or less constantly in the spleen, (*c*) very frequently, though not constantly, in the bone marrow, (*d*) not infrequently in the kidneys.

In the case of the liver, bone marrow, and kidneys, the changes consist of the presence of an excess of pigment derived from the blood; in the case of the spleen and bone marrow the evidences of this blood destruction are best recognizable on examination of the fresh tissue, and consist for the most part of morphological changes in the corpuscles and plasma, or of the presence of free hæmoglobin.

Nature of Pernicious Anæmia.

We are now in a position to consider what the pathology of this form of anæmia is. Do the changes in the blood, so

marked a feature of the disease, result from a profound disturbance in hæmogenesis, or are they to be traced to some equally marked disorder of hæmolysis?

The answer to this question has already been in part supplied by the consideration just given to the anatomical changes most commonly found.

As regards the *Blood-forming organs*, I find nothing to explain why pernicious anæmia should differ so markedly from other forms of anæmia.

In the case of the *Spleen* and *Lymphatic Glands*, there is little or no evidence of any failure of blood-forming function, [unless the sparing presence of nucleated red corpuscles in the former be considered as such].

In the *Bone marrow* the evidences of this kind are still more marked—viz., the presence of large numbers of *nucleated red corpuscles*. The presence of these corpuscles in such large numbers has been interpreted as pointing to some failure or imperfection in the blood-forming function on the part of this tissue—some interference with the proper development of the red corpuscles. The appearances may, I consider, be interpreted in another and entirely different way,—viz., as pointing to an excessive activity on the part of this tissue in blood formation, such as is met with, for example, after loss of blood. So far from pointing to any interference with blood formation, the presence of nucleated red corpuscles rich in hæmoglobin seems to my mind rather to indicate that the conditions are by no means so unfavourable to blood formation as is often assumed. Their presence in such numbers points, undoubtedly, to 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 time of death.

Unless, in pernicious anæmia, the conditions were rather favourable than the reverse to active blood formation, one would expect to find fewer nucleated cells in the bone marrow, and a hæmoglobin ratio lower than usual, rather than higher. Of these conditions, the chief appears to me to be the presence, in this disease, of a large supply of material suitable for purposes of blood formation. So far from iron being wanting in pernicious

anæmia, as is the case in chlorosis, the evidence I have adduced shews that there is a great excess; and although this is found for the most part in the liver, an organ not primarily concerned in the formation of corpuscles, a considerable excess is not infrequently found in the bone marrow. It is in the latter tissue, as all observations shew, that the formation of red corpuscles chiefly goes on, both in health and disease. In fact this, we find, affords a ready explanation of one of the most characteristic features of the blood in pernicious anæmia, viz., the relative richness of the blood in hæmoglobin—a condition the very reverse of that found in chlorosis.

Failure in blood formation plays, therefore, I consider, little or no part in the production of pernicious anæmia.

The foregoing observations appear to me, for reasons already detailed, to denote that the *essential nature of the blood change is excessive blood destruction.*

Explanation of Chief Clinical Features.

The most characteristic clinical features of the disease all find their simplest explanation in this view.

Changes in the Blood.—I have already shewn how the relative richness of the blood in hæmoglobin can be well explained by this view. I have now to add that the same statement applies to the other characteristic changes in the blood. Thus my experiments shew that all the characteristic features of the blood can be reproduced by destructive agents—such as pyrogallic acid and toluylendiamin, while, on the other hand, they cannot be reproduced by loss of blood, however great. Thus:

1. *Oligocythæmia.*—A profound degree of oligocythæmia is more readily producible in animals by means of blood-destroying agents than by repeated losses of blood. (Exp. 58, chap. xv.)

2. *Poikilocytosis.*—The destruction is accompanied by changes in the form and size of the red corpuscles, similar to those constantly met with in pernicious anæmia. (Exp. 77, chap. xv.)

3. *Eichhorst's Corpuscles.*—In certain cases, the destruction is accompanied by the appearance of small yellow spherical micro-

cytes in the blood, resembling in all respects those so frequently found in pernicious anæmia. In their most typical form I am therefore inclined to regard these bodies as products of blood destruction; *not* as stages in the evolution of young red corpuscles, as Eichhort thought.

4. *Jaundice.*—Further, the fact that the liver (as shewn by its richness in iron) has a specially prominent part to play in this disease, either in the blood destruction itself or in the disposal of the products of this destruction, serves at once to explain the disturbances in liver function so common in the course of the disease, *e.g.* bilious vomiting, yellow jaundiced appearance, and sometimes attacks of actual jaundice.

The observations of Stadelmann and Afanassiew on animals have shewn how frequently some degree of jaundice is associated with the increased destruction of blood induced by the action of such drugs as toluylendiamin. Their observations also afford, in part at least, an explanation of the jaundice. The increased flow of bile (polycholia) is soon followed by thicker consistence of the bile, greater viscidity, and consequent stagnation in the bile ducts. A similar explanation doubtless applies in many instances to cases occurring in man; and it is by this fact, as afterwards shewn, that this peculiar condition so often associated with pernicious anæmia is, I consider, to be explained. (See Part IX.)

Addendum.

Since the foregoing conclusions—(already foreshadowed and partly formulated in 1886)—were published (1888), the additional attention drawn, thereby, to the condition of the liver has increased considerably the data on which to base conclusions.

These data affect in no way the conclusions just expressed: on the contrary they confirm them, in my opinion, in all essential particulars.

1. With regard to the conclusions based on *micro-chemical tests*, my own further experience has only served to confirm their general accuracy. The excess of pigment in the liver, as determined by those methods applied in the way described, anatomically distinguishes pernicious anæmia from those forms of anæmia hitherto regarded as secondary varieties of the

disease, namely, the anæmia of wasting or malignant disease, and the anæmia of loss of blood. In my opinion these latter are absolutely distinct from pernicious anæmia.

The condition which most nearly, in my experience, approaches pernicious anæmia, in respect of richness of the liver in iron, in certain cases only, not constantly, is leukæmia—a disease easily distinguishable in other ways from pernicious anæmia.

2. With regard to the results of *Chemical Analysis*, a large number of additional analyses are recorded by various observers. The chief of these are *two* by Dr. Mott, *four* by Dr. Hopkins, *twenty-one* by Dr. Stockman, *five* by Dr. Beaven Rake, and *ten* by myself. These are tabulated on the next page.

The most numerous and extended series of analyses are those of Professor Stockman. They are, in my opinion, *of special value*: first on account of their numbers and the fact that they have been carried out by one observer; and secondly because Dr. Stockman adduces these analyses in support of his own view, namely, that pernicious anæmia is only an extreme condition, not a special form of anæmia.

Dr. Stockman regards his analyses as supporting his conclusions, that there is no real difference between pernicious anæmia and the anæmia of hæmorrhage or of wasting disease; that the former is simply the latter aggravated by the occurrence and absorption of interstitial capillary hæmorrhages throughout the body; that the condition of the liver in pernicious anæmia is merely the result of the absorption of blood from these multitudinous capillary hæmorrhages.

On the contrary it will be seen how remarkably they bear out the conclusions already expressed as to the distinctive character of the pigment changes in the liver in pernicious anæmia.

Of special interest, also, are the analyses in tapeworm anæmia and ankylostomiasis made by Dr. Stockman and Dr. Beaven Rake.

These analyses have been arranged in groups, so as to be readily comparable one with another.

[TABLE IX.

TABLE IX.—*Analyses shewing Percentage of Iron in the Liver and Spleen in various Diseases.* (1888–1900.)

No.	Disease.	Liver.	Spleen.	Observer.
1	Pernicious Anæmia, . .	1·038	0·301	Dr. Gowland Hopkins.[1]
2	,, ,,	0·204	0·325	,, ,,
3	,, ,,	0·400	...	,, ,,
4	,, ,,	0·190	...	,, ,,
5	,, ,,	0·230	0·086	Dr. Stockman.[2]
6	,, ,,	0·140	0·170	,,
7	1. Pulmonary Embolus (W. 49), . . .	0·070	0·144	,,
8	2. Obstruction of Bowel (M. 52), . . .	0·090	0·150	,,
9	3. Myxœdema (W. 60), .	0·090	...	,,
10	4. Acute Tuberculosis (M. 16), ...	0·070	0·400	,,
	(In these 4, "organs healthy.")			
11	Tapeworm Anæmia, .	0·166	0·366	,,
12	,, ,, .	0·262	...	,,
13	Malaria (chronic), . .	0·257	0·110	,,
14	Leucocythæmia, . .	0·337	0·290	,,
15	Addison's Disease, . .	0·120	0·120	,,
16	Chronic Nephritis (W. 24),	0·035	0·210	,,
17	Hæmorrhage into Pancreas; very anæmic, .	0·160	...	,,
	(*Loss of Blood.*)			
18	Gastric Ulcer and Hæmatemesis, . . .	0·018	0·041	,,
19	Anæmia with bleeding into Bowel, ...	0·029	0·020	,,
20	Anæmia from bleeding Uterine Polypus, . .	very little	...	,,

[1] "Five Cases of Pernicious Anæmia with Determinations of Iron in the Viscera, and some Observations on the Urine," *Guy's Hosp. Rep.*, 1893.

[2] "Remarks on the Analysis of Iron in the Liver and Spleen in various Diseases affecting the Blood," *Brit. Med. Jour.*, i., 1896.

TABLE IX.—*continued.*

No.	Disease.	Liver.	Spleen.	Observer.
21	Anæmia from Ankylostomiasis, . . .	0·021	...	Dr. Stockman.
22	Anæmia from Ankylostomiasis, . . .	0·020	...	,,
23	Anæmia from Ankylostomiasis, . . .	0·030	...	,,
24	Anæmia from Ankylostomiasis, . . .	0·050	...	,,
25	Anæmia from Ankylostomiasis, . . .	...	0·094	,,
26	Ankylostomiasis,	Trace	0·040	Dr. Beaven Rake.[1]
27	,,	0·260	3·280	,,
28	,,	0·207	...	,,
29	,,	0·012	0·059	,,
30	,,	0·023	0·071	,,

No.	Disease.	Liver.	Spleen.	Kidney.	Observer.
31	Pernicious Anæmia,	0·310	...	...	Hunter.
32	,, ,,	0·207	0·097	0·068	,,
33	,, ,,	0·515	0·023	0·043	,,
34	,, ,,	0·360	0·069	0·033	,,
35	,, ,,	0·240	0·094	0·042	,,
36	,, ,,	0·363	0·141	0·133	,,
37	1. Bronchitis, . .	0·092	...	...	,,
38	2. Chronic Myelitis with Bedsores, . .	0·093	0·025	0·004	,,
39	3. Cancer of Stomach (typical lemon colour), .	0·022	0·013	0·003	,,
40	Leukæmia, . . .	0·140	0·029	0·086	,,

[1] "A Note on the Percentage of Iron in the Liver in Ankylostomiasis," *Jour. of Path. and Bact.*, iii., 1896.

In one case described by Dr. Mott (*Lancet*, i., 1889, p. 521), the analysis shewed twice as much iron in the liver as in the same amount of liver taken from a man dying of paraplegia; in another (*Lancet*, i., 1890, p. 287) 112·3 grammes of liver contained 0·3237 gramme of ferric oxide, whilst in health there should be mere traces. The spleen and kidneys shewed a trace of iron.

Summary.

	Liver.	Spleen.	Kidney.
1. *Health.*			
Stockman (4 Analyses), . .	0·080	0·231	...
2. *Pernicious Anæmia.*			
Hopkins (4 Analyses), . .	0·458	0·313	...
Author (6 Analyses), . . .	0·332	0·085	0·064
Stockman (2 Analyses), . .	0·185	0·128	...
	0·325	0·175	0·064
3. *Wasting Disease.*			
Stockman (Chronic Nephritis), .	0·035	0·210	...
Author (3 Analyses), . . .	0·072	0·021	0·003
	0·053	0·115	0·003
4. *Loss of Blood.*			
Stockman (3 Analyses), . .	0·019	0·023	...
5. *Ankylostomiasis.*			
Stockman (5 Analyses), . .	0·030	0·094	...
Rake (5 Analyses), . . .	0·125	0·862	...
	0·077	0·478	...
6. *Tapeworm Anæmia.*			
Stockman (2 Analyses), . .	0·214	0·366	...
7. *Blood Diseases, etc.*			
a. Leukæmia.			
Stockman (1 Analysis), .	0·337	0·290	...
Author (1 Analysis), . .	0·140	0·029	0·086
	0·238	0·159	0·086
b. Chronic Malaria.			
Stockman (1 Analysis), .	0·257	0·110	...
c. Hæmorrhage into Pancreas.			
Great Anæmia (Stockman),	0·160	...	...
d. Addison's Disease, . .	0·120	0·120	...

RESULTS.

The results are as follows:

Health.

1. Four analyses of normal livers yield an average of 0·080 per cent.[1]

Pernicious Anæmia.

2. Twelve analyses in pernicious anæmia yield for the liver an average of 0·325, *i.e.*, *more than four times the average of health.*[2]

Wasting Diseases.

3. Four analyses in wasting diseases yield an average of 0·053, *i.e.*, less even than that of health, and *only about one-sixth that of pernicious anæmia.* Of special interest is the contrast afforded in my list of analyses, betwixt pernicious anæmia (0·332 per cent.) and cancer of stomach, with typical lemon colour of patient (0·022 per cent.).

Loss of Blood.

4. Three analyses in anæmia from loss of blood yield an average of 0·019, *i.e.*, only one-fourth that of health, and *only one-seventeenth the average for pernicious anæmia.*

Ankylostomiasis.

5. Ten analyses in ankylostomiasis yield an average of 0·077, *i.e.*, *less than one-fourth that of pernicious anæmia.*

Tapeworm Anæmia.

6. Two analyses in tapeworm anæmia yield an average of 0·214, *i.e.*, approximating the average in pernicious anæmia; denoting therefore, in my opinion, that hæmolysis is in excess in that form of anæmia (cf. p. 49).

Leukæmia and Malaria.

7. The nearest approach to the average in pernicious anæmia is made in leukæmia and malaria, *i.e.* conditions which present clinically no difficulties in regard to diagnosis

[1] Compare Table II., p. 85. [2] Compare Table III., p. 85.

from pernicious anæmia, and are pathologically quite distinct from it. In both, hæmolysis is obviously increased.

Relative Richness of Liver and Spleen.

8. With regard to the *relative amount of iron in liver and spleen*—in health and in general diseases, the average for the spleen exceeds that for the liver sometimes five or six fold. In pernicious anæmia, it is less than one-half that of the liver.[1]

Kidney.

9. Five analyses of the kidney in my cases of pernicious anæmia yield an average of **0·064** per cent.; while two analyses in wasting diseases yield an average of only **0·003**, *i.e., the increase in pernicious anæmia being thus twentyfold.*[2]

As regards the question, how far the excess of iron in the liver in pernicious anæmia is to be regarded as distinguishing anatomically this anæmia from the anæmia of wasting disease or of loss of blood—the point which here concerns me chiefly—the remarkable contrasts brought out in the preceding summary (2, 3, 4, 5) appear to me to strengthen, and in no way to weaken, the conclusion I have already arrived at as to the distinctive importance of this change in pernicious anæmia.

Of special interest are the analyses by Dr. Rake and Dr. Stockman relating to ankylostomiasis. They appear to prove, as Dr. Rake concludes, that this anæmia is really the result of loss of blood, and that its clinical resemblances to pernicious anæmia are of precisely the same nature as those of traumatic anæmia. It is to be noted, however, that in two cases the percentage of iron in the liver was as high as **0·260** and **0·207**—figures denoting that, in certain cases, there is some increase of hæmolysis. The result accords with the varying clinical features which cases often present (cf. p. 49).

[1] Compare Conclusion, p. 41.

[2] These analyses were carried out for me with special care and accuracy by Mr. Percy Richards, F.C.S., of the Chemical Laboratory, Charing Cross Hospital. (For method see *Lancet*, ii., 1900.)

PART III.—EXPERIMENTAL.

INTRODUCTORY.

THE foregoing observations established the fact that pernicious anæmia was essentially *hæmolytic*, not *hæmogenic*, in its nature. Its nature was, however, in my judgment, by no means thereby fully elucidated. Increased destruction of blood was characteristic of other diseases, notably of paroxysmal hæmoglobinuria, and to a less extent of malaria. How did the increased blood destruction of pernicious anæmia differ from that found in these diseases? Some difference there must be, since the diseases otherwise present little in common with each other. Was this difference one of kind, or merely one of degree?

Such were the questions which presented themselves very early in the course of these inquiries. It was probable that this destruction of blood in pernicious anæmia was merely an exaggeration of that occurring in health. At this point, however, the greatest difficulty of all presented itself. Of the nature and seats of blood destruction in health, or the conditions regulating it, our knowledge was as vague as it was limited.

Nature of the Experiments.[1]

The experiments now to be described were therefore undertaken with a twofold object:

(1) To ascertain the nature and seats of blood destruction in health.

(2) To endeavour to produce a condition of the liver and other organs similar as regards *quantity* and *peculiar distribution* of pigment to that found in pernicious anæmia.

The nature of the experiments was to induce in various ways an increased destruction of blood in the body. The methods used for this purpose were transfusion of blood, and the injection of various destructive agents. The chief agents employed were distilled water, glycerine, pyrogallic acid, and toluylendiamin. The changes in the blood in different parts of the circulation, and in the different organs of the body during the progress of the destruction, were then observed; and a careful study was afterwards made of the changes presented by those organs specially concerned in the disposal of the products of this destruction—viz., the liver, spleen, and bone marrow.

These observations and experiments were made on animals representative of the different classes: on dogs and cats, as representing the carnivora; on rabbits, as representing the large class of the herbivora; on pigeons and ducks, as representing birds; and on frogs, as representing cold-blooded animals. The experiments in all numbered about a hundred and fifty. The largest series were made with pyrogallic acid and toluylendiamin.

They were varied in a number of ways. The effects of large toxic doses were studied, as well as the cumulative effects of smaller doses administered over longer or shorter periods of time.

[1] The results of the experiments were recorded in the following papers:—

1. "Intraperitoneal Transfusion and the Fate of Extravasated Blood," *Jour. Anat. and Phys.*, 1886.

2. "The Life-duration of Red Corpuscles as Ascertainable by Transfusion," *Proc. Roy. Soc. Edin.*, 1887.

3. "An Investigation into the Pathology of Pernicious Anæmia," *Lancet*, ii., 1888.

4. "Arris and Gale Lectures on Transfusion," Royal College of Surgeons, England, *Brit. Med. Jour.*, ii., 1889.

5. Grocer's Lectures on "The Physiology and Pathology of Blood Destruction," *Lancet*, i., 1892.

With the object of determining what part was played by certain organs in blood destruction, other series of experiments were made. In a number of experiments the spleen was excised; and the effects of certain of the destructive agents were then noted, and compared with the results obtained after the administration of the drug in the healthy animal. In a few experiments on pigeons, the liver was similarly removed or cut off from the circulation, previous to the administration of the drug.

These experiments on blood destruction in health and disease, with special reference to the true pathology of pernicious anæmia, engaged my time and attention during the years 1885–1890. They will be found detailed in Part VIII.

In relation to our present subject, the nature of pernicious anæmia, they may conveniently be considered under the three headings:—

(1) Physiology of the Blood.
(2) Hæmolysis in Health.
(3) Hæmolysis in Pernicious Anæmia.

CHAPTER X.

PHYSIOLOGY OF THE BLOOD.

THERE are certain points connected with the physiology of the blood, a knowledge of which is essential to a right understanding of its pathology.

What are the functions of the blood in health, and how is it fitted by structure and composition to discharge them?

The physiology of the blood presents problems of peculiar difficulty, arising from its fluid nature, and its close relation to all other tissues of the body—a relationship peculiar to it alone. Its quantity and quality appear to be constantly varying. Are we then entitled to regard it as a tissue, seeing that it apparently has no stable composition? When we speak of the blood, do we speak not so much of a tissue, as of a mass of fluid of varying quantity and quality, holding certain corpuscular elements in suspension, and presenting merely a certain average composition in virtue of the united action of all the tissues? Unlike all those structures to which we give the name of 'tissue,' it appears to possess no single characteristic property, its composition being determined solely by the quantity and quality of the material poured into it by the various tissues. Hence it is considered, by some, to be far more profitable, indeed necessary, to treat of the blood, not as a tissue, but as the great means of communication of material between the tissues properly so called,—to regard it as a mass of material by which the tissues are bathed. Hence the title frequently given to it, of 'the nutritive fluid of the tissues.'

To regard the blood in this light seems reasonable enough in health, where we have to do with a certain average activity of

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all the organs of the body. Even as a working hypothesis—and it is as such that this view chiefly recommends itself—this view completely breaks down, in the presence of the far more difficult problems presented by the blood in disease. So far from the blood being a mixture of water, proteids, carbohydrates, salts, etc.—a simple 'nutritive fluid'—a consideration of all the evidence afforded by a study of its behaviour in health and disease points irresistibly to the conclusion, that it is a highly organized tissue of remarkably stable structure.

The most notable feature presented by the blood is not, as is usually supposed, its varying composition, but the remarkable power it possesses of maintaining a composition as rightly entitled to be termed stable as that of any other tissue of the body,—notwithstanding that its close relation to all the other tissues renders it peculiarly subject to changes.

The evidence pointing to this conclusion is of two kinds: (1) that derived from a study of the behaviour of the blood both in health and disease, under conditions tending to alter its composition, both in quantity and quality; (2) that derived from a study of the nature and composition of the plasma.

The former evidence—functional evidence—shews, that the blood possesses one of the most characteristic properties of living tissues, namely, great irritability; evidenced in its case by its intolerance of the presence of bodies, even those normally present in it, such as water, sugar, peptones, salts, if they do not reach it by the ordinary channels, or if they reach it in too great quantity, even by the ordinary channels.

> The use of salts for purposes of transfusion is, to a great extent, based on the assumption, that the composition of the plasma, as regards its richness in inorganic solids, is constantly varying, and that the injection of a little more or less is immaterial. So far is this from being the case, that there is every reason to believe that its composition in inorganic solids remains, consistently with its discharge of great carrying functions, as constant as that of any tissue of the body.
>
> This constancy in composition is most noticeable in the case of chlorides, which form more than one-half of the total percentage of salts in the ashes of the plasma; but it doubtless also is the same for other inorganic constituents. When a rich supply of chlorides is given in the food, the excess is at once excreted by the kidneys.[1]

[1] St. Klikowicz, "Die Regelung der Salzmengen de Blutes," *Archiv f. Physiologie*, 1886, p. 818.

When withheld altogether, the percentage in the blood at first falls very considerably, but ultimately rises again to the normal, while the excretion of chlorides by the kidneys falls to a minimum. The difficulty experienced in removing the chlorides from the serum by osmosis, even with the aid of large quantities of distilled water (Hoppe-Seyler), may be regarded as likewise pointing to the same conclusion; namely, that the inorganic solids of the plasma, as of the red corpuscles, are present, not in free form as such, but in combination with the other constituents. They must be regarded, therefore, as constituting portions of an organized structure built up by the agency of cells; and their amount is, therefore, solely regulated by the activity of these cells. This is specially true of the phosphoric acid of the blood, a considerable part of which is derived from the phosphorus contained in lecithin,—one of the most complex, as it is one of the most widely spread, organic compounds in the body. It is also true of the sulphates, some of which are derived from the sulphur of proteids. Hoppe-Seyler has recently shewn, that even the hæmoglobin of the corpuscles is not present in the corpuscle as such, but is in intimate combination with other organic and inorganic solids.

The importance of these various facts and observations lies in this, that they point clearly to the conclusion, that all salts injected directly into the blood form no part of the blood while present, but are in the position of foreign bodies. They are removed from the blood, and excreted from the body, with the same rapidity as sugar, peptones, hæmoglobin, and large quantities of neutral saline solutions similarly injected. So far from being inert, most of them are injurious. Thus phosphate of soda (5 per cent. solution) exercises a most markedly hæmolytic action on the blood (see page 129, fig. 11).

The latter evidence—structural evidence—goes to shew, that not only in the corpuscles, but also in the plasma, we have to do with proteid material built up into organized form, differing from the proteid material introduced into the blood from the food.

The key to the solution of the problems presented by the blood, both in health and disease, is to be found in the recognition of this fact—that, what are termed changes in its composition are in the great majority of instances merely changes in virtue of its function as the carrying tissue of the body. A clear distinction is to be drawn between changes in the blood as a tissue, —*structural changes*, and changes in virtue of function, *func-*

tional changes. The latter, however marked—sugar in diabetes, uric acid in gout—do not constitute disease of the blood; the former, however slight—deficiency in hæmoglobin, in the number of corpuscles, etc.—do constitute disease; and their cause must always be sought, not in the tissues as a whole, but in certain organs specially concerned with the life of the blood—the so-called blood organs.

The conclusions pointed to by a study of the behaviour of the blood in health and disease are the following:

1. The blood is in all respects a tissue of highly specialized structure, adapted for the performance of certain specialized functions—chiefly, the conveyance of food material, gaseous liquid and solid, to all the tissues of the body.

2. It possesses, in common with all tissues, the power of maintaining a certain physical structure, and a certain chemical composition, in the presence of the most varying physical conditions.

3. The peculiar fluid nature of its matrix necessitates, in its case, special arrangements for the regulation of its composition not required by the other tissues.

This mechanism is to be found, partly in itself—its white corpuscles, and the endothelium of its capillary walls; partly in certain organs in specially close relation to the blood, so situated, that its composition even as a carrying tissue is regulated at certain convenient points in the circulation—namely, gastro-intestinal mucous membrane, more especially the follicular tissue around the portal radicles, the spleen, liver, bone marrow, and lymphatic glands. With the exception of the latter, these blood-organs possess in varying degree certain features in common—namely (1) slowness of circulation—common to all; (2) closeness of relation of cells to the blood—spleen and bone marrow; (3) power of accommodating large and varying quantities of blood, chiefly venous, which the portal system, including the spleen and liver, possesses in a special degree.

It may be convenient to regard the blood, as has just been said, as an organized tissue; and in the case of certain of its elements, namely, the *Leucocytes*, their living character cannot be gainsaid. It is necessary now to consider more particularly to

what extent this also applies to its other elements—its *Red corpuscles* or its *Plasma.* And first, with regard to the plasma ; and the evidence that it is a highly organized tissue, and no mere nutritive fluid.

I.—The Plasma.

Its Organized Nature.—Any nutritive value the blood may have, must depend on the presence of its proteid constituents. Of these the blood contains about 20 per cent., distributed unequally between the corpuscles and the plasma ; rather more than 15 per cent. being contained in the corpuscles, rather less than 5 per cent. in the plasma.

How is the blood affected in starvation? As the 'nutritive fluid of the tissues,' does it suffer in any special degree, at a time when the waste of the tissues is not being replaced by food material from without? We know that, under such circumstances, the loss of substance does not affect all tissues equally. Some, as the heart muscle and the brain, suffer but little ; others, as the muscles, generally lose much. Does the blood become poor in albuminous constituents out of all proportion to the loss in the other tissues, as might be expected if its substance is in the first instance used up as food? On the contrary, the observations of Voit, Panum, and Heidenhain shew, that the loss in weight of the blood is proportional to the general loss in weight of the tissues ; and that the proportion of its various constituents remains unaltered. In starvation, as in health, the blood suffers quantitatively and qualitatively as other tissues. It behaves, not as a mass of nutritive material, but as a tissue. Its *carrying function*, nutritive and respiratory, remains the same to the last. The fact, that some tissues, such as skeletal muscle, suffer much, while others, such as the heart muscle, functionally active to the very last, lose but little in weight, implies that the latter must have been nourished at the expense of the former ; that food material must have been conveyed by the blood from the muscles to the heart. The *nutritive function*, which the blood thus subserves in virtue of its carrying function, remains the same as in health. The same holds true of its *respiratory function.* Lastly, the quantity of blood never falls below the point at which the circulation is unable to be maintained ; so that the great

function of circulation, which the blood is enabled to discharge in virtue of its physical properties—fluidity, viscosity, etc., remains unaffected.

The stability which the blood thus displays in health it continues to display under adverse conditions. Thus, even after transfusion the evidence clearly shews that its proteid material is not broken up as so much food material, but persists. This evidence is of the following kind.

Any nutritive value the blood may have must depend on the presence of its proteid constituents. Now, one of the facts definitely established with regard to the fate of proteids introduced as food by the ordinary channels, is that their utilization as food by the tissues implies their breaking up in the first place, and the excretion from the body of a quantity of nitrogen, chiefly in the form of urea, closely corresponding to the amount contained in the food.

If to an animal in a state of starvation—whose excretion of nitrogen is entirely at the expense of its own tissues, and after a time remains fairly constant—we give a certain amount of proteid material as food, we might expect that the greater part of the material thus given would be built up into the tissues and but little be excreted. What we do find, however—as will be seen by reference to the accompanying charts, in which I have represented graphically the results obtained by Forster in his well-known experiments, confirmed by those of Tchiriew—is that the whole of the nitrogen thus introduced is excreted from the body at once; there is an increased excretion of nitrogen corresponding to the quantity given in the food.

If to an animal in a similar condition a certain quantity of blood be given by the mouth, we have a similar result; the increased excretion of nitrogen corresponds to the quantity of nitrogen in the blood administered.

> Thus, Tchiriew found that, in a period of three days, during which 13·19 grammes of nitrogen were given in the form of blood by the mouth, the excretion was 14·55 grammes; in another period of three days, the excretion was 14·43 grammes as compared with 14·38 grammes in the food; in a third period, the excretion was 15·42 grammes as compared with 15·28 in the food.

The proteid material, whether in the form of meat or in the

form of blood, had undergone disintegration; its nutritive value corresponded to the quantity of nitrogen it contained, and was expressed by the excretion of nitrogen after its administration.

Very different is the result after transfusion, when the blood is introduced directly into the vessels instead of by the mouth. As will be seen (figs. 2 and 3), there is little or no increase in the nitrogen excreted. Some slight increase there always is, but it in no way corresponds to the quantity of nitrogen con-

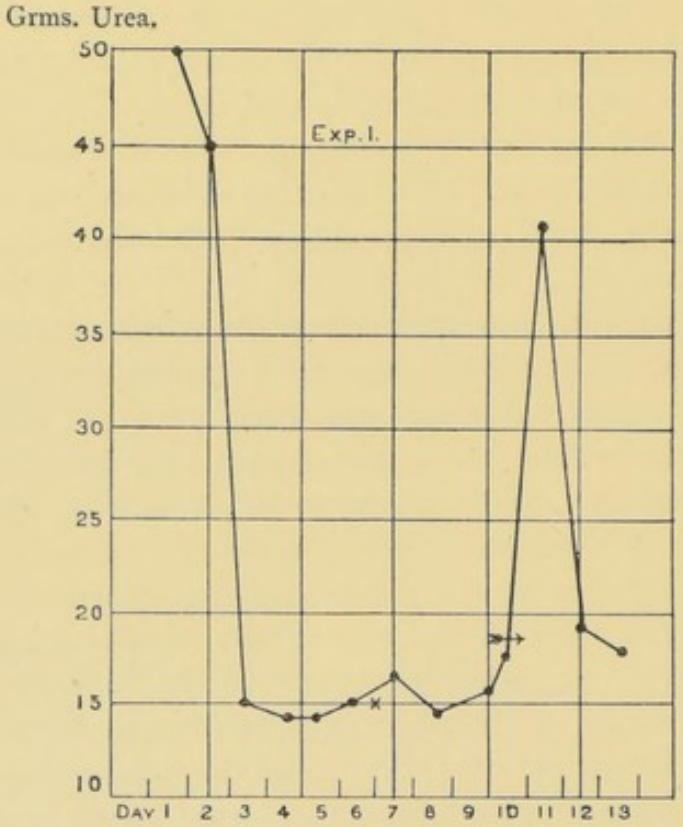


FIG. 2. × = 394 grms. blood transfused (15·06 grms. nitrogen).
→ = 375 grms. meat by the mouth (12·75 grms. nitrogen).

tained in the injected blood. Thus, of 19·09 grammes of nitrogen in the blood transfused, only 6·85, of 18·53 thus given only 10·60, of 7·84 only 4·39 grammes appeared in the urine in the periods over which the transfusions were made.

Similarly, in Forster's experiments (charts 2 and 3), while the transfusion of 394 and 611 grammes of blood (*i.e.* organized proteid) caused hardly any appreciable change in the excretion of urea, the administration of corresponding quantities of proteids by the mouth was followed immediately by an increased excretion of urea.

We must conclude, then, that blood transfused is not

immediately destroyed; its proteid is evidently more stable than that which reaches it by the food. Moreover, this is true of the proteids of the plasma as well as those of the corpuscles. This is well brought out by contrasting the results represented in figs. 2 and 3 with those represented in figs. 4, 5, 6, 7. *Plasma* (plus corpuscles) caused no rise in excretion of urea (figs. 2 and 3); whereas *Serum* (even without corpuscles) caused a distinct rise, precisely as if the proteid material had been given by the

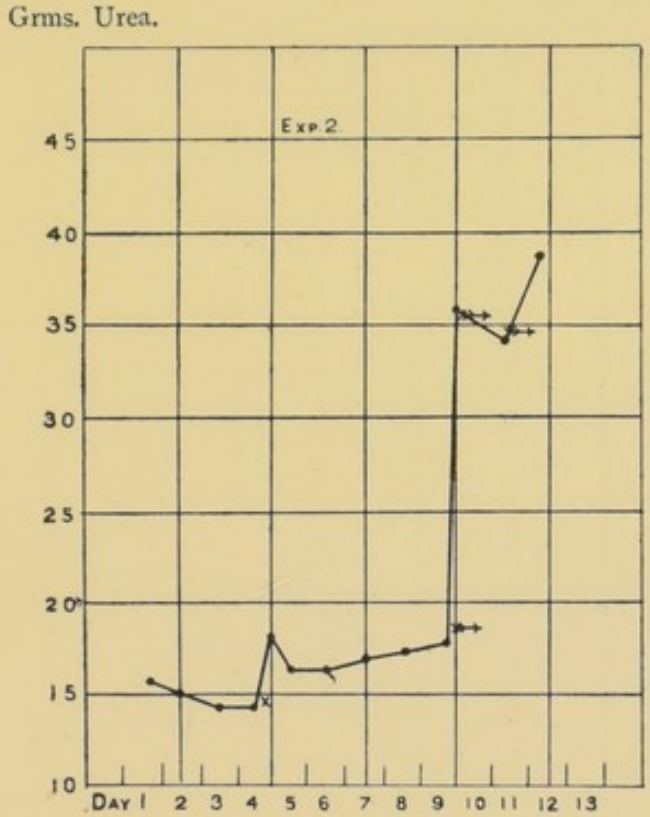


FIG. 3. × = 611 grms. blood transfused (19·92 grms. nitrogen).
→ = 600 grms. meat by the mouth.

mouth. Defibrination had, in the latter case, destroyed the organized character of the plasma, and its proteids were treated as if they were so much food material.

The nutritive value of transfused blood is therefore correspondingly less than the same quantity of blood given by the mouth. The two functions frequently ascribed to it at one and the same time—namely, of being an organized tissue and of serving as nutritive material for the tissues—are incompatible with each other.

Hence it is that the loss of weight in starvation is un-

affected by transfusion of blood in whatever quantities and however often repeated; and this is the case even although at death the blood may be not only increased in quantity, but actually richer in quality, than in health.

Thus in one of Tchiriew's experiments in which transfusion had been repeatedly made, and in which the weight had fallen steadily from 6·928 to 4·583 kilos., the quantity of blood obtained from the body amounted to about 8·7 per cent. of the body weight

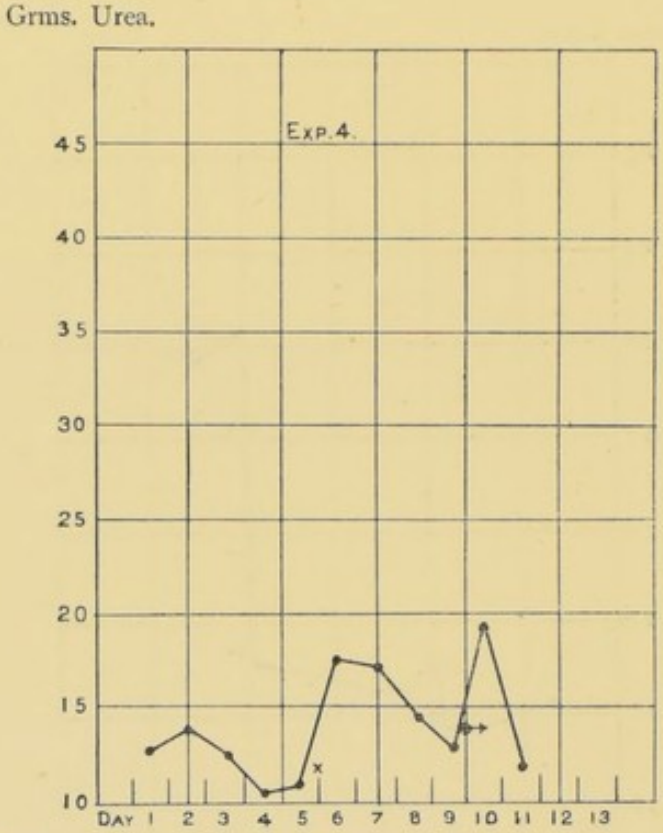


Fig. 4. × = 430 c.c. blood serum transfused (6·88 grms. nitrogen).
→ = 200 grms. meat by the mouth.

as compared with the 7 per cent. usually obtainable in health; and this blood contained 27·11 per cent. of solids with 4·21 grammes of nitrogen as compared with the 21 per cent. of solids containing about 3·2 grammes of nitrogen usually found in healthy blood. Similar results were gained by Panum—by a method, however, not so free from objection as that of Tchiriew, on whose results, as on those of Forster, the greatest reliance can be placed.

Bactericidal, Globulicidal, Immunizing, and Antitoxic Properties of Blood Serum. — Although defibrination thus alters essentially the relation of the proteids of plasma to each other,

these still retain many important properties, the very existence of which was unknown till they were revealed as the outcome of bacteriological research. These properties are variously designated, according to the particular way in which they manifest their existence, as *bactericidal*, *globulicidal*, *immunizing*, and *antitoxic*; and some reference to them, however brief, is here necessary, since they form the basis of that remarkable outcome of bacteriological research—the serum treatment of infective disease.

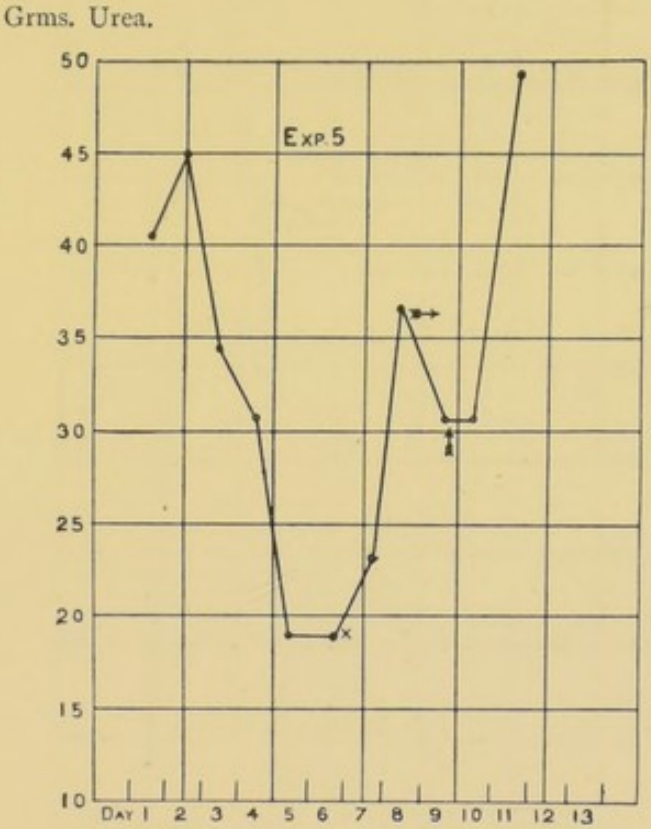


FIG. 5. × = 662 grms. serum transfused (6·38 grms. nitrogen).
→ = 600 grms. meat by the mouth.

1. The starting-point of the discovery of the existence of such properties of blood was the clinical observation that an attack of an infective disease so often confers more or less complete immunity against all subsequent attacks of the same disease.

2. Then followed the observations of Pasteur with regard to anthrax, that, by attenuation of the *living virus*, a milder form of the disease could be given which subsequently protected against the same disease.

3. Then came the important extension of this by Salmon and Smith (1887), that in certain cases immunity could be conferred

by injection of the *chemical products* of the virus, freed from all living elements by being filtered through porcelain—a result shewing that some chemical change underlay immunity.

4. About the same time came a series of observations (Fodor, Nuttall, Hankin, Behring, and Buchner), shewing that the body fluids, especially those of the blood, possess, under certain circumstances, *bactericidal* properties—these properties being associated

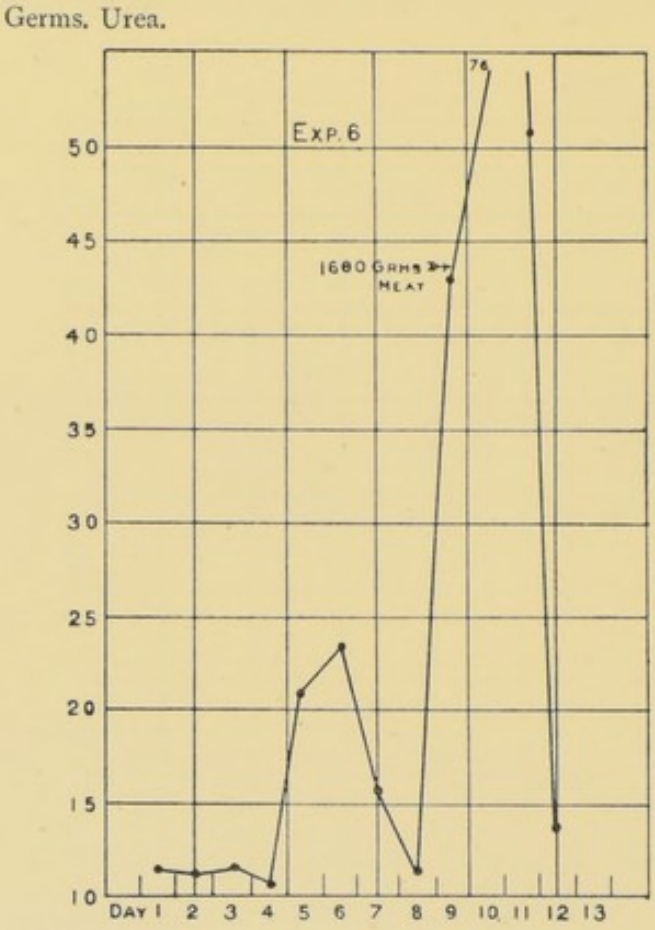


FIG. 6. × = 950 c.c. serum transfused (15·08 grms. nitrogen).
→ = 500 grms. meat by the mouth.

with certain proteids of the serum, and being of ferment-like nature, since they are destroyed at a temperature at which ferment action is arrested (55° C.).

5. The remarkable (hæmolytic) action which the serum of one animal exerts on the red corpuscles of another—*globulicidal action*—was shewn (Buchner) to depend on some similar ferment-like activity of proteids—since it also is entirely arrested at a temperature of 50°–60° C.

6. It is not, however, on any such bactericidal properties

of blood serum that immunity is dependent, as was at first thought. It remained for the epoch-making studies of Behring and Kitasato (1890) to shew that, apart altogether from any such properties, the blood serum of an animal *rendered immune* against an infective disease possesses the power of conferring a similar immunity on any animal subject to the same disease, into whose blood it is introduced in suitable quantity ('Behring's Law'). The serum possesses *immunizing* properties.

7. The same serum possesses, moreover, what for therapeutic

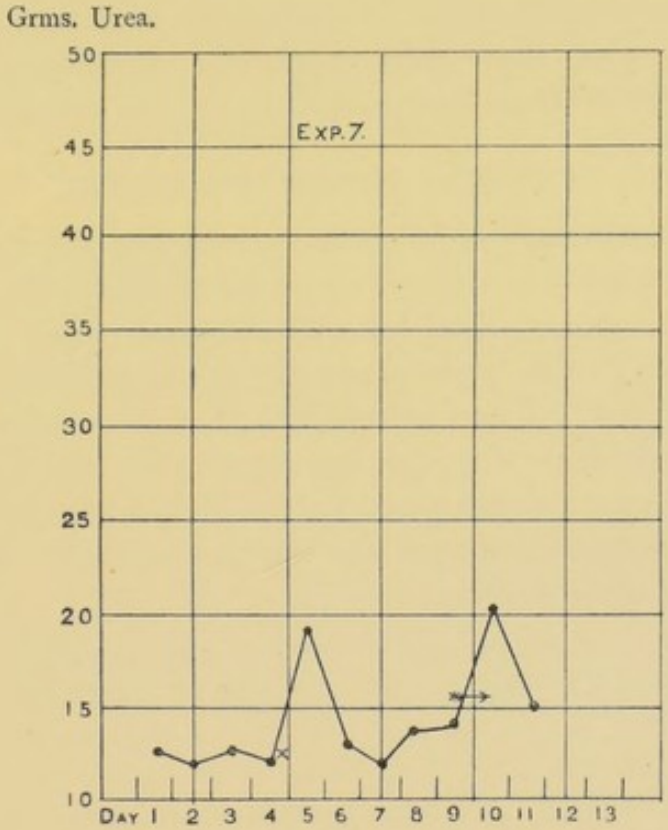


FIG. 7. × = 522 grms. serum transfused (30 grms. albumen).
→ = 150 grms. meat by the mouth (32 grms. albumen).

purposes is even more important — the power of destroying, antagonizing, or rendering inactive the poisons already present in the blood—*antitoxic* properties.

This law of Behring has been found to hold good for all diseases, *including even those of a septic nature*, which shew any degree of immunity.

The immunizing and antitoxic power of serum is in most cases a *specific* one—that is, it only applies to the particular disease against which the immunity has been conferred. But

there are exceptions even to this general rule. Thus anti-tetanus serum can protect not only against tetanus intoxication, but also against snake poison.

The foregoing facts bring out the two chief features of the blood plasma—namely (1) its *stability* in the face of all ordinary disturbances such as those of nutrition; (2) its *sensitiveness* to all influences of an infective or toxic nature, and the very varying manner in which these manifest their action.

The outcome of the investigation now to be recorded shews that the influences at work in pernicious anæmia are of this latter kind; and that their particular manifestation is a hæmolysis greater than that met with in any other disease.

II.—The Red Blood Corpuscles.

Their Life Duration.[1]—The normal persistence of red corpuscles within the circulation has hitherto been considered more a question for speculative inquiry than for experimental proof. Attempts have from time to time been made to solve it experimentally, by injecting the blood of one animal into another possessing blood corpuscles of different size and shape, and then noting how long the foreign corpuscles remained in the body of their host. As might have been anticipated, the success of such experiments has not been very striking.

Marfels and Moleschott, so early as 1856, arrived in this way at the conclusion that the life duration of corpuscles must be a very long one, since, even after the lapse of months, they could still recognize the corpuscles of the sheep in the circulation of the frog.

Brown-Séquard, also (1857), made some similar observations, with somewhat anomalous results; for whilst the blood corpuscles of the dog or rabbit were recognizable a month after injection into the circulation of fowls, on the other hand, the blood corpuscles of fowls were not to be found in the blood of dogs or rabbits even one hour after injection.

These different results were not easy to explain. The latter observation was probably the more correct of the two; since, as is now known from the experiments of Panum, Landois, Ponfick, and others, such a method of investigation, implying as

[1] The terms 'life,' 'living,' here employed are used only for convenience, as connoting that condition of the red corpuscle which enables it to circulate in the blood as an independent unit. Immediately it loses that condition, it is seized on as a foreign body (by leucocytes, splenic cells, etc.), and removed from the circulation.

it does the use of 'dissimilar' blood—blood derived from an animal of another species—is doomed from the outset to failure. The blood corpuscles of such blood, when introduced into the body of their host, always break down within a few hours of injection; in larger quantities they are directly poisonous to the organism into which they are injected.

It is only by transfusion of 'similar' blood—blood derived from an animal of the same species—that any results bearing on the question can be arrived at. That the corpuscles of such blood remain, for a certain time at least, in the body of their host, was to be assumed, from some of the very earliest experiments on transfusion made by Dr. Lower in 1666, in which dogs continued in good health, after all the blood in their bodies had been replaced by that obtained from other dogs.

The first observer, however, to make direct observations on the actual duration of the life of such transplanted or transfused blood corpuscles was Panum in 1863.

He judged the number of corpuscles present in any quantity of blood, by the *difference* in specific gravity between the blood serum and defibrinated blood. In this way, after withdrawing blood from a dog, and replacing it with defibrinated blood, he was able to shew, that two days later the number of blood corpuscles remained almost unaltered, and that five days later the majority of them still remained within the circulation.

It was naturally impossible, by this rough method, to determine more closely the further fate of the transplanted corpuscles. This could only be done by actual enumeration of the corpuscles before and after the injection, a method of investigation at that time unknown. Even since its introduction, the results obtained have not been so definite, as *à priori* might have been expected. They serve, however, to throw some light on the subject.

There are two ways, in which, by means of transfusion, information as to the duration of the life of red blood corpuscles may be obtained—viz., either by transfusion of blood without foregoing depletion, or by transfusion of blood after previous withdrawal of some of the animal's own blood.

In the latter case, the difficulty is to determine afterwards, what proportion of the blood corpuscles present belong to the animal, and what proportion is derived from the transfused blood; since by the withdrawal of blood, the standard of comparison—the number of corpuscles originally present—has been

lost. The difficulty is one which from its very nature it is quite impossible for us to overcome.

It might be thought, that in the former method—viz., transfusion without any foregoing depletion—we have at hand a ready means of ascertaining the duration of life of the red blood corpuscles; since the normal standard is in no way interfered with, and the time taken for the removal of the excess of blood corpuscles after the transfusion will, therefore, represent the longest period they have survived.

This is indeed the case, so far as the transfused corpuscles are concerned; but the question always arises, how far this period corresponds with the period the red corpuscles normally remain within the circulation. By transfusion of blood into the circulation of a healthy animal, an abnormal condition of the blood — a so-called plethora — is for the time being brought about, which, so far as we know, may very materially influence the duration of life of the injected corpuscles. The excess of blood corpuscles, thus introduced, can only be got rid of by a process of increased blood destruction on the part of the organism; and thus the transfused blood corpuscles are not placed under exactly the same conditions as those under which they normally run their life course. In spite, however, of these disadvantages, this method enables us to arrive at least at an approximate estimate.

Worm-Müller's Results.—Worm-Müller found, after such transfusions in dogs, that two or three days later the number of blood corpuscles present in the blood closely corresponded with the number of the original *plus* the injected corpuscles; a few days still later the blood corpuscles began to break down, and, by the end of a few weeks at most, the whole of the injected corpuscles had been removed from the body. The greater the quantity of blood transfused, the longer did this process of removal last; for whilst after the transfusion of 20 to 30 per cent. of blood the whole of the injected corpuscles were removed in the course of a few days, after injection of 60 to 80 per cent. their removal was not complete till about the end of the second or even the third week.

According to these results, therefore, the longest duration of life of transplanted corpuscles in dogs was about *two to three weeks.*

Quincke's Results.—Quincke's more recent observations, also

made on dogs, agree with this estimate, the duration of life according to him being at least *two to three weeks.* His method of investigation, however, is open to the objection, that the percentage amount of hæmoglobin in the blood, which he always estimated, does not necessarily correspond with the number of blood corpuscles present. With this reservation, his statement may be accepted as at least corroborative of that of Worm-Müller.

Author's Results.—The results of my experiments, made on rabbits, agree in the main with those of Worm-Müller and Quincke.

> The method of transfusion I adopted differed somewhat from that of previous observers. The blood was injected into the peritoneal cavity instead of being introduced directly into a vein. The absorption from this, as is well known, is so rapid and continuous, that peritoneal injection has claims to be considered a slow method of intravenous injection. In some respects, indeed, for experimental purposes, it offers advantages over the latter. The operation is easily carried out; and the subsequent absorption into the circulation (mainly through the lymphatics of the diaphragm and the thoracic duct) is so continuous and steady, prolonged as it is over a period of some twenty-four to forty-eight hours, that time is given during its progress for the removal of the fluid part of the blood; and hence little or no distension of the vascular system is likely to occur after the injection of even the largest quantities.
>
> The method is naturally open to the objection, that the fact of the blood corpuscles having been extravasated may possibly affect their vitality, and thus shorten the duration of their life. That a certain number of them, under such circumstances, always suffer death *in situ* is certain; but this number is relatively small; and, as will be seen, the results shew that the vitality of those absorbed appears in no way affected by their temporary sojourn in the peritoneal cavity.

The increase in the number of corpuscles in the blood, as ascertained by actual enumeration, after reaching a maximum on the second or third day, became gradually less and less; till at the end of a certain time, varying somewhat in the different experiments, the number of blood corpuscles had returned to their normal,—this period of time representing, therefore, the longest period the injected corpuscles had remained in the blood in that particular case. (See figs. 8, 9, 10, 11.)

The experiments were made both with pure and with defibrinated blood.

With pure blood the duration was:—In two experiments 26 days; in one 21 days; in one 19 days; and in one 14 days—*the longest duration being thus* 21 *days.*

With defibrinated blood, the time varied from 14 to 21 days or an *average of* 17½ *days* (figs. 9, 10).

The *longest* possible persistence of transfused blood corpuscles, in rabbits, may, therefore, be taken as from *two to four weeks.*

This applies naturally to only a few of the corpuscles injected, doubtless the most resistant at the time of injection. The great majority become destroyed at a much earlier period, oftentimes with great rapidity.

The quantities of blood injected were very large, varying from about 40 to 90 per cent.; but after the injection of smaller quantities the return to the normal was complete in a few days (5–7). The above period does not represent, therefore, the average life duration of transplanted corpuscles. On the contrary, all my observations go to shew, that the duration is regulated more by the activity of the general metabolism, than by the actual resistance of the corpuscles.

Small quantities of blood are, therefore, probably removed from the body in a few days, judging at least from the rapidity with which large numbers of corpuscles, *e.g.* 40 per cent., are destroyed in from 14 to 21 days, a destruction of blood at a rate of some 2 to 3 per cent. daily, in addition to the normal amount of blood destruction going on in the body.

This consideration is of importance, in view of the value to be attached to the operation of transfusion in man, in whom the quantities of blood transfusible are relatively very small.

The question then arises, how far the results obtainable in rabbits are applicable in the case of other animals. Since the metabolism of the body probably varies somewhat in each different species, may it not be, that the duration of life of the blood corpuscles likewise varies?

As has been seen, the results obtained in dogs and rabbits agree in a somewhat striking manner, and certainly do not lend much support to the above view. They both alike point to a period of some two to four weeks, as being the longest duration of life of transfused blood corpuscles.

On the other hand, from two experiments I made on dogs,

it would almost appear as if in them the process of blood destruction were in reality more rapid than in rabbits; in one case the normal being reached on the sixth, in the other on the eighth day. The quantities of blood injected were, however, relatively very small.

Summary.

The results of these experiments go, therefore, to shew, that the red corpuscles do possess an independent existence; since even under the relatively unfavourable conditions of being transfused into another host, they can remain a certain length of time (two to three weeks)—the time varying according to the activity of the blood-destroying organs. An excess of blood corpuscles is not tolerated by the organism for any length of time. Hence, it is more natural to assume that the period required for the destruction of the injected corpuscles is shorter than in the case of the normal red corpuscles than to assume the reverse —viz., that transfused corpuscles can remain longer in the circulation than the animal's own blood corpuscles.

Such are the results obtainable by transfusion without foregoing depletion. Although, as already indicated, they are more to be relied on than those obtained by transfusion after depletion, those obtainable by the latter method point to a similar period.[1]

The evidence thus obtained in so many different ways all agrees in pointing to a period of some *three or four weeks* as the longest persistence of transfused blood corpuscles.

It has already been seen that the probabilities are all in favour of this life-duration being shorter, rather than longer, than that of the normal red blood corpuscles.

Hence I conclude that three to four weeks represents approximately the average duration within the circulation of red corpuscles, in the rabbit, the dog, and presumably also in man.

Conditions influencing Life Duration.

As already said, the chief of these, according to my results after transfusion, appears to be the general metabolic activity; the more active this is, the shorter the life of the

[1] *Op. cit.* 2, p. 48.

corpuscles; the slower it is, the longer. This conclusion is opposed to the opinion generally entertained. According to Voit, in *Hermann's Physiologie*, we have hitherto had no knowledge, whether the corpuscles are destroyed in greater number in health than in starvation. "There is no reason why there

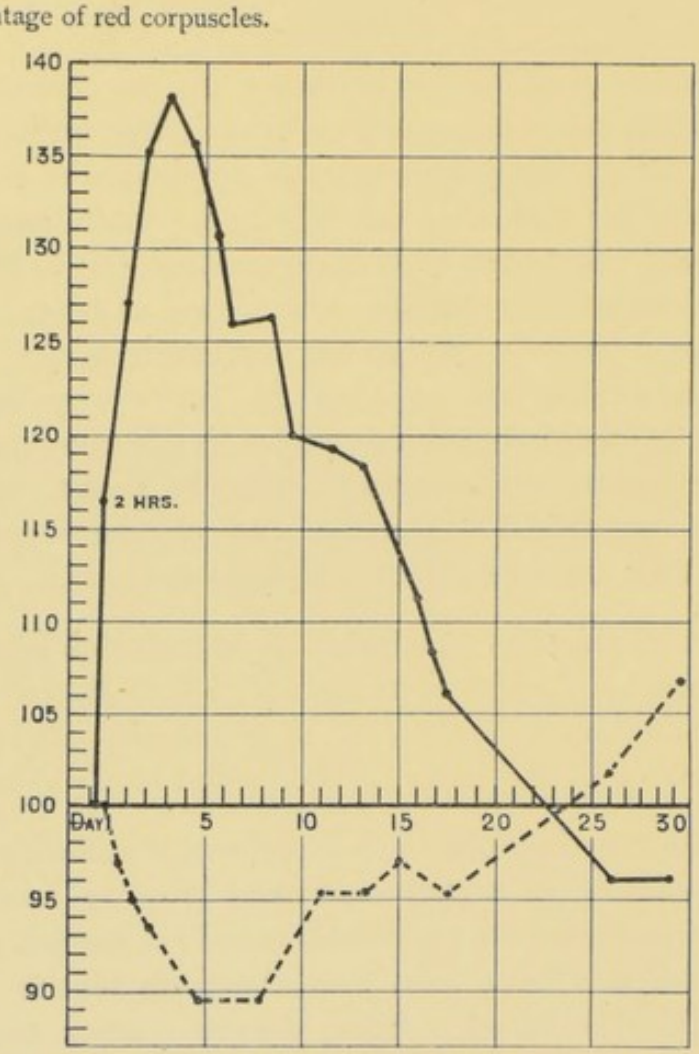


FIG. 8.—Life-duration of red corpuscles after transfusion of defibrinated blood into the peritoneal cavity (Experiment 10). The animal remained in good health throughout, although the original weight was not regained till close of the experiment. The weight is represented by the interrupted line.

should be a greater destruction of red corpuscles during digestion than during the fasting state." My own studies, as will be afterwards seen, shew, on the contrary, that it is precisely during starvation, that destruction of corpuscles is at a minimum, and during digestion that it is at a maximum.

After transfusion of large quantities of blood, there is a

gradual and steady fall in the number of corpuscles till the normal is reached two or three weeks later. This lengthened life duration is only found, when large quantities are injected, and only applies to rabbits. With smaller quantities, the life duration is correspondingly shorter. In dogs, a longer life

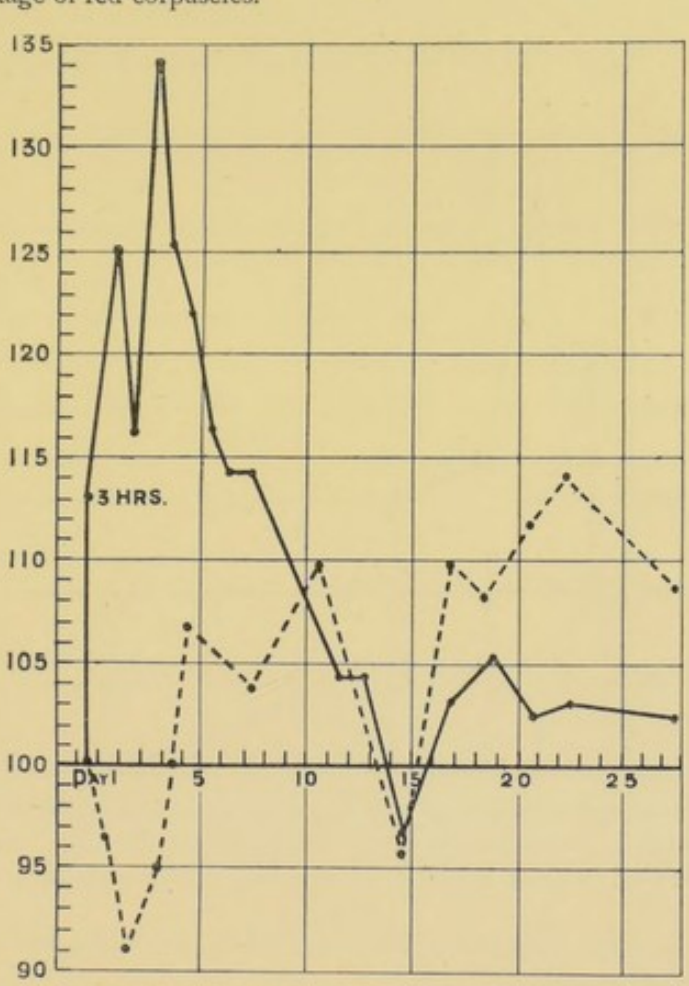


FIG. 9.—Life-duration of red corpuscles after transfusion of pure blood into peritoneal cavity. The health of the animal exceptionally good throughout.

duration than ten days was not observed. The two factors influencing it in all cases were—(*a*) the quantity of blood transfused ; (*b*) the condition of the animal at the time of the transfusion and subsequent to it. As regards the latter—the one applicable to the normal blood no less than to transfused blood—the following conclusions could be drawn from a study of the results obtained in my different experiments :

1. Any condition in which metabolism is diminished, as in

starvation, tends to prolong the life of the red corpuscles. This applies both to the animal's own corpuscles and to the corpuscles of transfused blood (fig. 8).

2. Any condition approaching that of health, in which metabolism is active, tends to shorten the life duration of the transfused corpuscles (fig. 9).

3. In any condition in which metabolism is increased, the life duration of the red corpuscles is shortest of all (fig. 10).[1]

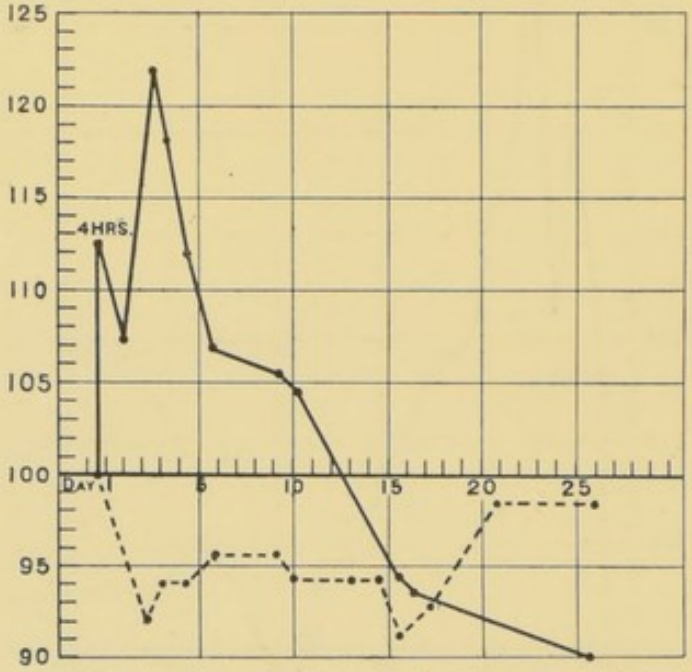


FIG. 10.—Life-duration of red corpuscles after transfusion of pure blood into peritoneal cavity (Experiment 9). The animal remained in poor health from the time of the experiment.

4. Lastly the life duration is very greatly influenced by certain drugs (fig. 11).

Effect of Defibrination.—Defibrination destroys the character of the blood as a tissue by destroying its matrix. On the red corpuscles, however, it has little or no injurious effect. Their life duration after defibrination is, under favourable circumstances, the same as when pure blood is transfused (fig. 8). This conclusion differs from the one arrived at by Hayem, according to whom, the corpuscles are by the act of defibrination doomed to a certain death — 'are killed, beaten to death.'

[1] For fuller discussion of these curves, see the author's paper in *Journal of Anatomy and Physiology*, vol. xxi., 1887.

They are ultimately destroyed, as the animal's own corpuscles are; but that they are not killed is clear from the circumstance, that they remain within the blood for days, sometimes even for weeks; whereas, as will be afterwards seen, red

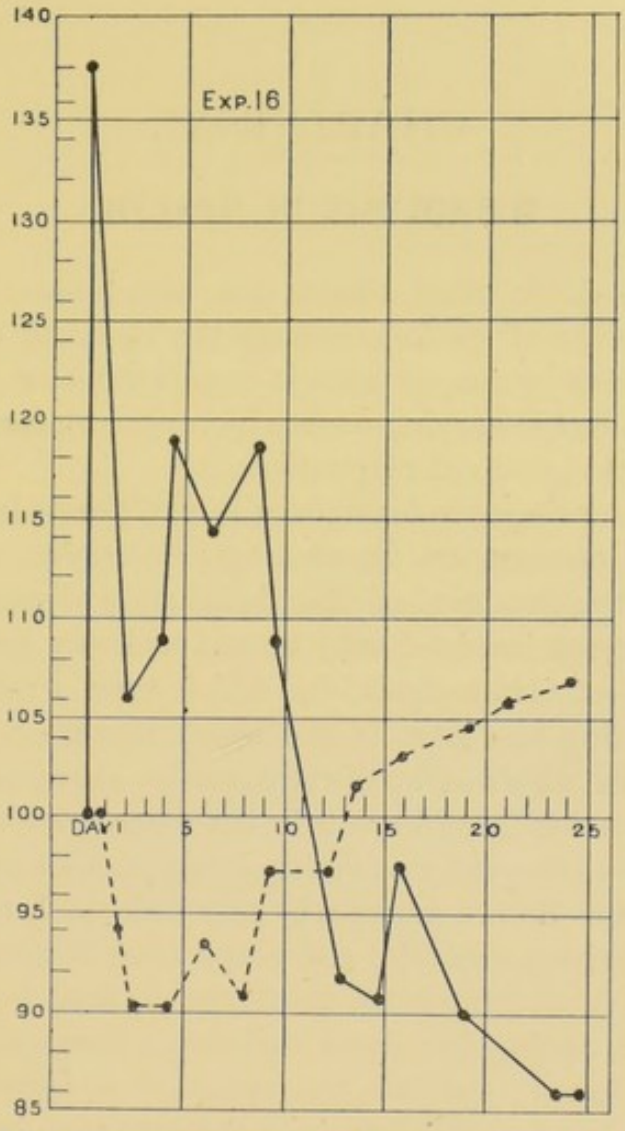


FIG. 11.—Injection of 100 c.c. of pure blood mixed with 30 c.c. of a 5 per cent. solution of sodium phosphate into the peritoneal cavity of a rabbit under the same conditions and with the same precautions as in the preceding series with pure and defibrinated blood. Greater quantity of blood transfused. *Life-duration of corpuscles shorter.*

corpuscles killed by the action of poisons—for example, by pyrogallic acid—are seized upon by the leucocytes, and removed from the circulation, in the course of a few hours.

CHAPTER XI.

HÆMOLYSIS IN HEALTH.

Introductory.—Like other tissues, the blood must be affected by the discharge of its functions as the carrying tissue of the body. A certain wear and tear is connected with this process, which must affect in varying degree its various elements—plasma, white corpuscles, and red corpuscles.

What, under these circumstances, is its ultimate fate? Where, and in what manner, are its elements destroyed, and in what manner are the products of this destruction disposed of. The various processes involved may be conveniently grouped under the one title of 'Hæmolysis,' by which term I mean no single process affecting one part of the blood alone, *e.g.* the red corpuscles, but the whole series of retrogressive changes which affect the blood as a whole, and result in the destruction and removal of its various parts—red corpuscles, leucocytes, or plasma.

The changes do not necessarily affect all these parts in equal degree; sometimes one (the red corpuscles), sometimes another (the leucocyte), sometimes the third (the plasma), being specially affected. To distinguish these variations, corresponding terms may be employed; and we can speak of a *Hæmocytolysis*, or a *Leucocytolysis*, or a *Plasmolysis*, as the case may be.

I.—Evidences.

Of these, *Hæmocytolysis* is the one which has received the little attention that has hitherto been given to the subject. The fate of the red corpuscles,—constituting, as these do, the chief bulk of the blood—has overshadowed what at first sight appears, the altogether subsidiary processes of leukocytolysis or plasmolysis. The reason for this, doubtless, has been, that

the process of hæmolysis can be most easily studied, as it affects the red corpuscles. One of their constituents—hæmoglobin—is of such a special character, that, unlike the proteid constituents of the leucocyte or the plasma, it cannot be got rid of without leaving some evidence of its fate behind,—in the form of either *Bile pigment*, *Urinary pigment*, or *Blood pigment*. Indeed, it would almost appear as if special provision had had to be made for getting rid of the bye-products of this particular body (hæmoglobin); since, cotemporaneously with its appearance in the animal scale, appears also the Liver, one of whose most prominent functions is the destruction of hæmoglobin, and the excretion of its pigment remains in the form of the bile pigments.

Prominent, however, as the evidences of hæmocytolysis may thus be, of no less importance, and, if looked for, hardly less prominent, are evidences of *Leukocytolysis* and *Plasmolysis*,—these two processes being considered together, since they are intertwined, and mutually affect each other greatly.

The chief evidence of the former is the extraordinary daily variations in the number of leucocytes—*Leucocytosis*—connected chiefly with digestion; variations that necessarily imply periodic increase, with subsequent diminution in their number. The chief evidence of the latter is a change of a less prominent character, but one nevertheless, when properly regarded, no less significant; namely, the *increased coagulability of the blood* (*i.e.* the plasma) at certain periods—a phenomenon (like leucocytolysis and doubtless related to it), most marked during digestion—in that portion of the blood where the leucocytic changes are most marked, namely, the portal circulation. The changes in the plasma include, moreover, others of a more easily demonstrable kind, namely; certain well-marked *morphological changes*—the presence of albuminous spheres and granules, undoubtedly derived from the plasma itself, as well as from the corpuscles; changes confined to those situations in which the plasmolysis is most active, especially the spleen.

All these evidences of hæmolysis, of varying prominence in health, become, under special conditions, as the following studies will shew, exceedingly prominent in disease; and their true value and significance can under such circumstances be much more readily determined.

II.—Nature.

As regards the *Nature* of hæmolysis, it is by no means the slow and gradual process of decay, which, notably in the case of the red corpuscle, it is represented to be by the only observer who has made any previous study of the subject.

> "The red corpuscles gradually lose their elasticity and become effete; and when they are to be eliminated, are taken up by white corpuscles, and by the cells of spleen, and bone marrow; and stored up, especially within the capillaries of the liver, the spleen, and the bone marrow. The enclosed corpuscles are then converted into yellow-coloured and colourless albuminates of iron, which are recognizable micro-chemically, partly in granular, partly in soluble form; part of the material being given up to the liver cells, and converted into bile pigment."[1]

On the contrary, as the subsequent studies shew—

(1) It is an active process, causing changes in the plasma, and consequent liberation of hæmoglobin from the red corpuscles.

(2) It involves all parts of the blood—leucocytes, plasma, and red corpuscles.

(3) It involves a daily liberation of hæmoglobin, and its destruction by the liver.

(4) It is greatest in youth, diminishes gradually with advancing age, and is very slow in old age.

(5) It is greatest during digestion; so much so, as practically to be confined to that part of the circulation specially affected by the processes of digestion, viz., the portal blood.

1. **Chronic Hæmocytolysis.**—The mode of death described by Quincke does occur; but it represents only one, and that the least important, manner in which red corpuscles meet their fate.

I designate it *chronic hæmocytolysis*, in contradistinction to acute hæmocytolysis, the process described later (see p. 135). It is the change in the corpuscles which occurs when they have not been subjected to any specially injurious influences; when,

[1] Quincke, *D. Archiv f. klin. Med.*, xxxii., 1883; also Kunkel, *Zeitsch. f. Physiol. Chemie*, Bd. v.

in consequence, they have been allowed to undergo a process of natural decay within the circulation.

This process, then, is a slow and gradual decay of the corpuscle; manifested chiefly, by slight changes affecting colour, shape, and resistance—namely, deeper colour, more spherical shape, and greater resistance offered towards reagents. The hæmoglobin remains within the corpuscle to the last. The corpuscle, as a whole, is ultimately taken up by cells, especially those of the spleen, but also by leucocytes; and is carried to certain situations—namely, the spleen, the *capillaries* of the liver (figs. 12



FIG. 12.

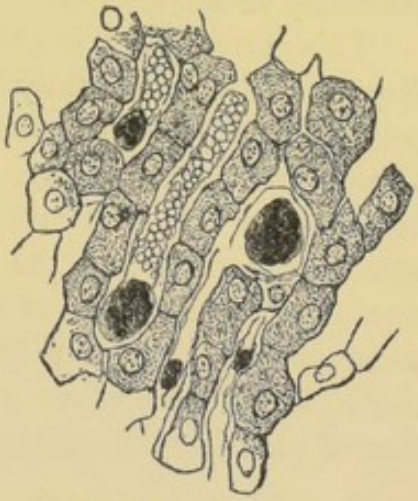


FIG. 13.

FIG. 12.—LIVER OF AN OLD PIGEON. Numerous pigment masses in the capillaries; no pigment in the liver cells; many of the pigment particles display the size and shape of the original red corpuscles from which they have been formed.

FIG. 13.—LIVER OF AN AGED DOG, shewing pigment masses in the capillaries; none in the liver cells; the size of many of the particles is seen to correspond to that of the original red corpuscles.

and 13), and the bone marrow. The pigment thus formed is *never found within the liver cells.* Within the cells, the hæmoglobin undergoes gradual conversion into blood pigment; the particular character of this pigment being, that it often forms conglomerate heaps, its particles varying in size and shape—many of them retaining the size and shape of the original red corpuscles. This feature is best seen in those animals possessing red corpuscles of special size and shape, *e.g.* frog, bird; for the larger the

original corpuscle, the larger the pigment particles formed (fig. 12, liver of an old pigeon). When once formed, this pigment is remarkably resistant; hence it can be recognized long after the death of the original corpuscle. Hence further, *pigment of this character and in the above situations affords no information as to the time of death of the corpuscles.*

As regards its significance *as an index of the amount of the preceding hæmolysis*, it may be said that this has usually been in inverse proportion to the amount of this kind of pigment present. For its presence denotes, that the conditions have been favourable to the slow and gradual decay of the red corpuscles,—that is to say, the changes in the blood have not been very active, otherwise these corpuscles would have been destroyed in the way presently to be described.

This statement holds true for health, and most conditions of disease. Experimentally it is possible, in the case of certain poisons, to inject such doses that the red corpuscles are killed almost instantly (within, it may be, a few minutes), without breaking up. In that case, they are enclosed bodily by leucocytes and splenic cells, and the pigment subsequently formed therein retains the characters of chronic hæmocytolysis. In disease, a somewhat analogous condition, albeit one of slower origin, is represented in malaria, where the corpuscle becomes individually the seat of parasitic infection, and yet often dies *en bloc* (Plate VIII.).

As regards *its relation to bile pigment formation*, it remains to be added, that for reasons that will be stated, the above process of chronic hæmocytolysis subserves the process of bile pigment formation in an altogether subsidiary degree.

In other words the process favours the accumulation of blood pigment in the body; and only slightly, the formation of bile pigment.

2. **Acute Hæmocytolysis.**—In marked contrast with the preceding is the process now to be described; the one connected with active hæmolysis in the blood. In this, the hæmoglobin is set free from the corpuscle; possibly sometimes as free hæmoglobin; but far more frequently, still retaining some combination with the proteid material of the stroma of the corpuscle. Its fate under these circumstances is a varying one. Part of it

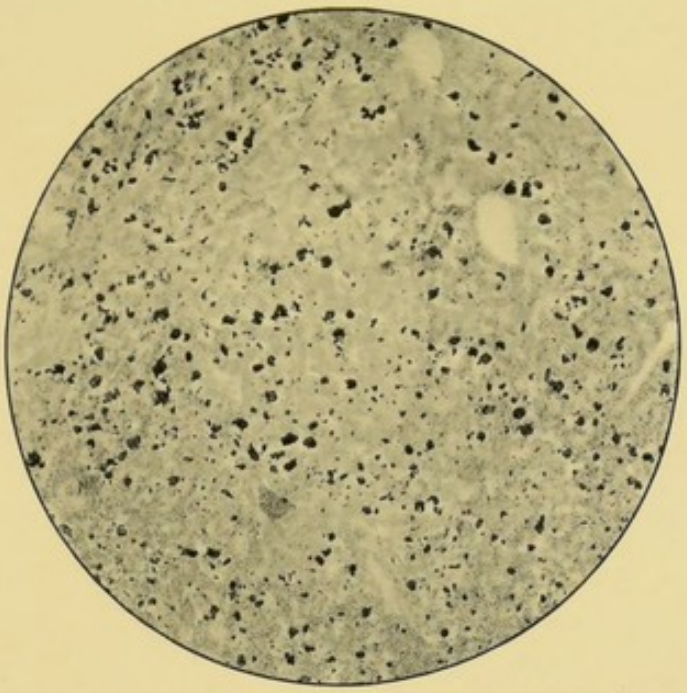


FIG. 1.—CHRONIC HÆMOCYTOLYSIS. LIVER OF A FROG × 25.

Showing large and varying size, and irregular distribution of conglomerate pigment masses resulting from chronic hæmocytolysis.

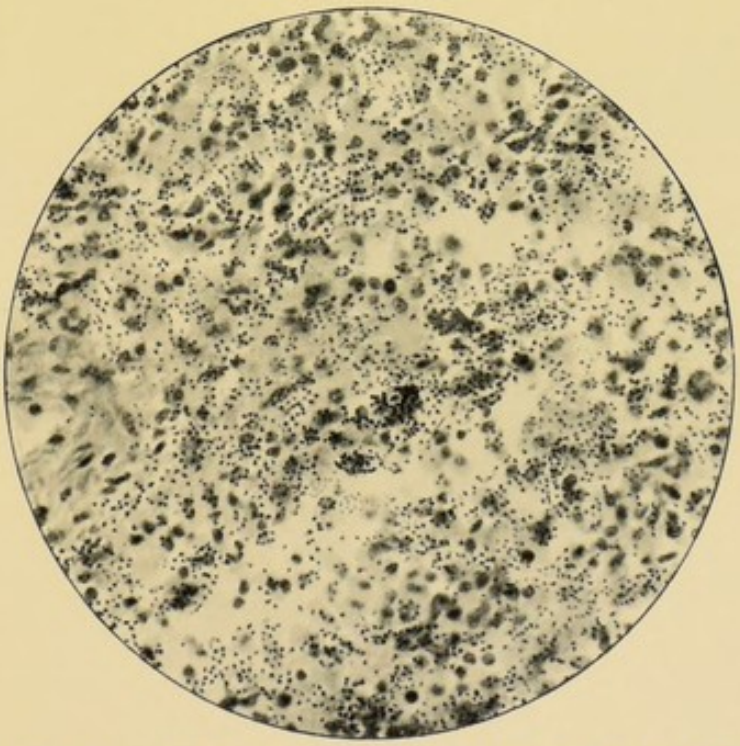


FIG. 2.—ACUTE HÆMOCYTOLYSIS. A LYMPH GLAND. × 350.

Showing in contrast with the above the small and uniform size of the pigment granules formed in acute hæmocytolysis in this case as the result of absorption of free hæmoglobin from extravasated blood.

may be utilized at once for purposes of blood formation, in the very sites in which it is set free (*v. postea*); part of it may be taken up by cells, and there undergo gradual conversion into blood-pigment; but the special feature of the change is, that part of the hæmoglobin is carried to the liver, taken up by *the liver cells*, and then broken up. *It is this process which subserves the biliary function of the liver;* it is this process which leads, *under particular conditions*, to an excess of iron and pigment *within the liver cells.* In health, the chief evidence of this change in the corpuscles, this acute hæmocytolysis, is the formation of bile pigment and, to an altogether subsidiary extent, the formation of blood-pigment, or deposit of iron—the latter chiefly within the liver cell. If pigment is formed, it possesses certain characters that serve to distinguish it from that formed as the result of chronic hæmocytolysis—namely, a greater uniformity in the size and shape of its particles, which are generally smaller. Moreover, these characters are not affected, as in the former case, by the size or shape of the original corpuscle. On the contrary, they are the same for all animals—frog, pigeon, or mammal (fig. 2, Plates VI., VII., VIII., and IX.).

Moreover, another feature no less distinctive is, that this pigment is the only variety found *within the liver cell*—a fact possessing a special significance, denoting, namely, that the hæmoglobin broken up by the liver cell has passed into that cell as hæmoglobin. In other words, any hæmolytic change that takes place in the liver occurs in the capillaries adjacent to the liver cells, not within the liver cells themselves. The latter deal with the hæmoglobin set free, and carried through the endothelial cells of the capillary walls into them; the actual liberation of the hæmoglobin from the red corpuscle—acute hæmocytolysis—occurs either in the capillaries of the liver, or—and still more, as will be afterwards seen—in the portal blood before it reaches the liver, notably in the spleen (Plate III.).

Further, the pigment formed in this way possesses the characters above described wherever it is found—*e.g.* in the splenic cells, the leucocytes, the endothelial cells of the liver, or in the cells of the convoluted tubules of the kidney. The condition in the blood antecedent to this change is thus, and this is the point of cardinal importance, what may be described as a *local hæmoglobinæmia*; that is to say, the hæmoglobin so acted

upon has first escaped from the individual red corpuscle concerned. The red corpuscle has not been taken up bodily by the cell in which the pigment is found. The hæmoglobin has been set free from the corpuscle into the plasma—whether actually as free hæmoglobin, or in combination, as is probably most common, with the proteid of the stroma, matters not from our present point of view—and has thence passed into adjacent cells, splenic, leucocytic, endothelial, or renal, as the case may be. That is its chief significance. It affords no information regarding the *site* of the antecedent hæmocytolysis, *not even in the case of the liver cell itself.* Even in cases in which these may be filled with such pigment, the evidence adduced clearly proves that the greater part of the preceding hæmocytolysis with its corresponding local hæmoglobinæmia has taken place elsewhere in the portal blood, notably in the spleen.

The use of this term *hæmoglobinæmia,* in the above defined sense, calls for some remark. The term has hitherto been generally used as signifying the presence of free hæmoglobin in more or less quantity in the plasma—in quantity recognizable by ordinary spectroscopic tests for hæmoglobin; such a condition, in fact, as must necessarily exist in every case marked by hæmoglobinuria. In that sense, it may be still employed, but not exclusively in that sense. In the strictest sense, it is also the appropriate term to designate any condition, *however slight,* in which hæmoglobin has been released from its red corpuscle, and has passed into the plasma; whether the escape be confined to a single red corpuscle, or to a multitude. In this sense, it is here employed, as being at once the correct, and the most appropriate, description of the condition referred to.

I thus find, that the significance attaching to blood pigment as an evidence of hæmocytolysis varies according to the characters of its granules, and its distribution. In the spleen and bone marrow, the character of the pigment is with few exceptions our guide as to its nature, whether chronic or acute. In the case of the liver we have to consider not only its characters, but also its precise situation, whether within the liver cells, or within the capillaries, or in both situations.



FIG. 1.—ACUTE HÆMOCYTOLYSIS. LIVER OF A PIGEON.

Showing the character and situation of the blood pigment formed from free hæmoglobin (acute hæmocytolysis) fine granules *within the liver cells*; none in the capillaries.

See also Plate facing page 184.



FIG. 2.—ACUTE HÆMOCYTOLYSIS. LIVER OF A RABBIT.

Showing the abundance and situation of the fine pigment granules *within the liver cells* after acute hæmocytolysis induced by toluylendiamin. Camera lucida drawing. Exp. 43.

III.—Causes.

As regards the factors which bring about this destruction, I find:

(1) The destruction is no mere senile decay.

(2) Nor is it the result of any mere physical action of products, *e.g.* food products, introduced into the blood during digestion.

(3) It is, on the contrary, the result of the activity of the cells, either within the blood (leucocytes), or lying in closest relation to it (gastro-intestinal mucosa, spleen, and liver); and of special changes (plasmolytic or globulicidal) induced in the plasma by the activity of such cells.

(4) Since the activity of this group of cells is mainly a question of gastro-intestinal chemistry—that is to say, is chiefly dependent upon the character and amount of the food taken, the hæmolytic changes which attend this activity are thus most marked during digestion. During starvation, on the other hand, they are at their minimum. It is also, however, during digestion that blood-formative processes are presumably most active, whether in plasma, leucocytes, or red corpuscles. It thus appears, that, in this as in other respects, the behaviour of the blood is that of a tissue. Just as in muscle the work which promotes its growth must always be attended by corresponding wear and tear; so also in the blood, it is affected most injuriously by the very influences which promote its renewal. In other words, in it, as in all other tissues, waste and repair are always associated together.

IV.—Seats.

With regard to the seats of these changes, it is necessary, in the first instance, to bear in mind that in hæmolysis two processes are involved, namely:

(1) The actual process of disintegration of the various elements,—leucocytes, plasma, and red corpuscles.

(2) The subsequent disposal of the various products derived from this disintegration, *e.g.* hæmoglobin and blood pigments.

The seats of these two processes are not necessarily the same. Thus, to confine for the moment our attention to the

red corpuscle, its hæmoglobin may be set free into the plasma by one set of agencies, in one situation ; and be ultimately carried to be broken up in another situation by quite another set of agencies.

Products of this destruction—*e.g.* blood pigment, may be found in one situation, and may appear to denote that that particular site has been the seat of the hæmolysis—a conclusion that may be quite erroneous.

This assumption seems a natural one, and is hence very widely spread. It has proved a source of fallacy in this relation, serving to obscure the significance that should rightly attach to blood pigment. It has led to the view that pigment within the spleen or liver denotes that particular organ to be the seat of the preceding blood destruction ; and further, that the amount of pigment is an index of the extent of the preceding destruction.

The evidence adduced in the accompanying studies proves conclusively that this is far from being the case. It shews that blood pigment is by no means a reliable index, either of the *amount*, or the *site*, of the preceding blood destruction.

With regard to *amount* : on the one hand, pigment may be absent when the blood destruction is most active ; its absence, indeed, for reasons given, being one of the evidences that the destruction has been active. On the other hand, its presence *in certain situations*, *e.g.* the spleen, even in large amount, may, and often does, denote that the destruction has been a slow and gradual one.

And as regards *the site* : absence of pigment from the spleen may be, and often is, quite consistent with the most active hæmolysis going on in that organ ; while its presence in the liver, even in large amount, so far from proving that the liver has been the seat of actual hæmolysis, may be, and often is, quite consistent with a preceding hæmolysis effected entirely outside the liver, namely, within the spleen and gastro-intestinal capillary area.

No part of the studies relating to this subject of hæmolysis proved to be of a more difficult character than this one just mentioned — namely, the significance to be attached to the presence of blood pigment as an indication of the seat of hæmolysis. It was only after some three years continual obser-

vations, and experiments, that the various facts could be grouped together, so as to come under one generalization.

Results.—The following, then, are the results of my various studies with regard to this particular point.

1. Hæmolysis does not occur in all parts of the circulation alike, as would seem at first sight to be most likely.

2. On the contrary, it is confined almost exclusively to the *portal area*, as distinguished from the area of the general circulation.

3. The chief seats of hæmolysis within this area are, in their order of importance,

(*a*) The Spleen.
(*b*) The Gastro-intestinal capillary area.
(*c*) The Capillaries of the liver.

4. Outside the confines of this area, the amount of hæmolysis in health is so small that it may be disregarded. The only site, where, possibly, a certain change may occur, is the bone-marrow. But this tissue is more concerned with the storage and disposal of old effete red corpuscles, than with the active destruction of normal corpuscles.

5. In health, it may be said, that apart from the changes occurring in the portal area and in the organs in relation to it, little or no evidence of any hæmolysis is forthcoming. The chief evidence is afforded by the liver—the formation, namely, of bile pigments. But anatomically, constant evidence is also to be found within the spleen, viz. changes in the plasma, and in the red corpuscles; also within the gastro-intestinal mucosa, although from their widespread distribution these are not so readily demonstrated as in the case of the spleen.

6. In health, all the products of hæmolysis are disposed of within the confines of the portal area, chiefly by the liver; and none of them ever reach the general circulation. Hæmoglobin in considerable amount may be liberated within the portal area, and yet never reach the general blood. On the other hand, the liberation of *the smallest amount* of hæmoglobin in the general blood outside the liver is at once evidenced by its appearance in the urine;—a condition exemplified *in disease* by paroxysmal hæmoglobinuria, the hæmoglobinuria of burns, etc.; *experi-*

mentally, by the action of agents such as glycerine or distilled water, which exert a *direct* injurious action on the corpuscles, as distinguished from substances, *e.g.* the food products, which influence hæmolysis only *indirectly* through the activity of cells.

V.—Amount.

The actual amount of hæmolysis, that daily occurs, could only be determined, if it were possible (as unfortunately it is not), to estimate the daily excretion of bile pigment, and express this in terms of the hæmoglobin required to furnish it. The fact, however, that bile pigment is daily formed, and that special provision is made for its excretion, may be taken as denoting that the amount of worn-out hæmoglobin requiring daily removal (and replacement) is no inconsiderable one; that is to say, it is too large to be met by such provision as suffices for the disposal of leukocytolytic or plasmolytic, *e.g.* proteid, products.

In any case, whatever the amount, whether considerable or inconsiderable, it is not such as can be neglected; for it certainly varies considerably under the influence of various factors even in health; and, what is from the point of view of our present subject the more important, it undoubtedly varies still more in disease.

In health, the chief factor influencing it is, I consider, the factor of *Digestion*; and as this necessarily includes all the possible variations in the activity of that process, and of the cells concerned,—connected with variations in quantity and quality of food, healthiness or otherwise of gastric, pancreatic, and intestinal digestion—it is obvious, that there are very wide limits within which the amount of hæmolysis may vary. Nor are the abnormal variations due to the above causes necessarily always in the direction of increase. On the contrary, insufficient hæmolysis may be, and in my opinion often is, a cause of ill-health. The beneficial and remarkably 'clarifying' effects of 'cholagogues' are by no means due simply to expulsion of bile already formed; but also, and probably even more, to the increased hæmolysis, *i.e.* blood change, of which the increased flow and richness of bile are only the sequels.

In disease this factor also comes into play; especially when, as already hinted at, it is modified by the gastric and intestinal disturbances so common in conditions of disease. But, in disease, a factor,—even in health not altogether wanting, namely, in connection with the putrefactive changes in the intestine—which affects hæmolysis even more than the one of digestion, is *Infection*; whether operating through the blood as a whole (general infection) or operating (by means of its products) from one particular area, especially from the gastro-intestinal area. In the latter case, its operation is doubly effective; inasmuch as in addition to its own *direct effects*, it also acts *indirectly*, by perverting the normal processes of gastric or intestinal digestion.

The influence of infection on hæmolysis is manifested in a large number of infective diseases,—in the general anæmia which so commonly accompanies, in greater or less degree, such infections. In the great majority of cases, however, the influence on hæmolysis is only one part of the general, and in most cases far more important influences—bactericidal, immunizing, antitoxic, agglutinating, and the like—exerted on the blood by infective agents.

It is only in certain cases that the influence is specially hæmolytic, *i.e.* globulicidal. In such cases, the blood-changes assume a special character, and usually a special degree of intensity. The most striking instance of this influence is shown in *malaria*, by the actual presence in the red corpuscles of the spores of the disease. But these cases are the exception. It is not by direct action of infective agents on the blood, that hæmolysis is usually affected; but indirectly by the absorption and action of the poisons produced. Even in the latter case, the poisons do not all operate in like manner. Some (a very few) appear to have an action analogous to that of distilled water, so immediate and direct is it. The result is then necessarily hæmoglobinuria; since the destruction is not confined to the portal area, but affects the blood corpuscles wherever they are brought into contact with the toxic agent. Examples of such a condition are afforded by paroxysmal hæmoglobinuria, and the various conditions characterized by this symptom. Some cases of malaria also exemplify this mode of action.

In most cases, however, the hæmolytic action of these toxins is, as in health, *indirect*; that is to say, they induce hæmolysis *indirectly*, by influencing the activity of the cells in closest relation to the blood. And hence their hæmolytic action is confined, as in health, to the portal area; and it is unattended with any hæmoglobinuria. This mode of action is exemplified by all those classes of infective disease in which there is evidence of increased hæmolysis without any accompanying hæmoglobinuria.

It is, however, most typically exemplified, in my judgment, by the disease which forms the subject of these studies—pernicious anæmia. In no disease, according to my observations, does such a degree of hæmolysis occur; in no disease are its evidences so numerous or so marked, whether regard be had to the degree of anæmia resulting, the character and amount of the biliary or urinary pigments or the anatomical changes (pigment accumulation) found *post-mortem*.

What its special characters are it will be the purpose of the next chapter to consider.

VI.—Relation to Blood Formation.

One point only remains to be considered, in connection with this general survey of hæmolysis as a whole,—namely, the relation of this process to the supplementary process of hæmogenesis. This has already been touched on incidentally, in connection with the sites in which hæmolysis occurs. It has been seen, that the sites of the two processes correspond; and no evidence has been forthcoming in these studies to indicate the wide separation between them that is often spoken of.

The fact that hæmolysis and hæmogenesis should occur in one and the same organ (*e.g.* the spleen), is often spoken of as if it involved a contradiction in terms; as if it were utterly impossible that within one organ processes so different should go on. In reality, properly regarded, this involves no greater contradiction in terms than the fundamental law regulating all cell growth, namely, that building up is always accompanied by breaking down. The material of no use to one cell may be utilized by the cell adjacent; so the worn-out hæmoglobin set free from a red corpuscle within the spleen may quite well be utilized at once by the cells adjacent.

And this, in my judgment, is probably what occurs. To adopt any other view would be to imply a useless waste of time and energy on the part of the economy,—of which, one may be certain, on *à priori* grounds alone, that it is quite guiltless. For it would imply that a material so valuable for blood formation as iron, when perchance set free in the spleen, was forthwith transported to the liver and got rid of; while at the very time a corresponding amount of iron was urgently necessary to replace it. It may be taken as certain that no such waste occurs. On the contrary, it is much more likely that a very considerable, if not the greater, part of the hæmoglobin set free from individual corpuscles during digestion, is again *immediately utilized* for purposes of blood formation, without ever reaching the stage of blood pigment, still less of bile pigment.

This conclusion involves the consideration of another point of importance, namely, the fate of the iron set free, not within an enclosed organ like the spleen, but within an excretory organ like the liver.

That iron is necessary for the proper discharge of the varied functions of the liver cell may be taken for granted—so constant a constituent is it of the protoplasm of this cell, as indeed of most cells. And this proportion of iron in the liver undergoes a periodic increase during digestion, as shewn by Professor Delépine; an increase so marked, that he has proposed to distinguish the process by a special name, viz., as an evidence, of a '*ferrogenic* function' of the liver, analogous to its glycogenic function. What the further fate of this iron is, apart from its use to the liver cell itself, is not clear. A certain amount is daily excreted in the bile. And this small amount probably suffices in health to maintain an amount within the liver cell just sufficient for its own purposes.

In disease, however, in which hæmolysis is greatly increased, —notably in pernicious anæmia, but also in many other conditions the amount of iron and pigment in the liver cell is often far in excess of its requirements. On the further fate of this pigment my observations throw no special light, *e.g.* whether it is again available for purposes of blood formation in other organs or not.

On the whole, it appears to me most probable, that once it

has passed into the liver cell, the iron of the hæmoglobin is less available for subsequent use for purposes of blood formation, than when stored up either within the spleen or the bone marrow.

As regards the fate of the hæmoglobin, it may thus be said, that this varies according as the destruction of the red corpuscles has been chronic or acute. Chronic destruction is conducive to the storing up of a large quantity of blood pigment within the body, chiefly within the spleen and the bone marrow. This pigment contains *all the iron* of the original hæmoglobin. Anything that tends to render destruction more acute favours the removal of the hæmoglobin from the body in the form of bile pigments; and along with the bile pigments a certain proportion of the iron is always excreted in the bile. The chief advantage of having iron in the system is, that it may afterwards be used for purposes of blood formation. This object is best served, when the iron is deposited in the organs concerned in that process, namely, the bone marrow, and the spleen. The presence of iron in large quantities within the liver cells, as in some forms of anæmia in which the destruction is very active, does not serve any useful purpose. It is in process of excretion, and probably interferes to some extent with the proper action of these cells.

In relation to transfusion of blood, this point is of interest. Transfusion has a certain hæmogenic value, in virtue of the presence of hæmoglobin in the form best suited to enable its iron to be stored up in the body. Free hæmoglobin introduced into the blood is removed at once as a foreign body, mainly by the kidneys, and in part also by the liver. Hæmoglobin introduced in the form of red corpuscles remains within the circulation, for a period commensurate with the life duration of the corpuscles. Under favourable conditions, it is afterwards stored up in the spleen and bone marrow, in the form of blood pigment. Little or none of it is then removed from the system.

Summary.

The foregoing is a brief summary of my results in relation to the subject of hæmolysis in health. The conception formed of this process, it will be seen, extends considerably beyond

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any such limited view of the process, as that represented by Voit's or Quincke's opinion noted at the outset. It also extends considerably beyond any conception of this process formed by myself at the outset; and that, too, not only in one relation, but in all relations,—its importance as a whole, its seats, the factors operating to bring it about, the significance of blood pigment in relation to it, and lastly, but not least, its relations to other processes, especially those of digestion on the one hand, or the biliary functions of the liver on the other.

1. *Function of the Liver.*

As regards the latter, hæmolysis is not a process necessary to subserve the biliary functions of the liver, as one might quite conceivably have asserted at the outset; but, contrariwise, the biliary functions of the liver, so far as pigments are concerned, are solely necessary in order to subserve hæmolysis. That is to say, the bile pigments are not necessary for any purpose they serve; they are merely derivatives of hæmoglobin which have to be got rid of; and the fact that any such necessity exists implies a corresponding necessity for continual removal of effete hæmoglobin. Perhaps in no respect more than this one,—the rôle of the liver in hæmolysis—are the conclusions more striking. On account of its biliary functions, this organ has been universally regarded, as not only a likely seat, but in all probability the most important seat, of hæmolytic change. On the contrary, the facts ascertained shew that the chief rôle of the liver in hæmolysis is that of an excretory organ. It is not in it primarily, nor yet in it chiefly, that the actual hæmolytic changes in the blood are produced. These are determined in great part before the portal blood reaches the liver—by the activity of the cells of the gastro-intestinal mucosa, and of the spleen. The chief function of the liver then declares itself, namely, to filter off, break up, and either utilize, or excrete, the various products carried to it. In short, in this relation *it is essentially the excretory organ of the portal system*, standing to that system in the same relation as the kidneys stand to the general circulation. The grounds for this conclusion will be found stated in detail.[1]

[1] See Part VIII.

2. *Function of the Spleen.*

While my results, so far as the liver is concerned, thus modify our views regarding the importance of the liver as a *seat* of hæmolysis, they serve, in no less striking degree to accentuate the importance of the spleen in this relation. No portion of the studies, indeed, in my judgment, are more conclusive than the series—experimental, histological, and chemical—throwing light on the important part taken by the spleen in hæmolysis.[1]

No organ presents conditions so favourable to action on the blood as the spleen.

> "Its arteries open directly into an open meshwork of channels devoid of definite walls from which the veins take direct origin. The interstices of this meshwork are filled with a delicate lymphoid tissue in which the various cellular elements lie embedded." [2]

In no organ are the relations between cells and blood so close or intimate.

If the blood can be affected by cellular activity at all, nowhere should this be more manifest than in the spleen; where, so to speak, all the cells lie bathed by the blood stream—not confined within capillaries as elsewhere. The remarkable effect of excision of the spleen in materially diminishing, —in the case of moderate doses, even abolishing—the hæmolytic action of so potent a hæmolytic agent as toluylendiamin, demonstrates, better than any other single fact could do, how important is the part taken by the spleen in this action.[3]

As evidenced, indeed, to the naked eye, no organ is more strikingly or immediately affected by hæmolytic agents than the spleen. Within less than half a minute after their injection into the blood, it can be seen to become greatly enlarged, and engorged with dark venous blood (see p. 377).

3. *Portal Area as the Seat of Hæmolysis.*

Of the various conclusions arrived at, however, the one that at once proved the most difficult, took the longest time to reach

[1] See Part VIII.

[2] Von Wittich, *Hermann's Handbuch der Physiologie*, Bd. vii. 345.

[3] *Vide* Part VIII., Chapter XXXVI.

(three years), and ultimately proved to be the most important, is the one regarding the distinction between the portal blood and the general blood as seats of hæmolysis. It was led up to by no one observation in particular, unless perhaps the remarkable effect of excision of the spleen; but, once reached, all the other facts and observations—many of them up to that time apparently of doubtful importance—seemed at once to fall into line with it, both supporting it, and being themselves explained by it.

Up to the time it was reached, the main difficulty was to account for the remarkably varying distribution of pigment betwixt various organs often seen, notably betwixt the liver and the spleen; sometimes the spleen (*e.g.* after transfusion), at other times the liver (*e.g.* pernicious anæmia), being, as judged by the evidences of hæmolysis discoverable in either, the chief, or even the exclusive, seat of the preceding destruction. Hence the working hypothesis on which the experiments were, for the most part, originally based,—namely, that sometimes the one, sometimes the other, took the chief part in hæmolysis; and that excessive hæmolysis in one or other probably indicated morbid activity on the part of that particular organ (see p. 74).

When the conclusion above referred to was ultimately reached, namely, that the portal blood as a whole was the seat of hæmolysis, attention was *for the first time* directed to the gastro-intestinal area, and the possible influence of the whole series of factors operating in connection therewith—to which attention has already been drawn (p. 140).

The influence of this conclusion extended, moreover, beyond the limits of health, namely, to the facts connected with hæmolysis in disease. In particular, it threw another and entirely new light upon, and originated fresh studies regarding, the nature of the hæmolysis in pernicious anæmia, and the possible significance of gastro-intestinal symptoms and lesions in connection therewith,—studies whose results will be presently seen.

In the light of the development the subject has since undergone, it is desirable to accentuate the sequence of events above related. The fact established by these studies that hæmolysis is a process confined mainly or entirely to the portal area has passed into general knowledge, and gained general acceptance. The natural corollary of this, also established by these studies,

that gastro-intestinal processes play an important part in determining these hæmolytic changes, has also been generally accepted; and finally, the further corollary, no less natural, that these processes may play a no less important part in the hæmolysis of disease, and that hence a new significance is to be attached to any symptoms pointing to disorders connected with this particular tract, has likewise received fair recognition.

In appraising, however, the proper value to be attached,—in my opinion rightly so—to conclusions of this latter kind, it is desirable to keep in mind the true sequence of events as above related,—a matter in some danger, to judge from certain criticisms to which my conclusions have been subjected, of being overlooked. That is to say, it was not the prominence or character of symptoms of gastro-intestinal disturbances *per se* that suggested :—

(1) *The portal blood* as likely to be specially affected, by any destructive action that such processes might exert upon the blood ; and consequently,

(2) *The liver* as the most likely organ to shew evidences of this increased hæmolysis in the shape of pigment.

On the contrary, the facts were arrived at in the reverse order. It was the detailed studies regarding the significance of blood pigment, and the nature and seats of hæmolysis, that *first pointed* to the portal area as the chief seat of this process; and it was this latter observation, that *for the first time* brought into discussion the probable importance and significance of gastro-intestinal processes in producing it.

In other words, the pathological facts were not ascertained by the help of a preceding clinical hypothesis regarding the possible importance of such gastro-intestinal processes ; but the importance of the latter in relation to hæmolysis was never realized, until the studies here detailed (anatomical, experimental and chemical) had established the fact that the portal blood was the chief seat of hæmolysis, and that the causes of the hæmolysis were to be sought in connection with the organs of the portal system.

CHAPTER XII.

HÆMOLYSIS IN PERNICIOUS ANÆMIA.

I.—Not a Physiological Exaggeration.

1. The hæmolysis in pernicious anæmia is no mere exaggeration of that which occurs in health.

After transfusion of blood, directly or intraperitoneally, a large excess of corpuscles has to be got rid of. No hæmoglobinuria occurs, such as would indicate a rapid dissolution. The destruction, as already seen, takes place gradually, a diminution in the number occurring day by day till the whole excess is removed. The time taken for this varied, from a few days to two to three weeks, according to the quantity injected[1] (figs 8, 9, 10).

Moreover, during this removal the health of the animals appeared in no way affected. On the contrary, the animals usually put on weight. The conditions were, in short, those of health, with the single exception of there being a large excess of corpuscles in the blood gradually being got rid of. What were the changes produced in the various organs by the removal of this excess?

The *degree of health* in the animals experimented on may be judged from the changes of the body weight.

	Increase in Weight.
Thus Exp. 1	12 per cent. in 4 weeks.
Exp. 3	19 „ „ 3 „
Exp. 5	13 „ „ 3 „

[1] Hunter, *Journal of Anatomy and Physiology*, vol. xxi. p. 139 *et seq.*, 1887.

The *amount of blood* successfully disposed of in these experiments without any apparent disturbance was:

Exp. 1: 200 per cent. (as the result of four transfusions) in the course of three months. That is to say, within this period, this animal, in addition to its own normal blood destruction, had to dispose of a surplus equal to twice the amount of its own blood.

Liver.—The slightest possible increase in the pigment within the liver cells, giving the slightest reaction to ammonium sulphide. None within the capillaries.

Spleen.—Pigment very abundant.

Exp. 3: 92 per cent., followed later, in course of two months, by 54 per cent.

Liver.—Here also the increase in pigment in the *Liver* was remarkably slight, just sufficient to give, with ammonium sulphide, a slight greenish tint around lobules. Large amount of pigment in *Spleen.*

Exp. 5: 70 per cent. Killed thirty-eight days later.

Liver.—Cells normal: faint trace of fine granular pigment in portal zone, recognizable by slight greenish coloration given by ammonium sulphide.

Spleen.—Pigment very abundant, giving intense darkening with ammonium sulphide.

Exp. 7: Blood (defibrinated) injected to the amount of 54 per cent. Killed eight days later.

Liver.—Gave no iron reaction with ammonium sulphide.

Exp. 10: 50 per cent. of defibrinated blood injected. Killed forty days later.

Liver.—Normal. No pigment.

Spleen.—Very large deposit of pigment. Tissue gave a coal-black reaction with sulphide of ammonium and deepest Prussian blue reaction of iron. (See Plate VII., fig. 1.)

The result of the destruction was a large increase of pigment in certain organs, invariably most abundant in the *Spleen* (Plate VII.), the *Liver* in contrast containing relatively little, and sometimes shewing no increase at all. The distribution of the pigment betwixt spleen and liver was thus precisely the reverse of that obtaining in pernicious anæmia. The increase in the spleen as compared with that of the liver was as striking and notable as is the reverse in pernicious anæmia.

In short, I found it impossible, by transfusion of even the largest quantities of blood, to reproduce in the healthy animal

PLATE VII.

FIG. 1.—SPLEEN OF HEALTHY RABBIT.

Stained with alum carmine and treated with ferrocyanide of potassium, and dilute HCl in order to develope Prussian blue reaction of free iron. Hardly a trace of any reaction.

FIG. 2.—SPLEEN OF RABBIT.

Stained and treated as above. Showing very considerable excess of blood pigment giving Prussian blue reaction. (After hæmolysis induced by injection of phosphate of soda into the blood.)

FIG. 3.—SPLEEN OF RABBIT.

Stained as above. Showing extraordinary excess of blood pigment. (Exp. 10 after transfusion of blood. The liver in this case contained no pigment.)

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Fig. 1.

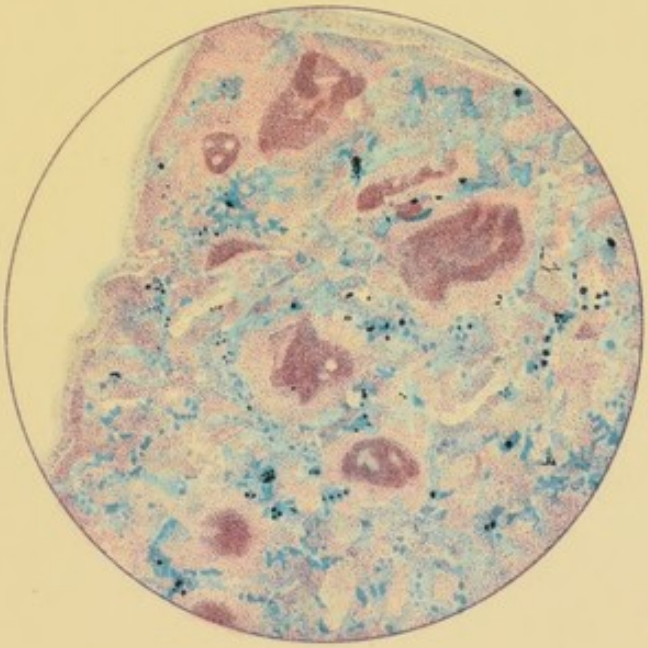


Fig. 2.

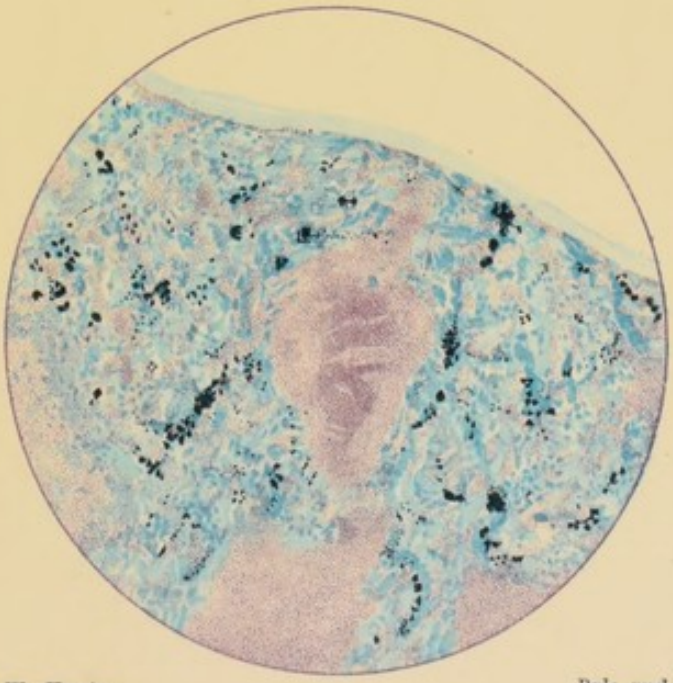


Fig. 3.

Pernicious Anæmia, Dr. W. Hunter.

Bale and Danielsson, Ltd., Lith.

the peculiar distribution of pigment betwixt liver and spleen characteristic of pernicious anæmia. And inasmuch as the conditions existing in the experiments were as nearly as possible those of health, and the increase of corpuscles was got rid of in a normal way, the conclusion I arrive at is that:

The blood destruction of pernicious anæmia is not simply an exaggeration of that which goes on in health, but differs from this in some essential respect.

II.—Not the Result of Extravasations.

2. The hæmolysis of pernicious anæmia differs from that which results from absorption of extravasated blood.

The transfusion experiments referred to above were undertaken, in the first instance, in order to ascertain whether excess of pigment in the liver could be produced by absorption of large extravasations; they were subsequently continued with special reference to pernicious anæmia, to ascertain whether not merely an increase, but a similar distribution of the pigment betwixt liver and spleen, could be caused by absorption of large extravasations of blood.

It will be seen from the figures quoted above, that it would be difficult to test the influence of extravasation in this relation more severely than was done in these experiments. Both animals being anæsthetized, the whole of the blood of the one (either pure or after defibrination) was transfused into the peritoneal cavity of the other. The quantities injected at one time varied from 32 to as much as 92 per cent. of the total quantity of blood estimated to be in the animal's own body. Moreover, the transfusions were in some cases repeated—in one case no fewer than four times.

Distribution of Pigment between Liver and Spleen after Absorption of Extravasated Blood.

The results were not those that I had expected.

I had thought in this way to produce a large excess of pigment in the liver. On the contrary, the increase was never more than slight, sometimes non-existent (*Exp.* 10), even in

cases in which such enormous quantities of blood had been injected as

200 per cent. in three months (*Exp.* 1);
92 per cent., followed by a subsequent injection of 54 per cent (*Exp.* 3);
50 per cent. of defibrinated blood (*Exp.* 10).

In the last case, indeed, there was no increase at all; and in none of the experiments did the appearances presented by the liver differ materially from those found in health. Nor was the result affected by the length of time after the transfusion. The animals were killed at varying intervals—two, seven, ten, twenty-one, thirty days, and up to three months after the injection.

The contrast between the condition produced in these experiments, and that found in pernicious anæmia, was, if possible, even more notable as regards the distribution of pigment between *liver* and *spleen*. For while the liver contained little or no increase of pigment, the spleen was in all cases packed with it —to a degree, indeed, more striking than ever obtainable by any other method of inducing excessive blood destruction.

The following may serve as a sample experiment:—

(Exp. 10.) Rabbit, weight 4 lb. 2 oz.; 50 c.cm. of defibrinated blood injected into peritoneal cavity (equivalent to about 50 per cent. of the total quantity of the animal's own blood).

Highest increase of red corpuscles per unit volume of blood reached on third day, namely, 38 per cent. Gradual fall in their number till the normal was reached on the twenty-third day.

Temperature.—Before operation 37·2° C. Day after injection 37·2° C. Following day, 37·6° C.; by which time animal seemed in every way well; eating as usual. On fourth day, 37·2° C.

After death (killed on thirtieth day) no trace of peritonitis.

Liver absolutely normal, shewing not the slighest increase of pigment, not even sufficient to give any darkening with sulphide of ammonium.

Spleen, on the other hand, packed with pigment, becoming coal-black in that reagent and deep blue with the Prussian blue test,—iron reaction (Plate VII., fig. 1).

The results of these experiments appear to me to prove, that, apart from other factors, extravasation of blood *per se* cannot be held responsible either for the excess of pigment in

the liver or for its characteristic distribution between liver and spleen, in pernicious anæmia.

Dr. Stockman's Views.—A contrary view has been put forward, and ably advocated by Dr. Stockman, of Edinburgh (1895);[1] and inasmuch as it constitutes a sort of compromise between the view which regards pernicious anæmia as an essentially hæmolytic (destructive) variety of anæmia, and that which regards it only as an extreme form of anæmia, his view calls for special notice.

Dr. Stockman in his studies of anæmia has been greatly impressed by the frequent mention of bleedings and extravasations of blood in the variety of anæmia we term pernicious; and he has come to the conclusion, that it is the occurrence of such extravasations that constitutes the difference between ordinary severe anæmia and pernicious anæmia.

The latter, in his view, is not a special form of anæmia. The large quantity of pigment found in various organs, especially the liver, is not, he considers, an evidence of a special hæmolytic process, but is merely the result of absorption of blood from a host of minute extravasations occurring from time to time in various parts of the body. In support of this view, he finds that an increase of pigment in the liver can be produced by injecting blood subcutaneously into rabbits.

A criticism of this view appears to divide itself under two heads.

(1) Do extravasations occur with the frequency, or to the extent, which is here assumed?

(2) Can the typical pigment changes found in the liver, spleen, and kidney, in pernicious anæmia, be caused by absorption of extravasated blood?

Frequency of Extravasations.—The first question it is not proposed to discuss at any length; for this reason, that the answer to it must naturally be determined by actual individual experience. I can only say that my own personal experience is entirely opposed to the view that the extravasations met with in pernicious anæmia are either of the frequency, or the importance, that such a theory presupposes.

[1] *Brit. Med. Jour.*, vol. i., 1895.

It so happens that shortly after the publication of Dr. Stockman's views, I had occasion to make autopsies on two cases of pernicious anæmia.

The changes in liver, kidneys, bone marrow, and spleen were those characteristic of the disease. In one, the retina shewed a few hæmorrhages; and there were a considerable number of punctiform hæmorrhages in the subdural arachnoid, especially over the right hemisphere. At one part, there was a small collection of sero-gelatinous fluid over the right frontal lobe. Elsewhere in the body, after most careful search, not the slightest evidence or sign of extravasation, small or great, could be found.

It is well known, that punctiform hæmorrhages are not uncommon in the retina and subdural arachnoid, in the disease, as in one of the above cases. That a degree of extravasation such as had here occurred was capable of inducing the great increase of pigment in the liver and kidney, found in that case, is, however, in my view, quite out of the question.

Percentage of Iron in Organs.[1]

Pernicious Anæmia.	Liver.	Spleen.	Kidney.
Case 1 (subdural hæmorrhages), . .	0·207	0·097	0·068
Case 2 (no subdural hæmorrhages), .	0·515	0·023	0·043

For comparison, an analysis made at the same time from a case of ordinary severe anæmia is appended.

Severe Anæmia.	Liver.	Spleen.	Kidney.
Case 3,[2] . . .	0·093	0·029	0·004

Dr. Stockman admits that in some cases no hæmorrhages at all are to be found; and he accounts for this by assuming that the blood has been very quickly absorbed, leaving no trace behind. Even if such were the case, evidence of this absorption would, it is reasonable to suppose, be found in the glands through which the blood had been absorbed.

[1] The author is indebted to Mr. Richards, of the Chemical Laboratory of Charing Cross Hospital, for kindly undertaking these analyses.

[2] All three cases were under Dr. Abercrombie's care, Charing Cross Hospital. Case 3 was a woman who presented during life various motor and sensory disturbances in the lower limbs, and died with cystitis and acute bedsores.

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In the experiments referred to, in which large intraperitoneal extravasations were caused, a large quantity of pigment was invariably found in the lymphatic glands through which the blood had been absorbed (Plate V., fig. 2). I have found no such changes in the mesenteric lymphatic glands in pernicious anæmia, although I have specially looked for them.

Summary.—(1) Extravasations in pernicious anæmia are not of the frequency or the magnitude to be themselves the cause of this variety of anæmia. They are not infrequently *entirely absent.*

(2) No evidences of such extravasations are to be found in the lymphatic glands, through which the blood must necessarily have been absorbed.

(3) The characteristic pigment changes in liver, kidney, and spleen in pernicious anæmia, and the no less characteristic distribution of pigment between these organs, cannot be produced by absorption of extravasated blood, however large in quantity.

(4) The conclusion must be permitted, that this form of anæmia does not owe its peculiar pathological features to the occurrence of extravasation. Both pathological and experimental data are in my experience quite opposed to such a view.

Nor is the blood destruction of pernicious anæmia such as is met with in two other conditions—*malaria and paroxysmal hæmoglobinuria,*—of which excessive blood destruction are likewise important pathological features.

III.—Differences between it and Malaria.

3. The excessive hæmolysis of pernicious anæmia differs in important respects from that which occurs in malaria.

It is not *a disease of the individual corpuscle*, with subsequent accumulation of pigment—chiefly in the capillaries of the liver, in the spleen, and perivascular lymphatics generally, to a subsidiary extent also in the liver cells,—such as one meets with in malaria. On the contrary, its chief feature is a *disintegration of the corpuscles* with liberation of their hæmoglobin,—with subsequent accumulation of pigment chiefly in the liver cells, to a subsidiary extent in the

capillaries of the liver, and only to the slightest extent in the spleen.

That an increased destruction of corpuscles occurs in malaria is evidenced by the quantity of pigment found in various organs of the body in that disease. This destruction is the result of actual morbid changes in the red corpuscles themselves.[1] The nature of this morbid change does not at present concern us. The result is, that while still circulating in the blood many of the red corpuscles present evidence of diminished vitality, and gradually become effete. Their fate is that of all other effete pigment particles circulating in the blood.[2] They are taken up by the leucocytes, and carried to various organs of the body, notably the liver and spleen, where they become ultimately stored up. In the liver, this pigment is often found very abundant, especially *within the capillaries*, enclosed in leucocytes, much of it presenting the general characters of pigment arising from chronic hæmocytolysis.[3] Sometimes, pigment is also found in the liver cells, in which case its character differs from that above described, and is that of pigment arising from acute hæmocytolysis.[4] In all cases, it is also found abundantly in the spleen (Plate VIII.).

In *pernicious anæmia*, on the other hand, the liver is invariably the chief, sometimes the sole, seat of the pigment accumulation which occurs. As has been seen, the spleen sometimes contains little or none. Further, within the liver, the pigment is generally most abundant, not within the capillaries as in malaria, but *within the liver cells* themselves. In some cases, moreover, I have found the pigment within the liver cells, and there alone, none being present in the surrounding capillaries (Plates II. and III.).

In all cases the pigment has the characters of that derived from acute hæmocytolysis.[4]

Source of the Pigment within the Liver Cells.—This peculiar distribution of the pigment granules in pernicious anæmia has been held by Quincke and Kunkel to indicate that the pigment has been originally conveyed to the liver in a granular form, probably by leucocytes, and afterwards stored up within the liver cells.

[1] Marchiafava and Celli, *Fortschr. d. Med.*, i.
[2] *Vide postea*, p. 181. [3] *v. antea*, p. 132. [4] *q.v.*, p. 135.



FIG. 1.—LIVER OF MALARIA. × 50.

Showing the abundance and irregular distribution of pigment. The darker masses represent pigment lying in capillaries around the lobules. In addition there is much pigment of a finer character *within the liver cells.*

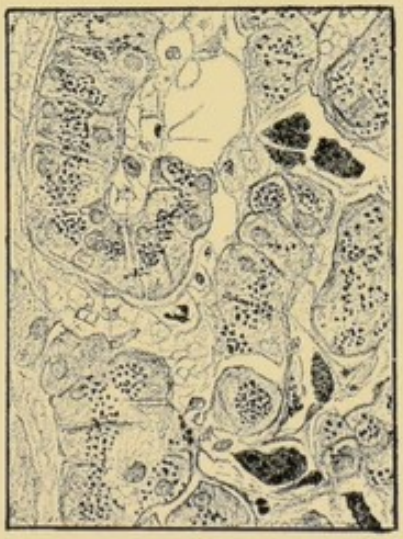


FIG 2.—LIVER OF MALARIA. × 300. (From same Section as Fig. 1.)

Showing the different size and appearance of the pigment granules in the capillaries and in the liver cells respectively—the pigment particles in the capillaries being of much larger size than those in the liver cells.

I am unable to accept this explanation as to the source of the pigment in such cases. It is opposed to what we know of the fate of pigment particles, such as carmine or ultramarine blue, after injection into the blood. My experiments, in agreement with those of Ponfick,[1] shew (*v. postea*) that, under such circumstances, the particles are never to be found within the liver cells; they are taken up by leucocytes, and deposited in the capillaries of the liver, and in the spleen (see p. 375).

In pernicious anæmia, on the contrary, I have sometimes found the pigment *within the liver cells, and there alone,* none being found in any other organ, not even in the spleen. This is, I consider, irreconcilable with the view that the pigment has been carried *in granular form* to the liver by leucocytes. My observations shew that the pigment found within the liver cells has been formed *in situ* from hæmoglobin,—which has passed into the liver cells *as hæmoglobin, not as granular pigment.* No evidence that the red corpuscles themselves pass into the liver cells could ever be found, although I carefully sought for it. Whatever hæmocytolysis occurs within the liver, takes place within the capillaries. It is only their hæmoglobin which passes into the liver cells themselves.

These various considerations involve, therefore, the conclusion already expressed; that the antecedent hæmolysis in the two conditions—malaria and pernicious anæmia—must differ in some essential particular; more especially, that in the latter, as shewn by the character and situation of the pigment, an actual disintegration of the red corpuscles is one of the special features of the hæmolysis.

In other words, it involves a *hæmoglobinæmia* in the sense I have already defined (p. 136).

[1] "Studien über die Schicksale körniger Farbstoffe im Organisms," *Virch. Archiv*, Bd. xlviii., 1869, p. 1.

CHAPTER XIII.

HÆMOLYSIS IN PERNICIOUS ANÆMIA—(*continued*).

IV.—Differences between it and Paroxysmal Hæmoglobinuria.

4. The hæmolysis in pernicious anæmia, although involving a hæmoglobinæmia, differs in important respects from that met with in paroxysmal hæmoglobinuria, and other similar conditions of which hæmoglobinuria is a marked feature.

In *Paroxysmal hæmoglobinuria*, and other conditions characterized by hæmoglobinuria, the destruction of blood corpuscles is excessive while it lasts. This is evidenced by the large quantity of hæmoglobin excreted by the kidneys during the attack. This destruction of corpuscles is only of short duration. In this respect it differs markedly from that occurring in pernicious anæmia.

This is, however, by no means the chief difference between these two diseases. In pernicious anæmia, hæmoglobinuria does not occur, notwithstanding that the actual amount of blood destruction during the progress of the disease—as judged from the anæmia during life and the evidence of blood destruction after death—is probably greater than that met with in any other disease.

The absence of hæmoglobinuria might conceivably be due to the fact, that, while in paroxysmal hæmoglobinuria the destruction is rapid, in pernicious anæmia it is more gradual, never equalling in amount at any one time that met with in the former disease.

Its absence cannot, however, be accounted for on these grounds alone. It is true that pernicious anæmia is a chronic

disease. It is also true, however, that its progress is often marked by exacerbations more or less acute,[1] in which, as evidenced by the diminution of the number of corpuscles—*e.g.* a diminution of 1,000,000 per c.mm. in the course of a few days—as great a destruction of blood probably occurs as in certain attacks of paroxysmal hæmoglobinuria.[2] Nevertheless, pernicious anæmia is not attended by hæmoglobinuria. Even during the severest exacerbations, I have never found free hæmoglobin in the urine in a form recognizable by ordinary tests, chemical or spectroscopic.[3]

How, then, account for the presence of pigment in the kidney in many cases of pernicious anæmia, possessing the characters of ordinary blood pigment, and giving the reaction of free iron? It is undoubtedly an evidence that hæmoglobin in some form or other has been excreted through the kidneys. Why, then, is it not recognizable in the urine by the ordinary tests?

According to Ponfick,[4] whose studies on this subject have been so important, the occurrence of hæmoglobinuria is simply a question of quantity. Hæmoglobinuria occurs when the quantity of free hæmoglobin exceeds the sixtieth part of the whole of the hæmoglobin contained in the body. When hæmoglobin appears in the urine, it is as an indication that the amount set free in the blood is greater than can be disposed of by the liver and other organs of the body. The presence or absence of hæmoglobin in the urine is thus, according to this view, simply dependent on the quantity of hæmoglobin free in the circulation.

How are we, on this view, to explain the differences in this respect in the two diseases—pernicious anæmia and paroxysmal hæmoglobinuria?

[1] See Case.

[2] See Dr. Bristowe's and Dr. Copeman's observations, *postea*, p. 162.

[3] Since the above statement was made, I have met with *one* case which *possibly* was an exception; a case of a man, aged 25, seen with Dr. Glover of Highgate (1898), profoundly anæmic (red corpuscles 22 per cent., hæmoglobin 15 per cent.), who died nine months later (red corpuscles 15 per cent., hæmoglobin 11 per cent.), with all the features of pernicious anæmia. His illness had commenced four years before with an attack of hæmoglobinuria; subsequent attacks occurred at intervals of about six months; and he had at least two attacks during the last six months. No *post-mortem* examination could be obtained; so that it could not be ascertained, *as could most definitely have been done by the condition of the liver with regard to pigment*, whether the anæmia was due simply to loss of blood, or to excessive hæmolysis.

[4] "Ueber Hæmoglobinurie," *Berl. klin. Woch.*, 1883, No. xxv.

In pernicious anæmia, for the reasons already stated, the pigment in the liver cells is formed *in situ* from hæmoglobin which has been set free from red corpuscles within some part of the circulation. In pernicious anæmia, therefore, some degree of *hæmoglobinæmia*—this term being used in the widest sense as applicable to the condition in which hæmoglobin is set free into the blood if only from one individual corpuscle—must at times exist. The condition resembles, then, to some extent that present in paroxysmal hæmoglobinuria. In both, hæmoglobin is set free from the corpuscle; but while in the latter the hæmoglobin is at once excreted, and appears in the urine, in pernicious anæmia hæmoglobinuria is absent. How account for this, on the above view that hæmoglobinuria is merely a question of the quantity of hæmoglobin free in the blood?

The occurrence of hæmoglobinuria is, I find, not a simple one of quantity, as Ponfick's observations might lead one to suppose.

(1) Thus I find that the injection of a small quantity of glycerine into the blood of rabbits is followed by hæmoglobinuria, although the destruction of corpuscles may be so slight in amount that scarcely any evidence of it is to be found, either in the blood or elsewhere. (*Exp.* 30, 31, 32.)

(2) On the other hand, the injection of even large doses of toluylendiamin in the same animals is most exceptionally attended by hæmoglobinuria, although the appearances subsequently presented by the liver, spleen, and blood clearly shew that a great destruction of blood has occurred.

Exp. 43: Rabbit:

Sept. 15.—0·5 gramme of toluylendiamin of solution injected subcutaneously.

Sept. 16.—Urine, 12 c.c., of a deep saffron yellow colour. Microscopically, groups of round spherical yellow globules and cast-like structures of colour of hæmoglobin made up of fine yellow granules.

Sept. 19.—0·4 gramme toluylendiamin (5 per cent. solution) injected.

Sept. 20.—Killed.

Post-mortem.—Spleen shews an extraordinary increase of pigment.

Bone Marrow.—Pigment greatly in excess of normal.

Liver.—Great abundance of fine granular blood pigment within the liver cells, notably within the cells of portal zone: *none within* the capillaries (Plate IX.).

I conclude, then, that *the occurrence of hæmoglobinuria is not simply a question of amount of blood destruction.*

On the contrary, other factors, as appears from my studies, come into play—namely :—

(1) *The Seat of the Hæmolysis*, whether in the *portal* or in the *general* circulation.

(2) The *Nature of the Hæmolysis*, determining as this does the form in which the hæmoglobin escapes from the corpuscle, whether as free hæmoglobin or still in combination with the proteids of the stroma.

And first, with regard to the first-mentioned factor: (1) *Hæmoglobinuria depends to a large extent on the seat of the preceding hæmocytolysis, whether within the portal blood, or in the general circulation.*

No portion of my investigation proved more difficult than this particular one—namely, to explain the extraordinarily varying occurrence or non-occurrence of hæmoglobinuria in connection with increased hæmolysis ; its absence, *e.g.* in rabbits, notwithstanding a very great and demonstrable hæmolysis ; its presence when that hæmolysis had been obviously slight. Ponfick's view was, that it was a mere question of quantity of hæmoglobin, and activity of the liver (and other organs) in getting rid of it ; that the liver was only able to dispose of a certain amount, and if this were exceeded, hæmoglobinuria necessarily ensued. So long as these appeared to be the chief factors responsible, no progress was made. For, as has been just stated, they were quite insufficient to explain the variations met with. Light was first obtained, when I ascertained that the *portal blood* might be regarded as exclusively the seat of hæmolysis in health ; and the following considerations soon evolved themselves, explanatory of a good deal that had been previously obscure.

As already seen, in all animals alike, the injection of even small doses of glycerine is followed by hæmoglobinuria, although no other evidence of blood destruction may be found. The glycerine acts *directly on the red corpuscles* wherever it comes into contact with them *in the general circulation*, and withdraws their hæmoglobin.

So also, in subjects of paroxysmal hæmoglobinuria, the mere dipping of the fingers for a short time in ice-cold water will suffice in some cases to bring on an attack. The actual disintegration of the corpuscles is confined apparently to the small portion of the general circulation exposed to the influence of the cold.[1]

> The hæmoglobinuria in such cases depends, I consider, not so much on the *quantity* of hæmoglobin set free, as on the fact that it has been set free *within the general circulation.*

Now so far as its *seat* is concerned, my studies shew that the hæmolysis of pernicious anæmia resembles that of health in being confined to the portal area, and the organs pouring their blood into it. It does not occur in the general blood as is the case in paroxysmal hæmoglobinuria, the hæmoglobinuria of burns, of glycerine poisoning, and the like.

This circumstance, although, as will presently be seen, by no means the only or even the chief factor, is one of the factors that account for the absence of hæmoglobinuria in this disease. The liver arrests the hæmoglobin as it passes through. Hence in all cases alike, whatever be their severity, the one constant anatomical change is found within the liver—namely, excess of iron, and blood pigment in the liver cells. Moreover, this pigment is found in relation to the portal capillaries—namely, within the outer two-thirds of the lobule. Evidence of hæmolysis may be wanting in every other organ of the body. But

[1] "Beitrag zur Lehre von der paroxysmalen Hæmoglobinurie," *D. Archiv f. klin. Med.*, Bd. xxxii., 1883, p. 371.

[See on this point a very careful study of a "Case of Paroxysmal Hæmoglobinuria," (*Med. Soc. Trans.*, 1889), by Dr. Bristowe and Dr. Copeman, published subsequent to the above studies.

The condition consists in a rapid and often apparently enormous destruction of the red corpuscles, and this depends on the direct influence of cold. On eight occasions observed, the loss varied between 129,000, and 824,000 corpuscles per c.mm., the destruction taking place with extreme rapidity, immediately after exposure of the patient to cold, and before any of the characteristic symptoms of the attack had revealed itself. During the whole time he was in hospital, he had no attacks excepting those brought on by exposure to cold. In the majority of cases, the morbid products found in the urine were hæmoglobin in an amorphous form, albumen, and hæmoglobin in free form.

The conclusions expressed in my above studies regarding the relation of hæmoglobinuria and pernicious anæmia, and the difference in the *seats of destruction* in the two cases are fully accepted by the authors as explaining the differences in the two diseases.]

in no case, however slight, can the liver escape: the products of the hæmolysis must always pass through it.

(2) The occurrence of hæmoglobinuria is in part dependent upon the *nature of the preceding hæmolysis*, determining as this does the form in which the hæmoglobin escapes from the corpuscle.

It is clear, from the changes found in the kidney in pernicious anæmia, that the hæmoglobin set free is not always retained within the confines of the portal circulation. For the pigment found in the renal cells is similar in character to that found within the liver cells—that is to say, it has the characters, already described, of pigment formed from hæmoglobin after its liberation from the corpuscle.[1] Free hæmoglobin has thus been excreted through the kidney. Why no hæmoglobinuria?

My studies shew that there are two different ways in which hæmoglobin may escape from a red corpuscle undergoing active disintegration; and that this difference is of importance in determining the subsequent fate of the hæmoglobin set free. The difference is one, moreover, that is mainly determined by the nature of the destructive agent.

(*a*) Thus as the result of the action of some agents, *e.g.* glycerine or distilled water, *the hæmoglobin is withdrawn from the stroma of the corpuscle*—the blood is laked. When in this (free) form, the hæmoglobin is excreted as such by the kidneys, chiefly through the glomeruli—*partly*, perhaps, because it is in a form not so easily acted upon by the liver cells as the other form presently to be described but *mainly* owing to the circumstance, that agents possessing this action destroy the corpuscles wherever they come in contact with them, both in the general and the portal blood. Their action on the corpuscles is precisely the same within and without the body. Their destructive action is a *direct* one, exerted on the individual corpuscle in the general circulation as much as in the portal; and consequently, however slight the destruction may may be, hæmoglobinuria ensues.

(*b*) In the case of certain destructive reagents, on the other hand, I find that the hæmoglobin, although set free from

[1] Compare fig. 2, Frontispiece, and fig. 1, Plate III.

the corpuscle, *remains still in combination with the albuminous stroma* of the corpuscles (see Plate II.). It oozes out from the corpuscle in the form of coloured droplets. When in this form it is no longer excreted as ordinary hæmoglobin, namely, through the glomeruli, but is taken up and excreted by the cells of the convoluted tubules (fig. 2, Frontispiece).

This change in the character of the hæmoglobin is, I find, characteristic of the action of certain destructive agents, notably of toluylendiamin. As already stated, the injection of even large doses of this drug into the blood of rabbits is not attended by hæmoglobinuria, although the appearances subsequently presented by the liver and spleen shew that there has been a great destruction of blood. Although hæmoglobin is not discoverable in the urine by the ordinary tests—spectroscopic and otherwise—microscopic examination of the urine shews numerous small yellow globules of varying size in the urine, easily recognizable as products of blood destruction by their bright yellow colour. These globules are always spherical in form ; and the larger of them may, on cursory examination, be mistaken for spherical red corpuscles. They have more usually been regarded as fragments of red corpuscles (Exp. 43, p. 160).

The interesting point regarding these globules of hæmoglobin—for such they are—is that in size, form, and colour they exactly resemble the 'yellow spherical corpuscles'—'Eichhorst's corpuscles'—which have already been described as occurring within the blood in pernicious anæmia. As regards size, they resemble the granules of pigment found in the cells of the convoluted tubules of the kidney in pernicious anæmia.

As to the nature and source of these yellow globules, the following observations appear to supply a clue. They show that *under certain circumstances hæmoglobin in solution can assume a corpuscular form.*

> *Action of Toluylendiamin on Red Corpuscles in vitreo.*—If a small quantity of blood, (5 c.mm.) be added to perfectly neutral (5 per cent.) solution of toluylendiamin, (995 c.mm.), the following changes may be observed. At the end of twelve or twenty-four hours the corpuscles have all disappeared. The solution is hæmoglobin tinted, and clear; and on microscopic examination not a single corpuscular element of any sort is to be found in it. After this time, a deposit begins to form at the bottom of the

vessel; and on examination, this is found to be made up, not of the original red corpuscles, but of innumerable spherical bodies, of deep yellow colour, and of the most varying size—identical, in fact, in all respects with the bodies found in the urine after the administration of the drug, (as also within the spleen). They are of viscous nature, the smaller fusing readily with one another to form larger bodies. The uniformly spherical form and deep yellow colour are, however, always retained.

If, instead of blood, a solution of pure crystalline hæmoglobin be used for the experiment, no such bodies are discoverable—only yellow granular debris similar to that often met with in the urine in ordinary hæmoglobinuria.

In the former case the hæmoglobin appears to have retained some combination with the viscous nucleo-proteid of the stroma, which enables it to resume a corpuscular form, even after it has been set free from the corpuscles.

As will be afterwards seen, the chief feature of the hæmolytic action of a drug like toluylendiamin, contrasted with that of an agent like glycerine or distilled water, is, that while the action of the latter is the same whether within or without the body—*i.e.* a *direct* one—the action of toluylendiamin differs markedly in the two cases; *outside the body*, in certain strengths, it actually preserves the corpuscles, while *inside the body* an equivalent strength would occasion most intense hæmolysis. Within the body, in short, its action is not a direct one on the red corpuscles themselves, but on the active cells in relation to the blood, especially those of the spleen, and only *indirectly* through them on the blood. Its hæmolytic action can, in short, be materially diminished, or altogether abolished, by previous removal of the spleen.

I conclude that a change of this nature occurs in the hæmoglobin in cases of pernicious anæmia; and indeed in severe cases the change in the corpuscles can be actually seen in progress (see Plate I.). Wherever it is taken up, whether by leucocytes, endothelial cells, or cells of liver, spleen, or kidney, it assumes the form of fine globules within these cells, a form subsequently retained by the pigment granules.[1]

As we have seen, it is only in certain cases that the kidney contains this pigment. According to the above observations, this may quite well be. So long as the destruction is

[1] Plate III., and fig. 2, Frontispiece.

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 the hæmolysis extend to the general circulation. Hæmoglobin in the modified form passes into the general circulation, and is excreted, as above described, through the kidneys,—not, however, through the glomeruli as free hæmoglobin, but through the cells of the convoluted tubules (see Frontispiece, also fig. 1, p. 93).

The most likely cases, therefore, in which to find pigment in the kidneys will be those in which the progress of the disease has been marked by specially severe exacerbations, in which, therefore, the destruction from time to time has been very great. Microscopic examination of the urine under such circumstances will probably reveal the presence of colouring matter in the form of small spherical globules similar to those just described.[1] I have not yet had an opportunity of seeing such a case. In the light of these observations I shall watch for one with interest.

[1] See *postea*.

CHAPTER XIV.

HÆMOLYSIS IN PERNICIOUS ANÆMIA—(*continued*).

V.—The Behaviour of the Spleen.

I REGARD these observations as establishing the fact that pernicious anæmia is due to an excessive destruction of blood occurring in the portal system. Presumably, therefore, according to my observations already recorded, the spleen plays a special part in the destruction.

How is this conclusion reconcilable with the fact that in certain cases of pernicious anæmia the spleen shews little or no changes either to the naked eye or upon microscopic examination? In some cases it is described as 'of small size,' 'firm and red,' or 'small and pale'; while in others, as in one which recently came under my notice, it is enlarged, swollen, soft in consistence, and of deep violet colour.

Variations in Size.—The explanation of these variations in size I find to be that

> *the size of the spleen is no reliable index to the amount of blood destruction which may have recently occurred in it.*

While active disintegration of the corpuscles is in progress, the spleen is usually found enlarged. On the other hand, two or three days later, while the blood still shews many remains of red blood corpuscles, and other evidences of blood destruction are numerous, the spleen, even when the destruction has been most excessive, may be found small, shrunken, and contracted, containing little blood, and shewing little evidence of having been at all concerned in the process.

Now, the course of pernicious anæmia towards the fatal termination is usually marked by relapses alternating with

periods of convalescence. Moreover, these exacerbations are always followed by further deterioration of the quality of the blood, (*i.e.* by greater oligocythæmia), also by high-coloured urine, and urobilinuria (*vide postea*). This indicates, that the excessive blood destruction occurring in pernicious anæmia is not constant. The process is marked by periods of activity alternating with periods of quiescence. It is this peculiarity of the process that determines the varying size of the spleen. The condition of that organ after death varies according as an exacerbation of the destructive process has recently occurred or not. If destruction is in active progress at the time of death, the spleen is found swollen and red; although sometimes even under the circumstances it may be small, since it was not uncommon in experiments for a spleen recognizably large and turgid during life to contract markedly immediately after death. If death occurs during a quiescent interval, it may be found small and contracted (see p. 380).

Varying Quantity of Pigment. — As regards the other characters of the spleen, we saw that after hardening, microscopic examination usually shews no changes at all; in particular, the percentage of iron it contains is in most cases by no means proportional to the great excess constantly found in the liver. I was for a long time inclined to regard this as an indication that the part played by the spleen in the destruction of blood in this disease was altogether secondary to that taken by the liver for the following reason. My experiments had shewn that after transfusion the spleen always contained much more pigment than the liver, and that this organ was a most important seat for the accumulation of pigment occurring in such cases, the conditions of the circulation in the spleen being, as already explained, specially favourable to the arrest and accumulation of effete red corpuscles and their conversion into pigment.

I ultimately found, however, that the presence or absence of pigment in the spleen was dependent to a great extent on the *nature* of the blood destruction which had occurred.

> If the corpuscles are broken down entirely, and their hæmoglobin liberated, the amount of pigment found in the spleen may be very slight, although the destruction of cor-

puscles may have been great. Thus, after injection of distilled water, little or no pigment may be found in the spleen, although marked hæmoglobinuria has occurred (see pp. 172, 173). Similarly, after poisoning with pyrogallic acid, the amount of pigment in the spleen may be small, although the appearances presented by the red corpuscles within the spleen itself shew that a great destruction of blood has taken place. The hæmoglobin of the corpuscles has been set free, and carried to the liver to be disposed of, or into the general circulation to be excreted by the kidneys.

The conclusion I have formed on these observations is, that, as regards the spleen, much more importance is to be attached to the recent appearances, both naked eye and microscopic, than to those presented by the organ after hardening. In many cases the spleen is found apparently normal on being examined after hardening; while examination of the fresh organ shews, (from the quantity of hæmoglobin in the spleen, and the numerous hæmolytic changes in the red corpuscles), that blood destruction had been in full progress at the time of death.

The same, I conclude, applies to pernicious anæmia.

In a case of pernicious anæmia, recently under observation, the spleen was much enlarged (weight 13 oz.), soft and flabby in consistence, and, on section, presented an extremely deep violet-red or dark-purplish colour. It seemed to be extremely rich in blood; and in this respect presented a marked contrast to the other organs, which were exceedingly pale and anæmic (a contrast I have found to be the general rule in pernicious anæmia).

On microscopic examination of the fresh organ, few red corpuscles were found. The colour of the splenic pulp was almost solely due to the *presence of free hæmoglobin*, the red corpuscles being in no greater number than in the other organs of the body. The splenic tissue gave little or no iron reaction with sulphide of ammonium. It contained *no excess of blood pigment.*

The explanation of these appearances appears to me to be the following:—Blood destruction had apparently been in active progress at the time of death; and the spleen was the chief seat of the disintegration of the red corpuscles. The hæmoglobin

was carried to the liver to be disposed of; the evidence of this in the present case, being, not only a great excess of pigment in the liver cells in the usual situation—the outer two-thirds of the lobule; but, also, the presence of a very large quantity of *intensely high coloured bile,* both in the gall-bladder, and in the upper part of the small intestine. The absence of any iron reaction is explained by the circumstance already alluded to—that iron, in the form it is present in hæmoglobin, gives no reaction with micro-chemical reagents.

CHAPTER XV.

HÆMOLYSIS IN PERNICIOUS ANÆMIA—(*continued*).

VI.—Its Special Character.

The Nature of the Blood Destruction in Pernicious Anæmia.

1. My experiments make it quite clear, that it is not simply a dissolution of the red corpuscles in the general circulation—a *general hæmoglobinæmia*—such as occurs periodically in paroxysmal hæmoglobinuria, or sometimes after burns affecting large areas of skin; and such as can be experimentally induced by injection of distilled water or glycerine into the blood. Under the circumstances enumerated, hæmoglobinuria occurs, usually with albuminuria; whereas, in pernicious anæmia, both these conditions are absent.

The destruction has rather the characters of a *portal hæmoglobinæmia—i.e.* of a blood destruction confined to the portal area; resembling in this respect the blood destruction of health, while yet differing from the latter in many important particulars.

As regards the Nature of the destruction *the condition of the liver*, as regards excess of pigment, and fatty degeneration, is of the greatest importance in this relation.

2. My observations shew, that mere excess of free hæmoglobin in the blood, (*e.g.*, due to distilled water, glycerine, etc.) cannot produce the pigment changes in the liver characteristic of pernicious anæmia. This conclusion is based upon the following experimental evidence.

Exp. 44: Rabbit: weight, 4 lb. 10 oz.

Date.	No. of Corpuscles.	Changes in Blood.	Remarks.
Sept. 29, 1887, .	6,310,000	Normal.	Urine 30 c.c., muddy, gives no reaction with Guaiac test.
,, 30, . . (10 A.M.),			10 A.M. 30 c.c. distilled water injected into jugular vein (etherized).
		11 A.M. No obvious changes in corpuscles—granules more numerous, but no *schatten*.	11 A.M. Animal shivering.
			4 P.M. 15 c.c. urine; contains fine granular yellow (hæmoglobin) débris; gives distinct reaction with Guaiac.
Oct. 1, .	5,250,000	. . . .	1 P.M. Animal recovered.
			2 P.M. Killed. Urine from bladder gives no Guaiac reaction; urine passed during night contains no hæmoglobin.

Blood of Inferior Vena Cava shews nothing abnormal.

Spleen.—Soft, and rather swollen; darkens very slightly in NH_4HS; contains no excess of pigment, and none seen after hardening, although Prussian blue reaction gives a slight diffuse staining.

Liver.—Purplish colour; cells very fatty; no darkening with NH_4HS; no pigment granules to be seen. After hardening, cells appear normal; no pigment.

Gall Bladder.—Contains a few drops of a light greenish bile.

Exp. 47: Rabbit: weight, 4 lb. 4 oz.

Date.	No. of Corpuscles.	Changes in Blood.	Remarks.
Oct. 7, 1887, .	5,650,000 Hb. 70 per cent.		1.30 P.M. Animal etherized. 50 c.c. distilled water injected into jugular vein.
		3 P.M. No débris, no *schatten*.	
,, 8, . .	5,480,000 Hb. 60 per cent.	. . . .	Animal recovered, eating as usual.

Exp. 47—(*continued*).

Date.	No. of Corpuscles.	Changes in Blood.	Remarks.
			50 c.c. of urine containing large quantity of yellowish granular deposit (hæmoglobin). Slight Guaiac reaction of hæmoglobin.
Oct. 10, 1887, .	5,290,000 Hb. 58 per cent.	. . . .	Animal looking ill. Killed at 2 P.M.

Liver.—Very fatty, especially in portal zone; no darkening in NH_4HS, and not a particle of pigment in liver cells. After hardening, no reaction of iron; cells appear normal.

Spleen.—Slight darkening in NH_4HS; gives pigment reaction, limited to large cells of pulp.

Bone Marrow.—No excess of pigment; no darkening with NH_4HS.

Kidney.—Shews nothing; no darkening in NH_4HS.

Exp. 48: Rabbit.

Date.	Blood.	Remarks.
Oct. 10, 1887, .	No changes. 4 P.M. No changes.	3 P.M. 70 c.c. distilled water injected into jugular vein (etherized).
,, 11, . .	Corpuscles perfectly normal. No débris. No *schatten*.	Animal eating; depressed. *Urine* dark and muddy. *Microscop.* large quantity of yellow granular remains of hæmoglobin, with casts of irregular yellow globules, resembling red blood corpuscles. Distinct reaction of hæmoglobin. No reaction of bile pigments. (Gmelin.)
,, 12, . .	. . . . .	Animal well. 11 A.M. Killed, *i.e.* 44 hours after operation. *Urine* 50 c.c. in bladder, muddy. No hæmoglobin reaction, but much granular and globular débris. Slight cloudiness on heating, and with HNO_3.

Spleen.—Dark, swollen; a large number of red corpuscles shew bud-like projections; and similar buds are seen free, also enclosed in cells. Distinct increase in pigment; tissue becomes almost black in NH_4HS; large quantity of colourless granular material.

After hardening, sections shew *slight excess* of pigment, diffused throughout large splenic cells.

Liver.—Cells fatty; no appearance of pigment, no darkening with NH_4HS.

After hardening, cells normal; free from pigment.

Gall Bladder.—Contains a quantity of dark green bile.

Bone Marrow.—Corpuscles shew no abnormal appearances, no buds; little or no iron reaction.

3. In certain respects, the characters of the blood destruction are more closely reproduced by a poison like pyrogallic acid—namely, as regards high *degree of oligocythæmia* (Exps. 78, 62, 77, 58); pronounced *poikilocytosis* (Exp. 77); and *fatty degeneration of the liver cells*, especially in the centre of the lobule (Exps. 62, 76, 58). In other respects, however, notably in regard to the *pigment changes* in the liver, this poison fails to meet the requirements. Despite the large destruction it occasions, as shewn *during life* by the reduction in number of corpuscles or by the hæmoglobinuria, and *after death* by the very large excess of pigment in the spleen there is, with rare exceptions (Exp. 58), a singular absence of pigment from the liver cells (Exps. 64, 78, 62, 76, 77). Moreover, the destruction is generally attended by hæmoglobinuria, and albuminuria.

Exp. 64: Rabbit.

Nov. 4, 1887, (11.20 A.M.),	5,350,000	No changes in blood during life.	0·5 gramme pyrogallic acid in 10 c.c. normal saline, injected simultaneously.
(12.20 P.M.),	5,090,000		
(3.20 P.M.),	5,150,000		
Nov. 5, . .	4,240,000		Animal killed, in good health.
,, 7, . .	4,400,000		

Spleen.—A very large amount of blood pigment; becomes coal-black in NH_4HS.

Liver.—Very congested; very slight darkening in NH_4HS; absolutely no pigment in cells.

Exp. 78: Rabbit: weight, 1500 grammes.

Date.	No. of Red Corpuscles.	Changes in Blood.	Remarks.
1888.			
Jan. 21,	. . .	. . . . .	12 A.M. 0·75 gramme pyrogallic acid, in 20 c.c. saline solution (¾% NaCl), injected into jugular vein. 4 P.M. 15 c.c. of dark, smoky urine passed; no albumin or blood; deep *red colour* with HNO_3.
,, 22,	. . .	A few *schatten* seen.	
,, 23,	3,735,000	Corpuscles normal in size and appearance.	
,, 24,	3,450,000	R.B.C. perfectly normal.	
,, 25,	3,410,000	R.B.C. perfectly normal.	
,, 26,	3,970,000	Some corpuscles larger than others, and a few poikilocytes.	
,, 27,	4,530,000	Normal.	
,, 28,	4,250,000	Normal.	
,, 31,	4,590,000		
Feb. 3,	4,780,000	. . . . .	0·75 gramme pyrogallic acid administered by mouth.
,, 4,	4,720,000	Normal.	35 c.c. urine, smoky, albuminous; port wine colour with HNO_3.
,, 6,	4,930,000	Normal.	
,, 9,	4,950,000		
,, 10,	. . .	. . . . .	1 gramme of pyrogallic by mouth.
,, 11,	4,240,000	Normal.	
,, 13,	3,870,000	Normal.	
,, 14,	4,480,000	Normal; colourless granules increased in number.	
,, 16,	4,930,000	Normal.	
,, 17,	. . .	. . . . .	Killed with chloroform.

Spleen.—Of normal size; red corpuscles mostly normal; considerable quantity of colourless granules, and also microcytes; darkens considerably in sulphide of ammonium; on examination shews considerable diffuse greenish staining; also a considerable excess of small dark spherules of pigment of varying size.

The protoplasm of certain of the large cells is of a diffuse greenish colour, studded with extremely minute dark pigment granules.

On examination with higher powers (Zeiss F.), the number of these granules is seen to exceed greatly that seen with low power; the cell substance seems full of them, the diffuse greenish colour being in great part caused by the particles thrown out of focus.

After *hardening*, gives no reaction with sulphide of ammonium; contains almost no pigment, a few granules only being seen.

Liver.—Healthy; not affected by sulphide of ammonium; cells normal; shew a few yellowish granules, probably fat.

After *hardening*, no reaction with NH_4HS; cells small; nuclei distinct; no pigment either in liver cells or in capillaries.

Exp. 62: Rabbit: weight, 1800 grammes.

Date.	No. of Corpuscles.	Changes in Blood.	Remarks.
1887. Nov. 24, .	4,750,000	. . . . .	Spleen excised; 0·75 gramme pyrogallic acid injected into jugular, (=0·41 gramme per kilo).
,, 25, .	4,780,000	A few *schatten*.	Animal not affected by operation; moving about freely; weight, 1700.
,, 26, .	4,470,000	Blood darker in colour; contains granular débris, but no *schatten*.	Weight, 1650; 70 c.c. pale straw coloured *urine*; no albumin or blood.
,, 28, . (1 P.M.),	5,180,000	No changes.	Weight, 1600; 1 gramme pyrogallic acid in 20 c.c. saline solution injected into vein.
(5 P.M.),		No *schatten* or other sign of blood destruction.	
,, 29, .	750,000	An extraordinary number of *schatten*, and many of the red corpuscles shew budding; the blood is of a dark chocolate colour.	*Urine*, 100 c.c., dark, smoky; no red corpuscles, but yellow hæmoglobin casts, also granular and epithelial casts.
,, 30, .	. . .	. . . . .	*Urine* very albuminous, almost pure blood. Death.

Blood of Portal Vein.—Shews red corpuscles in all stages of destruction, varying in size. Many *schatten*; and a number of red corpuscles shewing buds; numbers of large cells enclosing pigment and red corpuscles, some containing pigment alone.

Inferior Mesenteric Vein.—Pigment and corpuscle holding cells as numerous as in portal vein itself.

Inferior Vena Cava above Liver.—One or two pigment-holding cells, but much fewer in number than in portal vein.

Inferior Vena Cava.—Some corpuscles large, pale, twice or three times size of others. Not a single pigment-holding cell to be seen. *Schatten* very numerous.

Liver.—In a state of marked fatty degeneration; the surface mottled; lobules yellow in centre, with congested zones around.

Microscopically.—Numerous pigment cells in capillaries similar to those in portal vein ; also *schatten* in great number.

Tissue darkens very slightly in NH_4HS; after hardening, not at all.

Cells very fatty; loaded with fat globules, especially central part of lobule.

The absence of pigment from the Liver is very striking; especially when contrasted with the appearances presented by the liver (from another experiment examined the same day), where the pigment was very abundant, and yet the actual destruction of blood had been much less (drug used was toluylendiamin). Great dilatation of capillaries, especially around central vein.

Exp. 76 : Rabbit : weight, 2150.

Date.	Changes in Blood.	Remarks.
Jan. 19, . .	. . . . .	Spleen excised; and then 1 gramme of pyrogallic acid in 25 c.c. normal saline injected into jugular vein.
,, 20, . .	Blood from ear has not the dark colour of pyrogallic acid blood. Corpuscles shew absolutely no change.	(=0·46 gramme per kilo of weight, same proportion as Exp. 75.)
,, 21, . .	No change in blood.	Animal in perfect health; killed.

Liver.—Excessively fatty; contains absolutely no trace of pigment; no darkening with NH_4HS. Have hardly ever seen a liver so free from pigment.

Exp. 77 : Rabbit : weight, 1350 grammes.

Date.	No. of Corpuscles.	Changes in Blood.	Remarks.
1888. Jan. 20,	. . .	. . . . .	Spleen excised. 0·75 gramme pyrogallic acid in 20 c.c. saline solution injected into jugular (= 0·55 gramme per kilo).
Jan. 22,	1,360,000	*Schatten* in blood.	Hæmoglobin in urine.

Exp. 77—(continued).

Date.	No. of Corpuscles.	Changes in Blood.	Remarks.
Jan. 23,	1,360,000	Red corpuscles variously altered. Some very large and pale, others smaller than usual, $\frac{1}{3}$ or even less the normal size, *perfectly round and spherical, and retaining their colour.* Some of these seen in process of detachment from ordinary red corpuscles. In some of the corpuscles the hæmoglobin is seen as if withdrawn to one side of the corpuscle, in others it appears as if collected into centre. In the larger corpuscles these appearances resemble nucleated red corpuscles. Only one or two *schatten* seen amongst the red corpuscles, although the drop of blood withdrawn is thin, pale, and watery.	
,, 24,	1,760,000	Blood of a bright cherry colour, flowing freely. The appearances presented by corpuscles exceedingly striking. They vary exceedingly as regards both form and shape. Some, several times the size of normal red cells, others minute *spherical microcytes of bright yellow colour.* Some oval, others flask-shaped, others pointed, others throwing off buds, many of the latter being seen in process of separation from the corpuscles. The small microcytes resemble exactly in shape and colour the surrounding red corpuscles, except that the smaller ones shew no central depression. *The appearances presented by the blood agree in all particulars with those found in pernicious anæmia.*	Eating a little.
,, 25,	2,460,000	Blood from ear of a bright red colour, flowing freely. Some difficulty, indeed, in arresting flow from puncture. Poikilocytosis still very striking, although less marked than yesterday. Most of the corpuscles are fairly uniform in size; still some macrocytes, also microcytes, although fewer in number than before.	Animal looking better, has fed well since yesterday.
,, 26,	3,180,000	Character of blood visibly changed for the better, now bright red like normal blood.	Weight, 1250.

Exp. 77—(continued).

Date.	No. of Corpuscles.	Changes in Blood.	Remarks.
		Still, however, some tendency to bleeding from small puncture. A few macrocytes still seen, also microcytes. Some spherical, about half the size of a red corpuscle. Some oval, with pointed drawn-out ends. The great majority of the corpuscles are normal.	
Jan. 27,	3,500,000	Blood of normal colour. Still a few macrocytes and a few microcytes.	
,, 28,	4,150,000	Still a slight disparity in size of the corpuscles.	Animal well, 1300 grammes.
,, 30,	3,750,000	. . . . .	Animal looks depressed.
,, 31,	4,560,000	. . . . .	Weight, 1350.
Feb. 2,	4,720,000	Blood normal.	
,, 3,	. . .	. . . . .	0·75 gramme pyrogallic acid by the mouth.
,, 4,	4,160,000		
,, 6,	5,140,000	. . . . .	Weight, 1250.
,, 9,	5,420,000	A few microcytes still seen.	,, 1400.
,, 10,	. . .	. . . . .	1 gramme of pyrogallic acid by mouth, in 25 c.c. water.
,, 11,	5,050,000	Normal appearances.	
,, 12,	. . .	. . . . .	Urine smoky, deep colour reaction with HNO_3. Weight, 1300.
,, 13,	5,010,000	Slight poikilocytosis.	
,, 14,	4,700,000	Some macrocytes and microcytes.	
,, 15,	3,450,000		
,, 16,	3,790,000	Granular material, microcytes, bleeding from ear.	Killed.

Blood of Mesenteric Veins shews a few colourless granules, also some tendency to budding, and formation of microcytes. Some of the colourless albuminous granules are the result of disintegration of the red corpuscles, the stroma of which can be seen oozing out, breaking off, and floating away free.

Duodenal Veins.—Yellow microcytes and colourless granules.

Inferior Vena Cava.—Blood corpuscles perfectly normal, except that some of them are larger than normal. Almost complete absence of colourless granules, and no increase in the latter even after standing.

Hepatic Vein.—Same as inferior vena cava.

Liver.—Is somewhat small, flabby, atrophied looking. Gall-bladder empty.

Absolutely unaffected by NH_4HS, *and cells shew no trace of pigment.* After hardening no trace of pigment either in cells or in capillaries.

Summary.—In all these experiments, then, the most notable feature, as regards amount, and distribution of pigment, was the *singular absence of pigment from the liver*, despite the destruction, often excessive, occasioned by the drug.

In only one instance, with pyrogallic acid, did I succeed in producing a condition of liver similar in respect of increase of pigment, and fatty degeneration of centre of lobule to that of pernicious anæmia. But this was the result of a destruction which caused intense hæmoglobinuria, albuminuria, blocking of the renal tubules with hæmoglobin, viz., changes never met with in pernicious anæmia.

Exp. 58: Rabbit: weight, 3050 grammes.

Date.	No. of Corpuscles.	Changes in Blood.	Remarks.
Nov. 11, . . (12 A.M.)	6,280,000	. . . . .	Pyrogallic acid, 1 gramme, in 10 c.c. normal saline, injected subcutaneously. (=0·33 gramme per kilo.)
1.30 P.M., .	5,950,000	No changes.	
5 P.M., .	6,240,000	No changes.	
Nov. 12, . .	6,300,000	Normal. No *schatten* or granules.	
,, 14, . .	5,790,000	Corpuscles well preserved.	Weight, 2850.
,, 16, . . (12 A.M.)	5,890,000	. . . . .	Weight, 2850. 1½ grammes pyrogallic acid in 15 c.c. saline solution, injected intravenously. (=0·52 gramme per kilo.)
,, (2.30 P.M.),	5,560,000	A few fading corpuscles seen.	
,, (5.30 P.M.),	4,650,000	Circulation feeble. Blood of a dark colour; small spherical microcytes seen, much smaller than red corpuscles.	

Exp. 58—(continued).

Date.	No. of Corpuscles.	Changes in Blood.	Remarks.
Nov. 17, . .	1,100,000	Blood shews an extraordinary number of *schatten*, in number almost equal of the red corpuscles. Also an extraordinary increase of leucocytes.	Weight, 2650. Animal apparently well. Urine 140 c.c.; intensely dark, almost tarry; shews altered corpuscles and great quantities of granular and globular remains of hæmoglobin. Contains a large quantity of albumen; no reaction of bile, but spectroscopic appearance of hæmochromogen or acid hæmatin.
,, 18, . .	550,000	Enormous increase in number of leucocytes, as many as fifty in a field; large quantity of granular débris. *Schatten* in great number, although not so numerous as yesterday. Numerous destructive changes in red corpuscles, which are seen throwing off buds.	Animal looking very anæmic. Weight, 2550.
,, 19, . .	590,000	Blood very thin and watery, has lost its dark colour, shews a very large number of granules, and more marked alterations in red corpuscles. A number of them extremely large, pale, vacuoalated, deformed, pear-shaped.	Weight 2550.
		Leucocytes not so numerous—fourteen in a field.	Killed.

Spleen.—Swollen, of a dark slatey colour; enormous numbers of large splenic cells, filled with pigment. In NH_4HS, it becomes coal-black from large excess of pigment.

Liver.—Somewhat dark in colour, but not so dark as spleen; lobules on surface easily distinguishable by their pale yellow centre (fatty), and darker periphery. Tissue becomes black in NH_4HS. Large numbers

of pigment cells in its capillaries, similar to those in portal vein and in spleen; also a large excess of pigment in the liver cells in form of minute granules. The centre of the lobule is fattily degenerated to a marked degree, and shews little or no pigment. Some of the interlobular bile ducts filled with bile.

Kidney.—Tubules filled with yellow remains of hæmoglobin, very slightly darkened by NH_4HS.

Bone Marrow.—Dirty red colour; contains excess of pigment similar to that met with in spleen.

4. My studies, however, shew, that by the action of a drug, such as *toluylendiamin*, a condition of the liver can be produced closely resembling that found in pernicious anæmia as regards:

(1) *Richness in iron,*

(2) *Situation of the pigment within the liver cells,*

(3) *Occurrence of fatty degeneration in the cells in the central third of the lobule.*

A similar condition of the liver has been found by Stadelmann after chronic poisoning with toluylendiamin in dogs.

Exp. 42: Rabbit.

Sept. 19, 1887.—0·5 gramme (=0·18 per kilo) dissolved in 20 c.c. saline injected subcutaneously.

„ 26.—0·5 gramme injected subcutaneously (=0·18 per kilo).

„ 29.—1 gramme injected subcutaneously (=0·36 per kilo).

Oct. 13. Killed.

Spleen.—Of a pale red colour; not swollen at all; becomes coal-black in NH_4HS; contains excess of pigment, but not so much as liver.

Liver.—Appears healthy. Gall-bladder empty.

It is *loaded with pigment*; becomes coal-black in NH_4HS; more so than any yet seen.

Pigment is confined to the liver cells, in form of fine granules; most abundant towards the periphery of the lobule.

All the granules give the iron reaction.

Bone marrow.—Slight excess of pigment, but not so marked as in spleen. (See also *Exp.* 43, p. 160; Plates IX. and X.)

This peculiarity of the action of toluylendiamin, as distinguished from that of a poison such as pyrogallic acid, appears



LIVER OF RABBIT. × 300.

Showing large amount of fine granular pigment confined to the liver cells; none in the capillaries. Exp. 43. After administration of toluylendiamin.

to denote, that it combines with its destructive action on the blood a *specific*, not necessarily a *poisonous*, action on the liver cells.

I find a similar specific action exerted on the liver cells by phosphate of soda, a salt well known to be a stimulant of bile secretion.

I therefore conclude, that the agent, or agents, which induce the excessive destruction of blood in pernicious anæmia, have an action *on the blood* and *on the liver cells* similar to that of toluylendiamin; and this conclusion is strengthened by the consideration, that the form assumed by the hæmoglobin after its liberation from the corpuscles is, in cases of pernicious anæmia, similar to that assumed by it after poisoning with toluylendiamin (see p. 165).

Nature of the Poison.—With regard to the precise nature of the poison thus generated in cases of pernicious anæmia and responsible for the blood destruction which is at the basis of the anæmia, my observations have not as yet supplied me with any definite information.

The frequency of gastro-intestinal symptoms is a well-known feature of the disease. This finds its parallel in the frequency with which gastro-intestinal lesions are apparently the only, or at least the chief, lesions discoverable after death (p. 41).

The foregoing observations localizing hæmolysis to the portal gastro-intestinal blood attach a new significance and possible importance to these symptoms and lesions.

It is very probable, therefore, that the poison is of some special (cadaveric, i.e. *bacterial) nature produced within the gastro-intestinal tract; in excessively small quantity, however, and not necessarily constantly.*

On such a view, we can explain:

(1) Why changes in the gastro-intestinal tract—malignant disease, atrophy of gastric glands, presence of intestinal worms—may *sometimes* be important etiological factors in the production of this form of anæmia.

(2) Why, on the other hand, they may all exist without giving rise to the disease.

They are not themselves the cause of the disease. They,

merely *under certain circumstances*, favour the production of the essential pathological changes underlying the disease, viz., excessive destruction of blood, limited, for the most part, to the portal circulation, and its important *annexa*, the spleen and the liver.

[What these special circumstances were it became the object of my subsequent investigations to ascertain.]

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Fig. 1.—Liver of Pigeon.
After injection of 0·2 grammes of tolulylendiamine. Showing very large excess of iron. (Prussian blue reaction.) Exp. 84.

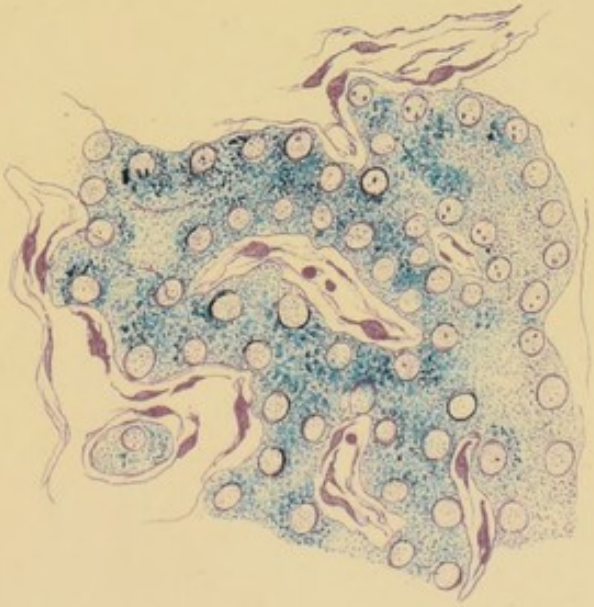


Fig. 2.—Liver of Pigeon.
Showing chief situation of pigment in above case, viz., within the liver cells.

CHAPTER XVI.

SUMMARY OF CONCLUSIONS REGARDING THE PATHOLOGY OF THE DISEASE.

THE following are the chief conclusions arrived at from the preceding anatomical and experimental studies regarding the pathology of this form of anæmia.

I. As regards its general *Morbid Anatomy:*

(1) None of the pathological conditions—*e.g.* malignant disease, atrophy of stomach, gastro-intestinal lesions, etc.—occasionally found associated with the features of pernicious anæmia, can be rightly regarded as the essential anatomical lesion underlying the anæmia present, or as reasonably accounting for the remarkable degree of its anæmia as compared with that of all other forms of anæmia.

(2) With regard to them all it is necessary to assume, in order to account for the high degree of blood change, that there have been superadded to these lesions certain others essential to pernicious anæmia.

(3) This conclusion is based chiefly on two considerations; (*a*) that similar anatomical changes, often far more marked, are constantly to be met with in cases presenting none of the features of pernicious anæmia; and (*b*), that still more frequently, cases of pernicious anæmia are met with without any such anatomical lesions.

II. As regards the changes in the *Blood and Blood organs:*

(4) The oligocythæmia met with exceeds in degree that found in any other condition. It is in itself distinctive, as between pernicious anæmia, and the anæmia of malignant or wasting disease. Except when very extreme,

it is not itself distinctive, however, as regards the anæmia producible by loss of blood.

(5) But in association with the high relative hæmoglobin ratio, the oligocythæmia is distinctive even in the case of the anæmia due to loss of blood; since, in the latter, the hæmoglobin ratio is invariably lower than the percentage of corpuscles.

(6) As regards the changes in the blood organs, the most marked and constant are those denoting a largely increased hæmolysis.

(7) In their order of frequency, these changes are found constantly in the liver, more or less constantly in the spleen, and very frequently in the kidneys.

(8) In the case of the liver, and kidney, the changes consist in an excess of pigment, rich in iron, derived from the hæmoglobin of the blood. In the case of the spleen, the evidences of hæmolysis are best—often, indeed, only—recognizable on examination of the fresh organ, comprising as they do morphological changes in the red corpuscles and plasma, sometimes also the presence of free hæmoglobin. The rich hæmoglobin colour of the spleen always contrasts markedly with the bloodless condition of all the other organs and tissues, with the single exception of the bone marrow.

(9) The pigment present is not the result of extravasation, either locally or elsewhere; but is distinguishable from such by important differences affecting both its character and its distribution.

(10) From its character, and amount, this pigment denotes an excessive hæmolysis as the most prominent, constant, and characteristic feature of the disease.

(11) Its presence, especially in the liver, serves to distinguish the condition sharply and clearly from those forms of anæmia, which *clinically* are supposed to most closely resemble it, namely,—the anæmia of malignant, or of wasting disease, and the anæmia of loss of blood.

(12) In these conditions, the above pigment changes are no less constantly absent.

(13) The anæmia of pernicious anæmia is thus essentially *hæmolytic*.

(14) Failure in blood formation plays little or no part in giving rise to the features of the disease. The evidence rather shews that it continues exceedingly active up to the very last.

III. As regards *Hæmolysis:*

(15) *In Health*, these studies shew that the process of hæmolysis differs in many important respects from the conceptions hitherto entertained; whether with regard to (1) its importance; (2) its nature; (3) the significance of blood pigment as an index of it; (4) its causes; (5) its seats; or (6) the relative importance of the various organs chiefly concerned.

(16) It is not a slow decay of the blood, but an active change occurring daily associated with digestion; involving the liberation of a certain amount of hæmoglobin, and, presumably, its immediate replacement by freshly-formed material; it is carried out through the agency of the mass of cells in relation to the portal blood; its chief seat consequently being the portal as distinct from the general blood; the chief site of hæmolysis within the portal area being the spleen as distinct from the liver; the chief function of the liver in regard to hæmolysis being as an excretory organ.

(17) In *Pernicious Anæmia*, the hæmolysis differs in important respects from that occurring in health; it cannot be regarded merely as an exaggeration of the normal process.

(18) It also differs in important particulars from the hæmolysis characterizing malaria and paroxysmal hæmoglobinuria.

(*a*) On the one hand, there is no evidence that in pernicious anæmia, as is the case in malaria, the red corpuscles are individually diseased.

(*b*) On the other hand, there is no evidence that in it, as in paroxysmal hæmoglobinuria, a dissolution of red cells takes place in the general circulation. In that case, hæmoglobinuria would result; and this is absent in pernicious anæmia.

(19) It resembles hæmolysis in health in the important particular that it is confined to the portal area, and carried out by agencies in connection therewith.

(20) Its features as a whole can, however, only be reproduced by drugs possessing a special hæmolytic action; notably toluylendiamin.

(21) Hence, inasmuch as it is confined to the portal area, and gastro-intestinal influences are those which, even in health, specially determine the occurrence of hæmolysis, it is reasonable to conclude, that the conditions that determine the hæmolysis in pernicious anæmia are also situated within that tract—moreover, that they are *of a special character.*

(22) In the light of these studies *establishing the portal blood as the chief seat of hæmolysis,* the comparative frequency of symptoms and lesions connected with the gastro-intestinal area acquire an entirely new significance.

PART IV.—THE INFECTIVE NATURE OF PERNICIOUS ANÆMIA.

CHAPTER XVII.

GASTRO-INTESTINAL CHEMICAL CHANGES.

Introductory.

THE foregoing investigation had indicated that the hæmolysis found in pernicious anæmia was not of an ordinary character, except in the one important respect, that it took place within the portal area. With regard to the nature of the products causing it, my observations did not supply any definite information. From resemblances between their effects, and those produced by toluylendiamin, especially in regard to the limitation of their action to the portal blood, I concluded, that "the poison was probably of a cadaveric nature produced within the gastro-intestinal tract—in excessively small quantity, however, and not necessarily constantly"; and that "the destruction of blood was effected by the action of such poisons absorbed from the gastro-intestinal tract."

The line of investigation required was of a different character from that up to that time pursued. It was essentially chemical; and no longer anatomical or experimental. In preparation for it, I therefore spent a winter working specially at gastro-intestinal chemistry in Professor Hoppe-Seyler's Chemical Laboratory in Strassburg.

In the first case met with subsequent to the foregoing studies (Case 1, 1889), I directed special attention to such characters of the urine, as might be capable of affording an insight into the nature of the changes occurring within that tract.[1]

[1] Hunter, *Brit. Med. Journ.*, 1890.

I.—Excretion of Aromatic Sulphates.

Considering how important a part is played by putrefaction in the changes within the intestinal tract, my first thought naturally was that excessive putrefactive change might be present, and might lead to the formation of special poisons in the disease. To this point, therefore, I early directed my attention.

We have a reliable index as to the amount of putrefaction within the intestine, in the excretion of aromatic compounds in the urine; compounds—such as phenol, indol, skatol, cresol—derived from the disintegration of proteid material in the process of putrefaction. These compounds do not appear in the urine as such, but in combination with sulphuric acid, in the form of ether sulphates, chiefly of potassium. Since the sulphuric acid excreted in this form is derived from the sulphur of the proteid constituents of the food, we can measure the total excretion of aromatic compounds in the urine, by determining the quantity of sulphuric acid with which they appear in combination. There are thus two forms in which sulphuric acid is present in the urine—(A) as free acid combined with the salts of the food, and derived directly from these salts; (B) as aromatic sulphuric acid, in combination with the aromatic compounds of the urine, and derived from the sulphur of the proteids of the food.

In health the ratio of these two to each other—of A to B—is fairly constant. The quantity of free sulphuric acid usually exceeds that of aromatic sulphuric acid in the proportion of 10 to 1; and this ratio remains fairly constant, independently of all changes of diet. The relation is affected, in all conditions, in which the amount of putrefactive change within the small intestine is in any way disturbed. In obstruction of the intestine, putrefaction may be so increased that the ratio of A to B becomes equal; or the amount of aromatic H_2SO_4 (B) may even exceed the free H_2SO_4 (A). On the other hand, by clearing out the intestines with purgatives, such as calomel, it is possible, for the time at least, to cause the total disappearance of B from the urine. In such cases there is

not only a disturbance in the ratio of A to B, but also in the total excretion of each. The former is, however, the more important, as the quantity of each is dependent to a great extent on the quantity of food ingested.

The important point is, that in health, whatever the quantity of food taken, the amount of putrefaction which occurs in the proteid constituents bears a more or less constant relation to the amount ingested—the ratio of aromatic to free H_2SO_4, being 1 to 10. Variations from 1 to 7, up to 1 to 15 are, however, still within the limits of health.

Method.—The method I used for estimating the sulphuric acid, was Salkowski's modification of Baumann's original method. The free H_2SO_4 is at once precipitated from the urine, on adding a solution of barium hydrate; while the aromatic H_2SO_4 is only precipitated after the aromatic compounds have been broken up by heating with strong hydrochloric acid. Each variety of H_2SO_4 is thus obtained in the form of a barium sulphate; and the actual quantity can be determined by subsequent ignition, and weighing.

In the following table are embodied the results of my observations in the case referred to (CASE 7):

Table shewing Excretion of Aromatic Sulphates in a case of Pernicious Anæmia.

Date.	Quantity of urine in c.c.	A. Total excretion of free H_2SO_4 estimated as barium sulphate.	A. Total excretion of free H_2SO_4 (A).	B. Total excretion of aromatic H_2SO_4 estimated as barium sulphate.	B. Total excretion of aromatic H_2SO_4.	Ratio of A to B.
1889.		grammes		grammes		
March 11 ...	1100	1·496	0·629	0·484	0·203	3 to 1
,, 18 ...	600	1·251	0·526	0·261	0·109	4½ ,, 1
,, 22 ...	1050	1·438	0·604	0·262	0·110	5½ ,, 1
,, 23 ...	1030	1·731	0·738	0·300	0·126	5·7 ,, 1
April 15 ...	600	3·030	1·274	0·276	0·116	11 ,, 1
,, 22 ...	...	(0·252 per cent.)	...	(0·030 per cent.)	...	8¼ ,, 1
May 2 ...	1100	2·090	0·879	0·275	0·115	7·6 ,, 1
,, 6 ...	1000	2·505	1·053	0·405	0·170	6·1 ,, 1
,, 10 ...	900	2·034	0·855	0·342	0·153	6 ,, 1

Results.—The results recorded in the preceding table bring out certain interesting facts. The amount of aromatic H_2SO_4 excreted in health varies somewhat, according to the amount of food taken. The average daily excretion, however, is about 0·25 gramme. In the above case the excretion never reached this amount, although, in the first instance, it closely approached it (0·203).

The absolute amount of putrefaction occurring within the intestinal canal in pernicious anæmia was thus not in excess of the normal.

Of greater importance, however, as an index of putrefactive change, is the ratio of *free* to *combined* H_2SO_4—of A to B. In the first instance, the ratio was 3 to 1 instead of the normal 10 to 1. This result indicated that of the very small quantity of food taken at this time (as evidenced by the small quantity of free H_2SO_4 excreted), the quantity destroyed by putrefactive change was three times greater than that which should have occurred. These figures thus indicated a disturbance of the normal ratio of very considerable extent and significance. Under the treatment commenced at this time, carbohydrate instead of a more nitrogenous diet, the ratio steadily but slowly improved; till finally, a month later, it had reached the normal—namely, 10 to 1. This alteration was coincident with a marked improvement in the patient's condition.

It was at this time, that the patient felt, and looked, better than at any time during the latter part of his illness. He was not only taking more food, as evidenced by the steady increase in free H_2SO_4 from 0·629 gramme to 1·274; but he was utilizing more of it for purposes of nutrition, as evidenced by the steady diminution in aromatic H_2SO_4 from 0·203 to 0·116.

At the same time, the colour of the urine was more normal than at any time observed. On April 15th, for the first and only time, it could scarcely have been distinguished from that of health. A few days later, however, an exacerbation of weakness occurred; and the urine rapidly regained its former high colour.

From this time onward, till death, the disturbance in the ratio of A to B was less marked—8 to 1, $7\frac{1}{2}$ to 1, and then 6 to 1. This disturbance was due, be it noted, more to an increase in the excretion of aromatic H_2SO_4 (B)—to a relative increase,

therefore, of putrefaction, than to any great diminution in the quantity of free H_2SO_4 (A).

The amount of putrefactive change, although relatively greater than it should be, was not, however, sufficiently great to be credited with being the cause of the special symptoms of so well-marked a disease.

II.—Excretion of Ptomaines.

At the time these observations were made, I made a further series, with a view to determine whether any special bacterial products of the nature of ptomaines were present in the urine. I had already been engaged for some time in investigating the nature of the ptomaines formed during putrefaction; and had been able to isolate certain of them in large quantity, and in a chemically pure condition.

Method.—The method employed was that of Brieger; modified in its later stages by a method I had learnt while working with Professor Hoppe-Seyler, of Strassburg, based on certain observations of Baumann and Udranzky. These last observers have recently shewn, that benzoyl-chloride forms remarkably stable compounds with all bodies of diamine nature; and certain of the more common ptomaines, such as cadaverine (penta-methylene-diamine), and putrescine (tetra-methylene-diamine); belong to this group of bodies.

The method employed was briefly the following. The urine was slowly evaporated to dryness; its various insoluble salts removed by extracting with alcohol; its various extractive matters with other salts, such as sulphates, phosphates, etc., removed by precipitating with alcoholic solution of neutral acetate of lead; the remaining alcoholic solution then precipitated with warm alcoholic solution of mercuric chloride. In this way, most of the organic bases present were thrown down, in the form of insoluble mercuric-chloride compounds. Some, however, always remained in solution. Both precipitate and filtrate were therefore kept; and treated separately; the mercury removed by sulphuretted hydrogen. The solution remaining

was then rendered strongly alkaline by addition of 10 per cent. caustic-soda solution, and shaken with benzoyl-chloride.

The method adopted was to treat the urine of different days, —sometimes of many days together, in the manner above described. In some instances, the hydrochlorate salts of the nitrogenous bases were converted into double platinum salts, or picrates. The benzoyl-chloride method yielded the best results; as it was also the one most easily applied. By the above method, there was isolated from both precipitate and filtrate a certain quantity of a double benzoyl compound in a perfectly pure condition. From a number of different portions of urine, thus treated during the last two months and a half of the patient's illness, a very small quantity of a benzoyl compound was obtained, possessing very definite crystalline characters and equally definite physical properties.

It was extremely soluble in alcohol, insoluble in water. It crystallized out of alcohol in the form of long fine needles, arranged in rosette-like bunches. On determining the melting-point of the first specimen thus isolated, I found this to be between 171° and 173° C. A specimen from another quantity of urine had at first a similar melting-point. On further purification, I obtained it constant between 174° and 175° C. From other specimens of urine, I obtained a similar compound.

In respect of crystalline form and melting-point, this body agrees with the double benzoyl compound of putrescine, (tetramethylene-diamine), a ptomaine first isolated by Brieger from putrefying meat. The melting-point of this compound, when absolutely pure, is 175° to 176° C.[1] Slight impurity tends always to lower the melting-point several degrees. Thus the melting-point of the double benzoyl compound of putrescine, obtained by Baumann and Udranzky from the urine in a case presently to be referred to, was 170° to 173° C. After repeated crystallization and purification, its melting-point remained constant at 175° to 176° C.

On comparing the compound obtained from the urine with a similar compound of putrescine prepared from putrefying meat, I found them in all respects identical. In most cases this

[1] Baumann and Udranzky, *Zeitschrift f. physiol. Chemie*, xiii., June, 1889.

ptomaine—as to the identity of which with putrescine I have little doubt—was obtained alone.

In other samples of urine, it was present along with another ptomaine, which also formed a double benzoyl compound, with very definite crystalline characters—long, elongated, rectangular prisms. Owing to the small quantities obtainable, I found it impossible to effect the separation of this latter substance. The characters of its crystalline compound were, however, those of cadaverine (penta-methylene-diamine), — another ptomaine always obtained from putrefying meat, and large quantities of which I had so prepared.

These two ptomaines—cadaverine and putrescine—are usually found in association ; sometimes the one, sometimes the other preponderating. In ordinary putrefaction, according to my observations, the cadaverine greatly preponderates.

Lastly, from one of the specimens of urine I isolated a compound in a perfectly crystalline form, of whose identity I am uncertain. Its double benzoyl compound crystallized in long rectangular prisms, resembling those of the cadaverine compound. The melting-point of this compound lay between 70° and 80° C.—a wide margin, indicating that more than one body was present. From its behaviour in other respects, I conclude, that it was not cadaverine, whose benzoyl compound it most resembled. The melting-point of the latter is 129° to 130° C. It will remain for further observations to shew what this body is. As I have not met with it in any of my observations on the ptomaines of putrefaction, I am inclined to believe that it is a special diamine body.

Significance of Diamines in the Urine.—As to the significance to be attached to the presence of these ptomaines in the urine in this case, I desire to speak with reserve. I am inclined, however, to attach not a little importance to it ; and for the following reason. Putrescine, as also cadaverine, belong to a group of nitrogenous bases, so-called 'ptomaines,' formed from proteids by the action of bacteria, and never formed as products of the metabolism of the tissues themselves. Neither of them has been found in the urine in health ;[1] nor are they met with in disease ;[2] even in conditions in which they might be

[1] Brieger and Stadthagen, *Berl. klin. Woch.*, 1889.
[2] Udranzky and Baumann, *op. cit.*

expected to occur. Udranzky and Baumann examined the urine in cases of scarlet fever, diphtheria, typhoid fever, pneumonia, tuberculous peritonitis, intestinal obstruction, and extensive suppuration—all of them conditions in which the putrefactive changes within the tissues or within the intestinal tract are increased without finding a trace of them present. In the foregoing case also, as already seen, there was no such increase. It is obvious, therefore, that *ordinary putrefactive changes cannot account for the appearance of these ptomaines in the urine in this case or in other cases; since they may be absent, when putrefaction is increased, and they may be present when it is not increased.*

Since, however, they are only formed by the action of micro-organisms, one must conclude that their presence in the urine points to the action of special micro-organisms. Such is the conclusion arrived at by Udranzky and Baumann, in the only other condition in which these two ptomaines have hitherto been found in the urine. In a case of cystinuria, these two observers found cadaverine and putrescine in large quantity, both in the urine and in the fæces; and Brieger has since confirmed this observation in two other cases of this peculiar condition. Their presence was in no way connected with excessive putrefactive change; for in their case, as in the present one, there was no increase in the excretion of aromatic sulphates, nor any unusual disturbance in the ratio of the free sulphates to the aromatic sulphates.

What, then, is their significance in the foregoing case of pernicious anæmia? Neither putrescine, nor cadaverine, possess any specially poisonous properties. Even if present in much larger quantity than they were, they could not, therefore, be held responsible for the production of the special symptoms of the disease. If further evidence on this point were wanting, it would be afforded by the case of cystinuria referred to; in which they continued to be excreted in the urine for over a year, without the health of the patient being in any way materially affected thereby. They derive their importance, therefore, from the following circumstances, now fully established by many observations. They are not formed in the body in health; nor yet as the result of increased putrefactive changes in the intestinal canal. They are products, however, of bacterial activity,—of bacteria, differing widely in pathogenic qualities; their forma-

tion is sometimes unaccompanied by that of special poisons (ordinary putrefaction); it may, on the other hand, be accompanied by that of very active poisons (cholera). *The formation of active poisons depends upon the character of the organisms, more than upon the conditions under which they act.* This being the case, the presence in the urine, of ptomaines, such as cadaverine and putrescine has a very special significance. *It points to the presence of special micro-organisms in the alimentary tract.*

Toxæmic Symptoms.—As will be seen from a study of the case, this conclusion received support from the character of some of the symptoms present (see CASE 1).

The exacerbations from which the patient from time to time suffered presented all the phenomena of toxic poisoning; whether regard be had to the *nervous phenomena*—the sudden onset of drowsiness, the contracted pupils, the slight fever, and the sweating, or to the more local manifestations of the action of such poisons—the *intestinal disturbance*, and the obviously *increased destruction of blood* which always attended such attacks.

The latter was evidenced, as will be seen, by: (1) the high colour of the urine, and the appearance of urinary pigments and chromogens differing from those of health; (2) by excretion of hæmoglobin through the kidneys, and its appearance in the urine in the form of granules of blood-pigment; (3) by increase of the pigments in the fæces; and (4) by more marked lemon tint, from the presence of pigment in the subcutaneous fat.

All these phenomena, viz.:—

(1) General toxic symptoms, with fever;
(2) Intestinal disturbance;
(3) Increased hæmolysis, shewn by high colour of urine and high colour of fæces;
(4) Profounder anæmia;

were so closely related to one another, in order of occurrence, and in degree, as to suggest the closest possible relation between them—the weakness being due to an excessive destruction of blood, caused by the absorption of specific poisons from the alimentary tract, some of which at the same time caused general toxic effects.

Intestinal Origin.—That the alimentary tract was the seat of production of these poisons there cannot, I think, be much doubt. The intestinal symptoms were always prominent on the occasion of these attacks. Moreover, Udranzky and Baumann, in the case of cystinuria referred to, found the ptomaines in large quantity *in the fæces.*

Relation to Gastric Lesions. — In my case, I found *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 irritation in the stomach wall itself.

There was, moreover, a definite history of infection in the case (Case 1), the patient's weakness dating from the time he was exposed to insanitary influences (see p. 227).

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 weakness, 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, or even primarily, one of gastric trouble; but one of steadily increasing weakness, with all the symptoms we have learnt to regard as characteristic of pernicious anæmia.*

This conclusion derives a special interest, from its bearing on the view I have expressed, as to the nature of the relationship between pernicious anæmia and the changes *occasionally* associated with it (p. 49).

These changes include, amongst others, malignant disease of the stomach, atrophy of gastric glands, gastritis, degenerative changes in the nerve plexuses of the intestine, and, lastly, the presence of intestinal worms. When present all these lesions have usually been regarded as the cause of the disease.

With regard to all of them, I concluded, that "as the essential morbid change in the disease, they could not possibly be regarded"; that "however important atrophy of the gastric glands, and other changes in the gastric mucosa, may be as etiological factors . . . they cannot be regarded as the essential anatomical lesions underlying this form of anæmia"; and that "malignant disease and other gastro-intestinal lesions are not fitted in any way to account for the peculiar features of this, as distinguished from other forms of anæmia." "With regard to them all, . . . it is necessary to assume, that there have been superadded certain anatomical changes essential to pernicious anæmia, on which the features of pernicious anæmia depend." That special change I have shewn to be an excessive destruction of blood, caused probably by the action of specific poisons absorbed from the intestinal tract.

The evidence adduced in the foregoing case supplements, and also confirms the conclusions thus arrived at. In the light of the observations just recorded, as to the presence of ptomaines in the urine for whose formation the action of specific micro-organisms is necessary, it is justifiable to draw the conclusion I now do, that *the special factor required to initiate the symptoms peculiar to the special disease—pernicious anæmia—is the presence under certain favourable 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*—a specially unhealthy condition of mucous membrane of stomach and intestine induced by the presence of intestinal parasites, or by prolonged bad nourishment.

CHAPTER XVIII.

PREVALENCE AND SIGNIFICANCE OF ORAL SEPSIS.[1]

Introductory.—After the foregoing observations the problem which the disease presented was mainly one as to the *nature* and *source of the infection* pointed to in the foregoing work.

The particular kind of problem was not one that lent itself to solution by direct studies (pathological, experimental, and chemical) such as had availed in former work.

To attack it by direct bacteriological studies implied:

(1) An elaborate investigation of the fauna and flora of the whole digestive tract in cases of pernicious anæmia.

(2) For purposes of comparison, similar investigations in other gastro-intestinal conditions.

(3) Experimental investigation of the virulence of the various organisms isolated; and that, too, not only individually, but in the various possible combinations ('mixed infections') met with in the digestive tract.

And lastly, presuming all these investigations to be successfully carried out, there was

(4) The certainty, that at the very best the results could only be suggestive, not conclusive; since it was quite impossible to reproduce, by experiment, the more or less unhealthy conditions of the digestive tract, possibly existing for many years, which were probably necessary to ultimate successful infection.

Great as my interest in the disease was, I did not care to enter upon such a task. My later observations were therefore made on individual cases as they presented themselves—observations mostly of a clinical character, supplemented, however, by such pathological observations as were possible.

[1] Hunter, "Further observations on Pernicious Anæmia—A Chronic Infective Disease," *The Lancet*, i., 1900.

The disease is not common; and cases under personal observation are necessarily few and far between. Moreover, for the particular purpose in view, they were even fewer than usual; for the only cases I deemed suitable, in the first instance, were those met with in private practice, as distinguished from those met with in hospital practice. In the former, rather than in the latter, the precise conditions as to previous health, food, occupation, and general sanitary surroundings could be definitely ascertained; and any deviation from the normal could be appraised at its proper value.

It was clear from my previous studies, and subsequent experience of the disease, that some such minute inquiry into individual cases was called for; that in this way, rather than by any process of collective investigation, light might be thrown on the mode of origin of the disease. For one of its peculiarities, according to my experience,—which differs, therefore, notably from the experience of earlier observers (see p. 15),—is, that it is met with alike in the rich, and in the poor; in the well-fed, as well as in the poorly nourished; in the athletic, as well as in the weakly; in the man whose whole life has been spent in the open air of the country, as much as in those living in the less pure atmosphere of towns; and in those previously healthy, as much as in those already the subject of disease.

These facts appeared to me to indicate, that it was not general conditions of life that were at fault, or that could be held responsible for the disease; but that its origin was rather to be sought in some special conditions—rare, fortunately, in incidence—common to all classes, irrespective of station, mode of life, food, and general surroundings.

Nature of Results.—The present observations are based on a series of seven cases of pernicious anæmia observed in private practice, to which are added five cases since observed both in hospital and in private patients. The result has been to draw my attention to the following points:—

(1) The frequency of unusually cario-necrotic conditions of the teeth in pernicious anæmia, as an antecedent to the onset of the anæmia (Chap. XXI.).

(2) The occurrence of glossitis, and stomatitis, among the first objective signs of the disease, sometimes as the first subjective and objective trouble (p. 204).

(3) The frequency of gastric symptoms, (sickness, retching, vomiting) pointing to gastric trouble (Chap. XIX.).

(4) "Septic" gastritis in pernicious anæmia (Chap. XX.).

(5) The origin of septic gastritis from necrotic and suppurating teeth (Chap. XXII.).

ORAL LESIONS MET WITH IN PERNICIOUS ANÆMIA.

The origin, and development, of my interest in the subject of Oral Sepsis in connection with pernicious anæmia will be afterwards traced (Chap. XXI.). In all the cases some morbid condition of the mouth was present sufficient by its character or its intensity to attract special attention. The actual conditions met with in twelve cases were:

(1) Marked cario-necrosis of the teeth, antecedent or existing, in all cases.

(2) Conditions of glossitis or stomatitis, characterized by great tenderness, presence of sores, or salivation, in seven cases. (Cases 1, 2, 4, 8, 9, 10, 11.)

(*a*) In no fewer than four cases, the condition of the mouth formed one of the chief subjects of complaint on the part of the patient (Cases 1, 2, 4, and 8).

(*b*) In nearly all cases, the morbid condition of the mouth seemed to be connected with the origin of the disease; either preceding the weakness (Cases 1, 2, and 8), or being most troublesome in the early stage of the disease (Cases 4, 9, 10, 11). In other words, the condition was not simply the result of weakness; on the contrary, it was most marked at the commencement when the anæmia was slight, and in each case became less marked as the anæmia increased.

(*c*) In two cases (Cases 2 and 8), the patients themselves connected the onset of their weakness in some mysterious way with the stomatitis. As one of the patients strikingly put it, "the trouble of the mouth seemed to go right through him."

(3) In all cases, there was evidence of gastric or intestinal trouble, or both—discomfort, sickness, retching, vomiting, diarrhœa; and in some cases, gastritis, or gastric catarrh, was proved to exist, either during life (Cases 8, 10), or after death (1 and 12).

(4) Lastly, the possibility of any connection between the oral and the gastric conditions was elucidated by one case (Case 7),

which demonstrated in the most striking manner the origin of "septic" gastric catarrh from infection with the organisms of dental necrosis (see pp. 231, 235).

I.—The Significance of Dental Caries and Stomatitis in Pernicious Anæmia.

In a subsequent section will be fully considered the relation between dental cario-necrosis on the one hand, and "septic" gastric catarrh, with general ill-health, on the other. What we have now to consider, is the significance to be attached to the oral conditions met with in the foregoing cases of pernicious anæmia, and their relation to the anæmia. To the various morbid conditions of the alimentary canal (p. 37), described as *occasionally* met with in cases of pernicious anæmia I have now to add certain morbid conditions of the mouth—viz., dental cario-necrosis, glossitis, and stomatitis. The other morbid conditions include:

(1) Atrophy of the mucous membrane of the stomach or of the gastric glands and chronic gastritis. (Fenwick, Nothnagel, Nolen, and Hunter.)

(2) Ulcers of the stomach and duodenum. (Zahn.)

(3) Duodenitis. (Homolle.)

(4) Chronic fibrotic changes in the colon, with more recent hyperæmia, and superficial necrosis. (Morley Fletcher.[1])

(5) Cicatrices of healed ulcers, and a little diphtheritic exudation in the large intestine. (Hale White.[2])

(6) Ulcers of colon. (Biermer, Bramwell.)

(7) Degenerative changes in the abdominal sympathetic ganglia (Banti), or in the nerves and ganglia of the intestinal walls (Sasaki).

(8) The presence of intestinal worms (Baumler, Reyher, Runeberg, Sahli).

(9) Cancer of the stomach.

In estimating the significance of these conditions in relation to pernicious anæmia, the standard of criticism I have employed is (see p. 50), that only in isolated cases have such changes been found; and that similar changes, sometimes even more marked, are constantly present without any of the features of pernicious

[1] *Transactions of the Pathological Society of London*, 1899.
[2] *Guy's Hospital Reports*, 1890.

anæmia. I cannot, therefore, regard them as the causes of the anæmia, *sometimes* found associated with them. To the oral conditions now described, the same standard has to be applied, and with a like result. Dental cario-necrosis is far too common to be itself the cause of so rare a disease as pernicious anæmia. Stomatitis and glossitis, although not so common, are also too common to be the direct cause of so rare a disease. I cannot, therefore, regard them as the essential anatomical condition underlying the disease, even in the cases in which they are most intense. Nevertheless, while they cannot be regarded as causes of the disease, they have a very special significance, especially the lesions found in the tongue.

Their mode of onset, character, and progress, all, I consider, denote their infective nature; and the special significance attaching to them in my mind is, that their existence points to an infection of a definite character localized to the alimentary tract.

II.—Special Features of the Glossitis.

Mode of Onset.—The origin of the stomatitis or glossitis was in all cases as mysterious, and sometimes as sudden, as the anæmia itself. The conditions were not simply the result of the anæmia. On the contrary, when they were, by discomfort or painfulness, of a character to attract the attention of the patient, they were generally noticed at the onset of the disease, or early in its course; in most cases, they actually subsided as the anæmia progressed. So closely connected were they, indeed, with the origin of the disease, that, in three cases, they were among the first symptoms noticed, and complained of; and in three cases, the patients dated their weakness from the onset of the trouble in the mouth.

Definite Character of the Infection.—In the first case observed, (Case 1) I was struck by the curious character of the sores on the tongue—localized inflamed patches, sometimes shewing vesicles filled with clear serum, situated under the tip of the tongue, the inflamed areas shifting from time to time, with atrophied appearance of the intervening mucosa. The condition thus described is not one of ordinary stomatitis, or glossitis, such as one finds *e.g.* as the result of the ordinary oral sepsis connected with decayed teeth. And this appears to hold true for my other

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cases described—both as regards the intensity, and the character of the glossitis, and the situation of the sores. Thus, in Case 1, the terms used to describe the condition of tongue are: "tongue extremely raw and tender"; "presenting a red and fiery appearance"; "tenderness on swallowing extending down the throat to the stomach," likened by the patient to that of 'swallowing fire.' Nine months later, the description was: "Whole tongue tender. On dorsum, and along edges, patches of more fiery redness; some under the tip of tongue shewing small inflamed vesicles full of serum." Compare this with the description given by the patient (Case 3), of the condition of his tongue for a period of seven months of his illness: "Tongue raw and tender, looking like a piece of raw liver . . . causing great pain." Or with that given by the patient (Case 8), when his illness began: "Some sort of painful sores in mouth under the tongue . . . not connected with the teeth . . . causing great discomfort," of such a character and intensity, that his subsequent illness he described—"as if the trouble in his mouth had spread down into stomach and right through him."

These are not the characters of an ordinary glossitis. They suggest an infection more deep-seated and severe.

'Periodicity' of the Stomatitis. Another notable feature of the glossitis is what may be termed its 'periodicity'—its variability from time to time, independent apparently of treatment; notably its greater severity at the outset of the disease, with tendency to subside, or at least to give less discomfort, as the disease advances.

This feature was very noticeable in Case 1. Thus, the illness was ushered in, (the autumn of 1886), with sore throat and diarrhœa, from which time "he continued to suffer at times from an inflammatory condition of throat and tongue, and his strength began gradually to fail." In January 1888: "With the exception of some congestion of the throat and certain pale red spots on the tongue, nothing further objective to be made out" (note by Sir T. Lauder Brunton). June 1888: "Tongue extremely raw and flabby, fiery, and tender, inflamed patches with smooth mucosa between." March 9th, 1889: "Tongue not so raw-looking. Presents a more atrophied appearance, still inflamed, vesicles full of serum, whole tongue tender, and mastication painful and difficult." March 20th: "Tongue lost its former fiery-red appearance, much paler, inflamed patches less marked, and

vesicles entirely disappeared." And from this time onward till the death of the patient two months later the tongue ceased for the first time since his illness began, to give him any trouble. It continued to present a smooth, flabby appearance ; but the tenderness on eating was entirely lost—"he could take all kinds of food and even condiments without the slightest discomfort."

The same 'periodicity' is noticeable in Case 3. For a period of some seven months, (October 1894 to May 1895) at the commencement of the illness, the tongue was raw and tender, 'like raw liver,' causing great pain. When seen by me (October 1895), the tongue shewed nothing to attract attention.

So also in Case 8. When the illness began, (June 1898), there were painful sores under the tongue, causing great discomfort. When the patient was seen in April 1899, there was nothing noticeably wrong about the tongue, although there was constant salivation. During the latter part of the patient's illness, (he died on 3rd December 1899) "salivation occurred when he had stomatitis : the latter was always a bother. The mouth was always clammy and uncomfortable."

The periodicity was no less striking in Cases 9, 10, 11, 13 (see p. 210).

This feature—*periodicity*—recalls one of the most striking characters of the disease itself. There is perhaps no single feature of the disease more notable than the mysterious way in which, whether under treatment or not, it varies from period to period without known cause. Here, then, locally in the mouth and tongue, one has had occasion to note equally striking and unaccountable variations in intensity of what is obviously a local infective process—an intensity varying from a fiery-red inflamed appearance of tongue with intense tenderness, coming and going over a period of several years, to a condition seen for a short time before death, when nothing was observable in the mouth except a slight atrophic appearance of the tongue, and all kinds of food and drink could be taken without discomfort of any kind. Had the patient been seen for the first time during the intervals between such attacks, no one could have judged, from the condition of his tongue, that anything special had been wrong ; the only sequel of the inflammation being a pale and atrophied appearance of the mucosa of the tongue.

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 stomach or intestine, or both, 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 limited to the portal area (p. 187).

(2) The prevalence of gastric and intestinal symptoms, *e.g.*, vomiting and diarrhœa during life (Chap. XIX.).

(3) The frequency with which morbid lesions when discoverable are confined to the gastro-intestinal tract, especially to the stomach—gastritis, atrophy of glands, etc. (p. 41).

III.—Frequency of Stomatitis in 250 Cases of Pernicious Anæmia.

The interest I attach to the stomatitis described is altogether apart from any question of its frequency, or of its importance, *qua* stomatitis. In the light of these observations, it was a matter of interest to me to examine the records of cases with special reference to the conditions observed in the mouth.

So far I have examined 250 cases; and I find references to stomatitis in 20 cases. These are appended. Few as the references are, they are of interest, chiefly in respect of the remarkable similarity of the appearances described by independent observers to those described above.

The fullest notes are those of Laache, who found the condition in 4 cases out of 11. His description of one of his cases (No. 3) might have been written for Case 1 of my own, especially in regard to the features above described as specially noteworthy—viz., the tenderness, the excoriations, and the 'smooth polished,' or 'atrophied,' appearance subsequently presented by

the tongue. It is also notable, as being the only one where I find mention made of a carious condition of the teeth. Cases (Nos. 4 and 10) are also noteworthy in regard to mode of onset. In both cases, the condition of the mouth was noted 'at the same time' as the onset of the illness. Dr. Bramwell's case is of interest in the same connection; there the condition of the mouth preceded the illness. Only one observer (Müller) draws special attention to the condition; and he was disposed to regard it as an effect of the blood condition. Eichhorst thought, that on account of the pain it caused, it might not be without significance.

I do not suppose for a moment, that the smallness of the number (20 out of a total of over 250 cases) accurately represents the frequency of this morbid condition of the mouth. When once noted, the condition is so striking that it is looked for in other cases; thus, I note, that out of a total of 20 cases, other than those which have come under my own observation, no less than 13 are reported by four observers, of whom Müller is responsible for 5, Laache for 4, M'Phedran for 2, and Hopkins for 2.[1]

References to Stomatitis.

1. Müller[2] (62 cases).

Cases 20 and 23: 'Stomatitis.'

Case 29: "Complains of very painful spots on the tongue which render eating almost impossible."

Case 38: "Small ulcers in mouth which make eating almost impossible."

Case 39: "Stomatitis (small ulcers on the tongue and on the mucous membrane of the mouth)."

Müller notes in general with regard to them, "that they were very resistant to local treatment, disappearing spontaneously or with temporary general improvement, to recur again without special cause, causing great discomfort to the patient, and great pain on eating and drinking." He thought that the stomatitis probably had some connexion with the alteration of the blood—that certain chemical products in the blood, mixing with the secretion of the mouth, caused irritation and ulceration; in a manner similar to that described by Mosler for the parotid secretion in other diseases.

[1] I may add, that I have seen ten cases of pernicious anæmia in the last nine months, and have found a well marked history of stomatitis or glossitis, or both, *in every case*.

[2] *Die Progressive Perniciöse Anämie*, Zürich, 1877.

2. Eichhorst[1] (91 collected cases) mentions the above observations of Müller; and concluded that sometimes, possibly on account of the pain they caused "they were not without significance." I find no mention of the mouth in any of his own (7) cases, except one (Case 6), where he speaks of a "bad taste in the mouth."

3. Laache's[2] (11 cases).

Case 1: "*Post-mortem.*—On the left aryteno-epiglottidean fold a round, greyish-white raised spot, the size of a pea, resembling an aphthous *erosion*, but shewing, on microscopic examination, no mycelium of *oidium albican.* On the back wall of pharynx, a slightly raised ulcerating patch, the size of a bean."

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.*"

Case 4: The illness began with sudden onset of diarrhœa. "*At same time* he became 'skinless' (*hautlos*) in mouth" (mouth feeling skinned).

Case 8: "Tongue moist, slightly furred: no excoriations here or on lips."

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."

4. Dr. Hale White[3] (29 collected cases).

Case 14: "Complains of a coppery taste in the mouth."

Case 20: "Tongue pale and flabby, partly furred, partly *raw* and *fissured.*"

Case 27: "Vomiting and a *burning sensation in the mouth* with epigastric pain."

5. Dr. Byrom Bramwell[4] (48 cases).

Case 43 (1898): Illness of several months' duration. Apparent *cause*, "the patient herself blames mental worry. A year ago she began to be troubled with sore gums (inflammation of the gums, buccal mucous membrane and side of tongue)."

[1] *Die Progressive Perniciöse Anämie*, Leipsic, 1878.

[2] *Die Anämie*, Christiania, 1883. The italics are mine.

[3] *Guy's Hosp. Rep.*, 1890.

[4] "Anæmia and Diseases of the Blood-forming Organs," Edinburgh, 1899.

6. Hunter (88 collected cases from the literature of the subject during the years 1890–1896).

(1) "Subject to attacks of diarrhœa at short intervals and irregular vomiting. The mouth sore and anus excoriated." Arsenic always caused disturbance of stomach and bowel in a few days, "with a *metallic taste and soreness of the mouth*" and increase of the anal affection.[1]

(2) A child, aged 2 years, admitted for ulceration, stomatitis, and anæmia. *Exacerbations in the stomatitis*, the latter finally extended, until it involved the alveolar spaces, and caused the loss of two or three teeth, and the separation of a sequestrum three-quarters of an inch long. *Post-mortem.*—Stomach "*evidence of acute or chronic gastritis.*"[2]

(3) "Often vomited. *Stomatitis was troublesome* and also diarrhœa."[3]

(4) Bleeding of the gums first noticed, then profuse nausea. "Tongue was clean; on left side was a deeply drilled-out *ulcer* which accounted for some of the blood which escaped. The gums were spongy and bled on being touched."[4]

(5) "For some time his mouth had felt very rough and dry." Nausea was present.[5]

(6) Case 3: "Tongue sore: vomiting; stools very loose."[6]

(7) Case 5: "Severe diarrhœa, stools colourless and slimy. Later on, tongue and mouth very sore."[6]

Additional Cases.—Since the foregoing was written in January 1900 I have observed the following additional cases. They serve to emphasize the points above mentioned with regard to time of onset, characters, periodicity of the glossitis.

Case 9: "For a fortnight, at onset of illness, great soreness of tongue, necessitating use of a soothing mouth wash." A condition of extreme dental caries; only six good teeth remaining; ten rotten stumps in gums; other teeth absent.

Case 10: Ill-health began four years ago, end of 1896. In February 1897, sore throat with considerable pain on swallowing, the pain seemed to run down into stomach. This lasted for fourteen to twenty-one days, when it disappeared. Since then he has had slight attacks of sore throat, at varying intervals, up to the present time. End of 1897, first had trouble with his tongue, slightly swollen around the edges, with several longish patches of a deep red colour, extremely tender. A few

[1] Dr. M'Phedran, *Medical News*, Philadelphia, 1890, pp. 367–368.
[2] Dr. Holt, *Medical Record*, New York, 1891, p. 410.
[3] Dr. M'Phedran, *Internat. Clinics*, Philadelphia, 1892, vol. i. pp. 39–47.
[4] Sir R. Douglas-Powell, *Clinical Journal*, London, 1893, vol. ii. pp. 241–244.
[5] Dr. Russell, *Brit. Med. Jour.*, vol. i., 1894, p. 298.
[6] Hopkins, *Guy's Hosp. Rep.*, 1895.

patches on the dorsum, less numerous and painful than those on the edges. Tongue very tender, especially to warm liquids. It got well in about a week's time. He has had repeated attacks of sore tongue since then, about once every two or three weeks, up till the last nine months; since which, they have been slighter, and at longer intervals (every two months). Since beginning of this year, (1900) has hardly noticed anything wrong with his tongue.

On admission, tongue slightly red, with a few transverse cracks, edges rather glazed on the dorsum; not tender. Gums swollen and inflamed, projecting betwixt teeth. Teeth all in a very bad state of preservation, all the incisors and canines loose.

Under treatment with antiseptic mouth wash, redness of tongue rapidly disappeared. Seven weeks later, tongue again became tender, red, shewing small red granulations on its right edge. Temperature at same time rose a little; patient looked ill. This continued for nine days; then it lost its general red colour, but continued to shew on its edges a number of angry red spots, size of a pin's head.

Case 11: Illness began two years ago; pallor, lemon-colour. Constant pain in the stomach and side (over spleen), and periodic attacks of severe pain in the mouth, and stomach. At this time, he was greatly troubled with 'a sore mouth.' It began by pain and swelling of the gums; the teeth became sharp-edged to the feel, and felt as if they cut his tongue. In twenty-four hours after this, the tongue itself became almost unbearably sore, and on examination shewed big red patches on the dorsum and edges.

His tongue felt "as if it had no covering; as if it was quite raw, so that when I put a piece of bread in my mouth, it felt like sandpaper." The attack usually lasted two or three days, after which the patient could eat beef-steak, or any other food. The attacks came on about every three weeks, and were always followed, or accompanied, by gastric symptoms. This continued till Christmas 1899. He had then three very bad teeth extracted, since which time the mouth condition has been considerably less. On admission dental caries and suppuration while under observation. Several attacks of "sore tongue."

Case 13: Three and a half months after illness began, patient noticed soreness of mouth and tongue. The degree of soreness has varied from time to time; at times the mouth causes no discomfort. During an attack the tongue "feels raw, as if it had been cut." On admission dental caries and stomatitis, and slight glossitis. (Patient died of acute congestion of the lungs a fortnight later. *Post-mortem*, the liver, spleen and kidney, shewed typical pigment changes—see Analysis, No. 35, p. 101—the stomach well marked subacute catarrhal gastritis. No hæmorrhages. Microscopic examination of organs not yet completed.)

CHAPTER XIX.

EVIDENCES OF GASTRO-INTESTINAL INFECTION.

Frequency of Gastro-intestinal Symptoms.—The symptoms of gastro-intestinal disturbance accompanying this anæmia include not only vomiting and diarrhœa, but almost every variety and degree of disturbance—*e.g.* indigestion, anorexia (sometimes alternating with ravenous appetite), nausea, sickness, pyrosis, salivation (rare), acidity, retching, vomiting, gastric pain, dilatation of the stomach with splashings, general discomfort over the stomach, looseness of the bowels, diarrhœa, and colicky pains.

An analysis I have made of a total of 279 recorded cases shews that the frequency of such symptoms is even greater than supposed.

Table shewing the Frequency of Gastro-intestinal Symptoms in 279 Cases of Pernicious Anæmia.[1]

Author.	Number of cases.	Number in which gastro-intestinal symptoms are recorded.	Per-centage.
Eichhorst (1878), ...	91	74	81
Laache (1883), ...	11	9	81
Hale White (1890), ...	29	25	86
Byrom Bramwell (1899), ...	48	40	83
Hunter (cases from the literature of 1890–1896), ...	88	73	83
Hunter (1900), ...	12	11[2]	91
Total, . . .	279	232	84

[1] I have not included in this analysis the very full and complete record of cases (103 in number) given by Dr. Pye Smith in his article in 1883; since this includes not only all the earlier cases recorded by Müller, and Eichhorst, but also many from the records of Guy's Hospital subsequently analyzed in Dr. Hale White's list of cases.

[2] The exception was Case 5. When I saw him, early in his illness, he had no

The most striking of these symptoms of gastro-intestinal irritation are vomiting and diarrhœa. Their prominence is well brought out by an analysis of 29 cases from the records of Guy's Hospital. The analysis was specially made by Dr. Hale White, in relation to my conclusions regarding the portal site of the hæmolysis, and the importance of gastro-intestinal changes.

Before admission: *Vomiting*, 12 (or 41 per cent.); *Diarrhœa*, 10 (34·5 per cent.).

After admission: *Vomiting*, 16 (or 55 per cent.); *Diarrhœa*, 12 (or 41 per cent.).

Dr. Cabot's analysis[1] of 50 cases (33 of males and 17 of females): *Nausea and vomiting* in 31 cases (62 per cent.); *diarrhœa in* 12 cases (24 per cent.); constipation in 13 cases, and bowels regular in 13 cases.

Gastric and Intestinal Lesions.—I have analysed 150 cases, and I find that the changes described in the stomach in individual cases, (and these constitute a very considerable proportion of those *microscopically examined*), include *every stage of catarrh of the mucosa and its effects, e.g.*,

Increase of mucus; *swelling of mucosa* (Laache, Case 8).

Punctiform hæmorrhages and submucous hæmorrhages (Eichhorst, Case 4).

Small-celled infiltration around the follicles with *increase of fibrous tissue, fatty changes in the glands*, and *atrophy of the glands*, (Fenwick, Nothnagel, Nolen, Hunter, Mader, Weichselbaum, Holt, and Nonne). The usual absence of macroscopic changes —*e.g.* congestion—is, I consider, in no way surprising, when the extraordinary bloodless condition of the tissues and organs in this disease is borne in mind. As a rule, microscopical examination alone can be relied upon to determine the presence or absence of lesions.

The changes found in the intestinal mucosa from time to time are, I find, of a closely similar character, viz.

Hyperæmia; *e.g.*, "the mucosa of the intestine, the upper part of the jejunum, the lower part of the ileum, and the whole of the

dyspeptic trouble. He recovered temporarily, but relapsed and died a year and a half later. I have no information as to the character of his symptoms during this later period of his illness.

[1] "A study of 50 Cases of Pernicious Anæmia." *Bost. Med. and Surg. Jour.*, 1896, pp. 104–107.

colon œdematous and swollen, with small hæmorrhages on the edges of the villi" (Eichhorst, Case 3).

Œdema; enteritis; erosion; ulcers; and thickening: e.g., "Cæcum œdematous; one or two blackish small spots on the mucous membrane almost diphtheritic-looking" (Hale White, Case 13).

"Large intestine; numerous cicatrices of ulcers, or ulcers newly healed, and a little recent diphtheritic inflammatory exudation in parts" (*Ibid.*, Case 3).

"Some patches of injection of ileum, and the mucous membrane of the large intestine irregularly injected" (*Ibid.*, Case 20).

"Chronic fibrotic changes in the colon with more recent hyperæmia and superficial necrosis" (Morley Fletcher).

Pathological Report on Case 12. This report is given here in full, since it illustrates the chief pathological features presented by the disease. It has proved to be one of especial interest in relation to the pathology of pernicious anæmia.

Nature of examination.—I was afforded the opportunity of being present at the necropsy, and made the following notes. I subsequently examined, microscopically, the following tissues and organs—viz., Blood, Spleen, Lymph glands (gastric and mesenteric), Liver, Kidney, Tongue, Gums, Teeth, Stomach, Small intestine, and Colon; also, chemically, the Liver, Spleen, and Kidney for iron; and, lastly, both microscopically and chemically, the Stomach contents. The number of sections so far microscopically examined has been close on 200.

Necropsy.—The necropsy was performed 12 or 15 hours after death. The weather was cold. There were no *post-mortem* changes. The body was fairly nourished. The *Blood* was watery. The *Liver* weighed 4 lb. 10 oz. and was fatty; the centre of the lobules was pale and the periphery was rust-coloured. A piece of liver placed in sulphide of ammonium gave marked iron reaction (blackening). The *Gall-bladder* was filled with extremely deep golden-yellow-coloured bile. The mucosa was normal. *Kidneys*; the right weighed 4½ oz. and shewed a cicatrix at the lower end, the result of an old crush. The left weighed 7 oz. It was compensatorily enlarged. The *Spleen* weighed 5 oz.; it was red and firm, not soft. The *Stomach* contained 120 cubic centimetres

of bile-stained contents, with food. There was no cadaveric softening. The mucosa shewed punctiform hæmorrhages; there was considerable increase of mucus. The *Duodenum* and *Intestine* contents were fluid and very deeply bile-stained. The jejunum was much dilated and the walls were considerably hypertrophied above the point of narrowing (from six to seven feet below the stomach). The mucosa above the stricture shewed a number of irregular ulcers, some of them cicatricial, others partially healed, and others still shewing hyperæmic edges. Elsewhere the mucosa of the intestine, colon, and rectum shewed nothing obviously abnormal. In the *Gastric* and *Mesenteric glands* there were no signs of hæmorrhages. Microscopically, there was no pigment. The *Heart* muscle was red and hyaline; there was no tabby-cat striation. The musculi papillares of the left ventricle were hypertrophied. There were a few punctiform hæmorrhages under the epicardium. The *Tongue* was very soft on the sides; there were no ulcers; compound papillæ on the back part of the dorsum in front of the epiglottis were slightly red and prominent. The *Tonsils* were red. The *Œsophagus* was normal in appearance. With regard to the *Teeth*, the incisors and canines were small, regular, and pearly white, looking quite normal. The bicuspids and molars were very bad, represented for the most part by necrotic atrophied-looking stumps, the gums around presenting a peculiar, whitish, sodden appearance. In the right upper jaw, the first bicuspid was represented by a black stump, very small and atrophied (10 millimetres long by 5 millimetres wide), with a small abscess sac of about the size of a pea at its apex. The fang at the apex was dead and necrosed. The second bicuspid and first molar were represented by black fangs, the second molar had a black carious cavity in the crown, and the third molar a dark carious cavity on the outer side of the crown. In the jaw, beneath these teeth, was a large abscess sac 13 millimetres in diameter, communicating by a fistulous sinus with the root of the second bicuspid or first molar above; bare tooth was felt at the upper end of the sinus. In the left upper jaw, there was a similar white sodden appearance of gums immediately around decayed roots. The wisdom tooth alone remained; the gum around it was swollen, and at the back part was detached from the tooth. It was red, granulating, and inflamed; the fang of the tooth beneath was exposed and carious. On opening the left *Orbital cavity* a large quantity of pus welled up, appearing at first as if coming from the orbital cavity; afterwards it was found to come from the ethmoidal sinuses. There were no subdural hæmorrhages in the *Brain*. With regard to the *Lungs*, there were subpleural, punctiform, hæmorrhages near the base. In

the *Marrow of the long bones* there was transformation of yellow into red marrow.

Summary of Results.

1. There were characteristic *pigment changes*: viz. large excess of iron in the liver and kidney, and intensely deep colour of bile, denoting excessive hæmolysis.

2. The percentage of iron in the liver, spleen, and kidney was:

Liver, ...	0·360
Spleen, ...	0·069
Kidney, ...	0·033

To shew the notable increase of iron in the liver and kidney, I append for contrast the results of a similar analysis recently made in a case of *gastric cancer*, one of the cases resembling pernicious anæmia in the high degree of lemon colour, and in the absence of any notable emaciation. Percentage of iron in the liver, spleen, and kidney in this case was:

Liver, ...	0·022
Spleen, ...	0·013
Kidney, ...	0·003

3. The ordinary *blood* changes of pernicious anæmia, including the presence of nucleated red corpuscles, in the blood, spleen, and glands.

4. Dental decay and necrosis, with pus sacs at the roots of the teeth; collection of pus in the ethmoidal sinuses; and foul granulations around a necrotic tooth.

5. *Stomach*: fatty infiltration, degeneration, catarrh, and desquamation of the glandular cells (oxyntic cells least affected); presence of *cocci* in the perivascular lymphatics of the submucosa, at certain parts.

6. *Intestine*: there were no *post-mortem* changes. There were a number of ulcers in various stages—active, healing, and healed, above the constricted portion of the gut. Elsewhere, there was thinning of the mucosa. On microscopic examination the cells of the glands generally were normal; here and there small areas of superficial inflammatory necrosis of the mucosa due to the presence of organisms; at other parts replacement

of glands by cicatricial tissue, amidst which *streptococcal organisms* were numerous ; and at others, *cocci* were present in the perivascular lymphatics of the submucosa.[1]

7. *Colon*: there were no *post-mortem* changes. The lymphoid elements of the mucosa were well preserved, and stained normally. (*a*) There was extreme degeneration of the glandular cells, hardly a normal cell remaining. The cells were represented by granular detritus crowded with organisms, most of them *cocci*, only a few bacilli ; (*b*) *cocci*, both single, and in chains, were very abundant in the deeper parts of the mucosa around the base of the glands (they were absent from the superficial mucosa); and at parts they were very numerous in the lymphatics of the submucosa. Their *streptococcal nature* in parts was very obvious.

8. *Pus of ethmoidal sinus*: " Staphylococcus pyogenes aureus and Bacillus coli communis, the latter being probably a *post-mortem* contamination " (Dr. Eyre, Bacteriologist, Charing Cross Hospital).

9. *Stomach contents*: Chemically, no free hydrochloric acid or butyric acid. Lactic acid was present. Microscopically, there were numerous organisms, including mouth bacilli. All of them were decolourized by Gram's method, with the exception of a *streptococcus* form (Streptococcus longus). The contents were deeply bile-stained, resembling closely in appearance and character the contents of the jejunum. No cultures were obtainable owing to excess of formalin.

[1] The areas of superficial inflammatory necrosis here described were quite independent of the ulcers met with above the point of stricture. They were only recognizable on microscopic examination.

CHAPTER XX.

RELATION OF THE INFECTION TO THE ANÆMIA.

Relation of the Gastric Infection to the Anæmia.—On this important point light is thrown by the observations made in Case 1, Case 8, and Case 12.

Case 1.—I had occasion, in Case 1, to note during life the condition of the mouth and tongue, as above described. In that case, there were no stomach symptoms; but *post-mortem*, subacute chronic gastritis and atrophy of the gastric glands were found—lesions of the stomach, in short, identical with the subacute and chronic inflammatory changes noted in the tongue during life.

Case 8.—In Case 8, there was an identical history as regards: (1) the mode of onset; (2) the mouth symptoms, including also salivation; and (3) the subsequent progressive anæmia. Here, however, an opportunity occurred to examine the watery vomit without admixture with food, brought up from the stomach; and I found evidence of a most intense septic catarrh, chiefly streptococcal—an infection of the stomach causing gastrorrhœa, precisely as the trouble in the mouth caused salivation.[1]

The infection was clearly pathogenic, not simply saprophytic, as was shewn by the effects of treatment. For both the gastrorrhœa and salivation, which had existed for five months, were in the course of a week brought incontinently to an end, by the administration of salicylic acid as an antiseptic.

[1] I have repeated and confirmed this observation as to the presence of streptococcus organisms in the vomit in three other cases: twice in Case 10. "Microscopical examination of the deposit after centrifugalization shewed the presence of bacilli and sarcinæ: cultivations from the deposit gave rise to a growth of the *B. subtilis* only. Examination of the scum, or uppermost layer, shewed the presence of bacilli (several

Further, *the infection thus arrested in activity had obviously some relation to the anæmia.* For, following its arrest, the red corpuscles rose, in a fortnight's time, from 1,290,000 (25 per cent.) to 2,200,000 (44 per cent.), a difference of 19 per cent.; while the hæmoglobin rose from 24 per cent. to 46 per cent., a difference of 22 per cent. I feel justified, then, in concluding, that the infective catarrh in the stomach was not simply saprophytic—a complication resulting from the anæmia; but that it had some causal connection with the anæmia; since on its removal by direct antiseptic treatment, so sudden and remarkable a recovery in the blood took place.

In this case, then, I *conclude, that an infection of the gastric mucosa similar to the infection in the mouth underlay the pernicious anæmia; and that the progressive anæmia was not due to the stomatitis, or the glossitis, or even to the catarrh of the stomach per se, with their attendant disturbances of nutrition—but to the special infection which underlay, and was the cause of them all.* The stomatitis and the gastritis were the local lesions of an infection—probably of a 'mixed' character, chiefly coccal; while the anæmia was the result of the hæmolytic action of the poisons absorbed into the blood.

Case 12.—The conditions found in Case 12 also support the above conclusion as to the relation betwixt the anæmia and the infection—and extend them, moreover, in relation to the probable oral source of the infection.

In it, as in the others, the anæmia was not due to any mere disturbances of nutrition arising from the stomatitis, glossitis, or any conditions of gastritis, or enteritis present; but to the destruction of blood occasioned by the special infection. The whole group of conditions in the alimentary tract "were the local lesions of an infection, chiefly coccal, the anæmia being the result of the hæmolytic action of the poisons absorbed into the blood."

1. *Nature of the Anæmia.*—That the case was one of pernicious anæmia is, I consider, conclusively proved by the results of chemical analysis, shewing a characteristic increase in

varieties) staphylococci, streptococci, and sarcinæ. Cultivations gave rise to such a growth of *B. subtilis*, that no other organisms could be isolated." Dr. Eyre, Bacteriologist, Charing Cross Hospital. Case 10, 23rd Aug., 1900.

the percentage of iron in the liver (also in the kidney). Microscopically, the pigment was found within the liver cells, in the outer zone of the hepatic lobule, with characteristic fatty changes in the centre of the lobule. The anæmia was thus hæmolytic in its nature. (See Analysis, p. 216.)

2. *Mode of Development.*—The patient suffered from more or less abdominal discomfort from the time of his accident[1] seven years before; without the development, however, of any special degree of anæmia, till the previous summer—*i.e.* seven months before his death. His great pallor then became noticeable; and he soon after began to suffer from shortness of breath, and palpitation—*i.e.* five months before death. The conclusion I form, then, is that at the time of his death he was in his first year of illness from pernicious anæmia. In his case, the unhealthy conditions of some part or other of the alimentary canal, which, according to my studies, always precede, and are necessary to, successful infection, were created in the intestine above the point of stricture. As shewn by the character and severity of his gastro-intestinal symptoms (pain and vomiting), these unhealthy conditions had existed from the time of his accident seven years before; and it is exceedingly probable that some of the healed ulcers found *post-mortem* above the seat of stricture were remains of lesions resulting therefrom. They did not, however, cause pernicious anæmia. *With comparative suddenness*, there was super-added to his general abdominal discomfort, the feature of intense pallor; with all the symptoms—*e.g.* palpitation, breathlessness, diarrhœa, and vomiting, varying febrile attacks (see Mr. Barker's account of the illness in September 1899)—which are so characteristic of pernicious anæmia. From that time forward, what troubled him most and induced him to seek admission into hospital was his extreme weakness and anæmia, complicated by periodic attacks of pain and vomiting connected with his intestinal condition.

This relation of events—*a history of antecedent gastric or intestinal trouble extending usually over many years, more or less suddenly followed by a rapidly developing anæmia out of all*

[1] The patient was run over, and sustained an injury to the jejunum which caused a stricture at the injured part. See History, Case 12.

proportion to the actual extent or severity of symptoms or lesions existing in the stomach or intestine—is, in my experience, the typical mode of development of pernicious anæmia. The more or less suddenness of development, with the extraordinarily high degree of anæmia exceeding anything ever met with even in the severest forms of wasting anæmia—these are the clinical features which I have come to regard as denoting the supervention of a new factor—viz., definite infection of some part or other of the alimentary canal.

3. *Evidences of Infection.*—In the present case, the evidences of infection of the mucosa of the stomach, and to a still greater extent of the mucosa of the intestine and colon, were undoubted—notably:

(1) The small areas of superficial inflammatory necrosis in certain parts of the mucosa of the small intestine, associated with presence of organisms *confined to these areas, and to the lymphatics of the submucosa.*

(2) The very striking degeneration and necrosis of the cells of the tubules in the colon, associated with presence of organisms also *confined to the tubules*, and *to the subjacent lymphatics* of the mucosa and submucosa.

That the invasion of the mucosa was no mere *post-mortem* phenomenon I conclude from the following:

(*a*) In the case of the stomach, in only one part examined was there slight superficial *post-mortem* change in the mucosa; and at this point no organisms at all were found. On the other hand, the organisms were found in the lymphatics of the mucosa, at parts where no *post-mortem* changes were shewn.

(*b*) In the case of the small intestine, the cells of the tubules generally shewed no change, and no organisms were present in them. On the other hand, where the organisms were present, they were surrounded by evidences of inflammatory reaction—viz., nuclear fragmentation, and necrosis.

(*c*) In the case of the colon, the organisms were confined to the degenerated and necrosed cells of the glands, and to the lymphatics underlying them. They were not present amidst the lymphoid tissue of the general mucosa.

4. *Nature of Infection.*—As regards the nature of the organisms present, and their relative importance, any decision from their microscopical characters alone is naturally impossible. The contents of stomach and intestine were much alike in character, and both were bile-stained; so that it is certain that the ordinary intestinal organisms (bacillus coli) were present in the stomach as well as in the intestine. In the mucosa, and especially within the lymphatics, however, the organisms present were not bacilli, but *cocci*, and especially *streptococci* (Zeiss, $\frac{1}{12}$ oil immersion); and a streptococcus was also present in the stomach contents. As this organism is undoubtedly pathogenic, I am disposed to attach to it the chief importance. The infection of the mucosa was chiefly coccal and streptococcal.

5. *Source of Infection.*—On this point—the one which will be dealt with in the next chapter—no information was forthcoming from the history of the patient. He was too ill to be questioned. He had been well fed, and had lived amidst healthy surroundings. With regard to any dental or oral trouble, his wife stated, in reply to inquiry, that he had not suffered in that respect. The examination, necessarily of a cursory character—made a few hours before his death, when he was already sinking—seemed to bear out this statement. For the front teeth, shewn on opening his mouth, seemed exceptionally good and healthy—so much so that the case appeared to be one affording no support to conclusions I had been led to regarding the prevalence of decayed teeth, and their importance as a possible source of pyogenic infection, in pernicious anæmia (p. 227).

As it turns out, the case is a rather remarkable one in this relation. For at the autopsy the very reverse was found to be the case necropsy. The front teeth alone were good. The remainder were mostly represented by black roots lying in white sodden gums. At the roots of these, in one side of the jaw alone, were two abscess sacs, the larger the size of a small hazel nut. Moreover, on opening the left orbital cavity, pus welled out in quantity from the ethmoidal sinuses.

Of this condition of mouth or nose, there was not, be it noted, the slightest suspicion during life, and not the slightest symptom. This was one of the points which had specially arrested my attention in previous observations. I considered it

"all-important in all cases of commencing anæmia that special attention should be directed to the condition of the teeth . . . by removal not only of old stumps, but also of all black teeth, and of teeth shewing commencing cario-necrosis . . . these precautionary measures being necessary, irrespectively of any statements made by the patient as to the degree of discomfort his teeth are causing. For in no single case observed, however bad I found the teeth to be, was my attention drawn to the teeth by the patient, or any complaint made of them by him. There is a stage in pyogenic conditions as in other forms of infection, when local reaction—*e.g.* pain or inflammation, is absent or insignificant, at the very time when the general septic effects are most marked."

The case just recorded fully bears out the correctness of these statements. Without occasioning the slightest local discomfort, there existed a profoundly septic condition both of jaw and ethmoidal sinuses. How long these decayed teeth had existed, there are no means of knowing. But one notes with interest the statement in his history, that "he had always suffered from 'heartburn'; worse since the accident," a symptom denoting the existence of chronic gastric catarrh. The close relationship between dental cario-necrosis and gastric catarrh is a subject that will be fully considered in a subsequent chapter. The two conditions are precisely those most favourable to infection of the mucosa of the stomach; and ultimately, if the conditions be favourable, as in the present case, to infection of the intestine lower down. For on the one hand, there is *diminished resistance* on the part of the stomach, from the diminished acidity of gastric secretion consequent on the catarrh; while on the other hand, there is *increase of dose* from continuous swallowing of pus organisms from the necrotic teeth. In the present case both these conditions were met. The patient had sepsis of the mouth; and the gastric condition preceding his anæmia was probably the one that I have designated *septic gastritis* (Chap. XXII.).

The relations of events in the case may then be summarized as follows:—

1. A man, temperate, well fed, and living in healthy surroundings.

2. Bad teeth, at no time occasioning local discomfort, even when they caused alveolar abscesses.

3. Always suffered from 'heartburn,' denoting chronic gastric catarrh—probably 'septic' gastritis.

4. Accident causing stricture of jejunum, with more or less severe abdominal and gastric symptoms lasting six years, *yet without anæmia.*

5. More or less rapid supervention of the features of pernicious anæmia, nine months before death.

6. *Post-mortem*—(1) Dental decay with alveolar and ethmoidal suppuration; and (2) definite infection (coccal and streptococcal) of the mucosa of the intestine and colon, causing localized catarrhal, inflammatory, and necrotic changes of the mucosa of intestine—and similar though less marked changes in the mucosa of the stomach.

PART V.—ETIOLOGY.

CHAPTER XXI.

GENERAL ETIOLOGY.

We have now to consider the probable source of the infection pointed to by the preceding observations.

On this point the evidence available is extremely limited, confined as it is to the observations on the cases which have been described. For the disease has hitherto been examined, and studied, *solely* with reference to its relations to the usual causes of anæmia—such as loss of blood, pregnancy and child-birth, wasting discharges (diarrhœa), bad nourishment, and unhealthy surroundings. It is under these headings that its etiology has been discussed, and beyond these nothing further has been investigated.

General Etiology. — In my own mind no fact stands out more clearly, in connection with the etiology of the disease, than that none of the above conditions can of themselves produce the disease of pernicious anæmia, with all its characteristic hæmolytic changes.

In the first place, I would point to the confusion which exists as to the importance of these so-called 'causes.' The same conditions—*e.g.* diarrhœa or vomiting—are arbitrarily regarded as causes or as effects, according to their prominence, or their severity. Sometimes they are regarded as both cause and effect. This is well illustrated in the grouping adopted by Eichhorst, and since generally accepted. Eichhorst grouped his cases (91 in number) *etiologically* under two headings:

I. 'Primary' pernicious anæmia (24 in number) where no cause was discoverable.

II. 'Secondary' pernicious anæmia (67 in number) caused by—

(1) Pregnancy and childbirth, . .	29
(2) Vomiting and diarrhœa, . . .	24
(3) Loss of blood and discharges, . .	7
(4) Unhealthy surroundings, . . .	7

The impression this last group naturally conveys is, that in only 24 out of 67 cases were diarrhœa and vomiting sufficiently prominent to excite attention, or be regarded as causes. Nevertheless, on examination of the records of the remaining 43 cases of Group II. assigned to other 'causes,' I find that vomiting or diarrhœa, or both (sometimes uncontrollable in degree), or other gastro-intestinal disturbances, were prominent features in no fewer than 34 cases—just as prominent, indeed, as the special condition selected to be the 'cause.' In other words, a total of 58 cases out of 67, (86 per cent.), might have been as reasonably assigned to gastro-intestinal disturbance as to 'causes' 1, 3, and 4.

And even with regard to the 24 cases of Group I. which he regarded as 'primary,' without any cause, one finds digestive troubles, diarrhœa, and vomiting (sometimes very marked in degree), mentioned in the records in no fewer than 16 cases (67 per cent.).

These facts appear interesting, not because, in my judgment, they point to gastro-intestinal disturbance, any more than to pregnancy or any of the other stated conditions as the 'cause' of the disease, but that they denote the unsatisfactory character of our present knowledge of the real 'etiology' of the disease. When it comes to be a mere question of degree, whether a condition is considered to be a *cause* or only a *symptom* of one and the same disease, it is obvious that knowledge is unsatisfactory.

My own conclusion is, that in all cases, these gastro-intestinal disturbances, however slight or however prominent, are of the same character as the blood changes—viz., effects of the disease underlying the anæmia. So far as the above-mentioned etiological factors are concerned, the whole question of the etiology of the disease is thus a completely open one.

The ordinary factors causing anæmia, however intense they may be, are not in my experience capable of causing pernicious anæmia.

Addison's original conclusion on this point, as opposed to the widely different one arrived at by Biermer, and accepted by most observers (see p. 15), has in my judgment proved to be the correct one.

Special Etiology.

The disease has, I consider, a special etiology underlying it.

The conclusions I have come to are:

1. Pernicious anæmia is a chronic infective disease.

2. It is the result of a special infection of the digestive tract, especially of the stomach; frequently, also, although to a less degree, of the mouth, and of the intestine.

3. The chief source of the infection is oral sepsis, arising in connection with long-continued and neglected cario-necrotic conditions of teeth; sometimes, possibly, arising from other causes, *e.g.* drain poisons.

4. The result of this infection is a chronic infective lesion of a portion of alimentary tract — mouth, stomach, or intestine, healing up in one part, and then spreading to another, causing in time deeper seated changes, *e.g.* ulcers of the mouth and tongue, chronic glossitis and atrophic changes in the tongue, and chronic gastritis with atrophy of gastric glands.

Oral and Gastric Sepsis in Pernicious Anæmia.

That a disease so rare as pernicious anæmia should prove to be a chronic infective disease, still more that it should appear to have any connexion with a condition so common as cario-necrosis of the teeth, may well excite surprise. For the former conclusion my former observations had already prepared me. For the latter, I was quite unprepared; and its gradual development—for it has been very slow and gradual—may be best traced by giving a brief summary of the cases in the order in which they occurred. The fuller details will be found in the CASES afterwards given.

Case 1 (1888).—This was a case of pernicious anæmia in a man of 59 years of age. There was a history of 'gastritis' six years previously. The origin of the illness was referred to a definite exposure to bad drains three years before, causing at the time sore throat and diarrhœa, and followed by a constantly recurring inflamed condition of the throat and tongue, and by increasing

debility. The teeth were loose, and the gums spongy. There were tender, inflamed sores under the tongue, and chronic glossitis. Retching and vomiting were present in the earliest stages of the illness, but in later stages they were absent. The blood shewed 950,000 of red corpuscles (or 19 per cent.) per cubic millimetre, and hæmoglobin 20 per cent. There were well-marked *toxæmic attacks*, marked by fever, sweatings, looseness of bowels, and intense urobilinuria. The *post-mortem* examination detected chronic and subacute gastritis, and typical pigment changes in the liver and kidneys. Duration three years.

It was this case that first drew my attention to the mouth as a possible source of infection, and particularly to the tongue (*v. antea*, p. 198). The condition of the teeth and the gums was noted as a part of the routine examination, but it made no special impression. If thought of at all, it was put down to weakness.

Case 2 (1894). — A man, aged 42 years, with a history of growing pallor for four years. The origin of his illness was referred by himself to a change of tooth-plate. He had a new set of upper teeth fixed in a gold plate, which tarnished and tasted 'like pennies,' and caused 'acidity' from the first day he used them. Then followed progressive weakness, vomiting of food, nervous disturbances, numbness and tingling in hands and feet, loss of knee-jerks, wasting of certain muscles, a *toxæmic attack* marked by delirium, constant vomiting, and general œdema. Under corrosive sublimate, there was a rapid recovery in three months' time, and the patient remained well for two years. Then came a relapse, with sickness and biliousness, fever, and looseness of the bowels. The blood shewed 1,800,000 (or 36 per cent.) red corpuscles per cubic millimetre, and hæmoglobin 38 per cent.

This case, striking as it was, failed to attract any special attention to the mouth or the teeth. I have no note of the condition of either. The absence of any note about the tongue may be taken as indicating, that nothing special was observed in its condition. As regards, however, the previous condition of the teeth, the fact that already at the age of 38 years, (four years before), he required a new set of false teeth for the upper jaw, speaks more eloquently, perhaps, than words could do.

Case 3 (1895). — A gentleman, aged 50 years, whose previous health had been good. The origin of his illness dated from 'influenza' two years before (in 1893), followed by another attack a year later

(in 1894), and then by loss of appetite for both food and drink. After 1893, he constantly complained of a faint, weak feeling in the stomach. There was temporary improvement from December 1894 to May 1895. Between October 1894 and May 1895 the tongue was raw and tender, 'like raw liver,' causing him intense pain. There were also *toxæmic attacks*, and acute relapses of fever with disturbances of liver, also sickness and vomiting and gastric pain. The blood shewed 1,860,000 (or 37 per cent.) red corpuscles per cubic millimetre, and hæmoglobin 54 per cent. No note as to the condition of the teeth was taken at the time I saw him; but it was subsequently learnt that he had bad teeth, with occasional neuralgia —seldom toothache. Latterly he would discover that a tooth was loose, and could be drawn out without the slightest force or trouble. The duration of the illness was about two and a half years.

Case 4 (1896).—The patient, aged 56 years, a country gentleman, active and athletic. There was a history of increasing weakness, with intermittent periods of betterment for two and a half years; specially marked for the previous three months. The tongue was soft, clean, moist, and not indented. The teeth were very bad, black, and decayed in both fangs and crowns. The stomach was dilated, with splashings and flatulence. There was no sickness, but uneasiness and discomfort. The patient had diarrhœa five or six times daily, with very offensive stools. There were nervous symptoms, numbness, tingling, loss of knee-jerks, and ataxia. The illness ended fatally. The blood shewed 760,000 (or 15 per cent.) red corpuscles per cubic millimetre, and hæmoglobin 18 per cent. The duration of the illness was two and a half years.

It was this case, that first particularly directed my attention to the teeth. The case was a typical one in its mode of origin—steadily increasing weakness, in a man previously strong and athletic, living a country, open-air, life, surrounded by every comfort, without exposure to any source of drain or sewer poisoning. What chiefly directed attention to the teeth in this case, was not, perhaps, so much that they were bad—although a blacker, and worse, mouthful of teeth one had seldom seen—as wonder, that anyone in this patient's station of life, with his comforts and surroundings, should have allowed his teeth to get into such a condition. Apart from the blood changes and their effects, which were very marked, the condition of the teeth was practically the only objective sign of disease that he presented. It was difficult to believe, that they could be the result of the disease; and the question arose, for the first time,

whether they could have had anything to do with causing the disease. Locally, in the mouth, there was no other sign of disease; and except for a dilatation of the stomach, with an ill-defined sense of discomfort, there was nothing special to point to disorder of the stomach. The only symptom of disorder of the digestive tract was the diarrhœa, which was marked by particularly offensive stools. My suspicions might prove to be quite groundless; but I resolved henceforth to note the condition of the teeth in all cases coming under my notice.

> Case 5 (1896).—A clergyman, aged 51 years, whose previous health had been good, for he had never had any illness till the present time. Its origin was undefined. There was no history of drain poisoning; but there had been increasing weakness for twelve months, especially the last four months. There was no history of indigestion, sickness, or vomiting, and the freedom from these symptoms continued; at most there was slight flatulence. The tongue was clean, but not specially smooth, and with nothing abnormal. Of the teeth, two or three were exceedingly bad, three being black rotten stumps in the lower jaw. There was no diarrhœa. Urobilinuria was present. The patient made a temporary recovery, but a relapse, followed by death (21 months later), ensued. Duration of illness two years and nine months.

This case, coming as it did within a fortnight of the previous one, served further to direct attention to the teeth; for here also, the teeth were the only diseased part of the organism, apart from the blood changes and their effects. There was no local trouble in the mouth; but the teeth were so bad, that if the patient had not been so weak, I should have had them all removed at once.

> Case 6 (1898). — A man, aged 52 years, with history of indigestion and poor appetite. The patient had been ill with anæmia six months before (in 1897), without sickness, but with irregularity of bowels, diarrhœa at times, and slight fever. The tongue was clean but flabby. The teeth were very bad, and covered with tartar and sordes. Three upper molars were gone, but the roots were left, and one of them was loose, and could be pulled out with the finger. The breath was very bad, the digestion was very feeble, and the bowels were irregularly loose. Towards the end of the illness there was gastric pain on eating. The case ended fatally. The blood shewed 1,390,000 (or 27 per cent.) red corpuscles per cubic millimetre, and hæmoglobin 34 per cent. The duration of the illness was about nine months.

In this case there was a history of chronic indigestion, very bad teeth, very feeble digestion; then, more or less suddenly, profound anæmia with gastric pain and irregular looseness of bowels.

The next case of interest in this relation was not one of pernicious anæmia, but of subacute gastritis, caused, and kept up, by three suppurating teeth, and permanently cured by removal of these teeth.

> Case 7 (1898).—Subacute gastritis in a lady aged 62 years. The patient suffered from severe intermittent sickness, and gastric pain necessitating the use of morphia, of eight months' duration, with loss of weight, and increasing weakness. Cancer was suspected, but on examination no sign of malignant disease was found in the stomach, the abdomen, the rectum, or the uterus. Constant complaint was made of a bitter taste in the mouth, nausea, with loathing and distaste for all food. The tongue was coated with a dirty moist fur. The patient had false teeth both in the upper and the lower jaws. The plates were scrupulously clean, and the gums beneath the plates were perfectly healthy. There were only four teeth in the jaws, three of them decayed, suppurating around the roots, with pus welling up on pressure. There was no other sign of disease. A provisional diagnosis was made of gastritis caused by continual swallowing of pus. The stumps were ordered to be removed. A week later, the tongue was clean, the sense of taste returned for the first time for eight months, and there had been only one attack of gastric pain. In another week, there was a return of the sickness, with vomiting and pain and slight fever. The vomit obtained two weeks later was watery, with rusty flakes consisting of mucus, fibrin, catarrhal cells, leucocytes, and blood, the whole being loaded with streptococcus, and staphylococcus (pus) organisms, and a few bacilli. A diagnosis was made of infective ('septic') catarrh. As a local antiseptic, three grains of salicylic acid were given thrice daily, peptonized milk as food, and counter-irritation was applied. There was complete cessation of all pain, and a steady recovery, from that time onward. When the patient was first seen, her weight was 9 st. 10 lb., and a month later (after her illness) it was 9 st. 6 lb. Two months later it had increased to 10 st. 6 lb. She reported herself well, and she has since remained well (two years).

Up to this time, my suspicions regarding the teeth were only suspicions. Knowing how infective the organisms of dental caries were, such unhealthy teeth seemed to me to be *possible* sources of infection. I had had no proof that infection from

decayed suppurating teeth might be the direct cause of gastritis. This case was, therefore, a particularly striking one in this relation. Had the teeth as a whole been very bad—*e.g.* a number of rotten stumps amidst a few fairly good teeth, the condition one so often meets with both in private, and still more in hospital, practice—and had they been all removed, and replaced with good artificial teeth, it would have been difficult to say, whether the resulting improvement was due to removal of the teeth as *sources of infection*, or to improved appetite, and better mastication. As it was, I made no change as regards her powers of mastication. The only change made was the removal of the three suppurating teeth, which had, the patient said, never caused her any trouble; indeed, she regarded them as 'old friends,' whose loss she greatly deplored. She said that "she had had them like that for twelve months or more"—her gastric trouble, be it noted, extending over the same period of time.

One was able to demonstrate further in this case, not only (1) the septic nature of the gastric catarrh—the catarrhal exudation vomited being loaded with pus organisms; but also (2) its permanency, since the condition continued *three weeks* after removal of the suppurating teeth.

Case 8 (1899).—A man, aged 53 years, whose health up to June 1898 had been good. There was a definite history of exposure for a period of some weeks to sewer gas. He suffered from retching, vomiting, and pain after food, with intense salivation, and gastrorrhœa. The upper teeth were all absent, except one in front, which was dark, decayed, and loose in its socket. Several molars and bicuspids were absent from the lower jaw. He had worn tooth-plates for the previous two years. At the commencement of illness, there were painful sores in the mouth under the tongue, which soreness, as he said, "seemed to spread down into the stomach, and right through him." Blood shewed 1,290,000 (or 25 per cent.) red corpuscles per cubic millimetre, and hæmoglobin 24 per cent. The vomited fluid was watery, with flakes of mucus and catarrhal cells, the whole being loaded with small cocci, often in zoogloœa-like masses. There were also bacilli and larger cocci, but in fewer numbers. A rapid temporary improvement was made under salicylic acid, but this was followed by a relapse marked by stomatitis, salivation, occasional diarrhœa, progressive weakness, œdema, acute epididymo-orchitis, and ultimately by death. The duration of the illness was one and a half years.

This case, coming so shortly after the observations made in Case 7, I regard as one of the most instructive up to that time met with, in respect not only of the history of its origin, but also of its oral and gastric symptoms. The illness dated from a definite exposure, lasting for a period of some weeks, to the odours of a cesspool, close to the window where he worked; the smells from which were so bad, that they often made him sick. Among the first troubles he noticed, were sores in the mouth; and his own description of his disease was, that this soreness seemed to extend right through him from the mouth to the anus. Then followed retching, and salivation, to a degree such as I had never before witnessed, pints of fluid being brought up daily either directly from the mouth, or indirectly by vomiting from the stomach. There was a history of dental trouble, all the teeth in the upper jaw being absent, with the exception of one which was markedly rotten and loose. This, however, he valued despite its looseness, and would not allow to be removed. Lastly, there was the microscopic observation made on the vomited fluid, demonstrating the presence of masses of cocci. The relation of events in his illness seemed thus to be—

(1) Previous dental trouble, extending probably over many years; (he had worn tooth-plates for two years, but still retained necrosed teeth).

(2) Definite exposure to sewer-gas infection, which, *either alone, or in combination with preceding infection from the teeth, set up* (*a*) *local infective trouble* in the mouth—sores under the tongue with salivation and stomatitis; and (*b*) *gastro-intestinal trouble*—septic gastric catarrh, with retching, vomiting, and pain.

(3) Rapid onset of anæmia; three months later, the patient became so anæmic that he could not work, and there was so much gastric trouble, that cancer was suspected.

(4) Subsequent history of the case—that of pernicious anæmia.

The problem as to etiology thus gradually in my mind resolved itself into the question: which of the above mentioned possible sources of infection was the more important? And first with regard to the possible importance of oral sepsis—on this point the following studies throw light, proving as they do that oral sepsis is a potent and prevalent cause of 'septic' gastritis.

CHAPTER XXII.

DENTAL DISEASE AS A CAUSE OF 'SEPTIC' GASTRITIS.

CASE 7 (recorded in the last chapter) is specially interesting in the above relation. It demonstrates a relationship between cario-necrosis of the teeth and gastric catarrh, of a closer and more direct character than any hitherto recognized.

That relationship may thus be described :—

(1) There is a limit to the capacity, even of the stomach, to resist indefinitely for periods of years the continuous presence of pyogenic (pus-forming) and other organisms derived from cario-necrotic conditions of the teeth.

(2) Its powers of destroying such organisms, although great, are never complete even in health; and are due solely to the presence of free HCl.

(3) These powers become progressively weakened, when through any cause an increased, and continuous, supply of pus organisms is associated with a diminished, and continually lessening, acidity of the gastric juice.

(4) These two conditions are precisely those produced by chronic cario-necrosis of the teeth.

(5) In time the catarrh of the stomach, so common a sequel of imperfect dentition—possibly of simply irritant nature to begin with (the result of fermentation), becomes *septic* in its character, and is really due to actual septic infection of the mucosa.

(6) Eventually, it may even lead to the deeper-seated changes which always result from chronic catarrh—viz., atrophy of secreting structures, with increase of fibrous tissue (chronic gastritis with atrophy of the glands).

These statements as to the relation between dental cario-

necrosis and gastric catarrh have been elucidated and supported by me elsewhere[1]; but some brief reference to the subject is here essential to a right understanding of our present subject —to wit, the significance of the oral sepsis met with in pernicious anæmia.

The Relation between Dental Disease and Ill-health.

That health is to a large degree conditioned by the state of the teeth—their presence or absence, their soundness, their freedom from pain—is generally recognized. But if inquiry were made as to the nature of the connexion, opinions would be found to differ.

1. In the minds of most, the relation is what one may term a 'mechanical' one. Carious teeth mean imperfect mastication; consequently, increased and unnecessary work for the stomach; this in course of time leading to the various ills connected with impaired digestion. Such a mechanical relation I consider by no means the only, or even the most important, relation of dental disease to general health.

2. In the minds of others, the connexion between bad teeth and bad health is supposed to be of another kind—viz., that bad teeth denote bad nutrition, and bad health. They are the result of ill-health, rather than the cause of it.

3. A third possible relationship—still very obscure, but one that appears to me to be altogether insufficiently recognized, and to be more important than either of the two above-mentioned—is, dental disease *as a cause of ill-health in consequence of being a continual source of septic poisoning, and septic infection, both local and general.*

Local Infections.—Among the obvious conditions of this nature, are the various local inflammatory and suppurative conditions met with in the mouth—(periostitis, alveolar abscess, suppuration around decayed teeth, and pyorrhœa alveolaris); or in the jaws—(periostitis, osteitis, osteo-myelitis, necrosis, and suppuration in maxillary sinuses); or in tissues adjacent to the mouth—tonsillitis, pharyngitis, otitis, enlargement and suppura-

[1] "Relations of Dental Disease to General Diseases and to Infective Gastritis," *Transactions of the Odontological Society of Great Britain*, February 6, 1899. "Oral Sepsis as a Cause of Disease, with Illustrative Cases," *The Clinical Journal*, September 12, 1900; *Practitioner*, December 1900.

tion of the glands of the neck, cellulitis of the neck, post-pharyngeal abscess, thrombosis of the veins, and even meningitis by direct extension.

Remote Infections.—Among the remote conditions of infective nature, obscure in origin, and in many cases probably traceable back to infection from the mouth, are such conditions as acute osteo-myelitis, acute necrosis occurring apart from injury, suppurative meningitis, empyema, ulcerative endocarditis, and acute nephritis and purpuric conditions generally. The special interest of dental disease in connexion with this class of cases arises from this: that dental cario-necrosis is the commonest and most prevalent septic infection in the body; and that this infection is of a 'mixed' character, including not only harmless organisms, but also the most active pathogenic (blood-poisoning) organisms —viz., streptococci and staphylococci.

Bacteriology of Dental Caries.—On this point—the infective nature of dental caries—I need not dwell. The evidence so abundantly furnished by the laborious bacteriological observations: of Miller (1884–1894) on no fewer than 250 cases of diseased teeth; of Galippe and Vignal (1889); of Jung (1893); and most recently of Professor Arkovy of Budapest (1878–1898) seem conclusive. With the minutest bacteriological precautions, the last-mentioned observer has, in 43 cases, studied in detail the organisms found in the most various conditions of teeth—*e.g.* gangrene of pulp (both acute and chronic), chronic alveolar abscess, old stoppings, etc. The chief result of the observations, from the dental point of view, is to shew, that one organism is constantly to be found in diseased pulps, and in dental caries, (the *Bacillus gangrænæ pulpæ*), possessing the power single-handed of producing gangrene of pulp, and of effecting softening of a tooth, *even in an alkaline medium.* Its frequency, as compared with other organisms, was 95·3 per cent. Next most frequent, and from the present point of view even more important, were various forms of pus organisms—viz.:—

Staphylococcus pyogenes aureus, 34·8 per cent. of cases.

Streptococcus pyogenes, 23·2 per cent.

Staphylococcus pyogenes albus, 18·6 per cent.

Bacillus pyocyaneus, 9·3 per cent.

Staphylococcus pyogenes citreus, 4·6 per cent., with nine other organisms, mostly harmless, in varying frequency. The pyogenic

organisms were always absent in teeth successfully dealt with antiseptically.

The significance attaching to these observations, in the present relation, is not the mere presence of such organisms in connexion with dental caries. Their mere presence in the mouth does not constitute disease of the mouth, or elucidate the pathology of stomatitis, any more than the almost constant presence of the pneumococcus in the mouth constitutes pneumonia, or elucidates its pathology.

Infective disease in the mouth, as elsewhere, is, fortunately, not a mere question of the presence of an organism, however pathogenic; but a question of *dose*, and *resistance*. In the case of the mouth, the question of dose becomes a very important one; when we have to deal, not with an isolated carious tooth, but with a whole series of such teeth—not only diseased themselves, but lying in foul, inflamed septic, possibly (as in Case 7) actively suppurating, sockets.

The effects of such a condition are twofold—first of all, locally; and, secondly, on the body generally. The *general* effect is a septic absorption from the diseased teeth and sockets, that must, in the aggregate, be of remarkable extent, continued as it often is over many years. The *local* effects are primarily on the mouth itself, and are sufficiently obvious in the oral sepsis so common in such cases, namely, inflammatory gingivitis and stomatitis of every degree of intensity—erythematous, pustular, suppurative, ulcerative, or even gangrenous.

But the effects are not limited to these; because if there is a continual source of septic generation around these teeth, septic infection may occur lower down, even in the stomach itself.

The continuous swallowing of mouthfuls of pus organisms is not tolerated indefinitely by the stomach mucosa. The number of organisms that enter the stomach from the mouth is very large. Most of them, fortunately, are destroyed by the gastric juice. But this is by no means true of all. A very considerable proportion, (as many as eight out of twenty-five, according to Professor Miller), are to be found in the stomach contents. The observations of Macfadyen and others shew, that only a certain proportion are destroyed by the gastric juice. It is *only* when the acidity of the gastric juice is considerable—*e.g.* an hour or two after food—that it exercises any direct bactericidal action,

not in the intervals between digestion. When the acidity reaches a low level, a large number may be quite capable of living in the stomach.

In long-standing dental disease, the conditions are, thus, precisely those most likely to produce infection of the stomach —viz., on the one hand, *diminished resistance, i.e.*, diminished acidity as a result of the chronic indigestion and catarrh ; on the other hand, *increase of dose, i.e.*, increased supply of pus organisms from the necrotic teeth, reaching the stomach not only during digestion, but in the intervals between meals when the free HCl is at a minimum, or absent. That under such circumstances disturbances may arise, from abnormal fermentative processes in the stomach, is a fact to which both clinical and pathological experience testifies—one, too, that is generally recognized. What, however, Case 7 demonstrates is, that the effect is not limited to a mere fermentation of food products; but that actual *infection of the mucosa* with pathogenic organisms may itself occur, causing what I would term a "septic"—as distinguished from a simple irritant—gastric catarrh. The mucosa of the stomach, continuously exposed to infection by influx of pus organisms from the teeth, becomes eventually infected. A septic catarrh is set up, and being continuously sustained by influx of septic organisms into the stomach never got rid of; if continued long enough, this chronic catarrh leads to the usual effects of a glandular catarrh—viz., glandular atrophy, with increase of interstitial tissue around.

These considerations as to the possible effects, both general and local, of long-continued dental and oral sepsis are of no mere pathological interest. On the contrary, they are of supreme practical importance, exemplified as they are (to a degree which is, in my judgment, and almost daily experience, altogether insufficiently recognized) by the cases one meets with of gastric catarrh in association with dental and oral sepsis.

The ashy-grey look, and general languor, which such patients in my experience characteristically present, are really manifestations of long-continued septic absorption ; the local symptoms of clamminess of the mouth, distaste for food, coated tongue, bad taste in mouth, which one simply looks upon as manifestations of gastric catarrh, are really, as in the case described (Case 7), the result of oral sepsis ; while the nausea,

indigestion, gastric discomfort are the results of the 'septic' gastric catarrh produced by direct infection of the stomach with the pus organisms.

Case 7 appears to me to present points of unique interest, in demonstrating the actual relations between dental infection and gastritis—viz., the history of nausea and vomiting; gastric pain extending over a period of months—the pain so severe as to necessitate the use of opium, and to suggest cancer; the scrupulous cleanliness of tooth plates, and the healthiness of the gums; the absence of all teeth except three carious ones, these latter discharging pus from their roots; the removal of these three; the immediate improvement, temporary in character; the recurrence of sickness and vomiting; the vomit *three weeks after removal of teeth* still loaded with pus organisms; the administration of salicylic acid as a local antiseptic; the entire cessation of all gastric symptoms three days later; in three months a gain of a stone in weight; and, lastly, the permanency of the cure. Fifteen months later the patient wrote that she had never had any return of the sickness.

CHAPTER XXIII.

THE INFECTIVE NATURE OF THE DISEASE, AND THE SOURCE OF INFECTION.

The Infective Nature of the Disease.—The facts already recorded denote in my judgment conclusively the *infective*, as distinguished from the *general*, nature of the disease. Moreover, they denote the infection to be a *local*, not a *generalized*, one. It is confined to the alimentary tract, its chief seat being the stomach; no part, however, of the alimentary tract, from the mouth to the anus being safe from it.

Further, in certain of the foregoing cases, the first site, or one of the first sites, of infection has apparently been the mouth —general discomfort, or soreness, or tenderness, of the mouth having been complained of, either before, or 'at the same time' as, the anæmia. There remains, then, the question, whence the infection has sprung in the first instance—from without, or from within, the mouth?

Source of Infection.—In this relation, the cases divide themselves into two groups—two cases, in which there was a most definite history of exposure to sewer gas, or drain, influences (Cases 1 and 8)[1]; nine cases, in which no such history could, on very careful inquiry on the point, be traced. This failure to trace infection to some outside source need not necessarily denote the absence of such a source; for failure of this kind is common at times with regard to all infective diseases. So clear is the history of exposure in the two cases mentioned, that, in the absence of any other facts, I should be disposed to suspect some similar origin in the case of the others.

But both in these two cases, and in the other nine, there existed a marked condition of either antecedent or co-existing

[1] I have recently seen a third—very striking—case of this kind.

dental cario-necrosis—in most of the cases, to such a degree as to amount to 'neglect,' the teeth being very carious in whole or in part. In the light of what I have described with regard to the infective power of the oral sepsis so created, and the possible effects on the stomach that may ensue, the question thus raised is—whether the 'mixed' infection underlying the disease may not have taken origin within the mouth itself in connexion with the teeth. Or, alternatively, whether the infection may not have found its first footing, so to speak, amidst the infective septic conditions prevailing around the diseased teeth. Either alternative is possible. The subsequent course of the infection is then determined by the relative amount of resistance offered by the mucosa of the mouth and stomach respectively. In the great majority of cases, the mucosa of the latter is the first to be affected—in certain cases possibly the only part to be affected. But, in some cases, direct infection of the mucosa of the tongue and of the mouth also takes place—if one may judge from the foregoing data (which, however, are probably too low) in at least 10 per cent. of cases (see footnote, p. 208).

It will remain for future observations, on a larger series of cases, to determine more precisely the points I have raised—viz.

(1) Whether dental decay is only important in creating the septic stomatitis and gastritis favourable to the later *special* infection;

(2) Whether the special infection may not, so to speak, be created around them in the first instance; or

(3) Whether direct infection of the stomach can occur from exposure to infection (drain smells), independently of any oral or dental trouble.

Whatever the precise source of the *special* infection may be —whether from within the mouth or from drains, *an antecedent condition of septic gastritis is in my judgment a necessary preliminary to successful infection.*

Hence, the fact of importance clear to me—that oral sepsis in this disease deserves more attention than has been hitherto bestowed upon it. The extraordinarily persistent overlooking of this subject of oral sepsis, and the share taken in it by diseased teeth, I have fully brought out elsewhere. It is well illustrated by my own experience—viz., that while actually interested in the occurrence of glossitis and stomatitis in cases of pernicious anæmia, I did not begin to note especially the condition of the teeth till many years later.

Nature of the Infection.—I have, throughout, designated the infection as a 'special' one, most probably of a 'mixed' character, *i.e.* brought about by the joint action of two or more organisms.

That it is no ordinary 'septic' stomatitis or gastritis, such as is a common sequel of dental decay—is clear from

(1) The rarity of the disease;

(2) The remarkably hæmolytic action of its poisons;

(3) The occurrence of an ordinary 'septic' gastritis without any of the blood changes of pernicious anæmia (Case 7).

That it is of a 'mixed' character appears probable from the following facts:

(1) The abundant presence (as in Case 8) of organisms of coccal and streptococcal nature, forming zoogloea-like masses amidst the catarrhal and inflammatory exudation contained in the vomit. These organisms were obviously related to the anæmia, the salivation, and the vomiting; since by administration of salicylic acid, the first was greatly ameliorated, and the two latter were abolished; and yet they are not such as are peculiar to this disease, but resemble organisms present in the stomach in other diseases.

In my other cases (four in number) in which the vomit has been examined, *Streptococcus longus* has been a form constantly found. Hence my suspicions are strongly directed to this, as one of the organisms concerned; but not to this exclusively. For the poisons of streptococcic infection are not specially hæmolytic in action, whereas such an action is in a special degree characteristic of the poison of pernicious anæmia.

It is hence to another form that this special action must be due. For the present, my suspicions are directed towards one of the character of a *proteus*. For this reason, that increased hæmolysis (with jaundice) is one of the features of its action, and the changes described in cases of 'infective jaundice' (Weil's disease) in which it has been found, agree in many particulars with those I have described for pernicious anæmia[1]—namely, fatty degeneration of liver and of epithelium of kidney, minute hæmorrhages, swelling of spleen, intestinal changes, observed in one case—namely, vascularity, numerous hæmorrhages, and superficial erosion of the mucous membrane throughout the whole intestinal tract.

[1] Hunter, "Weil's Disease," Allbutt's *System of Medicine*, vol. iv. p. 98, 1897.

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It must remain for future observations to determine the nature of the organisms concerned and their relative rôle.

(2) The disease, though very rare in incidence, is nevertheless common to all classes irrespective of station, mode of life, food, previous health, or general surroundings.

Professor Adami of Montreal, and his fellow-workers, Dr. D. Anderson and Dr. Ford, have recently made some interesting observations in this relation.[1] Their observations they consider suggest that possibly the colon bacillus may be concerned as a secondary factor in producing the gastric change.

They have examined bacteriologically the contents of the stomach in four cases of pernicious anæmia. They found (1) a complete absence of hydrochloric acid; with the presence, however, of considerable quantities of lactic and some butyric acid; (2) an abundant presence of the colon bacillus; (3) in one case a modified—diplococcoid—form of the colon bacillus within the walls of the stomach; and (4) the presence of the same forms in the liver cells—the bodies giving the iron reaction and constituting, indeed, according to Professor Adami, the granules hitherto regarded as pigment granules.

With this last-mentioned conclusion (one with which I am unable to agree) we are not here specially concerned. The matter, however, is otherwise with the second observation, as to the presence of the colon bacillus in the stomach, and its possible relation to the disease. On this point, Professor Adami is "very careful not to state that the colon bacillus is the primary or the essential cause of (either cirrhosis of the liver, or) pernicious anæmia. . . . probably not. In either case there is some primary or underlying factor favouring its entrance into the economy." The possible relation is one he describes by the term 'sub-infection'—"a condition, in which, as a consequence of chronic inflammatory disturbance in connexion with the gastro-intestinal tract, there may, for long periods, pass in through the walls of the stomach or of the intestine a greater number of the ordinary bacteria inhabiting the tract; and while the bacteria undergo the normal and inevitable destruction by

[1] "On Latent Infection and Sub-infection and on the Etiology of Hæmochromatosis and Pernicious Anæmia." The annual address before the Society of Internal Medicine, Chicago, November 29, 1899. *Journal of the American Medical Association*, December 23, 1899.

the cells of the lymph glands, the liver, the kidneys, and other organs, nevertheless the excessive action of these cells and the effect on them of the bacterial toxins liberated in the process of destruction may eventually lead to grave changes in these cells and in the organs of which they are part—changes of a chronic nature."

For the action of the bacillus, Professor Adami, it will be seen, predicates the existence "in the first place of some chronic inflammatory condition of the mucous membrane of the upper gastro-intestinal tract, leading often to atrophy." This is the very condition which according to my observations does exist; and which I regard, partly as the result of the septic gastritis preceding, partly as one of the local effects of, the special infection underlying the anæmia. Future observations must determine the actual significance of the colon bacillus infection thus described.

The presence of the colon bacillus in the stomach cannot itself be regarded as suggestive of disease; since it is a normal inhabitant of the intestine, and the vomit in pernicious anæmia is very often bile stained from regurgitation of intestinal contents into the stomach (see p. 222).

Definition of the Disease.

For reasons above indicated, the terms 'secondary' and 'primary,' used in connexion with the disease, appear to me to be no longer fitly applicable. To say that the disease is secondary to gastric or intestinal disturbances, *e.g.* vomiting, diarrhœa, is just as correct as to say that typhoid fever is secondary to the diarrhœa which attends it. To say that it is secondary to the very slight anatomical lesions above described, is just as correct as to say, that the whole features of diphtheria are secondary to the anatomical lesions found in the throat, or that typhoid fever is secondary to the lesions found in the intestine. In these cases, the relation of the local symptoms, and the lesions, to the disease are the same—namely, they are effects of the infection which underlies the disease—diphtheria or typhoid fever, as the case may be.

Hitherto the feature of the disease to arrest chief attention has naturally been the *anæmia*, the progressive blood change; and all other symptoms have been studied in relation to this. The disease has been regarded as an anæmia complicated from time to time by other disturbances—digestive, nervous, circulatory, etc. The result has been to obscure some of the chief characters of the disease, and certainly to hide much of their proper relation

to each other. For the future, it will, I consider, throw entirely fresh light on the disease, if it be studied as an *infective disease characterized by anæmia* with *definite local and general* effects, and no longer be viewed simply as an anæmia occasionally complicated with such effects.

The definition which I formulate for the disease is therefore the following :—

Pernicious anæmia is a chronic infective disease localized in the alimentary tract;

Caused by a definite infection of certain parts of the mucosa of the alimentary tract, chiefly of the stomach, occasionally also of the mouth, and of the intestine.

Characterized by—

(1) Intermittent destruction of blood, and increasing anæmia—and all the other pathological and clinical changes consecutive to these, *e.g.* anæmia, lemon colour, urobilinuria, hæmorrhages, dyspnœa, palpitation, œdema—as the result of the hæmolytic action of poisons on the blood.

(2) Periodic disturbance of the alimentary tract, chiefly of the stomach and the intestine, as local irritant effects of the infection on the alimentary canal; and

(3) Occasional 'toxæmic' attacks, characterized by fever, sweatings, general nervous symptoms; not infrequently by effects—*e.g.* numbness, tingling, ataxia, absence of reflexes, denoting deeper nervous changes, such as peripheral neuritis, sclerosis of the cord.

Summary of Conclusions regarding the Etiology and Nature of the Disease.

The conclusions I have come to are—

1. Pernicious anæmia is a chronic infective disease of septic nature.

2. It is the result of a special infection of the digestive tract, especially of the stomach; frequently also, although to a less degree, of the mouth and of the intestine.

3. The chief source of the infection is oral sepsis arising in connexion with long-continued and neglected cario-necrotic conditions of teeth; sometimes, possibly, arising from other causes—*e.g.* exposure to drain poisons.

4. The effects are chronic infective lesions of the mouth and

stomach or intestine, which heal up in one part, only to spread to another, and which cause in time deeper seated changes, *e.g.* ulcers of the mouth and tongue, chronic glossitis and atrophic changes in the tongue; chronic gastritis with atrophy of gastric glands.

5. In the vomit, the infective nature of the catarrh of stomach can be demonstrated.

6. One element in the infection is streptococcal. But this is not the only one. It probably derives its special (hæmolytic) characters from being of a 'mixed' character.

7. Such infection the more readily occurs if the stomach or intestine is already, from any cause, the seat of disease; the most potent antecedent cause is 'septic' gastritis arising in connexion with oral sepsis.

8. Gastric and intestinal symptoms—*e.g.* nausea, discomfort, pain, sickness, retching, vomiting, looseness of bowels, and diarrhœa, are features of every case, although varying much in intensity and character in individual cases. They are the local manifestations of the infection; while the excessive destruction of blood taking place in the portal area is the result of the action of its poisons absorbed into the blood.

9. The fever so commonly met with is not an accidental occurrence—the effect of weakness—but is a feature of the disease, a result of the infective process itself; its variations correspond to variations in the activity of that process.

10. Such variations are common—from week to week, sometimes from day to day—in the progress of the disease, even when it is running a fairly progressive course.

11. In addition, however, the course of the disease towards the fatal termination is often marked by one—sometimes by two or even more periods of marked improvement, lasting from a few months to a year or more, followed by relapses. This character of the disease I have come to regard as the result of a relative immunity, unfortunately only temporary in its nature, conferred by the disease itself—an immunity accelerated, and greatly strengthened, for a time by suitable medicinal treatment, notably by administration of arsenic.

12. The recurrence may, however—and perhaps still more likely—be due to the fact that the patient has hitherto been allowed to remain continuously exposed to fresh infection from the original source, namely, the neglected oral sepsis.

PART VI.—SYMPTOMS.

CHAPTER XXIV.

GENERAL CLINICAL FEATURES.

Introductory.

As regards the general features which go to make up the clinical picture this disease presents, no description ever given can better the original one of Addison ; a general anæmia occurring without any discoverable cause whatever, pursuing a similar course, and with scarcely a single exception, followed after a variable period by the same result ; making its approach in so slow and insidious a manner, that the patient can hardly fix a date to his earliest feeling of the languor which is shortly to become so extreme ; increasing pallor ; indisposition to exertion, with faintness or breathlessness on attempting it ; bloodlessness of lips, gums and tongue ; failure of appetite, extreme languor and weakness ; till the patient can no longer rise from bed, and at length sooner or later falls into a prostrate and half torpid state, in which he finally expires.

As regards the individual symptoms accompanying the progressive weakness, reference may be made to Biermer's account already given.

As regards the relation of these symptoms to one another and to the anæmia, their essential feature appears at first sight to be, that they are one and all referable to the anæmia. The latter is "idiopathic, primary, essential, without any symptoms during life that cannot be explained as directly due to the anæmia." (Pye-Smith.)

Even the *Fever* so commonly met with, appears to be "anæmic" in its character (Immermann) ; the *hæmorrhages*, likewise, are the result of fatty degeneration of the capillary walls,

consequent on the anæmia; the *nervous disturbances*, psychical, sensory, or motor, such as are not infrequent, have been referred to the capillary bleedings in the nervous system, (Eichhorst); and lastly, the *alimentary disturbances*, not infrequent, if only slight, seem merely results; if severe they appear to be possible aids in producing the disease, from the exhaustion and profound disturbances in nutrition they occasion. (Biermer, Eichhorst, and Fenwick.)

From the definition given at the close of the last chapter, it will be seen, that in the light of the foregoing studies, the various clinical features presented by the disease have, in my mind, assumed a somewhat different relation to one another.

I am accustomed to divide them into four groups.

Four Groups of Symptoms.

1. A group, to a large extent the *effects* of the anæmia.

These include most of the more prominent features of the disease, such as *pallor, weakness, breathlessness, palpitation, irritability, sleeplessness, incapacity for mental or bodily exertion, want of appetite, feeble digestion, sluggish intestinal powers,* and lastly, the general *characters of the urine,* as regards quantity, excretion of urea, freedom from albumen, sugar, bile, blood.

2. A group, the effect not of the anæmia itself, but of its *hæmolytic character.*

These include the *lemon colour*, varying greatly in intensity at different periods; the *urobilinuria,* with or without *high colour of the urine,* also varying greatly at different periods; occasionally also, deeply bile-stained fæces, likewise varying from time to time.

3. A group, related to the anæmia, neither as effect nor as cause, but denoting the *site of the lesion* underlying the disease.

These include the *oral, gastric,* or *intestinal* symptoms, varying in intensity from time to time; insufficient of themselves to account for the anæmia; and not to be accounted for by any mere weakness resulting from the anæmia; but important as marking the existence of some special irritant trouble in the portions of the alimentary tract affected.

4. A group, like the last, neither cause, nor effect of the anæmia *per se*; but denoting *the infective nature and severity of the agencies* causing the anæmia.

These include most prominently of all, the *fever*, which comes and goes in the most varying manner; but is, in my opinion, rarely or ever absent in any case that is actually advancing. It also includes other phenomena, not so general but often met with, all of them characterized by the same periodicity which has been seen to be so common with most of the other features — namely, *headache, perspiration, drowsiness, languor, feelings of intense weakness,* and illness; also a group of more pronounced *nervous symptoms,* denoting actual lesions in central or peripheral nervous system, namely, *pains, numbness,* and *tingling* in the arms and legs, *disturbances of sensibility, ataxic phenomena, loss of knee jerk,* and sometimes actual *peripheral palsies.*

I. General Clinical Features.

1. *Pallor* is always marked, and is one of the first signs of the disease; frequently commented on by the patient's friends, before he himself has noted it. It is usually accompanied by a more or less marked lemon colour, the latter varying much from time to time.

2. *Nutrition.*—This generally appears fairly good: often surprisingly so, considering the great weakness of the patient. The subcutaneous fat is often increased. The muscles are always very soft. Although wasting is not a special feature of the disease, a considerable loss of weight is, in my experience, the general rule; and recovery is always marked by an increase of weight. In one very acute case I recently saw—in which the diagnosis was confirmed by post-mortem examination,—the patient lost over two stones in weight in the course of three months.

3. *Skin.*—The skin is usually dry; and sometimes shows a slight desquamation. The hair is also dry. According to Eichhorst, a peculiarly bad odour is sometimes given off by the skin, shortly before death.

4. *Hæmorrhages* into the skin are met with now and again. They usually take the form of minute petechiæ of the size of a

pin's head or a pea; it is exceptional for more extensive ecchymoses to occur: I have not met with them in any case under my observation.

5. *Œdema* is usually present in the later stages, chiefly in the feet and ankles.

6. *Weakness.*—This is the chief complaint from first to last: in the later stages it is of the most intense character.

It is invariably associated with *Breathlessness* and *Palpitation*, in the later stages to such an extent that the patient is often unable even to sit up in bed, without feelings of faintness. The heart is dilated; and loud systolic murmurs are heard over the mitral, tricuspid, and pulmonary areas: also in the vessels of the neck. In the later stages, the heart-weakness is accompanied by some œdema at the bases of the lungs.

7. *Want of Appetite* is a constant and common complaint, amounting sometimes to a positive loathing for food. In rare cases, the opposite condition prevails: the patient desires to eat too much.

8. *Sleeplessness* is a common symptom, both in the earlier and in the later stages: In the later stages, it often gives place to a marked drowsiness presenting, in some cases, certain special features (p. 310).

9. *Urine* normal, or increased in quantity: of normal or subnormal specific gravity; acid in reaction; of varying colour, sometimes pale, sometimes darker; *urea*, either absolutely, or only relatively, increased;[1] *uric acid* relatively increased; often giving a reaction of *indican.*

10. *Retinal Hæmorrhages* distributed over the whole of the retina; sometimes single, sometimes in extraordinary number; usually very minute, sometimes as large as the optic papilla; in shape, round, irregular, or in lines; usually situated in the neighbourhood of a blood-vessel; if recent, of a bright red colour, afterwards, more brownish-red.

11. *Epistaxis* sometimes occurs early in the disease: at other times only late in its course; sometimes so frequent, and so marked, that it adds greatly to the anæmia existing.

[1] Regarding excretion of urea and uric acid, see valuable observations of Eichhorst (*op. cit.*); Laache (*op. cit.*); and Mott. *Lancet*, i., 1889.

Summary.—These, then, are the prominent symptoms which fall within the first group mentioned as being apparently referable to the anæmia itself. The relation between them and the poverty of blood seems obvious. If they comprised the whole of the symptoms of the disease, one might reasonably consider, that the disease was without any symptoms other than those referable to the degree of general anæmia itself.

And yet with regard to many of these, I have to point out that they are only *in part*—not *wholly*,—caused by the degree of anæmia present. That is to say, the weakness, lassitude, inability for exertion, breathlessness, palpitation, etc., are *not* always proportionate to the degree of anæmia present. On the contrary:

(1) *They may all be extremely marked, with a relatively good condition of blood;* or

(2) *They may all be absent, with a much poorer condition of blood.*

In other words, with regard even to these general features, *some other factor than mere degree of anæmia is at work.*

A patient may be *very ill*, with over 60 per cent. of red corpuscles and hæmoglobin; while another may feel *very well* with only half that proportion. And even in the same patient at different times: he may be so ill that he can hardly walk or even sit up, with his blood shewing 26 per cent. of corpuscles, and 40 per cent. of hæmoglobin: and two months later he may be able to go about from morning to night, take walks, go up and down stairs, eat well, and describe himself as "feeling better than he had done for several years"—yet his blood only shew 28 per cent. of corpuscles and 35 per cent. of hæmoglobin (Case 10).

I consider this a remarkable feature of the disease—one which demonstrates that the clinical features, even the simplest of them, are not referable to the degree of anæmia, and to these alone.

CHAPTER XXV.

II. HÆMOLYTIC CHANGES IN THE URINE.[1]

A. Urobilinuria.

The Urine:—*Quantity.* The quantity placed at my disposal from day to day during the last two and a half months of the patient's illness varied from 18 to 52 ounces. These figures represent only approximately the quantities daily passed, for in the earlier periods there was a good deal of intestinal disturbance, and much of the urine was therefore necessarily lost. During the last three weeks, when there was less disturbance of this nature, and the patient was in a condition of exceeding weakness, taking little nourishment, the quantity varied from 40 to 52 ounces.

The *Reaction* was acid throughout; sometimes very acid.

Specific Gravity.—This varied from 1010 to 1020. The time over which the observations extended may be divided into three periods. During the first the average specific gravity was 1016; during the second 1015; and during the third 1014. The fall in the third period was doubtless due to the circumstance that the patient's diet at this time was mainly milk.

[1] The observations here recorded under this title were made on Case 1 during the last two and a half months of his illness (1889); they supplement in some important particulars my observations regarding the hæmolytic nature of the disease. They were published under the title "Observations on the Urine in Pernicious Anæmia."

Ex. 1. "Excretion of Pathological Urobilin," *Practitioner*, Aug. 1889; *Proc. Cambridge Medical Soc.*, May 1889.

2. "Excretion of Blood Pigment," *Ibid.*, Sept. 1889.

3. "Excretion of Iron," *Ibid.*, Oct. 1889.

General Characters of the Urine.

Date.	Quantity.	Reaction.	Specific Gravity.	Colour.
	ozs.			
March 9	35	Acid.	1015	Clear, and very high coloured.
,, 10	—	,,	1020	,, ,,
,, 11	38½	,,	1020	,, ,,
,, 12	18+	,,	1020	,, ,,
,, 13	18+	,,	1016	,, ,, No sediment.
,, 14	34	,,	1016	Slightly muddy; a heavy deposit of uric acid crystals. After filtration, less high coloured than before; rosy-red deposit on filter.
,, 15	19+	,,	1014	Still muddy, but less so than yesterday; colour appreciably less than that of the 13th; a heavy deposit of uric acid crystals.
,, 18	21+	,,	1015	Urine clear, and of dark sherry colour. No deposit of urates or uric acid.
,, 19	22+	,,	1016	
,, 20	22+	,,	1017	Cloudy; heavy deposit of urates.
,, 21	20+	,,	1018	Very high coloured, but clear.
,, 22	37	,,	1014	Colour not so high.
,, 23	36	,,	1016	*Colour very high;* urine clear. No deposit of urates or uric acid.
April 17	20+	,,	1010	Lighter in colour than at any time yet seen.
,, 18	20+	Very acid.	1018	*Very high coloured;* deposit of uric acid.
,, 23	37	Acid.	1017	Still very high. Clear; no deposit.
,, 24	28+	,,	1016	Colour high; heavy deposit of uric acid on standing.
,, 25	37	,,	1016	,, ,,
,, 26	27+	,,	1015	,, ,,
,, 29	42	,,	1015	Urine slightly muddy.
,, 30	28+	,,	1014	,, ,,
May 1	42	,,	1016	Colour very high.
,, 2	40	,,	1014	,, ,,
,, 3	49	,,	1010	,, ,,
,, 4	35	,,	1012	,, ,,
,, 6	35	,,	1013	,, ,,
,, 8	52	,,	1013	,, ,,
,, 9	42	,,	1014	,, ,,
,, 10	35	,,	1015	,, ,,
,, 11	49	,,	1014	,, ,,
,, 13	35	,,	1014	Exceedingly high coloured.
,, 14	52	,,	1016	,, ,,
,, 15	52	,,	1016	,, ,,
,, 16	42	,,	1014	,, ,,
,, 17	41	,,	1015	,, ,,
,, 18	52	,,	1015	,, ,,
,, 20	42	,,	1016	,, ,,

Colour.—The colour of the urine was the most striking feature throughout. This was exceedingly high, varying slightly from time to time, sometimes even from day to day, but in all cases remaining very much higher than ever observed in conditions of health. I only saw the case from time to time, in consultation with his doctor; but I found myself able, to some extent, to judge of the condition of the patient, from day to day, by the colour of the urine sent to me.

The colour was that of an extremely dark sherry, presenting generally at the same time something of an olive tinge.

The urine was lightest in colour on April 17, and this change was associated with an improvement in the condition of the patient the most marked at any time observed. On this day there occurred a sudden and marked exacerbation of all his symptoms, with great weakness, drowsiness, marked lemon colour, dark colour of stools; and the urine again became very dark.

The same relation between these attacks and the colour of the urine was observed on April 23. In neither instance did the specific gravity rise correspondingly, as usually occurs in fever. This absence of relation between the colour of the urine and its quantity or specific gravity was best observed in the later stages of the illness, when, as I have stated, the quantity was greatest and the specific gravity lowest; and yet it was at this time that the colour was highest.

The urine was usually perfectly clear, and transparent. On two or three occasions, it was slightly muddy; and on two occasions (March 14th and 15th), at a time when arsenic was being pushed a little too rapidly, it was very muddy, and threw down a heavy deposit of urates with uric acid crystals. At the same time, there were some pain and difficulty in micturition, which soon, however, passed off.

Pigments.

Bile Pigments. — With regard to the cause of this high colour of the urine, at no time were any *bile pigments* to be detected. In addition to the ordinary method of applying the Gmelin test, I used the one recommended by Hoppe-Seyler, when other colouring matters such as hæmoglobin or urobilin are present—namely, precipitating the urine with a moderate quantity

of milk of lime, shaking well, then filtering off the precipitate, and washing with water. A few drops of impure nitric acid, allowed to fall on the precipitate on the filter, gives the well-known colour reactions, if any bile pigments are present.

Uro-erythrin.—On a few occasions, when there was a heavy deposit of urates, there was a considerable quantity of *uro-erythrin*, the colouring matter so frequently found in the urine of fever patients, giving a well-marked rose-red colour to the paper when filtered. Hæmoglobin was never found, either on chemical or on spectroscopic examination.

Urobilin.—On spectroscopic examination, however, I found a well-marked absorption band lying close to the line *F* of the spectrum, and fading off toward the line *b*, with at the same time a considerable absorption of the outer part of the blue portion of the spectrum (1 and 2, fig. 14).

The colouring matter, which gave this spectrum, I was able to separate in large quantities, by shaking the urine gently for some time with half its volume of chloroform, decanting off the solution, and then evaporating to dryness. After again being taken up in chloroform, filtered, and evaporated, a residue of a brownish-red colour remained, readily soluble in alcohol, the solution shewing the same well-defined spectrum band as the urine itself.

On addition to the urine of a few drops of an alcoholic solution of chloride of zinc, a very marked green fluorescence was developed; the band became somewhat narrower, its darkest part being still on the side next *F*, and at the same time displaced more towards the line *b* (3 and 4, fig. 14). On further addition of a few drops of ammonia the spectrum still shewed an absorption band between *F* and *b*. Its characters, however, were changed, its darkest portion now being seen close to *b*, and the band fading off towards *F* (5, fig. 14).

Both as regards its spectrum and its chemical behaviour (green fluorescence with zinc chloride), the colouring matter present in such large quantities had all the characteristics of the pigment termed *pathological urobilin*, as described by Dr. MacMunn,[1] from a case of intraperitoneal hæmorrhage.

[1] "On the Origin of Normal and Pathological Urobilin," *Journal of Physiology*, x. p. 71, plates x. and xi.

Uro-hæmatoporphyrin.—It is possible, that in addition to the pathological urobilin, there was also present in the above case some *uro-hæmatoporphyrin*, since, as MacMunn shews, the presence of a band at *F* in an acid solution, the development of a green fluorescence with zinc chloride and ammonia, and the

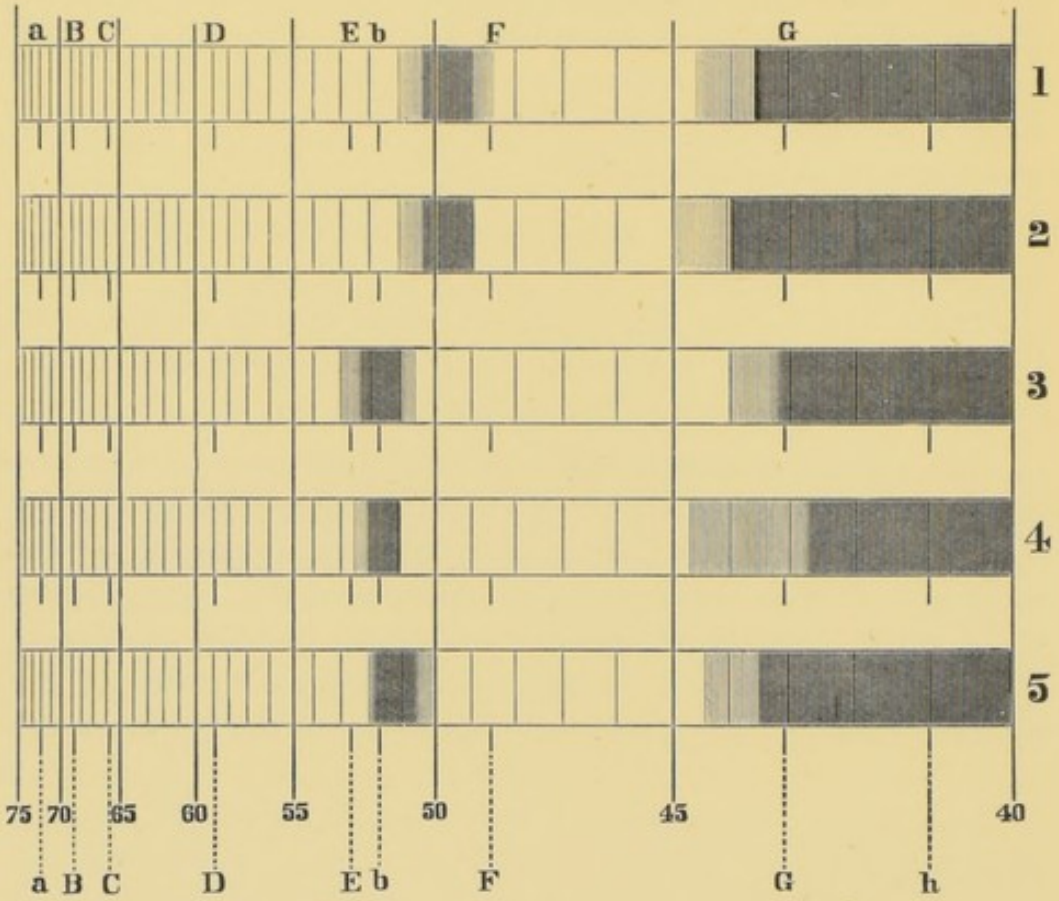


FIG. 14.—ABSORPTION-SPECTRA OF URINARY PIGMENT IN PERNICIOUS ANÆMIA.

1. Solution of pigment in alcohol.
2. The same, more diluted.
3. Solution after addition of a few drops of zinc chloride.
4. The same, diluted.
5. The same, after further addition of a few drops of ammonia.

shifting of the band towards the red with ammonia (5, fig. 14) are as characteristic of uro-hæmatoporphyrin, as of pathological urobilin. The fact, however, that the green fluorescence was so marked on the addition of zinc chloride alone, leads one to conclude, that in the above case the colouring matter was mainly pathological urobilin.

The presence of this colouring matter in such quantities in pernicious anæmia appears to me to have a twofold significance, both pathological and diagnostic.

Pathological Significance.—That in all cases pathological urobilin is a product derived from the disintegration of hæmoglobin there is no doubt. As MacMunn has shewn, pathological urobilin is quite distinct from the urobilin of healthy normal urine. However deep the layer of fluid may be, the absorption band at *F* of this normal urobilin never appears broad and black like that of pathological urobilin (1, fig. 14); and further, with the former, no green fluorescence is developed with zinc chloride. This observation I consider to be one of great value and importance. It points to a difference in the conditions leading to the appearance of normal and pathological urobilin in the urine.

Both of them have, in all probability, a double origin—from hæmatin; and, by a process of reduction, from the pigments of the bile.

MacMunn's observations go far to shew that normal urobilin is in all probability derived from hæmatin in the tissues, perhaps also from the hæmatin of the food. It is with difficulty obtained from bile pigments, while it is easily obtained from hæmatin.[1]

Origin from Bile Pigment.—On the other hand pathological urobilin is in all probability derived mainly from the bile pigments, and to a less extent from hæmatin. In the bile MacMunn has indeed found a urobilin-like substance, convertible by oxidation into one closely resembling pathological urobilin.

Whether derived therefore from the bile pigments, or from this urobilin-like substance excreted with the bile, we have at least ample evidence, in the above case, that the excretion of pathological urobilin was connected with a largely increased secretion of bile.

A darker character of the fæces was noted from time to time in association with the recurrent aggravations of weakness.

[1] [The later exhaustive studies of Dr. Gowland Hopkins and Dr. Garrod and others shew that urobilin is formed from bile pigments within the intestinal canal.]

At the same time, the urine contained much more colouring matter.

In one case of pernicious anæmia, I found still more certain evidence of this increased secretion of bile. The duodenum and upper part of the small intestine contained a very large quantity of highly concentrated bile, extremely rich in pigments.

I think there can be no doubt, therefore, that in the excretion of such large quantities of pathological urobilin, we have further valuable evidence as to the essential nature of this disease, namely, that it depends, as I have maintained elsewhere, on an excessive destruction of blood:—in other words, that pernicious anæmia is hæmolytic in its nature.

In the present case the richness of the urine in colouring matters could have had absolutely no relation to the absorption of colouring matter derived from the food; for during the latter part of the illness the patient's diet was as little nitrogenous as possible, and consisted mainly of milk.

In this connection, namely, the derivation of this colouring matter indirectly from hæmoglobin through the bile pigments, it may be pointed out that the cases, hitherto described, in which pathological urobilin has been found in greatest quantity, have been instances in which large extravasations of blood were in process of absorption,—a largely increased formation of bile pigments following the destruction of the hæmoglobin, supplied to the liver, in increased quantity, under such circumstances.

Origin from Hæmatin and Blood Pigment.—In addition to its origin from the pigments contained in the bile, I conceive it likely, however, that another probable source of the pathological urobilin in pernicious anæmia, is the pigment found, as my former observations shew, in such great abundance within the liver.

I am the more inclined to arrive at the conclusion from the appearances presented, *post-mortem*, in the foregoing case. The urine remained of high colour to the very last; but, on *post-mortem* examination, no excess of bile was found in the duodenum or small intestine. On the contrary, the mucous membrane was covered with only slightly bile-stained mucus. The probable origin of pathological urobilin in other organs of

the body from products of blood-destruction, as well as from the pigments of the bile within the intestinal tract, is thus to be kept in mind.

Diagnostic Significance.—As regards its bearing on diagnosis, the excretion of such large quantities of colouring matter in the urine—entirely independent, be it noted, of fever, or of any diminution in the quantity of the urine, or rise in the specific gravity—is, I think, of the greatest interest and importance.

In former observations, my conclusions regarding the hæmolytic nature of this disease were based on :—

(1) A consideration of the pigment changes to be found after death, especially in the liver.

(2) The possibility of inducing experimentally similar changes in animals by the action of blood-destroying agents.

As I stated, evidence of this destruction would in all probability be found in the urine. But, as it happened, I had no case at the time to make the necessary observations upon.

The high colour of urine has been noted and commented on in this relation by other observers—Eichhorst, Pye-Smith, Bristowe, and most recently by Mott.[1] Dr. Mott has pointed out, that the high colour of the urine observed in his case "bears out strongly" my views; and "strongly supports the conclusions" I have arrived at in the foregoing studies, as to the hæmolytic nature of the disease. He states that to his mind these studies have "very definitely shewn that the essential features of pernicious anæmia are excessive destruction of blood corpuscles, the seat of the disintegration being the portal system, more especially that portion of it contained within the liver and spleen, the process seeming to commence by a liberation of hæmoglobin in the spleen, which was carried to the liver to be disposed of."

He thinks it likely that the urobilin is split off from the hæmoglobin molecule within the liver, the iron remaining within the liver.

With this conclusion as to the significance of high coloured urine in this disease, I agree. In the light of the foregoing observations, it will become more and more a matter of import-

[1] "A Case of Pernicious Anæmia." *The Lancet*, i., 1889, p. 520.

ance to observe the condition of the urine in all cases of anæmia of doubtful nature.

The only anæmia liable to be mistaken for pernicious anæmia, both as regards its general features and the degree of change in the blood, is the anæmia resulting from loss of blood. I have already indicated, that as regards the changes in the blood in the two forms, important differences exist, which enable one to state with some degree of certainty, whether the anæmia is *pernicious* or *traumatic*,—the chief one being the relatively high hæmoglobin percentage in pernicious anæmia.

It now becomes clear, that an equally important difference must exist as regards the condition of the urine in the two forms. The urine of traumatic anæmia is invariably extremely pale; and I have found this the case, even when some degree of fever is present.

The pathological processes underlying pernicious anæmia must, on the other hand, always be associated with a formation of effete pigments, and colouring matters, evidence of which ought invariably to be found. Such evidence in the above case I judge was found in:—

(1) The marked lemon-colour presented by the patient, which varied, as I have stated, in a remarkable manner, the variations corresponding with a variation in colour of the urine.

(2) The slight degree of jaundice observed at one time, and so frequently met with in other cases (see Part IX.).

(3) The increased formation of bile pigments, as shown by the dark colour of the fæces.

(4) The high colour of the urine.

If, in addition, in any case of severe anæmia presenting the group of clinical features I have described, the colouring matter present be found to be pathological urobilin, I should consider this fact (in the absence of fever, with urine undiminished in quantity, and of low specific gravity) as absolutely diagnostic of the existence of pernicious anæmia.[1]

Dr. Mott has since recorded[2] another case of this disease in which the pigment found by himself and Dr. Halliburton was urobilin. In reference to the foregoing observation of mine, Dr. Mott expresses the opinion, that it is of comparatively little

[1] Hunter, *op. cit.*, *Practitioner*, 1889. [2] *Lancet*, vol. i., 1890.

importance which variety of pigment is present; the chief interest attaching to the presence of "urobilin" in such large quantity is that it serves to explain the presence of iron in the liver in such cases, both being evidences of an "exaggerated physiological process" of blood destruction. With reference to this, I have to note, that the pigment I found was *not in itself the cause of the high colour of the urine.* After its removal from the urine by means of chloroform the urine retained much of its original colour. Furthermore, it was present in *very varying* quantity at different times, even in urine presenting the same high colour. Thus, while its characteristic absorption band was sometimes lost on dilution of the urine twice, *at other times it was still recognizable after the urine had been diluted as much as six or seven times.*

My conclusions as to the character of this pigment were based on numerous observations, both chemical and spectroscopic, made from day to day. I have since repeated these observations with the pigment then separated, and still in hand in considerable quantity. I have satisfied myself once more that it *differs in important respects, both chemically and spectroscopically, from any pigment present in the urine in health, or obtainable by the method I employed from the high coloured urine of fever.*

So far as my observations go, the distinction drawn by Dr. MacMunn between the pigment present in the urine in health, and in high coloured urines generally, to which he gives the name of "normal urobilin"—and that obtainable from the urine under certain special conditions, for example, absorption of large extravasations of blood, to which he gives the name "pathological urobilin," is a valid one.

While a high significance attaches to the presence of high coloured urine of low specific gravity, and in undiminished quantity, *an altogether special significance attaches, in my opinion, to the presence of pathological urobilin in such cases.* It is most usually found in the urine during absorption of large extravasations of blood—under conditions I would therefore define, as primarily those in which an undoubted extensive destruction of blood is going on, unattended by hæmoglobinuria.

With regard to the large excess of pigment in the liver, in my judgment it is the special character of the preceding blood destruction rather than blood destruction *per se* that determines

the presence of iron in such quantities in the liver in these cases. I found it impossible, namely, to reproduce a condition of the liver similar to that found in pernicious anæmia, by injection of such reagents as distilled water, glycerine, or even pyrogallic acid. I succeeded, on the other hand, with toluylendiamin. And this fact appeared to suggest that the drug had not only a peculiar destructive action on the blood, but had also "a specific, not necessarily poisonous, action on the liver cells." One result of its peculiar action on the blood, I found was, that the hæmoglobin remained combined with the albuminous constituents of the corpuscles or plasma. As the result of its action on the liver cells, part of the hæmoglobin was reduced *in situ* to the form of an albuminate of iron, which remained within the liver cell in the form of pigment granules. That, under these circumstances, the bye-products of pigment nature, split off from the original hæmoglobin molecule, should differ from those split off in health, seems to me quite likely. In health, such bye-products are the bile pigments, and the pigments and chromogens of the urine, including normal urobilin. Under other conditions, for example, changes in large extravasations of blood, special bye-products may appear, differing, it may be slightly, but still recognizably, from the pigments usually formed.

I consider "pathological" urobilin to be such a bye-product. It is formed, not only from the bile pigments within the intestinal canal, but also possibly from hæmoglobin through the agency of cells. Between it and normal urobilin I conceive important differences exist. *Its appearance in the urine in pernicious anæmia points therefore—far more than any excess of ordinary pigments—to a preceding extensive destruction of blood of a special nature.* Both it and the excess of iron in the liver are explained by the same special cause—a destruction of blood proceeding along lines, and due to causes, differing from those found in health.[1]

[1] Hunter, *Brit. Med. Journ.*, i., 1890.

CHAPTER XXVI.

HÆMOLYTIC CHANGES IN THE URINE—(*continued*).

B. Excretion of Blood Pigment.

In the case described, there were certain other changes in the urine, which seem to me of some interest and importance.

In my study of the pathology of pernicious anæmia I was led to the conclusion, from a consideration of the anatomical changes found in the kidneys, that microscopic examination of the urine might be found in certain cases to throw not a little light on the nature of the anæmia we had to deal with. This conclusion I find fully borne out by the results of observations in the present case.

The chief result of these observations, it will be recalled, was to shew :—

(1) That the essential feature of this form of anæmia is excessive destruction, and not in the first instance any impaired formation of blood.

(2) That the characteristic feature of this blood-destruction, by which it is in the first place to be distinguished from that occurring in paroxysmal hæmoglobinuria, is that it is initiated in, and for the most part limited to, the portal circulation—the chief seats of the destruction within this area being the spleen, the capillaries of the liver, and the radicles of the portal system within the gastro-intestinal walls.

This limitation of the destructive process serves to explain why the liver is so constantly the seat of the important and characteristic changes then described, inasmuch as all the hæmoglobin set free is necessarily carried to that organ in the first instance. It also serves to explain why hæmoglobinuria is not a symptom of the disease, notwithstanding that in many cases

a considerable, and sometimes very sudden, destruction of blood takes place. The hæmoglobin liberated by such an occurrence is, within certain limits, entirely disposed of while passing through the liver, either by being excreted in the form of bile-pigments or by being stored up in the form of blood-pigments.

I concluded, however, that the blood-destruction is not always confined within these limits. The course of the disease is usually marked by exacerbations more or less periodic, during which the amount of blood-destruction may be so great, that the liver is unable to dispose of all the hæmoglobin supplied to it. The hæmoglobin then passes into the general circulation, and is excreted by the kidneys. Evidence of such an excretion I found in the large quantity of pigment present in the kidneys in certain cases of the disease I had examined, the situation and character of which alike pointed to hæmoglobin as its source.

That under such circumstances hæmoglobin, or any of its immediate derivatives, had never been found in the urine was a remarkable fact, and seemed to me at first sight to negative the view that hæmoglobin in any form was excreted by the kidneys.

In the case now under consideration I had an opportunity of satisfying myself as to the freedom of the urine from such evidences of blood-destruction. During the last three months of the patient's illness there were two well-marked exacerbations such as I have referred to; both of them sudden in their onset, and attended by great weakness, drowsiness, slightly increased temperature (not exceeding, however, 100° F.), a more marked lemon tint of the skin, and an exceedingly high colour of the urine.

Certain of these clinical phenomena, more especially the excretion of the large quantities of 'pathological' urobilin already described, undoubtedly pointed to an increased destruction of blood, comparatively sudden, too, in its occurrence. Nevertheless, at no time was hæmoglobin or any of its immediate derivatives, such as methæmoglobin or acid hæmatin, to be found in the urine.

The discrepancy between the clinical phenomena and the pathological events I have supposed to occur at this time is, however, more apparent than real.

As I have already pointed out, the absence of hæmoglobin or any of its immediate derivatives from the urine in such cases is to be explained by the *special form* in which the hæmoglobin reaches the kidneys. Instead of being free, the hæmoglobin liberated from the corpuscles remains combined in some peculiar way with the albuminous constituents of the corpuscle or of the plasma.

The evidence pointing to this conclusion was considered in Chapter XIII., and need not therefore be dwelt upon here. I need only add, that urine containing hæmoglobin in this form does not shew any of the reactions of the hæmoglobin. When it appears in the urine, it does so in form of small yellow viscous droplets, only recognizable on microscopic examination.

Corresponding with this difference in the *form* of the hæmoglobin, there are, I find, important differences in the actual channel by which it is excreted. There is a marked difference between the changes in the kidneys in pernicious anæmia, and those in ordinary hæmoglobinuria. In the latter, the chief changes are the presence of *menisci* of hæmoglobin in and around the glomeruli, and sometimes similar hæmoglobin casts in the tubules; in pernicious anæmia, the hæmoglobin is excreted through the cells of the convoluted tubules. The changes are limited to the renal epithelium, and consist in the presence of fine granular blood-pigment within the epithelium of the convoluted tubules, none being found in the glomeruli.

This difference in the character of the changes in these two conditions points, I conclude, to a difference in the channels of excretion of the colouring matter in the two cases.

In ordinary hæmoglobinuria, the principal (most observers consider the only) channel by which the hæmoglobin passes into the urine is through the glomeruli. If any excretion at all takes place through the epithelium of the tubules, this is altogether of secondary importance to that which occurs through the glomeruli. On this point my observations are in agreement with those of other observers.[1] Hence it is that the chief evidences of this excretion are to be found in and around the glomeruli.

In pernicious anæmia, on the other hand, the absence of

[1] Adami, *Jour. of Physiology*, 1887.

pigment from the glomeruli, and its presence in the epithelium of the convoluted tubules, must, in my opinion, be regarded as pointing to the epithelium as the chief channel of excretion of the hæmoglobin, for the pigment has the characters of that formed from hæmoglobin.

An analogous case of a similar difference in the channels of excretion is afforded after injection of salts of iron or indigo-carmine into the blood. Glævecke[1] found, that after injection of salts of iron into the blood, their excretion takes place through the epithelium of the convoluted tubules, and not through the glomeruli; and the preponderance of evidence goes to shew[2] that the same holds true for indigo-carmine when similarly injected, the granules being found in process of excretion within the renal cells.

The idea naturally suggests itself in this connexion, that in pernicious anæmia we have really to do with an excretion of some remote derivative of hæmoglobin, containing all the iron of the original hæmoglobin molecule; and this idea cannot be altogether set aside as unfounded. On the other hand, the character of the pigment-granules is precisely that of pigment formed from hæmoglobin according to my observations. Hence I conclude that it is not merely an iron-derivative of the hæmoglobin, but a modified form of hæmoglobin itself, which passes into the renal cells and is excreted.

In the case described, I found clinical evidence of these pigment changes in the kidney—in the presence during the exacerbations of the disease of renal cells and casts containing granules of blood pigment.

"*March* 9.—At the time I first saw the patient, the most striking character presented by the urine was its high colour. On microscopic examination nothing abnormal was detected.

"*March* 10.—A number of faintly granular cast-like structures are to be seen, holding yellowish pigment granules which resemble blood pigment very closely in appearance, size, and colour. The casts are short and fragmentary, and made up of partially degenerated cells, apparently of renal origin, the outlines of the individual cells being indistinct. The yellowish pigment granules are confined to these cells,

[1] Glævecke, *Maly's Jahresbr. ü. Thier-Chemie*, 1883, p. 182.
[2] Foster, *Text-book of Physiology*, 5th ed., vol. ii. p. 667.

none being seen free. The granules are sufficiently large to shew distinct outlines with the power used (× 250). Cells from the bladder are also seen, but they are free from any such pigment.

"*March* 11.—Similar cells are seen arranged as before in cast-like groups of three, four, or more, and containing yellow pigment granules.

"*March* 12.—A few isolated cells are seen, containing the same yellowish granules. The pigment is not so abundant as before, and the cells, which are small and round, and appear to be renal in their origin, are not so numerous. They are no longer arranged in groups.

"*March* 13–18.—Daily examination of the urine has failed to reveal any cells such as were before seen. The urine on several days threw down a heavy deposit of urates and uric acid crystals. Its colour has in the meantime improved.

"*March* 19–22.—Colour of the urine has again become higher, the specific gravity, however, still remaining 1015 to 1018. On the afternoon of *March* 22 the patient had a marked exacerbation of all his former symptoms—profound weakness with drowsiness, increase of lemon tint with apparently some slight degree of icterus of the conjunctivæ, looseness of bowels, and darker colour of stools.

"*March* 23.—The urine markedly changed for the worse. Although the specific gravity is not increased (1016), the urine presents a very high colour; it is perfectly clear, however, and throws down no deposit on standing. On microscopic examination, a number of degenerated renal cells are seen, partly single, partly arranged in cast-like groups of three, four, or more, most of them containing yellow-pigment granules. These granules present exactly the appearance of blood-pigment, and are so numerous that some of the cells seem filled with them. No granules are to be seen free; they are all contained within renal cells, or their remains. The appearance of these cells contrasts markedly with that of the few cells from the bladder also seen, the latter being perfectly free from this pigment. The urine is singularly free from amorphous urates, so that the appearance presented by the yellow pigment granules is all the more striking. The more these cells are examined, the stronger becomes the conviction, that they are renal in their origin, and that the pigment they contain is blood-pigment. The uniform size of the pigment-granules, their spherical shape, and yellow or brownish-yellow colour, are precisely the characters of blood-pigment granules.

"I did not see the patient after this for a period of three weeks. In the meantime he had recovered from his attack of increased weakness, and had indeed gained ground. I found him on my return

considerably improved in health, his appetite better, the colour returning to his lips and gums, and he himself feeling altogether stronger and better.

"*April* 17.—Urine lighter in colour, and more nearly normal than at any time yet observed. On the afternoon of this day, there was a second exacerbation in all respects similar to the first.

"*April* 18.—Colour of the urine again very high. On microscopic examination, renal cells seen as before containing yellowish pigment granules, easily distinguishable by their colour and appearance from the surrounding urates. Some of the cells are grouped together in cast-like form, but most of them are single."

Further details of these examinations during the remainder of the illness need not be given. Cells, similar in character to those already described and with similar contents, continued to appear from time to time in the urine. For the patient's condition from the time of this last exacerbation became rapidly worse, the colour of the urine remained continuously and persistently high, higher even than before, notwithstanding that the quantity was undiminished, and the specific gravity lower (1014).

What was the meaning of these changes found on microscopical examination? The consideration already given to the histological changes met with in the kidney supplies the answer.

I was at first unwilling to accept the view, which naturally suggested itself, that the pigment found in such small quantity came from the kidney. The gradual diminution in the number of cells, and in the quantity of pigment, from *March* 10 onwards, and the final disappearance of both cells and pigment after *March* 13, led me, however, to conclude that such was the case. For this disappearance was connected with a change in the patient's diet, with what appeared to be a resulting slight improvement in his general condition.

The diet of the patient at the time he was first seen was of a highly stimulating and nitrogenous character, consisting of meat juices, beef-tea, &c. Since my observations on the nature of blood-destruction denoted that such a diet was perhaps the best fitted of any to ensure an increased destruction of blood

even in health, a blander and less nitrogenous one was substituted on *March* 11, two days after he was first seen.

The disappearance of pigment-cells from the urine, and the slight improvement in the health of the patient, seemed at first to justify this step. But the change for the better was only of short duration. Exacerbations more or less acute occurred at intervals, apparently uninfluenced by the treatment adopted.

With each exacerbation there was a reappearance of these pigment-carrying renal cells in the urine. The connection, in point of time, between the two occurrences was so close, as finally to satisfy me, that they stood to each other in the relation of cause and effect: the greater blood-destruction initiated by the exacerbation was, in fact, evidenced by the excretion of blood-pigment in the urine. The cells were such as had probably become detached from the convoluted tubules under the extra strain thrown upon them in the excretion of the pigmentary material supplied to them from the blood. The character of the pigment they contained was precisely such as that already described, and such as I afterwards found *post-mortem* within the kidney in this case.

Significance.—It is perhaps unnecessary to point out on the pathological bearing of this excretion of pigment, or its importance from a diagnostic point of view. The observations recorded speak for themselves.

As regards its pathological significance, the appearance of this pigment in the urine, in the form I have described, bears out fully what I have already said regarding the excretion of hæmoglobin by the kidneys in cases of pernicious anæmia, and the channels by which this excretion takes place.

As regards its bearing on diagnosis, the discovery of pigment cells in the urine in a doubtful case of anæmia, if combined with a high colour of the urine, and especially with an excretion of pathological urobilin, would undoubtedly in my opinion go far to establish the case as one of pernicious anæmia.

CHAPTER XXVII.

HÆMOLYTIC CHANGES IN THE URINE—(*continued*).

C. Excretion of Iron.

In the light of the observations already recorded regarding the excretion of hæmoglobin, and its appearance in the urine in the form of blood-pigment, it became a matter of some interest to determine what was the excretion of iron in pernicious anæmia as compared with that of health.

My former observations had shewn that as the result of the excessive blood-destruction prevailing, there was an accumulation of iron in certain organs of the body—notably within the liver, and occasionally also within the kidneys. It seemed not improbable, therefore, that the urine might shew some evidence of this greater destruction in the form of an increased excretion of iron.

At the time my observations were made, I was naturally unaware of the condition of the kidneys in the particular case described, that is to say, of the presence of a very large excess of pigment lying within the cells of the convoluted tubules. This condition obviously rendered a considerably increased excretion of iron all the more likely.

Iron in the Urine.

Iron is a constant constituent of the urine in health. It is present, however, in exceedingly small quantity, and in such a form as only to be recognizable on very careful analysis of the ash. The presence of free iron in the urine can be recognized, as Hamburger[1] has shewn, by its characteristic reaction with sulphide of ammonium, even when in such dilution as 1 to 10,000. The iron normally present in the urine gives

[1] Hamburger, *Zeitschrift für physiol. Chemie*, ii. 191 (1878).

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no reaction with this reagent. We must conclude, therefore, that it is present in organic combination with other constituents of the urine.

Whether this combination is similar to the one we are acquainted with in the case of hæmatin, or is of the same nature as in the nuclein combinations of the yolk of egg and in milk, we are as yet ignorant. In all probability it is of the former kind, and has its origin therefore in the hæmoglobin of the blood.

Methods of Estimation.—The methods we at present possess for the estimation of the iron in the urine are unfortunately very imperfect; a matter of the more consequence, as the quantities we have to deal with are so small, as to render the errors that arise of the greatest possible importance. Iron is so abundantly present in nature, and is so frequently present in the various reagents used in its detection, that the greatest care is necessary to rid ourselves of this ever-present source of fallacy. Nearly all the observations hitherto made suffer in accuracy from fallacies arising in this way.

The methods hitherto in use have been chiefly two, that by weighing, and that by titration with a standard solution of potassium permanganate.

By Weighing.—The urine after evaporation to dryness in a platinum capsule is reduced to charcoal; and then carefully extracted with a moderate quantity of warm water, and filtered to remove the soluble salts (Filtrate No. 1). The insoluble residue left on the filter, along with the filter itself, is then completely ignited, till only a white ash remains. This is extracted first with dilute and afterwards with strong hydrochloric acid, and again filtered (Filtrate No. 2). The filtrate thus obtained contains, according to Hoppe-Seyler, the whole of the iron. So far is this, however, from being the case, that I find that a trace, although a small trace, of the iron occasionally passes through in the first filtrate, especially if a considerable quantity of water be used. It is desirable, therefore, to evaporate the first filtrate to dryness, extract with a small quantity of hydrochloric acid, filter again, and add the filtrate thus obtained to Filtrate No. 2.

The two filtrates thus combined contain the whole of the iron. On adding ammonia, a white flocculent precipitate is thrown down, made up of the phosphates of magnesium and calcium, along with phosphate of iron.

The phosphates of magnesium and calcium are readily soluble, with the aid of heat, in acetic acid, in which reagent the phosphate of iron is insoluble. The separation of the latter can therefore be effected by digesting in warm acetic acid, and subsequently carefully filtering through a small filter of known ash-composition. After being carefully dried and ignited, its quantity can be determined by weighing. The precipitate thus obtained contains the iron in the form of a ferric

phosphate (Fe_3PO_4); and since this latter contains 37·09 per cent. of iron the quantity of iron present may be determined.

According to Hoppe-Seyler, this method gives results of sufficient accuracy in the case of fluids, such as the urine, that contain phosphoric acid in large excess; the iron present is then converted into a phosphate. It was the one I employed in my earlier estimations. It is one, however, on whose accuracy we cannot by any means constantly rely. The results obtained give in most cases too high an estimate. It is difficult, in any case, to be certain that the precipitate finally obtained is made up entirely of phosphate of iron, although by carefully warming with acetic acid this can in many cases be accomplished.

It need scarcely be said, that in all these operations every care must be taken to avoid introduction of iron from dust in the air, through the reagents employed, or through the filter paper. In the case of the filter paper it is necessary to use one of definitely known ash-composition. The weight thus determined is subtracted from the total weight of the precipitate after final ignition.

By Titration.—In all cases it is better and safer to estimate the amount of iron by reducing it to the form of a ferrous salt, and then determining its reducing power on a solution of potassium permanganate of known strength. For this purpose the iron is converted into ferric sulphate, and then reduced to a ferrous state by means of zinc. Titration with the permanganate solution is then carried out in the usual way.

Certain sources of error are met with in using this method also. There are not infrequently impurities in the zinc, and these may have a reducing action on the permanganate solution, even when no ferrous salt is present. The error arising in this way has been regarded by one observer (Jacobi) as constant, being equivalent to not less than 1·8 milligramme of pure iron per litre. When it is remembered that, as will presently be seen, the whole of the iron in the urine frequently amounts to little more than 1 or 2 milligrammes, it will be understood how grave a source of error this may prove to be.

Another method has recently been proposed and carried out by Gottlieb.[1] This is based on an entirely different principle from the above, namely, the conversion of the iron into Prussian blue and its determination by weighing. The method is complicated and requires the use of a large number of reagents, in itself a source of grave error.

In Gottlieb's hands, however, it seems to have yielded remarkably constant results, and if his observations are confirmed the method may prove a valuable addition to those we already possess. It has the advantage of being specially suitable for determining very small quantities of iron.

[1] Gottlieb, *Archiv f. experim. Pathol. u. Pharmakol.*, November 1889.

Excretion of Iron in Health.

Owing mainly to the imperfections in our methods, partly also to the slow and tedious nature of the investigation, the observations hitherto made with regard to the daily normal excretion of iron in the urine have been but few.

In a healthy man Magnier[1] found the excretion to vary from about 4 to about 16 milligrammes per day, a wide range of variation, equivalent to an average daily excretion of about 10 milligrammes.

Hamburger found traces of iron constantly present in the ash of the urine, both in health and disease. In two healthy women he found a daily excretion of 10·1 and 15·6 milligrammes respectively, giving an average for the two of a little over 12 milligrammes. There cannot, I think, be a doubt that this estimate is too high. The method Hamburger used was that of titration, the iron being reduced to a ferrous state by warming with sulphurous acid instead of zinc. My experience of this method is that it is difficult afterwards to get rid of all traces of the sulphurous acid; and this exercises a very strong reducing power on the permanganate solution, in many cases even exceeding that of the ferrous salt actually present.

The results of Gottlieb's observations give a much lower estimate. In five cases he found it to vary from 3·69 to 1·59 milligrammes, giving an average of 2·59 milligrammes per day.

The excretion from day to day in each individual case remained remarkably constant, the widest range of variation in any one case being 0·21 milligramme, and the average range of variation from day to day in the whole series being only 0·15 milligramme.

These results differ widely from those obtained in the fewer and more limited observations of Magnier and Hamburger. If they are to be relied on, and the narrow range of variation found is their best recommendation, they indicate a daily excretion of iron considerably less than that of 10 milligrammes hitherto accepted.

Author's Observations.—My own observations (four in number), presently to be recorded, shew that the average daily excretion

[1] Magnier, *Maly's Jahresbr. ü. Thier-Chemie*, 1875, p. 138.

may most probably be taken as ranging from 3 to 5 milligrammes. In a *healthy individual* I found the daily excretion to be 5·65 milligrammes. After allowing for the error of excess which usually attends the method of estimation employed in this instance, that by weighing, this result agrees with the above estimate.

In three cases of *chlorosis*, in two of which the patients were getting large doses of iron, the daily excretion found was 1·71, 1·96, and 1·61 milligrammes respectively, giving an average of 1·76 milligrammes. The average in the two conditions was thus 3·70 milligrammes, any error of excess in the first being counterbalanced by the slight diminution in excretion which probably existed in the second.

Influence of Various Conditions.—This appears to be remarkably slight. The excretion seems to remain fairly constant for each individual.

It is not affected, at least directly, by changes in the quality or quantity of food. Thus Hamburger found, in a dog, that the daily excretion remained the same whether the animal was receiving 300 or 500 grammes of meat daily. What is more remarkable, it is apparently not affected by the administration of even large quantities of iron by the mouth.

The observations with regard to this point divide themselves naturally, both in point of time and in point of result, into three series.

The view long held, that iron administered by the mouth was absorbed as such, and utilized for purposes of blood-formation, had to be abandoned when Hamburger (1878) shewed that the absorption of iron in such cases was infinitesimal. In one experiment, out of 441 milligrammes of iron administered in the form of ferrous sulphate by the mouth, an excess of only 12 milligrammes was to be found in the urine over the period of time during which the administration lasted. That even this increase, slight as it was, was indirectly brought about, and was dependent on increased metabolism in the tissues rather than on increased absorption of the iron, was shewn by the fact that in no case, however great the amount of iron given by the mouth, could free iron be detected in the urine.

Following on these observations came those of Kobert[1] (1883) and Cahn[2] (1884). Hamburger's observations had pointed to a slightly increased excretion as the immediate result of the administration of iron by the mouth. Kobert and Cahn found that under such circumstances no absorption at all took place from the intestine, and hence any increased excretion of iron if present must be solely an indirect result.

Lastly, differing still more from those obtained by Hamburger, are the results obtained by Gottlieb. His observations appear to shew that so far from being increased the excretion is diminished while iron is being administered by the mouth. The immediate effect of the administration was to diminish for the first two or three days the quantity excreted in the urine. The excretion rose again in the following days, but never above that at which it previously stood. Thus in a healthy man, in whom the daily excretion of iron for three days had averaged 3·68 milligrammes, the excretion while iron was given by the mouth fell to 1·19 and 0·70 milligrammes, and on the third day the iron disappeared altogether. After the administration of the iron was stopped, the excretion rose again to 0·56 and then to 2·54 milligrammes.

In two other cases the same result was observed. It is extremely difficult to explain how such a result is produced, —nor need we stop to discuss it. The chief interest of these observations lies in this, that they seem conclusively to shew that the excretion of iron in the urine is as little affected by iron administered by the mouth as it is by diet. This conclusion is one of some importance in endeavouring to determine what significance should be attached to any increased excretion in disease.

Excretion of Iron in Disease.

This subject has as yet received scarcely any attention. The only observations hitherto made are those of Hamburger, already incidentally noted, in which he found traces of iron con-

[1] Kobert, *Mangan und Eisen, Archiv f. exper. Pathol. u. Pharmak.*, xvi. (1883).

[2] Cahn, *Resorptions und Ausscheidungs-verhältnisse des Mangans im Organismus, ibid.*, xviii. (1884).

stantly present in the ash of urine in a large number of diseases, including, amongst others, jaundice, pneumonia, diabetes, typhoid fever, puerperal fever, pleurisy, chlorosis, and leucocythæmia. No attempt, however, was apparently made to estimate the quantities present in these diseases.

Some of Gottlieb's observations were made on patients suffering from nervous diseases, the excretion of urine in whom, as he took for granted, was a normal one. In a healthy individual, the average excretion was 3·68; in a case of general paralysis it was 2·62; and in a case of "motor aphasia" it was 1·58 milligrammes. It is possible that Gottlieb may have been in error in regarding these cases as normal; and since he uses these results in arriving at his conclusion as to the average excretion in health, it is probable that this may account for the lowness of his estimate, namely, 2·59 milligrammes.

My own observations number seven in all, one made in health, three in chlorosis, and three in pernicious anæmia. The results are represented in the following table:—

No. of Observation.	Condition.	Quantity of Urine in c.cm.	Specific Gravity.	Excretion of Iron in milligrammes.	Remarks.
1	Health	1500	1018	**5·65**	
2	Chlorosis	900	1018	**1·71**	Has been receiving 6 grs. reduced iron daily for three weeks. Greatly improved.
3	,,	1175	1014	**1·96**	Has been receiving 30℥ tr. ferri perchlor. daily for three weeks. Improvement great, although not so marked as in No. 2.
4	,,	1365	1015	**1·61**	Treatment not commenced.
5	Pernicious Anæmia	1100	1014	**32·26**	*May* 2. (Death on *May* 22.) Urine of very high colour, contains much pathological urobilin. Not examined microscopically, but on *May* 1 contained a considerable number of renal cells, shewing blood-pigment.
6	,,	1500	1014	**6·52**	*May* 14.—Patient profoundly weak. Colour of urine as high as before.
7	,,	1200	1016	**1·00**	*May* 20.—Patient in a moribund condition. Urine still of high colour.

Results.

1. *Health.*—The excretion *in health* was 5·65 milligrammes. It is considerably higher than the average obtained by Gottlieb (2·59), although at the same time considerably lower than the average obtained by Magnier and Hamburger (10 milligrammes).

2. *Chlorosis.*—The observations in chlorosis are not sufficiently numerous to enable one to speak with certainty as to the excretion of iron in this condition. They shew a diminished excretion: 1·71, 1·96, 1·61, the average of the three observations being 1·76 milligramme. This is considerably lower than the average obtained by Gottlieb in health, and still lower than the average estimated by myself. When the poverty of the blood (in hæmoglobin) in chlorosis is borne in mind, this is what one might expect, assuming what is most probable, namely, that the iron excreted in the urine is derived directly or indirectly from the hæmoglobin of the blood.

Observations Nos. 2 and 3 are also of interest as shewing how little the excretion is influenced, directly at least, by the administration of iron by the mouth. Both patients had been receiving iron in considerable doses for three weeks previously, and both had improved under the treatment, without any apparent influence on the excretion of iron. This remained almost the same as that found in No. 4, where no iron had been given. The improvement was most marked and most rapid in No. 2; and the smaller excretion of iron in this, namely, 1·71 milligrammes, as compared with that in No. 3, namely, 1·96, was in all probability related to the circumstance that the attack was the third in a comparatively short period of time, from which the patient had suffered. At the time of admission, she presented in a very marked degree the symptoms of extreme chlorosis.

3. *Pernicious Anæmia.*—The most striking feature of these observations, however, and the one of most interest in the present relation, is the enormous excretion found in one instance in the case of pernicious anæmia. My observations on the excretion of iron in this case were unfortunately not made till near the fatal termination of the case, when the patient was already in a state of profound weakness. Notwithstanding his condition in

this respect, the urine shewed a large excretion of iron, on one day as high as 32·2 milligrammes, on another as high as 6·5 milligrammes. This must undoubtedly be ascribed to the excessive blood destruction constantly going on, as evidenced more especially by the high colour of the urine associated with the presence of so much pathological urobilin,[1] and the presence from time to time of considerable quantities of blood-pigment.[2] Under these circumstances, therefore, it is not surprising that there should be an increased excretion of iron as was found on *May* 2, even to such an amount as 32 milligrammes.

A very small amount of blood-pigment in the urine would amply account for an increase to this, or even to a still larger amount. The urine on this particular day was not examined microscopically; but on the day before, I found a considerable number of renal cells in the urine, the most of them containing pigment in considerable amount. It is very probable, therefore, that a similar condition existed on *May* 2.

How far an increased excretion of iron in pernicious anæmia is a constant condition, or how far, on the other hand, it is intermittent, occurring from time to time associated with the periodic exacerbations of the destructive process, it will remain for future observations to determine.

The results obtained in the present case point to the latter conclusion. Another estimation was made on *May* 14, a week before death, when the patient was in a condition of exceeding weakness, with occasional wandering and mild delirium. The excretion found (6·52 milligrames) must be regarded as, relatively speaking, a very large one, considering the condition of the patient's blood at the time. So poor was the blood in hæmoglobin, that it scarcely sufficed to give a red tint to a white cloth, as was observed on one occasion when there was a slight attack of epistaxis. The excretion on *May* 20, two days before death, had fallen still lower. This relatively large excretion, observed on *May* 14, I am inclined to regard as of equal significance to the much larger excretion observed on *May* 2. Both alike pointed to the conclusion that there was a largely increased destruction of blood, the excess of iron being derived from the blood-pigment, probably also from other iron-containing products of this destruction present in the urine.

[1] *Practitioner*, September 1889. [2] *Ibid.*, November 1889.

[Dr. Hopkins[1] has since repeated these observations, and confirmed them. He found the excretion

In a *normal urine*, 3·5 milligrammes.
In *Pernicious Anæmia* (Case 1) 8·3 „
„ „ a few days later a mere trace.
„ „ (Case 5) a mere trace.]

[1] *Guy's Hospital Reports*, 1895.

CHAPTER XXVIII.

SUMMARY REGARDING THE HÆMOLYTIC CHANGES IN THE URINE.

THE results regarding the hæmolytic changes in the urine observed in the foregoing case may be shortly summarized as follows :—

1. They shewed, first, a largely *increased excretion of urinary pigments*, evidenced by an extremely high colour of the urine without any diminution in quantity, and with a low specific gravity. During the last three weeks of his illness, for example, when there was little intestinal disturbance, and the whole of the urine could be obtained, the quantity varied from 40 to 52 ounces, with an average specific gravity of 1014. The reaction was at all times extremely acid. At no time were bile pigments found in the urine. Uro-erythrin appeared from time to time during the slight feverish attacks from which he suffered. The chief interest attached to the presence in large quantity of a urinary pigment, having all the characters (chemical and spectroscopic) of that termed by Dr. MacMunn as *pathological urobilin*, itself not accountable for the high colour of the urine, but presenting such definite characters that I regard it as of special significance: its presence denoting a hæmolysis of a special kind, and when found in severe anæmia being almost diagnostic of pernicious anæmia.

2. The observations shewed, secondly, occasional *presence of blood pigment* in the form of granules enclosed within cells of renal origin. For a time these pigment cells were absent, and their absence corresponded with the period of improvement in the health of the patient. They reappeared, however, in increased numbers on each occasion of an exacerbation of his weakness.

The renal cells and pigment granules found in the urine during life were identical with those found in the tubules of the kidneys after death; and their origin from the latter cannot, therefore, be doubted. The significance to be attached to their presence has been fully discussed.

3. They shewed, lastly, a greatly *increased excretion of iron.* In one case in health I found the daily excretion to be 5·65 milligrammes; and this represents about the average. In three cases of chlorosis, I found the excretion reduced to 1·76 milligramme. In the above case of pernicious anæmia, three weeks before death, when the anæmia was most intense, I found the enormous excretion of 32·26 milligrammes, and even a week before death it was 6·52 milligrammes.

So far as I am aware, no previous observations have been made on the excretion of iron, or the presence of renal cells containing blood pigment, in this disease. Taken together with the large increase in the urinary pigments, and especially with the presence of pathological urobilin in the urine, they point clearly to a preceding excessive destruction of blood; the amount of destruction, as evidenced by the varying colour of the urine, and excretion of pigment, varying from time to time.

These clinical observations in the present case bear out fully the conclusions arrived at in previous investigations as to the essentially hæmolytic nature of this disease. The changes found after death in liver, spleen, and kidneys point equally to the same conclusion. The situation and character of the pigment within the *Liver* were such as I have formerly described. The pigment was more abundant in the present case than in any I have yet met with. The enlargement of the *Spleen* recognized during life, and confirmed *post-mortem*, is of some interest in connection with the important part played, as my observations shew, by that organ as one of the chief seats of blood destruction both in health and disease. The congested purplish appearance presented by the pulp was the same as that found by me in another case I have described. It was also due apparently to the same cause—not to the presence of red corpuscles, few of which were to be found, but to the presence of free hæmoglobin. The presence, also, of well-formed crystals, presumably of hæmoglobin, is also of special interest in connection with the

interesting observations of Dr. Copeman as to the readiness with which crystals of hæmoglobin are obtained from the blood in this disease.

[POSTSCRIPT.]

In the foregoing observations, it will be noted, that the point which specially arrested my attention was not the *high colour* of the urine—a point drawn attention to by previous observers (Eichhorst, Pye-Smith, Bristowe); nor yet the presence of *urobilin*—whose presence and possible hæmolytic significance had been noted and commented upon by Eichhorst—but what appeared to me to be the *special character of the urobilin.*

It was not in itself the cause of the high colour, that being due to other pigments; it was present in very varying quantity, sometimes recognizable after dilution of the urine as much as six or seven times. "Its appearance in the urine in pernicious anæmia pointed—far more than any excess of ordinary pigments—to a preceding extensive hæmolysis of a special nature," rather than to any mere exaggeration of the physiological progress.

The subsequent observations of Dr. Mott and Dr. Halliburton, above referred to, appeared to shew, as against such conclusions, that the urobilin present was normal urobilin; and that its presence in excess merely denoted therefore an excessive hæmolysis proceeding along the ordinary lines of health.

These hæmolytic changes in the urine have since been made the subject of study by Dr. Gowland Hopkins (1895). His results confirm those arrived at by me, with reference to the excretion of aromatic sulphates, and the increased excretion of iron.

His observations regarding the pigments present are of special interest, inasmuch as the subject of urobilin—its character and relationships to other pigments—is one of which, in association with Dr. A. E. Garrod, he has made a special study.

The following are his results in his own words. (The italics are mine.)

Dr. Hopkins' Observations.—He concludes from his observations, that the urobilin of pernicious anæmia is normal urobilin. As to the existence of pathological urobilin, he considers it would be extremely easy to confound a mixture of ordinary urobilin and hæmatoporphyrin with the published description of it.

This latter pigment is one (as shewn by Dr. A. E. Garrod (*Journ. of Phys.*, 1892), and confirmed by Dr. Hopkins) that appears in small quantity in very many normal urines.

In general, according to Dr. Hopkins, the quantity of it in the urines of pernicious anæmia was not in excess of what may be found in normal urines. Its bands could never be seen in the original sample without treatment.

As to the quantity of urobilin present, he finds that even if the urobilin in pernicious anæmia be of the normal variety only, it yet remains *a characteristic feature of the disease that the absorption band at F should be present in the perfectly fresh urine.*

On the other hand, a definite, easily observed band is certainly absent from normal urines when fresh; though one may appear after the urine has stood in the air, or sometimes after acidification with a free acid. In febrile conditions the band is very usually to be observed; but it is most exceptional for it to appear when the pyrexia is so slight as that found in pernicious anæmia; it may, indeed, be well marked in this disease, when the temperature is almost normal.

Such observations as he had been able to collect seem to shew that it is, on the whole, an *uncommon phenomenon in other diseases.* If this be so, the *observation of the band* (which can always be seen with a pocket spectroscope) *would be more valuable as a point in diagnosis than is the mere darkness of the urine*, for the band may be often seen in specimens which would be described as pale.

As to its appearance in the fresh urine—it might be due to increased excretion of urobilin (or urobilinogen), or due to independent variations in the character of the urine, which so conditions the urobilin as to render the band visible. The latter factor, he thinks, is at least contributory.

So far as his estimations shewed, the *actual excess of urobilin did not seem to be sufficient at any time to account for the difference between a normal urine shewing no band at all, and one with a very dark band.* Indeed, one may find, at times, a normal urine which yields quite as much urobilin, and yet shews no band either before or after acidification.

With the evidence to hand, he doubted if the morbid processes of pernicious anæmia are accompanied by any very

startling increase in the excretion of urobilin. This latter is certainly not responsible for the hyper-pigmentation of the urine; for other pigments are also increased in quantity, and take a large share in this.

The characteristic appearance of the band is at least in part *a matter of condition* and not of quantity; but it is, none the less, a prominent and important phenomenon of the disease.

Pathological urobilin he considered to be an admixture of a larger proportion of urobilin with a smaller one of hæmatoporphyrin.

It will thus be seen, that Dr. Hopkins is of opinion that the urobilin of pernicious anæmia is normal urobilin; and that the abnormal spectroscopic appearances which I regarded as denoting a special variety of urobilin—"pathological" urobilin—are in all probability due to a mixture of urobilin and hæmatoporphyrin.

Despite this conclusion, opposed as it seems to be to the one I arrived at, Dr. Hopkins' observations appear to me to draw attention afresh to the very points which arrested my attention, and which induced me to emphasize their importance as denoting the special character of the urobilin present.

For what do they shew? He notes:

"As a characteristic feature of the disease, that the absorption band at F is present in the perfectly fresh urine;"

"That the actual excess of urobilin did not seem sufficient at any time to account for the difference between a normal urine shewing no band at all and a pernicious anæmia urine with a very dark band" (*a fortiori*, still less for the band after 5–7 times dilution);

"Indeed, at times one may find a normal urine which yields just as much urobilin, and yet shews no band either before or after acidification;" and, lastly,

"The observation of the band would be more valuable as a point in diagnosis than is the mere darkening of the urine."

In all these respects, then, the urobilin offers a marked contrast to the normal urobilin. It was precisely these points that "satisfied me that it differs in important respects, both chemically and spectroscopically, from any pigment present in the

urine in health, or obtainable by the method employed from the high-coloured urine of fever."

As regards the possibility that the spectroscopic appearances might be due to a mixture of normal urobilin and hæmatoporphyrin, Dr. Hopkins' observations appear to me also conclusive. For they shew:

(1) That the hæmatoporphyrin "is not in excess of what may be found in normal urines, and its bands could never be seen in the original sample without treatment";

(2) That the actual *amount* of urobilin was apparently little in excess of the normal amount.

Under these circumstances, how a combination of the two pigments, neither of them in excess, can be accountable for a spectroscopic band, far in excess of anything ever met with in health, one recognizable in the fresh urine of pernicious anæmia—sometimes even after 5–7 times dilution—is not very clear.

Dr. Hopkins' observations amply justify his conclusion, that the characteristic appearance of the band is "at least in part a matter of condition and not of quantity."

This special "condition" of the pigment (urobilin) present in such cases was the feature that appeared to me to be the notable one. So much so, that I concluded "its presence in severe anæmia" (in absence of fever, and in a urine of low specific gravity and undiminished quantity) might be regarded "as absolutely diagnostic of the pernicious anæmia."

My later observations give me no grounds for modifying the above conclusion. If sought for, this character of the urine is to be recognized in every case of pernicious anæmia; but, as I duly warned, not constantly at all times.

I have often had occasion to examine a urine *which appeared normal in colour* to the naked eye, and nevertheless found the urobilin band quite distinct—far more so, than in the high-coloured urine of fever (Case 10).

The variations from time to time, and the relations of these to the general condition of the patient, are notable features: I have recently made a series of observations in this relation in one of the cases now recorded (Case 10). Employing for my purpose the simpler and better methods for the separation of urobilin with which the work of Dr. Hopkins and Dr. Garrod have

made us acquainted, I have estimated (and indicated by figures, quite roughly) the varying amounts of urobilin present at different times and separable by means of chloroform, from 100 c.c. of urine (after saturation first with ammonium chloride and afterwards with ammonium sulphate).

From the time of admission the quantity of urobilin steadily diminished, until one period (25th May) when it suddenly, and apparently unaccountably, went up.

Two days later the patient suffered from sickness and vomiting: in other words, he passed through an exacerbation of his disease.

In short, the sequence of events I have described in the foregoing case, I have constantly had occasion to observe and demonstrate in other cases.

Moreover, I have constantly had occasion to demonstrate in connection with a urine *apparently normal in colour* two facts, viz.

(1) The colour would be *normal* for a person in health possessing 100 per cent. of hæmoglobin and corpuscles, but is really *abnormal* for a patient reduced to the last stage of exhaustion, with possibly only 20 per cent. of corpuscles and hæmoglobin.

(2) Even in such apparently normal urines, the spectroscopic band of urobilin can often be recognized; whereas in ordinary febrile urine of *much higher colour*, it cannot be detected.

Whether the variety of urobilin here described is identical with that termed "pathological urobilin," by Dr. MacMunn, is open to question.

But the facts themselves remain, namely, that there is something "pathological" about the urobilin present in such cases. That is the point emphasized in my original observations; confirmed, as it appears to me, by Dr. Hopkins' later observations; and further confirmed by my own later experience regarding the condition referred to.

CHAPTER XXIX.

III. GASTRO-INTESTINAL SYMPTOMS.

THE foregoing observations regarding the portal area as the chief seat of the hæmolysis in this disease attach a new interest and significance to the group of symptoms denoting gastro-intestinal disturbance.

Historical.—Addison made no mention of any such symptoms.

The occurrence of gastro-intestinal symptoms was noted by Biermer. He attached a double significance to them. If slight, they were effects of the anæmia. If severe, they were causes. "The most common cause was chronic diarrhœa with or without gastric disturbance."

Following this teaching, almost all observers have attached a similar double importance to them. When severe, they have been held to be themselves the cause of the disease; when insufficient to be accounted causes, they have been regarded as effects (Eichhorst). This point I have already had occasion to bring out (p. 225).

In Eichhorst's experience, "*Vomiting* was not often observed." In his own cases, it was never of any special intensity; nor did it last any length of time; it appeared to be caused by the iron administered. The vomit was watery, smelt sour, and had a greenish black colour. He noted, that in the experience of others it was not uncommon, Muller having seen it in two-thirds of his cases (not all of them, according to Eichhorst, of equal value). Eichhorst himself considered that it had a double significance: as a *cause*, and as a *complication*. Several cases shewed, in his judgment, that a persistent vomiting either in connection with pregnancy, or arising independently,

had finally led to pernicious anæmia. On the other hand, vomiting was often met with as a consequence of pernicious anæmia that had arisen from other causes; occurring sometimes early in the course of the disease, sometimes towards the end of life. When very persistent and severe, it might lead to the suspicion that cancer of the stomach existed. As regards the microscopical characters of the vomit, he had not himself made any observations; but Muller had examined it several times, without discovering any abnormal constituents. *Diarrhœa.*—Changes in the frequency and character of the stools were met with in a majority of recorded cases. Constipation was exceptional, while diarrhœa was the rule. Like the vomiting, this also had a double significance. Sometimes it caused the disease, sometimes it was merely a result. For the rest, it had no special relation to the vomiting. Vomiting could occur without diarrhœa, or diarrhœa could occur without vomiting. In duration, and frequency, the diarrhœa could vary within very wide limits; and it was met with at very different periods of the disease, sometimes early, sometimes late. Sometimes it occurred periodically without the slightest discoverable cause. One peculiarity it had, namely, it was remarkably resistant to all therapeutic measures. In his own cases, intestinal disturbances were remarkably little observed. In his first five cases, the regularity of the bowels was specially noted. The stool was firm, well formed, and presented a deeply bile stained ('almost remarkably so') colour. Blood was observed only exceptionally, as in one case described by Sir Samuel Wilks.

According to Dr. Pye-Smith, "In not a few cases, vomiting and diarrhœa are marked symptoms, and this when no gastro-intestinal symptoms have preceded the appearance of anæmia. Anorexia and some degree of nausea are almost constantly present." Considering how often the disease came on with no assignable cause, one might well doubt, whether preceding dyspepsia (or slight hæmorrhage, or pregnancy) should be regarded as more than a coincidence. At most, dyspepsia and diarrhœa might be regarded as predisposing causes, if we admitted that the 'secondary' form of the disease described by authors was the same disease as the 'primary.'

As regards the primary form, he made no special mention

of such symptoms. His view of the relation of such symptoms to the anæmia was presumably embodied in his statement, that the disease was "without any symptoms (and without any lesions) which could not be explained as directly due to the anæmia."

Significance.—The special significance I have been led—as *the result of my studies*—to attach to these gastro-intestinal symptoms differs essentially from that enunciated in the above views. They do not, in my opinion, suggest the 'gastro-intestinal origin,' nor yet the 'gastro-intestinal cause,' nor yet the 'gastro-intestinal nature' of the disease. Their significance is, that they denote the *gastro-intestinal site of the infection causing the disease.* They derive their importance not from their severity, or their character. It is the fact of their occurrence at all in connection with this area that is the most significant feature; and this solely in relation to my foregoing studies regarding the portal area as the seat of the hæmolysis.

They stand to the disease in precisely the same relation as the intestinal symptoms stand to typhoid fever. They may be severe; they may be moderate; they may even be so much in abeyance as hardly to arrest attention at all, as the intestinal symptoms in typhoid fever may be. Yet all these variations are, in its case, as in the case of typhoid fever, compatible with the presence of lesions in this tract—very obvious and definite in the case of typhoid fever; obscure, and requiring to be sought for, but nevertheless there, in the case of pernicious anæmia.

I have already described the varying character of the gastric and intestinal symptoms; also the similarly varying character of the oral symptoms, accompanied, in their case, by recognizable lesions which can be seen to come and go.

It has also been brought out, how constantly gastro-intestinal symptoms occur, irrespective of their severity; disturbances of some kind or other being actually recorded in over 86 per cent. of cases—a frequency which may be regarded as denoting that they are rarely, if ever, absent. Their severity indeed varies much, both in different cases and in the same case at different times. This variability is of importance. A case may appear to be without symptoms of this kind at one time; yet at another later period, when the case is possibly not under observation, gastric or intestinal symptoms may be

present. The important point about them in my judgment is, that they are not of sufficient severity or persistence to be *themselves* the cause of so grave and remarkable a form of anæmia; any more than the pain and discomfort of the throat or the slight fever can be adjudged to be the cause of the profound effects of diphtheria; or the gastric and intestinal symptoms in typhoid fever be held accountable for the remarkable effects and course of that disease. They are mere symptoms. If very severe, *e.g.*, vomiting, or diarrhœa, they, of course, as in typhoid fever, add gravely to the exhaustion occasioned by the disease. Still, even then they are *not the cause* of the disease, 'pernicious anæmia.'

Oral Symptoms.—These I have already discussed in detail. I attach great significance to them. The most marked feature is oral sepsis. The chief symptom is recurrent tenderness of the tongue. They are usually but little marked except when tenderness of the tongue is present. The only one requiring special note is *salivation*, which seems to be a rare symptom. It was intense in one of my cases, and a similar case is described by Müller.

Gastric Symptoms.—The most common are *anorexia*, sometimes amounting to a loathing for food, and a *sense of fulness* and *gastric discomfort*, such as one would naturally ascribe to feebleness of digestion in an anæmic individual. Taken by themselves, they might be, as indeed they generally have been so regarded.

But very often, at periodic intervals, they assume a different character—*pain*, *distress*, *nausea*, *retching* and *vomiting*, having no constant relation to food; often in the morning on awaking. When obtained free from food, as it often is, the vomit usually consists of thick viscid mucus, whitish in colour. When severe, it is often bile stained, or actual bile may be brought up.

In some cases, instead of anorexia, the opposite is found—namely, not only good, but even *inordinate appetite*. The latter is not common. It was a marked feature in no fewer than three out of eleven cases described by Laache. It was a very marked feature in one case observed by me. Up to the very last, even when moribund, with only some 10 per cent. of hæmoglobin and

15 per cent. of corpuscles, the patient insisted on having jugged hare for his supper.

Intestinal Symptoms are, on the whole, less common and severe than the gastric, and they are of less varying character. The most common is a slight *looseness of bowels*, sometimes, *diarrhœa*. These are only noticed occasionally. The *general* condition is one akin to the anorexia in the case of the stomach —namely, a want of tone of the bowels, necessitating the regular use of a slight aperient.

One symptom I have observed in two cases—in both cases greatly complained of as the chief distress of the whole illness—namely, a great burning heat at lower end of rectum, either with or immediately after stool, with most intense subsequent weakness. This burning sensation one meets with as a result of arsenic; but in neither case referred to was arsenic being given. This weakness is not simply the result of the exhaustion entailed in going to stool. On investigation it is found really to precede, and merely to culminate in the effort. It is really antecedent to it; great relief always follows the movement of the bowels, and the patient then feels better than at any other period of the day. I take it to be of the same nature, and due to a like cause, as the nausea and retching in the case of the stomach. These also are apt to occur chiefly in the morning. It denotes, in my judgment, the existence of a lesion low down in the rectum; in these cases it is the effect of the gradual accumulation (and absorption) of toxic products during the preceding twenty-four hours—especially marked in the lower part of the bowels where the intestinal contents accumulate.

Conclusions.

This conception of the significance of the gastro-intestinal symptoms in pernicious anæmia differs, as I have said, from that which would regard these symptoms as either the *cause* or the *effect* of the disease, according to their severity.

It also differs, I would now point out, from the much vaguer and looser sense in which the term 'gastro-intestinal' has come, mainly as the outcome of a misconception as to the import of the preceding studies, to be employed by many in connection with this disease—namely, as involving some 'theory' regarding

the 'gastro-intestinal origin,' 'gastro-intestinal cause,' or 'gastro-intestinal nature' of the disease.

Of this 'theory,' or 'hypothesis,' I find myself in certain writings, credited with being the chief exponent, and with having carried out various observations and experiments, which I regard as supporting it.

If I have been at pains, in the historical summary of the views of the earlier and chief observers on this subject, to bring out as clearly as possible how they regarded this group of symptoms, this has been done purposely—not with a view to accentuate the differences between their views, and any led up to by these studies, but rather to support the correctness of the conclusions they drew from the *data* at their disposal.

Their conclusions were, I consider, the only ones they could legitimately come to, in the light of the clinical and pathological facts they observed. Moreover, even now, in the light of the same clinical facts, they are the only conclusions that any careful clinical observer could reasonably come to. To say or teach, as one observer has recently done, that it is 'natural' to think of gastro-intestinal intoxication as the cause of pernicious anæmia, is nothing more or less than 'an intelligent anticipation of events after they have occurred.' It is no more natural now, *having regard to the clinical facts alone*, than it was at the time when Addison and Wilks, Bristowe and Pye-Smith, Biermer, Quincke, Immermann and Eichhorst, Bramwell, Mackenzie, Coupland—observers second to none in either clinical or pathological acumen—could either pass such symptoms by without notice, or regard them sometimes as causes, sometimes as complications.

My conclusions regarding these gastro-intestinal symptoms were based originally not upon clinical facts, but upon *pathological and experimental data* acquired in the course of my work.

My pathological studies were not begun in relation to any particular hypothesis—least of all one connected with a gastro-intestinal origin of the disease. On the contrary, they were carried out without the slightest suspicion that they were eventually to lead back to the gastro-intestinal tract, and to suggest that tract as the seat of some abnormal processes in the disease.

It was the result of the experimental portions of my studies pointing to the portal area as the chief seat of hæmolysis, that

for the first time suggested the gastro-intestinal tract as the possible seat of trouble in this disease, and *for the first time* attached a new significance to

(1) the frequency of morbid conditions in connexion with the tract;

(2) the frequency of gastro-intestinal symptoms.

Up to that time, as I have shewn, the general teaching was: *as regards morbid conditions* that any morbid condition, if only severe enough—and altogether irrespective of site—could give rise to the features of pernicious anæmia; and that *as regards gastro-intestinal disturbances* these could be considered either as the effects or as the cause of the disease, or as both combined.

It is desirable to draw attention to these details, and their true relation to one another, if only in justice to the experiments on which they were chiefly based; for misapprehension on these points forms the basis of the chief criticisms to which my conclusions as to the importance and significance of the gastro-intestinal symptoms have been subjected.

Based in the first instance, not on clinical evidence, but on *experimental* evidence, these conclusions as to the importance and significance of the gastro-intestinal symptoms cannot rightly be divorced from the facts from which they were originally derived. *Without those facts*, I should not consider myself justified in attaching to such symptoms any significance other than was attached by previous observers. The detailed studies in every case since observed have only served to confirm the conclusions arrived at; as have, indeed, all the subsequent analyses of recorded cases regarding the frequency of gastro-intestinal symptoms.

To judge from the references which I find in the literature of the subject subsequent to 1890, no portion of my conclusions has excited more attention than the one above dealt with relating to the significance of gastro-intestinal symptoms—this conclusion, as already stated, being based upon the fact that the portal area is the chief seat of the hæmolysis.

I have at the outset described in detail the views regarding the disease held by the chief observers in this country.

Most of these have since contributed valuable studies of the disease: notably Dr. Bristowe,[1] Dr. Stephen Mackenzie,[2] Dr. Coupland,[3] Professor

[1] *Principles and Practice of Medicine*, 7th ed., 1890; Preface, i. p. 611.

[2] "Lettsomian Lectures on Anæmia," *Trans. Med. Soc.*, Lond., xlv. p. 191, 1891.

[3] *Allbutt's System of Medicine*, vol. v. pp. 531, 532, 534, 1898.

Osler,[1] and Dr. Byrom Bramwell[2]; and to these studies reference may be made by those interested in tracing the gradual evolution of knowledge regarding the disease.

In addition valuable contributions have also been made by other observers:—

Dr. F. W. Mott,[3] Dr. W. Russell,[4] Dr. Crozier Griffith,[5] Dr. Hale White,[6] Dr. George A. Gibson,[7] Dr. Gowland Hopkins,[8] Professor T. R. Fraser,[9] Professor Stockman,[10] Dr. James Taylor,[11] Dr. Robert Muir,[12] Dr J. Craig,[13] Dr. Risien Russell,[14] Dr. Frederick Taylor,[15] Dr. F. P. Henry.[16]

Most of these observers deal with individual points in connection with the disease, and to many of them I have already had occasion to refer. Most of them accept the general teaching of my studies regarding the hæmolytic nature of the disease, the portal site of the hæmolysis, and the new significance thereby attaching to gastro-intestinal symptoms and lesions.

The only one who puts forward an alternative view regarding the disease as a whole is Professor Stockman, 1895.

He traverses the whole of my conclusions regarding the hæmolytic nature of the disease—accepting the general facts, but putting a new and entirely different interpretation upon them. In so doing, he is not content merely to take exception to my conclusions; but supports his contentions by a detailed study of the whole features of the disease; and by a most valuable series of chemical analyses of various organs, to which I have already referred.

Professor Stockman, as already seen, considers that the whole features of the disease, including those I consider as denoting its hæmolytic character, can be explained as due to the repeated occurrence and absorption of small hæmorrhages; although he admits he cannot explain why such hæmorrhages should occur in the first instance. He says:

"The evidence seems convincing that pernicious anæmia follows usually on well-recognised debilitating causes. The cause is sometimes, however, obscure, and is not detected, but we are rapidly reducing this unknown territory, and if it be remembered that only a few years ago all cases of tape-worm anæmia were regarded as 'idiopathic,' we may

[1] *The Principles and Practice of Medicine*, p. 691, 1892.

[2] *Anæmia and Diseases of the Blood-forming Organs, and Ductless Glands*, p. 82, 1899.

[3] *Lancet*, 1889, i. p. 520; *Practitioner*, 1890. [4] *Brit. Med. Jour.*, 1889.

[5] *Keating's Cyclopædia of Medicine*, iii., 1890. [6] *Guy's Hospital Reports*, 1890.

[7] *Edin. Med. Jour.*, 1892; *International Clinics*, iii., 1893.

[8] *Guy's Hospital Reports*, 1893. [9] *Brit. Med. Jour.*, i., 1894.

[10] *Brit. Med. Jour.*, 1895. [11] *Trans. Med. Chirurg. Soc.*, lxxviii., 1895.

[12] "On Changes in Bone Marrow," *Jour. Path. and Bact.*, ii., 1894.

[13] *Dublin Jour. Med. Sci.*, 1897. [14] *Lancet*, ii., 1898.

[15] *Brit. Med. Jour.*, 1896. [16] *The Medical News*, Philadelphia, Oct. 1889.

hope in the near future to elucidate the hitherto unrecognised causes. Further, I do not think that a hypothetical destruction of red blood-corpuscles by the liver cells or by a ptomaine or ferment can be considered the cause of the condition. I hold rather that anæmia from any cause induces in some persons degenerative changes in the whole vascular system; that these permit the occurrence of numerous minute internal bleedings, more rarely of external ones also, and that a persistent continuance of these leads ultimately to excessive anæmia and death."

"These bleedings being so small disappear very rapidly and completely, this being assisted by the well-known tendency of the blood to resist coagulation in extreme anæmia (Eichhorst). They usually produce no special symptoms (unless they occur in the central nervous system or organs of special sense, and even in those very rarely), but if they do cause paresis or other symptom, this passes off in a very few days, and no trace of bleeding may be found *post-mortem* owing to rapid absorption of the small extravasations. 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 the number must diminish just before death, I believe in such cases they had previously been much more numerous."

"These bleedings are, to judge from the exacerbations and partial remissions of symptoms, more numerous at one time than at another, and according to the amount of blood loss the case progresses rapidly or slowly."

"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 poison breaks down the blood in some cases; and if this be so, debilitating conditions with haemorrhages need not necessarily precede the 'pernicious anæmia.' It is possible, too, that degenerative changes in the small vessels may occur spontaneously in certain people; in these, also, there might be no preceding causes or illnesses of a marked kind, and few *post-mortem* lesions would be observable except in the light of our very recently acquired knowledge. But conclusive evidence is wanting on all these points. As I have previously pointed out, the capillary haemorrhages 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."

I have already explained why I cannot, either on anatomical or experimental grounds, accept Dr. Stockman's conclusions. But I desire here to pay my tribute to the detailed nature of the study on which he bases them. With regard to the general question so fully raised by him as to the significance of these haemorrhages, I can merely repeat what I have already said, and what Dr. Stockman himself admits, that many cases show no trace of any such hæmorrhages. And with regard to their possible significance in those cases in which they occur, even if Dr. Stockman's view was accepted, the whole problem of the disease would in my judgment still remain—namely to explain why hæmorrhages should occur in the first instance, and why, despite all treatment, and despite the remarkable temporary recovery, they should continually recur, so as to confer on the disease its characteristic features of progressiveness and perniciousness.

CHAPTER XXX.

IV. TOXÆMIC SYMPTOMS.

THE class of symptoms I here designate 'toxæmic' are those which, in my judgment, cannot be ascribed to the anæmia *per se* —*i.e.* to the actual poverty in corpuscles or in hæmoglobin; but denote rather the influence of agencies of a *toxic character.* They have one character in common—*periodicity*.[1]

They really include many of the commonest and most characteristic features of the disease. That is to say, the intense feeling of illness and weakness which the patient experiences is not constant, but varies remarkably from time to time, sometimes even from day to day, independently of any recognizable changes in the blood sufficient to account for it.

The characters of the urine also change periodically without any assignable cause.

The gastro-intestinal symptoms also display a no less marked periodicity; but the group of symptoms which I desire to draw attention to, by the special title 'toxæmic,' are those connected with the temperature and the nervous system—namely, *fever* and *nervous disturbances.* The symptoms connected with increased hæmolysis and gastro-intestinal irritation are evidences

[1] With reference to my first account of this group of symptoms (Case 1, p. 310), Dr. Hale White (*Guy's Hospital Reports*, 1890) writes:—

"From the cases I have watched, and as a result of carefully reading the reports of 31 cases, I am inclined to think that fits of coincident increase of weakness are quite the exception in genuine pernicious anæmia; and that toxic symptoms are very rare."

This conclusion is not surprising. For, previous to the publication of my studies, such attacks had not before been drawn attention to, and hence it is quite possible that they are not mentioned in the *records*. The attacks will, however, be found in the *cases* themselves. My own experience has been that they constitute one of the most striking and instructive features of the disease; and I have had occasion time after time to demonstrate them at the bedside. Moreover, it is only in 'genuine' cases that they are to be observed.

of more *local* disturbances—namely, of the gastro-intestinal mucosa and the portal blood respectively. The fever and the nervous symptoms are evidences of more general and widespread disturbances.

Fever.—Fever is, in my experience, an interesting feature of the disease, not so much from its character or its severity as from its existence at all. It is quite irregular in type, and very variable in degree. It may be, and often is, absent for considerable periods of time; but even in such cases it will be found that a slight rise of temperature at night—to between 99 and 100° F.—is the rule. Variations of a much more marked character occur from time to time, apparently without any cause. It will be noted in the records of CASES appended how often such attacks are referred to 'influenza.' During these attacks all the other symptoms undergo exacerbation—namely, sense of illness and increase of weakness, increase of hæmolytic changes in the urine, occurrence of sickness or looseness of bowels—sometimes one, sometimes another predominating. (See Charts, CASES 10 and 11.)

These latter symptoms are not necessarily proportionate to the degree of fever. In other words, sometimes the *local*, at other times the *general*, disturbances predominate. Hence an interesting feature I have often had occasion to observe—most marked perhaps in CASE 2—that patients who have had a particularly sharp attack of fever with general disturbance have often had a no less marked and sudden respite in the progress of their disease, whereas those who shew more or less continuously a slight rise of temperature often display the most continuous deterioration of the blood (CASE 1).

As regards the nature of the fever, it has been regarded as 'anæmic' (Immermann), due to want of hæmoglobin; as 'humoral' (Biermer).

My own view of it is, that it is essentially *septic*, and that all its peculiarities find in this fact their fullest explanation, both as regards its possibly slight degree when the disease is progressing, and its sometimes high degree followed by amelioration. That is to say, fever denotes the *degree of reaction* of the body, not necessarily the actual amount of septic absorption. It is the equivalent to inflammatory reaction locally.

Local reaction, in my judgment, denotes relatively healthy conditions; inasmuch as it shews that the tissues still have the power to react against the irritant. The case is different when sepsis is extreme.

There is a stage in septic conditions, as in other forms of infection, when the absence of local reaction is not only compatible with profound septic effects, but even, more than any other circumstance, denotes the severity of these effects. I have known a patient to be utterly prostrate—with subnormal temperature and feeble pulse—as the result of blood-poisoning; his hands and arms covered with a number of sluggish, dirty boils, none of them giving the slightest pain, or accompanied by any local inflammation; and I have seen in the same patient, a month later, when he was on the road to recovery, the most violent local inflammation, abscess formation, lymphangitis, and fever arising in connexion with one of the sores on his hand.

In that case the septic effects were greatest when the local effects were least. If the latter had been as marked at the outset as they were at the termination, it would have denoted that the patient was a healthier subject; and the general toxic effects would not have been so marked as they were.

In pernicious anæmia two factors co-operate in giving to the fever its peculiar irregular character—namely, (1) local inflammatory changes in connexion with the infective lesions in the mouth, stomach or intestine; (2) 'septic' absorption from these lesions.

The gastro-intestinal irritation is due to the former, the general toxic effects to the latter; sometimes the one, sometimes the other predominating, according to the general resistance of the tissues. Under such circumstances, as has just been seen, the effect on the temperature is variable enough, even when the blood is normal. But in pernicious anæmia these variable factors operate on a blood profoundly deteriorated in character, so that the wonder is that one ever gets a sharp febrile reaction at all.

Nervous Disturbances.—The other group of symptoms which I regard as in a special degree toxæmic are those connected with the nervous system. They include not merely slighter

effects, such as I have already dwelt on—*e.g.* intense feeling of illness, weakness, perspirations, headaches, drowsiness, etc.—but also more serious effects denoting actual lesion of the nervous system, sensory, motor, and trophic disturbances. That they should occur at all constitutes the significant feature; the degree of their intensity is a point of secondary importance.

It will be seen that in no fewer than three out of my twelve cases such disturbances were a marked feature.

Case 2.—One of the first symptoms complained of was a sensation of numbness and tingling in the hands and feet, with loss of knee jerk, marked wasting of certain muscles (deltoids and extensors of thigh).

Case 4.—Nervous symptoms, ataxia, numbness, paræsthesiæ, and loss of knee jerk.

Case 11.—Numbness and tingling in forearms and fingers, of which the patient made constant and grievous complaint; these symptoms being as marked when the blood shewed 80 per cent. of hæmoglobin as when it shewed only 35 per cent.

As to the nature of the changes associated with these disturbances, reference may be made to the very complete account of this subject given by Dr. James Taylor (1895).[1]

They include—

> Almost complete degeneration of the columns of Goll, with similar but slighter affection of the pyramidal tracts; also small foci of degeneration in other parts of the lateral columns and in the anterior columns. (Lichtheim, 1887.)
>
> Small sclerotic foci, which on microscopical examination were found to be the results of hæmorrhages; distinct degeneration in the posterior columns, differing in intensity in the different cords, and not restricted to the posterior columns, although most evident in these. (Lichtheim, 1889.)
>
> In six cases—all except one shewed ataxy, and complained of subjective sensations, while most had actual sensory impairment in the limbs and bladder weakness. The cords in all shewed similar degeneration, chiefly marked in the posterior columns, and in one case confined to them; also degeneration in the lateral columns; in two, also in the anterior columns; while in all, the posterior roots, the grey matter and the peripheral nerves were described as free from changes. (Minnich, 1892.)

[1] "On Nervous Symptoms and Morbid Changes in the Spinal Cord in certain cases of Profound Anæmia," *Trans. Royal Med. Chirurg. Soc.*, London, 1895.

In a case in which the prominent symptoms were anæmia, paræsthesiæ in the hands and feet, impaired sensibility in the legs, motor weakness in the arms and legs, with spontaneous jerkings in the former, and finally complete inability to walk, with absence of knee jerk, there was found complete degeneration of the posterior columns, except of a part next the posterior roots, and also in the lateral columns of the cord. (Van Noorden, 1891.)

A case of pernicious anæmia with motor weakness and paræsthesiæ, with, later, loss of the control over the sphincters, and loss of knee jerks shewed degeneration in the posterior columns of the cord, and scattered foci in the lateral columns. (Eisenlohr, 1892.)

Two cases of anæmia, with nervous symptoms, numbness and weakness of the lower extremities, girdle sensation, loss of control over the sphincters, varying knee jerk, numbness in hands and feet present *for some months before the anæmia was obvious*, shewed changes in the posterior columns especially, but also in the lateral and anterior columns. (Nonne, 1893.)

A case of anæmia, with great weakness, ataxy in the arms, legs rigid and semiflexed, with painful spasmodic jerkings, and impairment of sensibility in the lower limbs shewed marked changes in the cord, degeneration in the posterior columns, with extensive changes also in the lateral and anterior; posterior roots and grey matter normal. (Bowman, 1894.)

Two cases: Case 1.—Numbness in the legs and difficulty in walking, with, later on, extreme anæmia. Changes found—extensive sclerosis in the anterior, lateral and posterior tracts of the cord.

Case 2.—Sclerosis in the lateral columns, well-marked degeneration on each side of the median fissure, in the anterior columns. Nowhere any changes in the grey matter. (Taylor, 1895.)

From a consideration of all these cases Dr. Taylor concludes that we have in them no mere accidental association of anæmia and spinal cord changes. The anæmia was a prominent feature in all, and the spinal cord changes were so similar and constant that they must be regarded as in some way dependent on a similar cause. In most of the cases, he notes, the anæmia seems to have preceded the spinal symptoms, except in one (Nonne's), where the spinal symptoms are expressly stated to have preceded the anæmia.

Hence he considers it most natural to regard the anæmia and the spinal cord changes with their symptoms as both resulting from a common cause.

"Such a cause we should most naturally look for in some toxic blood condition, having regard especially to the bilateral sym-

metry of the changes, and to the constancy with which certain tracts are affected and others spared. But while I believe that this is the chief cause of such changes, I think there may be, in addition to this degeneration, other minor changes, probably the result of that tendency to the occurrence of hæmorrhages which is so marked a feature of pernicious anæmia."

The subject of these spinal cord lesions in pernicious anæmia has also been fully dealt with by Dr. Risien Russell.[1]

The whole subject of the influence of toxic agencies in producing degenerations in the neurone has since received most admirable elucidation at the hands of Dr. Mott,[2] in his Croonian Lectures for 1900.

My own observations entirely agree with the conclusion expressed by Dr. Taylor as to the toxic nature of these nerve lesions.

Oral Sepsis as a Cause of Toxic Neuritis.

My foregoing studies regarding the prevalence of oral sepsis in this disease appear to me to supply the clue as to the source of the toxic products responsible for these lesions.

The case that first directed my attention particularly to the nervous complications of pernicious anæmia was Case 2 (1894). Up to that time I had felt inclined to regard nervous symptoms, such as numbness and tingling, as possibly the results of too free use of arsenic. The history of the case referred to was remarkable (*q.v.*); for the effects were not limited to paræsthesiæ, but resulted in permanent paralysis of certain muscles.

Since then I have satisfied myself that they are really related, not to any such accidental cause, but to the actual disease itself. That is to say, they are part effects of the same cause that produces the anæmia.

One of my recent cases (Case 11) illustrates this very well. When he first presented himself, no diagnosis of pernicious anæmia had been made, consequently no arsenic had been given. One of his chief complaints then was, of numbness and tingling in hands and forearms.

[1] *Lancet*, ii., 1898.

[2] "The Croonian Lectures on the Degeneration of the Neurone," June 19, 21, 26, and 28, 1900.

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Under treatment with antistreptococcic serum, intestinal antiseptics, and antiseptic mouth washes, he made a rapid recovery in four weeks' time from 30 per cent. of red corpuscles and 35 per cent. of hæmoglobin to 64 per cent. of corpuscles and 73 per cent. of hæmoglobin. He then went to the country, and returned three weeks later, looking and feeling still better, with 64 per cent. of corpuscles and 80 per cent. of hæmoglobin. No arsenic up to this time had been given. His chief complaint was of numbness in the fingers of both hands, extending up to the elbows, so bad that he could hardly pick up any article from the table and could not button his clothes.

The problem which these nervous symptoms present to me is: are they the effects of the *special infection* underlying the pernicious anæmia; or are they the effects of the *antecedent oral sepsis*, which, in my experience, usually precedes the onset of the actual hæmolytic anæmia?

I am disposed to refer them to the latter, and for this reason—that in my experience *precisely similar nervous lesions are met with apart altogether from pernicious anæmia, in connexion with extreme conditions of oral sepsis*, and in my judgment as toxic effects of the sepsis thereby occasioned—an observation, so far as I know, now made for the first time.

I append the notes of three cases which have recently come under my notice.

In all cases the nervous effects were of the same character as those met with in pernicious anæmia.

In all cases the most intense condition of oral sepsis prevailed, lasting for many years—in Case 3 for fourteen years.

In all cases immediate improvement resulted from removal of this condition.

Case 1.—D. P., 33. Theatrical employé.

Ill 2½ months with wasting in both arms. Illness began with diarrhœa and pains in stomach, vomiting, lasting about three weeks. About a month after, noticed weakness in hands, with feeling of stiffness, and the weakness extended up both arms. It was accompanied by a sensation of 'pins and needles.' At this time he also suffered from acute pain in the stomach, was very depressed, and anæmic. He was treated for this in the out-patient department; and he passed some blood-stained and mucoid stools, after which he felt better.

He came to the Electrical Department under my care for treatment of his arms. He was a spare man, ill-nourished, with a peculiarly dirty-grey sallow look. He suffered from a marked weakness and atrophy of all the muscles of both arms, as far up as the deltoids, and especially of the deltoids.

Trapezius, scapular and rhomboid muscles not affected.

They all reacted, although with diminished force, to faradism, with the exception of the posterior part of the deltoids. This last gave no reaction with faradism, and shewed reaction of degeneration—viz. K.C.C. nil, sluggish reaction with A.C.C.

His mouth presented the most intense condition of oral sepsis, dirty black teeth, many of them loose, and extreme gingivitis.

This condition he had had for twelve years.

Three years ago was employed in mixing of paints. While thus employed he says he suffered from 'muscular rheumatism.' No recent history of lead-poisoning. He had rheumatic fever sixteen or seventeen years ago. His present illness began early last June, with violent vomiting and diarrhœa.

20th Sept. 1900.—*Treatment.*—Gums thoroughly swabbed with 1–20 carbolic acid, and a mouth-wash given of same (℥ 1 in half a tumbler of water); also syr. ferr. hypophosphit. ℥ 1; liq. arsenicalis ♏ 2, *ter die.*

25th Sept. 1900.—Gingivitis and stomatitis much less. Some teeth still loose, greater power in arms. Can now flex arms freely at elbows.

2nd Oct. 1900.—Improvement continues.

4th Oct. 1900.—Loose teeth removed.

9th Oct. 1900.—Mouth now clean, marked improvement in arms, muscles still wasted, but all movements now free except those of shoulders.

Case 2.—Mary G., 33.—Confined three months ago. Complaint since then weakness, numbness, and wasting of muscles of left thumb and third and fourth fingers. Pains up the arm to the left shoulder; great nervousness. Illness began with numbness in third and fourth fingers, followed by 'pins and needles' sensation.

23rd Sept. 1900.—Some tenderness of left median nerve. Marked wasting of muscles of thenar and hypothenar eminences.

She presents a dirty, sallow-looking colour of face.

Mouth.—Tooth-plate upper jaw, covering a number of teeth broken off; most intense gingivitis around roots. She has suffered greatly from teeth, and has suffered from indigestion for years.

Treatment.—Gums swabbed with 1–20 carbolic, and an antiseptic mouth-wash ordered to be used morning and night. Salicylate of soda, 15 grs. dose thrice daily.

Tooth-plate not to be worn.

2nd Oct. 1900.—Mouth condition much improved, again thoroughly swabbed. Power in left hand much better, no 'pins and needles.'

9th Oct. 1900.—Declares herself 'wonderfully better.' She has lost her former sallow look, and is now fresh complexioned. Mouth very clean, although necrosed roots still remain.

She can now grasp freely with left hand.

Case 3.—Aged 34. 3rd Oct. 1899.—Sought advice for wasting of muscles of left upper arm, and fore arm and hand, commencing with the triceps and biceps. Muscles of shoulder (deltoid and trapezius) little if at all affected. The muscles affected correspond to distribution of musculo-spiral and median nerves. Both these nerves sensitive to pressure, and especially sensitive to electrical stimulation.

Electrical Reactions.—Stimulation with faradic and galvanic currents causes much pain, especially over nerves, and over internal and external cutaneous nerves. Faradic reactions much diminished; galvanic reactions increased, but K.C.C. still greater than A.C.C.

History.—Illness came on a week before confinement, with 'pins and needles' sensation: a week after, great pain with weakness in left arm and shoulders.

Diagnosis.—Peripheral neuritis, especially of musculo-spiral nerve.

Treatment.—Faradic bath (feeble current), with a view to prevent further wasting of muscles.

24th Oct. 1899.—Condition improved. Faradism not so painful.

2nd Oct. 1900.—Returned after having discontinued visits. Some improvement.

Mouth.—Shews extreme oral sepsis, which she states has lasted since age of 20,—*i.e.* 14 years. Between ages of 24 and 27 she suffered severely from indigestion; at age of 28 she had severe gastritis.

Present Condition.—Extreme stomatitis and gingivitis. Incisors of upper jaw loose, and at root of one of them an abscess cavity opening by a sinus from which pus wells out freely. This she states has existed since age of 20. Only thirteen teeth serviceable, the remainder are represented by necrotic roots.

CHAPTER XXXI.

CASES.

Case 1.—The patient, a gentleman in good circumstances, came under my observation in June 1888, suffering from anæmia and profound weakness, which had already confined him to his bed for three months.

Antecedent History.—With the exception of an attack of ague, which he had had as a youth while studying on the Continent, his health had up to the onset of his present illness been exceptionally good. About six years previously he was under treatment for a short time for a gastric attack, stated to be 'gastritis' by Sir George Paget, who attended him.

Mode of Onset.—Present illness dated from the autumn of 1886. During a holiday in the country he was exposed for a time to unhealthy sanitary conditions in the house in which he stayed; and he suffered at the time from sore throat and diarrhœa. From that time onward, he never entirely regained his former health. He continued to suffer at times from an inflammatory condition of throat and tongue; and his strength began gradually to fail, so much so, that late in 1887 he was induced to seek medical advice.

Condition in 1888.—In January 1888 anæmia was already very marked; but, with the exception of some congestion of the throat, and certain pale red spots on the tongue, there was nothing further objective to be made out. At times there were retching and vomiting, especially in the morning. Although still able to go about, his condition at this time was such as to occasion anxiety to his friends. A month later, the number of corpuscles was found reduced to 860,000 per cubic centimètre (17 per cent.); and the corpuscles themselves shewed all varieties of change both in form and size. Under treatment he recovered considerably during the spring and summer of that year.[1]

I first saw him in June 1888. He complained much of great weakness and exhaustion, on the slightest exertion. There was no emaciation;

[1] For the notes as to his condition at this time I am indebted to the kindness of Sir Lauder Brunton, to whom I here desire to express my thanks.

but the pallor was marked, without any trace of lemon tint, or of jaundice of conjunctivæ. 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, nor any symptoms connected with, the *Stomach* itself.

Blood.—Number of red corpuscles 3,200,000 per cubic millimètre, with 56 per cent. of hæmoglobin; the corpuscles shewing no specially marked changes, either as regards their size or shape. This condition of the blood represented, therefore, a considerable improvement on that found four months previously.

He went to the country for a time, and returned early in August somewhat improved in health. The improvement, however, was more apparent than real. The condition of the blood on his return I found to be almost the same as before. From this time onward he began to lose ground, and became weaker and weaker till he had to take to bed early in December.

Condition in 1889.—He again came under my observation, on March 9th, 1889, and the following are the notes taken at the time. He presented an extremely pale, slightly lemon-coloured appearance, without jaundice of conjunctivæ, or œdema, or other obvious signs of disease. No emaciation, although patient has lost all the appearance of stoutness, which he formerly possessed. No fever; pulse 108, soft and regular; weakness, very great; unable even to sit up for any time. Muscles of arms and legs very soft and flabby.

Alimentary System.—Appetite very poor, no desire for food, and much discomfort in taking it, especially if of a hot or stimulating character. *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 shewing 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 (castor-oil in capsules); *looseness* at times, especially at nights, alternating with *constipation.* While the former weakens him, the latter occasions him

even more discomfort. He always feels very uneasy, when the bowels are not moved daily.

Nothing abnormal to be found on physical examination of the abdomen. *Liver* dulness natural. *Spleen* enlarged; dulness extending from upper border of eighth to lower border of eleventh rib.

Blood shews marked changes. Number of red corpuscles 1,730,000 (34 per cent.), with 30 per cent. of hæmoglobin. The red corpuscles are well preserved, but shew marked changes, both as regards size and shape; the former, however, being much more marked than the latter. The corpuscles vary in diameter from three to ten or fifteen μ; most of them under examination spherical, including those of small size; some, however, oval, flask-shaped, and pointed. In addition, a certain number are seen, throwing off buds, varying in diameter from one-third that of the original corpuscle upwards. In all respects, except size, these buds resemble the original corpuscles—their shape, colour, and appearance being the same. A certain number of the red corpuscles, surrounded by paler, more colourless spheres, derived apparently from the corpuscles themselves. The material of the corpuscles seems to ooze out, and then assume the spherical form, frequently remaining attached for a time by slender processes to the main body of the corpuscle. No increase in the number of *blood plates*, or of *white corpuscles*. No small extremely high-coloured spherical corpuscles—Eichhorst's corpuscles—to be seen. No nucleated corpuscles.

Urine very high-coloured, clear, very acid; quantity, thirty-five ounces, in addition to some unavoidably lost. Specific gravity 1015. Free from albumen; no bile pigments—the possible presence of which was suggested by its colour; no hæmoglobin, or acid hæmatin. Urea, 1·7 per cent. It deposits on standing a flocculent cloud of mucus. On microscopic examination, a number of *desquamated renal cells*, in small irregular cast-like groups, *holding granules of blood-pigment*. The yellowish granules of blood-pigment are confined to those cells, none being seen free, or within any of the epithelial cells of the bladder.

Vasomotor and Nervous System.—Mental faculties absolutely unaffected. Troubled a little with *sleeplessness* at night, also with occasional and somewhat profuse *perspirations*, especially in the early morning. These latter are usually connected with the attacks of looseness of the bowels, from which he at the same time suffers. The other systems present nothing abnormal.

Subsequent History.—The patient had been steadily losing ground since the preceding December. His temporary recovery, the previous summer, had taken place under the administration of phosphorus and strychnine. Arsenic had failed then to do him any good, and it had not since been tried. He was now receiving iron, in the form of small

doses of the tincture of the perchloride, without apparently any benefit. He was taking various meat and beef extracts, in addition to such solid meat, fish, egg, chicken, etc., as he could be induced, or as the condition of his tongue would allow him to take. It was the latter that occasioned him most trouble, *the taking of food being, in fact, a painful effort, owing to the tenderness of the tongue.*

Mild astringent lotions were ordered for the mouth; the diet was changed to a less nitrogenous one, milk and farinaceous food being substituted; and, in addition to the iron he was already receiving, arsenic in 2-minim doses of the liquor arsenicalis was ordered. Under this 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 March 20. The *tongue* was then 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, 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* 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.

Under the change of diet, a corresponding improvement—more gradual, however, and less obvious in its character, was also noticed for a time in his general condition. The arsenic was found to disagree, and was stopped five days later (March 15th). Its administration had been pushed too rapidly, with the result that the patient suffered from frequent micturition, and some symptoms of strangury. At the same time, the urine threw down, for the first time, a heavy deposit of uric acid crystals, and amorphous urates. This condition entirely disappeared, and never recurred after the arsenic was stopped. As arsenic had been found in an earlier stage of his illness to be without effect, I did not again try it.

April 13.—The improvement that occurred for a time, may be judged of by a note made a month later (April 13th). Notwithstanding that during the intervening period he had several exacerbations of weakness of the kind presently to be described, and on two occasions had had slight bleedings from the nose, his general condition was on the whole considerably improved. His appetite was better, and he was taking much more food than before.

The pallor was still extreme, mixed with a slightly lemon hue; but there was a slight return of colour to the mucous membranes and finger

nails. He felt considerably stronger, and was now able to sit up for half an hour daily. He was still troubled with occasional *looseness of the bowels*, especially at night, *accompanied by sweating*. The improvement evident in his general condition was most manifest in the urine. The latter was of more natural colour than at any time observed throughout the latter period of his illness, and presented nothing abnormal on microscopic examination.

'*Toxæmic*' *Attacks.*—The improvement which had thus set in, slight though it was, had not, however, been an uninterrupted one. He was subject from time to time to peculiar exacerbations of weakness, usually more or less sudden in onset, and of comparatively short duration, which always left him in a more exhausted condition than before. They occurred without any recognizable exciting cause, and were marked by certain *highly characteristic* features well fitted to arrest attention.

The first of these attacks, I had occasion to note, occurred on March 22nd. For two days previously, he had presented a much more lemon tint than usual; and the urine at the same time had become still more highly coloured. The night of the 21st had been disturbed by perspiration; but on the morning of the 22nd, he felt comparatively well, and took breakfast as usual. Shortly afterwards, he was seized with a feeling of *intense weakness*, ushered in by *drowsiness* so marked in character, that at the time of my visit the patient lay in a dreamy soporific state, as if under the influence of a slight narcotic, answering questions slowly and languidly, and taking no interest in his surroundings. This was all the more marked, as his natural disposition at all times was lively and excitable. While the attack lasted, the patient presented a *ghastly hue*, the lemon tint becoming so pronounced, that the medical attendant at one time feared an attack of jaundice. The pulse was slightly increased in rapidity, and more compressible; *temperature* 99·4°; pupils contracted. The drowsiness continued till late in the afternoon, gradually passing off. During the night there were several *free motions of the bowels*, the *stools being much darker in colour than usual.*

The *urine* passed at the same time was of *remarkably high colour*, clear, very acid in reaction, specific gravity 1016, quantity obtained (excluding some unavoidably lost) being 36 ounces. On microscopic examination, I found a large number of *renal cells containing granules of blood-pigment*, some of the cells being full of such granules. The appearance of these renal pigment cells in the urine at this time was all the more striking, as they had been entirely absent from the urine for more than a week previously (March 13th to 22nd).

The day after such an attack as has been described, the patient always expressed himself as feeling relieved, although always feeling much

weaker. Slight attacks occurred from time to time; constituting what came to be termed his 'bad days.' Their onset was always heralded by a more yellow or lemon hue of skin; when at their worst, his weakness was such, that the worst was occasionally feared. Nevertheless, he recovered from these in the most marvellous way; so that, as already mentioned, on April 13th considerable improvement had taken place in his general condition since the time he came under my observation.

On April 17th he had another sharp exacerbation of weakness, from which he never again fully recovered. It was marked as before by *drowsiness*, *increase of lemon colour*, *profound weakness*, *slight rise of temperature*, *flushing of head with perspiration*, and *contraction of pupils*; and was followed by several free *motions rich in pigments*, and by the passage of *very high-coloured urine*, extremely acid in reaction, with renal cells and casts containing granules of blood pigment.

He rallied from this, and was able to sit up for an hour on April 23rd. Next day, however, he had a return of the weakness, and was languid and drowsy the whole day. Examination of the *Blood* the following day shewed: number of red corpuscles 950,000 (19 per cent.), with 20 per cent. of hæmoglobin; poikilocystosis extremely marked; the red corpuscles presenting the most marked changes in shape and size; some of them throwing off buds, others surrounded by pale colourless discs still adhering to the corpuscles by slender processes. The pallor of the patient at this time was extreme; lemon colour very marked, the appearance presented by the conjunctivæ being that of slight jaundice. *Tongue* soft and flabby, slightly red at margins, smooth on the dorsum. He had not been troubled so much with his bowels during the last week. Perspirations had also been checked by $\frac{1}{100}$-grain of sulphate of atropine at bedtime. Pulse 100, soft and regular; temperature normal, slightly raised during the last three nights—never, however, above 99·5° F. At times a feeling of great heat over the head. Systolic murmurs over the heart. Splenic dulness still increased.

From this time onward, he rapidly lost ground, his weakness steadily increasing, uninfluenced apparently by diet—mainly milk,—or medicine —β-naphthol, on which he was now put. The urine remained of persistently high colour, notwithstanding that the quantity was undiminished —varying from 40 to 52 ounces, and its specific gravity was low (1014). Slight attacks of drowsiness became more common, with mild delirium at nights. On May 3rd slight epistaxis occurred, the blood, of a pale yellow colour, merely tinged with hæmoglobin. The heart's action became weaker, murmurs louder, weakness greater; till finally death occurred on May 22nd, preceded by wandering delirium. Consciousness was retained till within a few hours of death.

Morbid Anatomy.

Extreme pallor of body; subcutaneous fat of a bright lemon colour present in considerable quantity. All the organs of the body, *with single exception of spleen*, pale and bloodless.

Heart shewed slight fatty degeneration of its muscle.

Liver, on section, presented a rusty and somewhat mottled appearance. Centre of lobules pale, fatty; periphery of a more brownish tint, due to the presence of much pigment. On micro-chemical examination the tissue was found exceedingly rich in blood pigment. A piece of it placed in sulphide of ammonium became coal-black in a few seconds—the characteristic reaction of free iron. On microscopic examination, the pigment was seen in the form of granules, for the most part of fairly uniform size and appearance, lying within the liver cells, and most abundant in the outer two-thirds of the lobules. Similar pigment granules, although much fewer in number, also seen within the capillaries, lying enclosed in leucocytes. These changes were best seen, after developing the Prussian blue-reaction of the iron in the pigment, by placing the sections first in solution of ferrocyanide of potassium, and afterwards for a short time in dilute hydrochloric acid.

Spleen weighed 11½ ounces, enlarged and soft, presenting a purplish appearance. Pulp soft and diffluent. Its appearance that of a congested spleen. On microscopic examination of fresh pulp, red corpuscles very sparse, in no greater number than in other fresh organs. *Rich purple colour due to the presence of free hæmoglobin.* Large irregular rhomboidal crystals, probably of hæmoglobin, seen here and there. A piece of the fresh tissue, placed in sulphide of ammonium, became rapidly coal-black. Blood-pigment present in very large quantity, in the form of minute spherical granules lying within the cells of pulp. *After hardening of tissue this reaction altogether less marked.*

Kidneys, pale and bloodless. Large quantity of blood-pigment in the form of fine granules lying within the cells of the convoluted tubules, also, in certain of the ascending loops of Henle.[1]

In the case described, the kidneys shewed the usual pigment changes. The convoluted tubules shewed a large quantity of pigment in process of excretion, the form and distribution of the pigment being precisely similar to that described. In many of the tubules the epithelial cells were filled with pigment granules. A number of these shewed signs of fatty degeneration. Some of the pigment was contained within cells that seemed to have become detached, and lay free within the lumen of the tubule.

[1] For full description of these changes in the kidney in cases of pernicious anæmia, as well as of their significance, see my paper, "On the Excretion of Blood Pigment," *Practitioner*, November 1889 (Chapter VIII.).

Stomach.—Walls of stomach and intestine very thin and almost transparent. No trace of malignant disease. *Lymphatic glands* lying along the main lympathic trunks on the smaller curvature of the stomach enlarged, soft, pinkish, and translucent in appearance, the largest of them five centimètres in diameter. *Stomach* empty, its mucous membrane covered with a thin layer of mucus, slightly bile-stained near the pylorus. Mucous membrane very thin, but presenting to naked eye no obvious morbid appearance. After hardening—portions of it in Müller's fluid and then in spirit; other portions in spirit, most extensive changes are revealed, affecting both the submucous and the mucous coats. The cardiac end of the stomach is the seat of chronic, subacute, and acute inflammatory processes, the changes varying in degree and character at different parts. At parts, the gastric glands have entirely disappeared, and are replaced by fibrous tissue; at others, the glands are still seen surrounded, and pressed on, by connective tissue, the glandular cells themselves in a state of proliferation. At parts, the changes are even more acute, large groups of actively proliferating connective tissue and glandular cells replacing the original gland structure. Around these inflammatory foci, capillaries are seen greatly distended, extending in from the submucosa. Changes of this kind are present throughout the greater part of the mucous membrane; only here and there are portions seen, where the glandular structure remains intact. The changes in the submucous coat are as striking as those in the mucous membrane itself. The submucous coat is greatly thickened; so much so, that it is difficult at parts to trace the transition between it and the mucous membrane; this thickening is due to increase of fibrous tissue, resulting from chronic inflammatory processes. The change involves in a special degree the vessels, the walls of which are greatly thickened; at parts, however, the process is more subacute in its character, the walls of the vessels being seen infiltrated with groups of proliferating connective tissue cells. In the pyloric portion of the mucous membrane, the chief change is the increase in the interstitial connective tissue between the glands; the more subacute and acute inflammatory changes are absent.

Small Intestine.—Walls very thin. Mucous membrane of duodenum covered with a thin coating of slightly bile-stained mucus. No swelling or other obvious change. On microscopic examination nothing abnormal found.

During the last two months and a half of his illness the *urine* of this patient was made the subject of the series of observations already described relating to (1) Excretion of urobilin; (2) Excretion of blood pigment; (3) Excretion of iron; (4) Excretion of aromatic sulphates; (5) Excretion of ptomaines.

Case 2.—The origin of illness in this case was referred to the use of a new tooth-plate. Sickness, looseness of the bowels, toxæmic attacks, and nervous symptoms, were the presenting conditions. The illness lasted for four and a half years.

The patient, a gentleman, aged 42 years, was sent to me by Dr. R. Honeyburne, of Idle, Bradford, with the following graphic history of the case.

Mode of Onset.—"He began to look paler nearly four years ago, and consulted me then. He dates his illness himself from a new set of upper teeth fixed in a gold plate, which tarnished and tasted 'like pennies' from the first day he wore them, until by my advice they were removed, and a vulcanite plate substituted. In addition to a general feeling of *ill-health*, one of the first symptoms he complained of was a *sensation of numbness and tingling* in his hands and feet. He became progressively more and more anæmic, lost his knee-jerk, developed *hæmic murmurs*, *vomited his food*, and certain of his muscles (deltoids and extensors of the thigh) wasted markedly. There was no wrist drop. By this time his *pallor* was most *marked*, his skin having a yellowish tinge; his pulse got quicker and weaker, till he lay in bed *œdematous* nearly all over (on the chest, back, legs, backs of hands, face, etc.); he was *delirious*, *vomiting* nearly everything, his blood being pale, and, on examination, containing very few perfectly-formed cells and a mass of granular *débris*—in short, he got so bad that I did not think he could live another week. All this time he had been taking large quantities of iron, and latterly arsenic. An addition of one twenty-fourth of a grain of corrosive sublimate was now added to his medicine (five minims of liquor arsenicalis every four hours), and his improvement under it (or, at any rate, after it) was marvellous. The vomiting stopped, the œdema subsided, and he began to gain colour. In about three months he was quite well again, with the exception of the wasted muscles, which still remained stiff, and made his gait somewhat awkward. They in about six months more had also recovered except the knee-jerk."

"At this time, looking back on the case, I thought it one of lead-poisoning, though Dr. J. E. Eddison, of Leeds, then leaned to the view that it was a cured case of pernicious anæmia. The patient remained well for two years, then he had an attack of melancholia, which soon passed off, leaving him again quite well (better in health than he had ever felt before, so he says). There was no anæmia. This state of well-being lasted for about six months, when small-pox, being prevalent, I vaccinated him. This occurred last October (1893), and from that date he gradually declined in health until about Christmas, when his anæmia was well marked, and he began to take his former medicine—mercuric chloride and arsenic. He immediately

improved, and continued to do so until he had an attack which looked like influenza, but may have been one of the febrile attacks common to the disease, since which time he has remained nearly stationary in spite of the medicine he has been taking regularly, with the exception of a short time when we were obliged to remit it because of an attack of arsenic poisoning—scaly eczema on the backs of the wrists and elbows, with marked bronzing of the skin in other parts. I think that is about all I have to tell you concerning his history. If there is anything else you want to know, he will be able to give you an intelligent account of it himself. With regard to my theory of lead-poisoning, I must say that I was never able to find any possible means of lead ingestion except the doubtful one of the tooth-plate; also, about the vaccination origin of the relapse, it occurred exactly in point of time, but I never heard of such an origin of pernicious anæmia. Still, it is a disease of which we have much to learn."

Antecedent History.—In May 1894 when I saw him I ascertained that the family history of the patient was good, and his own previous health had been good. The present illness dated from four years previously. He had changed his tooth-plate in May, and had suffered from acidity and a pricking feeling in the hands; in December he began to get weak. In January 1891 he had to take to his bed for six weeks, with great weakness, swelling of the hands, sickness, and constipation. He was 'unconscious for a week.' He woke up suddenly conscious, and asked for a glass of beer. He could eat anything, and he got well, and in June was going about; there was, however, stiffness in the legs, and the muscles were wasted. He remained well till early in 1893, when he had business worry; not a great one, but it seemed to 'knock all the nerve' out of him. He went away for three weeks, and came back better. During that summer (1893), he had never had such good health. His usual weight was 13 st. 6 lb.; it then rose to 13 st. 12 lb. Now in May 1894 it was 11 st. 6 lb.

In December 1893 came the small-pox scare. He got frightened and was vaccinated. Two weeks later, he had sickness, and he suffered from biliousness. After being three weeks under treatment, he again got well, or seemed to do so. In January 1894 he had a sudden fit of chilliness—a rigor. The temperature was 102° F. The patient, who was ill for two days, got well from this; but he 'hung fire' ever after.

Condition.—He was then sallow, lemon-coloured, very weak and breathless. He complained of *numbness and tingling* of the legs; and there was marked *bronzing of the skin* over the back and in patches on the legs. The *knee-jerks were absent.* He suffered a good deal from *sickness*, which came on regularly morning, afternoon, and evening, and was sometimes *bilious* in character. The *bowels* had been

very free, acting two or three times daily up to a week previously to the time of my seeing him. There was no pain or loss of blood.

Blood.—The red corpuscles numbered 1,800,000 (36 per cent.) with poikilocytosis; hæmoglobin, 38 per cent.

The patient died in December 1894, after an illness of four and a half years' duration.

Case 3.—This was a case of pernicious anæmia of indefinite origin. There were febrile attacks, sickness and biliousness, and the tongue was raw and tender, 'like raw beef.' The duration of the illness was two years.

The patient was sent by Mr. Corner of Poplar.

Mode of Onset.—His previous health had been good. Two years before (1893) he had suffered from 'influenza.' A year later (1894), he had had another attack. He did not suffer from indigestion before his first influenzal attack in 1893. After that, he constantly complained of a *faint* and *weak feeling in stomach*. Since then, there had been loss of appetite for both food and drink. From Christmas (1894) to May (1895) there was improvement, when he went back to work, at which he continued till the middle of August. He was still, however, *very weak*, since he noted, as a mark of improvement, that he could walk a mile or so. His appetite at this time was fair. On September 7 he was seized with a *chill* and with *shiverings*. The temperature was 104°. On the next day, the temperature was normal. He picked up a little, and went to business; but grew feebler day by day. He felt *sick*, and fainted at times.

Condition.—On October 10, 1895, when I saw him, his condition was extremely anæmic; the lemon hue was noticeable, and there was slight conjunctival jaundice. He had lost 1½ st. in weight in the last twelve months. There was *sickness* occasionally, usually after eating. The *stomach* was slightly *dilated*; there was no tenderness, but some flatulence. The bowels during the past year had been regular; formerly they were constipated. There was no pain or discomfort in connexion with them, and no loss of blood from them. The rectum was normal. Between October 1894 and May 1895 the *tongue* was *raw* and *tender*, 'like raw liver,' causing him great pain. He had *bad teeth*, but they caused him very little pain. He was scarcely ever known to have toothache, but now and again he suffered from neuralgia. Latterly, he would discover that a tooth was loose, and could be drawn out without the slightest force or trouble. He never wore false teeth or a tooth-plate of any kind.

Blood.—The red blood corpuscles numbered 1,860,000 (37 per cent.), with slight poikilocytosis; hæmoglobin, 54 per cent. There were no retinal hæmorrhages. There was a sensation of numbness and tingling in the fingers. The knee-jerks were absent.

Subsequent History.—The patient died in January 1896. From the time I saw him up to the time of his death, he suffered from sickness and vomiting. During the last month or two of his illness, the faint and weak feeling in his stomach he described as agony. Mr. Corner reported that "he had acute relapses of fever, with disturbances of liver, etc., and increased failure of heart."

Case 4.—In this case the prominent symptoms were nervous symptoms, the teeth were all decayed and black, and there was diarrhœa, but no sickness. The illness lasted for two and a half years.

History.—The patient was a gentleman aged 56 years, whom I saw with Dr. Aldren Turner on January 24, 1896. There was a history of increasing weakness, with intermittent periods of betterment for the previous two and a half years; the weakness specially marked during the last three months. The patient had come under Dr. Turner's care on account of nervous symptoms, ataxia, numbness and paræsthesia, and loss of knee-jerks; but there was no loss of flesh. He had formerly been a very active, athletic man, and had lived a healthy outdoor life.

Condition.—He was slightly built when I saw him, and appeared very anæmic, and slightly lemon-coloured. The tongue was soft, clean, moist, and not indented. The *teeth were very bad*, all decayed; they formed a lot of black decayed fangs and crowns. The *stomach* was dilated, and there were splashing sounds; the abdomen generally was flatulently distended and full. Flatulence was present, but there was no sickness. The *bowels* were *loose*, acting five or six times daily, and the stools were very offensive. There was no malignant disease in the rectum. The *blood* was exceedingly pale; the red corpuscles numbered 760,000 (15 per cent.), and were small and misshapen; and there was much granular *débris*; hæmoglobin, 18 per cent. *Systolic* bruits were heard in the heart. There was some œdema of the ankles. The pulse was 84, of fair strength, and regular (the patient had been taking digitalis). He was extremely excitable, talking almost incessantly, and was very difficult to manage. The colour of the urine was normal; there was no albumin. The spleen was not enlarged.

Treatment.—As much milk as possible; five grains of salicylate of bismuth with five grains of salol were administered every four hours; five minims of liquor arsenicalis thrice daily; and calomel at night for three nights.

On February 3 (ten days later), I learnt that he had been better since my former visit; but had been very weak for the last two days, with weak, intermittent, and irregular pulse. He had been very excitable, seeing visitors, altering his will, and constantly talking. He had become hoarse. His colour was better, and his fingers were warmer. The abdomen was much less distended, and was soft; there was

no splashing. In that respect, the patient had felt much better. The tongue was clean and moist. The bowels were still loose, and had acted three times during the night; the stools were no longer offensive, and they were not so coloured (they were black before, but now they were of the colour of the yolk of an egg). The pulse was 84, soft, and regular.

The *blood* shewed notable difference in colour. Red corpuscles, 1,250,000 (25 per cent.); hæmoglobin 40 per cent.; there was no granular *débris*.

The hoarseness formed the prelude to an attack of bronchitis, from which the patient died a week later.

Case 5.—This was a case of pernicious anæmia of ill-defined origin. The teeth were necrosed. The duration of the illness was two years and eight months.

History.—In company with Dr. Rowland Coombs of Bedford, I saw the patient, a man, aged 51 years, on February 8, 1896. He was a healthy man, who had never suffered from any severe illness till the present one. There had been increasing weakness for the last twelve months, especially for the last four months; and for the last week he had been confined to bed.

Condition.—He was very pale, with slight lemon colour of the skin, and slight conjunctival jaundice. He had never suffered from indigestion, sickness, or vomiting; and was free from them now. At most, there was only a slight degree of flatulence. The tongue was clean, but not especially smooth, and there was nothing abnormal. There were two or three exceedingly bad, black, rotten stumps of teeth in the lower jaw. The bowels were regular, and there was no diarrhœa. The weakness was greatest, almost to faintness, when the bowels were moved. He had suffered a little from piles, which used to bleed two or three years previously, but not at this time. There was no trace of malignant disease in the rectum. The abdomen appeared somewhat full, and there was considerable distension of the colon, especially of the transverse colon, but nothing abnormal was felt. In the liver and spleen, the dulness was normal. In the heart loud bruits were heard. The urine was dark; an urobilin band could be detected.

Blood.—The hæmocytes numbered 1,230,000 (24 per cent.), with poikilocytosis; leucocytes, 4000 per c.mm.; hæmoglobin, 40 per cent.

On May 8, 1896, the following note was made by Dr. Coombs:—I think him much better. Looks better. His anæmia and breathlessness on exertion much improved. He still complains of rectal trouble, due wholly, I think, to hæmorrhoids. A later note stated: "He has taken on a part of his work again and apparently without hurt." The patient died about two years later in December 1897.

Case 6.—This was a case in which there was a history of chronic indigestion, very bad teeth, and diarrhœa. The illness lasted for nine months.

History.—The patient, a man, aged 52 years, was seen by me in consultation with Dr. A. H. W. Clemow, of South Kensington, on January 31, 1898.

History.—He had suffered from anæmia six months previously; and after getting better had experienced a relapse three weeks before we saw him. He had always been healthy; but had suffered from indigestion, poor appetite, and a 'bad cook.'

Condition.—He was thin, spare, very anæmic, and of a light lemon tint. The tongue was clean, but flabby. The *teeth* were very bad, all covered with tartar and sordes. Of three of the upper molars, only the roots were left; and one of these was so loose that it could have been pulled out with the finger. *Digestion* was very feeble. The *bowels* were loose irregularly; and the breath was bad. The abdomen was sunken; there were no pains or tumour in the epigastrium. In the liver and spleen, the dulness was normal. The urine was dark in colour, with urates but no albumin.

Blood.—The red corpuscles numbered 1,390,000 (27 per cent.); hæmoglobin, 34 per cent.; there was poikilocytosis; there was no increase of leucocytes, but an increase of granular material.

The patient died three weeks later, on February 12, 1898.

The following note was subsequently furnished me by Dr. Clemow: "In the earlier attack of anæmia, I find he had no sickness; but there was irregularity of the bowels, with diarrhœa at times. When I first saw him, his temperature was raised about a degree, and pulse rapid, 112. Under iron, these symptoms gradually subsided; but I had made a diagnosis of probable pernicious anæmia. During the last week of his illness, everything he took into the stomach caused considerable pain."

Case 7.—(Septic gastritis. See p. 231).

Case 8.—This was a case of pernicious anæmia in which the origin of the illness was referred to exposure to sewer-gas. The teeth were decayed, and there were sores in the mouth. Intense gastrorrhœa was present, with sickness and vomiting. Microscopical examination of the vomit shewed intense septic catarrh.

Mode of Onset.—In consultation with Dr. Aldren Turner, I saw the patient, a man aged 53 years, on April 21, 1899. He had been well till June 1898 when for several weeks he was much exposed to sewer-gas, during his occupation as a builder. It appeared that close to the window of an office where he worked there was a cesspool, the smell from which was so bad, that it often made him sick. He had lost flesh, but not much. By October, he was too ill to work; and was noticed to

be very pale; he suffered from retching, vomiting and pain after food. This continued. His complaint was thought to be cancer. He saw a physician, who put him upon a milk diet for a week or ten days, and then on ordinary diet; but there was no improvement. When the patient was seen by Dr. Turner on April 11, 1899, the chief symptoms were constant retching, with salivation and flow of watery mucus from the mouth, and periodical daily vomiting of still large quantities. The red corpuscles in the blood numbered 1,600,000 (32 per cent.); hæmoglobin 28 per cent. No malignant disease was discoverable in the stomach or in the rectum.

Present Condition.—On April 21, when first seen, the patient was very anæmic, and he presented a marked lemon-coloured appearance. The pulse was 90, and the temperature remained steadily between 90° and 100°. There were hæmic murmurs.

Blood.—The red corpuscles numbered 1,290,000 (25 per cent.) with marked poikilocytosis; hæmoglobin 24 per cent. There were constant *salivation*, and expectoration of large quantities of watery mucus (pints daily); and during the periodical *attacks of sickness*, still larger quantities were vomited. The stomach was dilated, but there was no splashing. The patient suffered from no pain; but from time to time he experienced a feeling of great discomfort with nausea, which was relieved by *vomiting* large quantities of mucus, after which he felt easier, and was usually hungry. Meat disagreed with him, and gave him pain. The upper teeth were absent, except one in front, which was dark, decayed, and loose in the socket. Several molars and bicuspids were absent in the lower jaw. The patient had worn tooth-plates for the last two years; previously, the teeth had been in a bad condition. When the illness began in June 1898, he had some sort of painful *sores in the mouth* under the tongue, which were not connected with the teeth. His own description was, that his illness seemed somehow or other connected with this—"it seemed to spread right down into the stomach and right through him." The *liver* and *spleen dulness* was normal.

The specimen of the vomit, which I obtained for microscopical examination, was fluid with rusty flakes. The flakes were found to consist of mucus, with inflammatory exudation (leucocytes and fibrin) catarrhal cells in great number, the whole being loaded with cocci, both within the catarrhal cells and in zooglœa-like masses. No yeast fungi were found to exist.

A diagnosis of pernicious anæmia with subacute infective catarrh of the stomach ('septic catarrh') was made.

The treatment consisted of the administration of from three to four pints of peptonized milk daily; liq. bismuthi sedativa (Schacht) with salicylic acid (three grains) thrice daily; mustard leaves over the stomach at night; and two grains of calomel at night.

On April 28, Dr. Turner reported: "Under new treatment (com-

menced on Friday), improvement noticeable on Monday; since then steady and marked. Amount of fluid brought up much diminished; no vomiting since Tuesday; patient has lost the sense of discomfort about stomach, he has had for months; likes the milk. Improvement in colour very marked. *Blood*: red corpuscles 1,600,000 (32 per cent.); hæmoglobin 40 per cent."

On May 5 the patient was again seen by me. There was very marked improvement. All the stomach symptoms had gone; and there was no further expectoration or vomiting, so that it was impossible to get any stomach material for another examination. *Blood*, the red corpuscles numbered 2,200,000 (44 per cent.); hæmoglobin 46 per cent. The patient left for home three days later.

Subsequent History.—The subsequent history of the case, for which I am indebted to the medical attendant (Mr. R. C. Kirkby), was as follows: "The vomiting and constipation improved steadily after he returned home; but the blood condition fluctuated, the highest count being about 3,000,000 red corpuscles. He developed *acute epididymitis* and *orchitis*, in September, while I was away for my holiday. This was followed by cystitis and albuminuria, the albumin being in excess of the amount attributable to pus. Œdema of the feet and legs followed, and congestion of the bases of the lungs. The urine became clearer during the administration of urotropine; but the patient had some attacks of syncope, and gradually faded out on December 3, 1899. The vomiting recurred three or four times after he returned home; but the intervals between the attacks increased, and the matter vomited latterly was merely bile-stained milk. *Salivation* occurred when he had *stomatitis*. The latter was always a bother. The mouth was always clammy and uncomfortable. *Diarrhœa* occurred several times during the illness, the bowels being opened four or five times in the twenty-four hours; but usually the motions were formed, sometimes scybalous and coated with mucus; occasionally there were streaks of blood."

Case 9 (1900).—A lady aged 55, seen 14th March 1900. Ill for a year: profound weakness and anæmia. *Blood*, red corpuscles 930,000 per c.mm. (18 per cent.); extreme poikilocytosis; numerous red corpuscles shewing 'oozing' of their stroma, more marked than ever observed. (See Plate I.) *Hæmoglobin* 22 per cent. Intense urobilinuria.

History.—Ill for a year. Began about Easter 1899, great pallor, yellow tint, thought she had jaundice; sickness, biliousness, no vomiting. *For about a fortnight during this period, great soreness of tongue*, necessitating use of a soothing mouth wash. Went to the seaside for two weeks; came back worse. Confined to bed from May till August; put on arsenic; recovered sufficiently to go to Scotland in August till

middle of October (felt so well she stopped taking arsenic while away); she came back much better. But from that time fell off, till February 1900, when she was able to be out for the last time.

March 14, 1900.—Now confined to bed; extreme pallor; weakness; hæmic murmurs; slight œdema of feet; no sickness or gastric pain; slight looseness of bowels, especially at night.

Mouth.—Breath very bad; tongue clean, smooth; teeth *very bad*, only six good ones remaining. No fewer than ten small rotten-looking stumps; remainder absent.

A week later, red corpuscles 730,000 per c.mm. (14 per cent.). Hæmoglobin 15 per cent. Death, April 6th.

Case 10.—F. C., 57, builder foreman (sent by Dr. Benjafield). Admitted into Charing Cross Hospital 24th April 1900.

Family History.—Father drowned at sea. Mother died of paralysis. He is the youngest of eight children. One sister alive and well.

Previous Illnesses.—Congestion of lungs twice. Influenza about twelve years ago. No other illness. No history of specific disease, malaria, or rheumatism.

Personal History.—Married about thirty years. Has six children alive and well at present time; two dead—one aged six weeks, the other aged sixteen (pneumonia and peritonitis).

He has been in building trade almost all his life; has worked pretty hard in his younger days, but since he has been foreman he had more mental than manual labour.

He has been a teetotaller all his life, never indulged in excess of any kind, and has led a cheerful existence, never being subject to attacks of melancholy, but always looking on the bright side of things.

Present Illness began about four years ago (*i.e.* 1896). He began to feel tired and to lose his usual energy, especially towards the latter part of the day. He always used to have a sinking feeling in the pit of the stomach whenever he went up an incline, or ascended a ladder. His friends, too, noticed that he was gradually getting paler and thinner.

His bowels were fairly regular; no attacks of pain in his stomach; no sickness; no attack of hæmorrhage; breathless on exertion.

For the first three weeks or so of his illness he stayed at home quietly by the doctor's orders. He improved considerably, and then commenced work again.

Three months later he commenced to get gradually worse, his breathing more difficult on walking, the sinking feeling in pit of the stomach worse; became somewhat thinner.

He kept at his work, but at the end of another six months (1897), as he did not improve, he went to the Isle of Wight for fourteen days.

On his return he felt slightly worse if anything.

August 1897.—About a month later he went to Bartholomew's Hospital and saw Dr. Norman Moore, under whose treatment he remained for twelve months (1898).

During this period, especially during the latter part of this time, patient had several attacks of sickness. This sickness was, as a rule, independent of food, would vary in amount generally about half a pint, often distinctly yellowish.

He had also some attacks of fainting.

His face was also of a yellowish colour at this time. There was no pain in stomach; and his bowels were pretty regular.

He noticed and often complained of palpitation on exertion, generally accompanied by a throbbing in the head.

One interesting fact was that although patient often used to get very tired after his day's work in the open air, he used to feel still more so after his rest at home on Sunday.

He discontinued going to Dr. Moore somewhere about the middle of August 1898. He immediately began to go downhill and had to give up work. So very weary that he had great difficulty in getting home.

August 1898.—He stayed at home for a few days, then tried to go up to town again to see Dr. Moore, but had an attack of sickness and fainted on the way; and another attack of sickness before he reached home.

The following day, so weak he could not walk upstairs, but had to be carried up. Next day tried to walk down but fainted, and for the following three days he lay in a semi-conscious state, with high temperature.

After four to five days the temperature fell to normal, and he felt considerably better, although he was confined to bed for six weeks and did not return to work for three weeks later.

He was then given arsenic and iron, and improved till July 1899, when he felt almost quite well but was rather thin.

His improvement continued till Christmas 1899, when he again got weak.

Sickness commenced about three weeks ago, average once or twice a week, and he was then admitted into Charing Cross Hospital April 24, 1900.

Teeth and Gums.—In the latter part of 1898 patient first became aware of the condition of his teeth. *For some years previously* they had been gradually decaying; at the end of 1898 he noticed that the incisors and canines of upper jaw were gradually becoming loose; there was, however, no trouble with the gums.

Patient saw the surgeon dentist at Bartholomew's Hospital, who

removed some of his teeth; there was not much bleeding; since that time several others have become loose.

He has neglected the care of his teeth, cleaning them occasionally at intervals of a month or longer.

Two years ago, after having several decayed teeth removed, he had some false teeth put in. These he removed and washed every night. He gave up wearing them about two months ago, as they were uncomfortable, and difficult to put in and take out.

Throat.—In February 1897 patient had a sore throat with considerable pain on swallowing, and the pain seemed to run down into the stomach. This lasted for about fourteen to twenty-one days, when it disappeared. Since then he has had slight attacks of sore throat, and these have continued with varying intervals up to the present time.

Tongue.—It was in August 1897 that patient first went to see Dr. Norman Moore. About six months later he first had some trouble with his tongue. It appeared to become slightly swollen, and especially around the edges; he noticed several longish patches of a deep red colour which were extremely tender. There were a few patches on the dorsum, but these were less numerous and less painful than those on the edges. The tongue was very tender, and became specially irritated by warm liquids. The tongue got well in about a week's time. He has had repeated attacks of sore tongue since then, about once every two or three weeks up till the last nine months, since which the attacks have been very slight and separated by longer intervals (once every two months). In fact, since the beginning of this year, he has hardly noticed anything wrong with his tongue.

In the first attack two years ago, the tongue was very sore, lasting three or four days at a time. The soreness would then pass off without treatment, and the tongue would remain all right for about a month, when he would have another attack. When the tongue was bad, dark red, almost purple, patches appeared on it, chiefly around the edges; very painful and tender, so that he had trouble to eat anything.

Stomach.—Patient had had poor digestion for the last four years; a feeling of weight in his epigastrium after meals; and also about half an hour to an hour after food he feels hungry though not inclined to eat more.

Two years ago he used often to vomit in the morning soon after getting up, before he had eaten his breakfast. At times he vomited after meals, but not often.

He suffered from discomfort in the region of his stomach, not amounting to actual pain.

When under Dr. Moore he had several attacks of sickness and severe fainting fits.

Within the last month he has had several attacks of sickness in the morning, but no fainting fits.

Intestinal.—Patient usually more or less constipated, and frequently takes medicine, but during the last two years he has had occasional attacks of diarrhœa; on two or three occasions the attack lasted for a week, but generally only two or three days.

PRESENT STATE.

April 25th.—R.B.C. 1,030,000. H.C. 40 per cent. Urobilin in quantity.

April 27th.—Examination of Patient.—Patient lies in bed, complains of no pain, looks considerably older than his years. Face slightly pinched, slightly yellowish, conjunctivæ have yellowish tinge. The whole of the body is stained yellow, the colour being deeper on the trunk, where there are numerous spots more deeply pigmented.

Thorax.—Slight amount of emphysema.

Heart.—Apex beat neither visible nor palpable. Heart sounds are regular, but a murmur, systolic in tune, can be heard at the apex. This is conducted slightly outwards. The pulmonary second sound is accentuated. A murmur, systolic in tune (not musical), can be heard on both sides of the neck, and over both aortic and pulmonary cartilages.

Abdominal.—No alteration in size of liver; spleen cannot be felt; but dulness can be made out over the splenic area extending further forwards towards mid line than normal.

Urine.—Acid, 1020. Turbid, clears on heating. No albumin.

Condition of mouth on admission.—Tongue slightly red at the margin; slightly enlarged, with a few transverse cracks on the dorsum. No tenderness complained of; tongue also slightly furred. The *gums* swollen somewhat and projected between the teeth; they were red and injected.

The Teeth.—All in a very bad state of preservation, discoloured and covered with a considerable amount of sordes.

Upper jaw.—The left lateral incisor and right and left canine are quite loose; the other incisors have been extracted.

In the lower jaw all the incisors and both canines are very loose.

Since his admission into hospital, patient has used an antiseptic mouth wash. The effects have been very marked. The redness of the tongue at the margins has disappeared, and the tongue is cleaner. The condition of the gums has much improved; they are cleaner, less red and less swollen.

April 28th.—R.B.C. 1,170,000. Leucocytes 5000 per c.mm.; poikilocytosis.

May 1st, 1900.—Last night eight teeth removed (under gas), viz., 2 canines, 4 incisors, 2 back molars (carious). P. 78; 97°·2. Urine much paler than on admission, deposit of urates, looks natural.

May 2nd.—Lemon colour more marked. Slight feeling of sickness early this morning. P. 84; T. (morn.) 98°·4; (even.) 99·2. Last two days, T. 99°·2; lemon colour more; urine more normal in colour.

May 3rd.—P. 78; T. 97°·8. Urine 36 ozs.; very slight deposit (triple and feathery phosphates); S.G. 1016. Distinctly darker in colour; heavy white deposit of triple and feathery phosphates; several small cast-like masses of yellowish pigments. No nausea.

Blood.—R.B.C. 1,100,000. H.C. 25 per cent. W.B.C. very few.

May 4th.—Urine S.G. 1018—heavy deposit. No albumin. Rosy pink colour with HNO_3. No sickness; feels weak. P. 84. Temperature normal.

May 7th.—Evening of 4th; T. 100°; 5th, 100°; 6th, 99°·4; this morning 98°·4. Has not seemed to feel rise of temperature. Eats well, sleeps. P. 96; regular. Bowels regular. Urine 1015; colour of sherry; very clear; no deposit of urates; slight cloud of mucus. Wants to get up.

May 8th.—Up yesterday for an hour. 8 p.m.—10 c.c. of Jennerian Institute antistreptococcic serum injected. T. (evening) 98°·8, slept well. This morning P. 90, T. 98°·4; E. 100°·6. No urobilin.

May 9th.—Urine 1013—natural colour. P. 84, T. (morn.) 99°; (even.) 99°·2. 2nd serum injection 8 p.m. R.B.C. 1,260,000. H.C. 34 per cent.

May 10th.—T. this morning 98°·4; P. 84. Did not sleep so well. No headache or sickness. Urine light sherry; clear; floating deposit; S.G. 1015.

May 11th.—Urine pale, 1013, and yet urobilin considerably increased. 3rd injection of serum in the evening.

May 12th.—P. 84. Temperature last night, 99°·2; this morning, 98°·8. Urine 1017.

May 14th.—T. this morning rose to 103°. Now (10 a.m.) it is 101°·8. Sickness about 5 this morning. *Vomit*, greenish in colour, watery, with mucus flakes. No food, mixed with it microscopically, *numerous streptococci*. P. 108. Feels a heavy dull headache across eyes. Urine 1016; pale—not high coloured.

Blood rouleaux formation—marked increase of leucocytes. R.B.C. 1,210,000. H.C. 30 per cent. W.B.C. 10,000 per c.mm.

May 15th.—No sickness since last night. P. 102—soft. T. last night—102°·6. This morning 99°. Feels better; slight headaches still. More lemon colour—urine deposits urates.

May 16th.—Urine 1017. Sickness over. P. 102.

May 17th.—No sickness. Slight erythematous, urticarial-like rash over front of abdomen and flanks, causing discomfort during night—still persisting this morning. Urine 1016—as before. P. 108. No sickness. Taking peptonised and ordinary milk.

May 18th.—Examination of chest.—Rhonchi can be heard over whole of chest in front. Resonance not impaired. *Behind*—some impairment of resonance in both bases, over which area, moist râles are heard. Breath sounds weak on right side. R.B.C. 800,000. W.B.C. 2500.

May 25th.—P. 96. Poikilocytosis marked. Urine not high-coloured. Urobilinuria, 1015.

May 27th.—[Clinical Lecture.]

May 29th.—P. 96. Liq. arsenicalis, ℥3 ; liq. hydrarg. perchlor. ℥ 30 *ter die.*

June 1st.—R.B.C. 1,260,000. H.G. 22 per cent. W.B.C. 10,000.

June 5th.—P. 84. No sickness. Eats well; 5 pints milk, plus biscuits.

Lungs.—Right lung clear to base. Left lung, slight dulness at base ; sounds weak. Weight now 9 st. 4 lbs. ; former weight, 8 st. 13 lbs. Urine clear, natural.

June 7th.—P. 84, as before.

Lungs.—Right lung clear to base. Left, slight dulness, with crepitations at extreme base.

Blood.—Much better colour. Urine, pale ; urobilin + +. R.B.C. 1,340,000. H.G. 30 per cent.

June 11th.—Feeling much better ; takes food ; enjoys meals ; appetite good. For first time since admission slight tenderness on right side of tongue, a small red point size of a pin's head on side of tongue. Pulse 84 ; better strength.

June 13th.—T. last night rose to 100°·8. P. 90. Feels well. Urine paler than usual. Tongue sore on edge ; brushed with 1·20 carbolic.

June 15th.—T. last night 98°·8 ; this morning 98°. P. 84, good. Appetite good. Feels better, but looks pale and sallow. Tongue yesterday and to-day painted with 1·20 carbolic. No tenderness in it now. Looks somewhat red, smooth.

Blood.—1,350,000. H.G. 35 per cent.

June 20th.—Tongue still generally red, with whitish areas at edges ; still a little sore. P. 84, good strength. Appetite good. Getting up.

Red Corpuscles.—1,372,000 (50 sqs. counted). Hæmoglobin, 40 per cent. (A. G. Pitts).

June 23rd.—Up and about last two days, from 6 a.m. to 6 p.m. ; feeling very well ; can move about without weariness ; appetite good. To go out. Tongue lost once more its red colour, but on right side a number of minute (pin-head) angry red spots. 1·20 carbolic rubbed in as before. Urine 1015 ; normal colour. T., morning, normal or sub-normal ; night, 98°·6, 98°·8, 99°.

June 27th.—Red Corpuscles 1,563,000 (average of 50 squares).

Hæmoglobin 42 per cent.

June 28th.—Last two days water very clear ; paler than at any time,

yet quantity increased. Thus 30 ozs. and 60 ozs. last two nights. Tongue still reddish. Urine 1010; no urobilin at all.

June 29th.—Red, 1,420,000. H.B. 35 per cent. Going about feeling very well. T. normal; appetite good; urine very pale, more so than at any time, and increased in quantity.

June 30th.—Went out to go to Isle of Wight; improved. For the last ten days has been moving about freely, going up and down stairs, walking in the parks; all without any sense of fatigue or breathlessness. Yet his blood contains only 28 per cent. of corpuscles and 35 per cent. of hæmoglobin.

This compares with 20 per cent. of corpuscles and 40 per cent. of hæmoglobin when admitted. He *feels* a totally different man, better, he says, than for some years; yet his actual *anæmia* is little if at all improved.

Subsequent History.—Was at the seaside for six weeks; continued to improve for first month; weight reached 10 st., then suddenly went back; increase of weakness; no sickness. Re-admitted 17th August 1900; colour very lemon-tinted; complains of discomfort about the stomach, without actual sickness; bowels regular; systolic bruits in heart; T. 99°·2; tongue rather red; smooth in parts, not furred; cough troublesome (moist sounds base of left lung).

Blood.—Red corpuscles 1,230,000 (24 per cent.); hæmoglobin 34 per cent. For next ten days he had very considerable and irregular temperature (see Chart), with repeated attacks of sickness, the vomit, when free from food, being extremely mucoid. Very marked lemon colour, and high colour of urine. ("Toxæmic attack.")

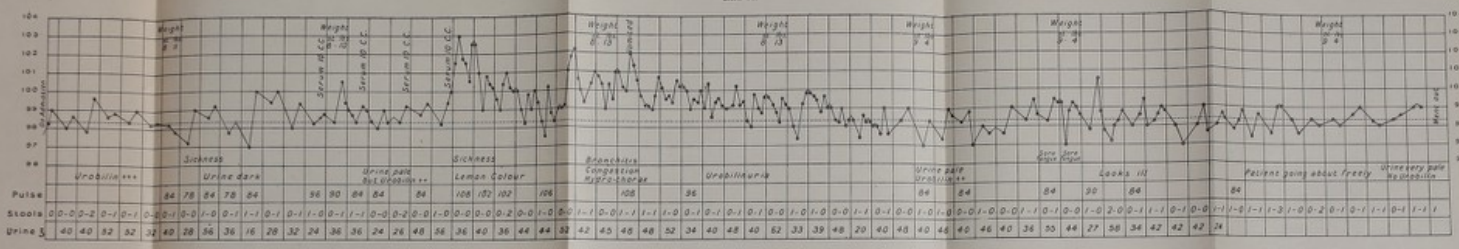
On 28th August, and again, 30th August, he received an injection of 5 c.c. of antistreptococcic serum (Jenner Institute); and again on 3rd September 1900. (See Chart for temperature subsequently.) Improvement.

On 6th September, blood shewed corpuscles 1,480,000 per c.mm. (29 per cent.), and hæmoglobin 35 per cent., and the urine was paler than at any time since readmission; pulse 84, good. He was allowed to get up the following day, and on following days. On the 14th the blood shewed 1,140,000 (28 per cent.), and hæmoglobin 30 per cent. Pulse 96. Urine still pale.

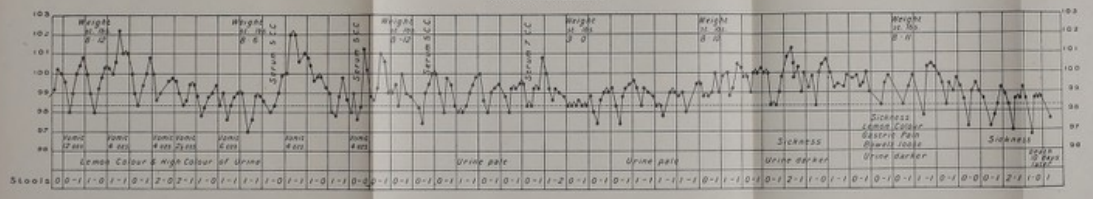
On 19th.—Pulse 96. Sickness, with empty hungry feeling before food; flatulent distension after food; bruits in heart very loud; crepitations at both bases (hypostatic congestion); urine of slightly darker colour. Temperature risen.

On 21st.—More lemon tint; sickness; fever; soreness over stomach; colour of urine much higher; bowels slightly loose; drowsiness. ("Toxæmic attack.") Patient looks very ill.

CASE 10.



CASE 10 ON RE-ADMISSION.



Pernicious Anæmia.]

[*Dr. William Hunter.*

LEEDS & WEST RIDING
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On 27th.—Sickness less; urine paler.

29th.—Sickness three times; went home 2nd October; died 10th October.

Post-mortem.—12th October 1900, fifty-six hours later.

Post-mortem lividity marked over chest and abdominal wall.

Heart.—Slight hydropericardium; cavities empty; muscles extraordinarily flabby and fatty, marked tabby-cat striation; muscle substance pale, and looks greasy throughout; slight atheroma of coronary arteries. Microscopically, extreme fatty degeneration.

Lungs.—Moderate hydrothorax; lungs healthy; slight emphysema; œdematous.

Liver.—Surface in contact with intestine blackened; fatty; blackening also of periphery of those lobules situated near large veins; fatty.

Kidneys.—Also blackened on surface; on section pale.

Spleen.—Weighs 8 ozs.; soft, red; resembling in appearance a febrile spleen.

Stomach.—Shews slight *post-mortem* change at cardiac end; walls very thin; mucosa over greater part exceedingly thin and atrophied-looking.

Duodenum.—Nothing obviously abnormal.

Small Intestine.—Slight catarrh lower end close to ilio-cæcal valve.

Colon.—Nothing obviously abnormal.

Rectum.—Nothing obviously abnormal.

Analyses of Organs for Iron.

Liver.—0·363.
Spleen.—0·141.
Kidney.—0·133.

Case 11.—Charing Cross Hospital.—Name of patient, A. L.; age, 37; occupation, traveller; admission, July 4th, 1900, under Dr. Mitchell Bruce, by whom he was placed under my care.

Complaint on Admission.—"Great weakness, breathlessness, and palpitation."

Duration.—About two years.

Family History.—Father died at 37 from the effects of a "*stroke of lightning.*" Mother alive and well, 63 years old. Two brothers alive and well. Three sisters also alive and well. One sister died of cancer of breast at 36 years of age. Nothing else of importance in family history.

Past Personal History.—(*a*) Twenty years ago the patient, while killing pigs condemned for swine fever, was inoculated by a wound in the finger. He was very ill for a few days, with high temperature,

urticarist-like rash on body surface, great swelling, etc., but eventually recovered completely. (*b*) He had typhoid fever while a child. Recovery complete. (*c*) Four years ago he suffered from three accidents all within a short space of time, viz.:—(1) Head injury caused by falling out of a trap; (2) Kick from a horse over the left eye; (3) Kick from a horse over the spleen. He seems to have recovered almost completely from all these injuries, the only indications nowadays being occasional sensations of numbness in the regions of the first two injuries, and a certain tendency or liability to headaches upon slight provocation, such as an unusual amount of brain work (calculations, etc.), excitement or irritation; and, again, he is liable to giddiness on stooping down for any length of time. (*d*) He has also suffered from influenza twice, the first occasions being three years ago, when his principal symptoms were "head," and again six months ago, when they were again most prominent, and after which his present condition became much more aggravated.

Habits and general surroundings always seem to have been excellent. He describes himself as being a very "careful living man," particular about his food, health, and general comforts. He always appears to have been in a position to gratify these desires. He has passed through several grades of occupation: (1) He began life on his father's farm in Bedfordshire; then became (2) butcher at Kilburn for three years; (3) charge of stables at Bon Marché for twelve years; (4) bought a public laundry for himself at Willesden, and kept this going well until April of this year, when he gave it up, owing to the great decline in his general health and consequent inability, through weakness, to give that care and attention to his business which was essential for its success. Latterly he has had a very easy and profitable occupation as a traveller for a brewery in Kilburn, which gives him very little anxiety and exertion, but even this he has recently been compelled to give up.

Height 5 ft. 6 in. *Weight*, 9 st. 7 lbs.

Present Illness began two years ago, when the patient noticed his appetite was poor, weight coming down; colour, which had always been red, disappearing and becoming yellowish at times, and what was most prominent of all, an almost constant pain in the stomach and side (over spleen), and periodically acute attacks of *severe pains in the mouth and stomach.* On investigation still futher into these curious periodical attacks of pain which he complained of, it was ascertained that at this time (two years ago) he was greatly troubled by what he describes as a *sore mouth.* It began by pain and swelling of the gums, then the teeth became sharp edged in feeling, so that they tasted like "china" in his mouth, and seemed as if they would at any moment cut his tongue to pieces. In twenty-four hours after this the tongue itself would become almost unbearably sore, and on inspection patient noticed big red patches

on the dorsum and edges. In endeavouring to describe the sensation of this sore mouth, he said : "The tongue felt as if it had no covering, as if it was quite raw, so that when I put a piece of bread in my mouth at meals, it felt like sandpaper." It never seems to have bled ; and it is interesting to notice that when the attack, which usually lasted two or three days, was over, the patient could eat beef-steak or any other food. During the attack, his food consisted of milk and bread sop. The attacks came on almost every three weeks, and were followed, and accompanied, by gastric symptoms which will be referred to later.

This state of matters continued until about Xmas '99, when patient had three very bad teeth extracted ; and he is certain that from that date the mouth condition diminished very considerably in severity. He has had mild complaints since ; but *the* complaint which has been most prominent since that time has been the *gastric pains*. He has constantly suffered during the last twelve to eighteen months from a gripping, vice-like pain in the region of the epigastrium, always more marked at times, *e.g.* after a mouth attack, when he had worked hard and exhausted himself, or when annoyed or irritated by anything. His appetite was very variable, depending to a great extent upon the condition of his mouth, but always improved after the mouth trouble was over for a time (interval between two attacks). He has always had recently a tendency to *nausea* ; which became aggravated in its severity, when anything unpleasant or distasteful to sight, smell, or taste was present. He was never actually sick, except after taking some medicine which he had had during an intermittent illness (influenza). Nausea and *retching* were often present ; and the latter was particularly severe if the stomach was empty.

During the last twelve months the patient has felt himself grow perceptibly weaker, and incapable of hard work.

Breathlessness, *palpitation*, and *giddiness* have gradually forced themselves upon him ; and now he can distinctly recollect how he has noticed the gradual onset of the *lemon yellow colour* of skin all over the body, but states that it has constantly varied in intensity. The most marked features of late have been the great *weakness*, together with the nausea, etc., referred to above ; and in addition, *pains shooting down the limbs*, *numbness*, *tingling in the shins*, acute pains in the clavicular regions at times which almost arrested breathing. The patient has been treated all along for chronic catarrh of the stomach, and his mouth has been relieved by borax, glycerine, and chlorate of potash lozenges. His diet was never the subject of special comment ; he generally took what he thought would suit him. He came to Charing Cross Hospital on June 29th for examination ; and after hearing the history and examining the blood, the case was diagnosed as "Pernicious Anæmia," and was recommended to come in as soon as possible for

treatment. At the time of examination on June 29th the physical conditions observed in the blood were shortly:—The red blood corpuscles were markedly altered in size and shape, showing poikilocytosis; numerous nucleated R.B.C. were present. Hæmoglobin 35 per cent., and R.B.C. 1,500,000 per c.mm. (30 per cent.).

Condition on Admission.—The patient came into the Hospital on July 4th, and on examination—(1) *Alimentary System.—Teeth*—Two incisors, lower jaw, exposed and covered with tartar at their necks; gums receding, inflamed. They have been in this condition for ten years, and have bothered him. *Upper Jaw: Right Side.*—Bicuspids and two molars absent, Wisdom tooth remains. Shews carious cavity, and gum around slightly swollen and inflamed. *Left Side.*—Canine represented by a necrotic root. *Lower Jaw.*—Back tooth, left side, represented by a rotten root, other teeth sound. *Tongue* normal, gums somewhat anæmic; otherwise normal. The *stomach* was slightly enlarged, but the only sign of importance was the localized severe pains over the epigastrium. Patient could not bear the least pressure here. The *Liver* was quite normal. *Spleen* slightly enlarged. *Bowels* somewhat loose, and fæces paler than normal.

(2) *Circulatory System.—Heart* slightly enlarged in its transverse diameter. Over pulmonary and mitral areas, systolic murmurs, soft and low in character.

(3) *Respiratory System*, with the exception of the breathlessness, normal.

(4) *Nervous System.*—Complains of tingling and numbness, shooting pains, etc., as described above.

(5) *Urinary System.*—Urine dark brown in colour; large quantity of urates appeared in urine on the 1st and 2nd days succeeding injections.

(6). *Blood:*—

		R.B.C.	H.B.	
	June 29th	1,500,000 (30 per cent.)	35 per cent.	W.H.
	July 7th	1,350,000 (27 ,,)		
1st Inject.	,, 9th			
(10 c.c.)	,, 12th	1,580,000 (31 ,,)	35 per cent.	
2nd Inject.	,, 13th			
(10 c.c.)	,, 16th	1,800,000 (36 ,,)		
	,, 20th	2,530,000 (50 ,,)		
	,, 23rd	2,685,000 (52 ,,)	50 per cent.	
	,, 31st	2,845,000 (56 ,,)		
	Aug. 1st	2,390,000 (65 ,,)	75 per cent.	W.H.
3rd Inject.	,, 2nd	W.B.C. 17,000 per cum.		
(5. c.c.)	,, 7th	2,750,000 (55 per cent.)	70 per cent.	W.H.
	,, 10th	2,360,000 (47 ,,)	72 per cent.	W.H.

R.B.C. normal; no poikilocytosis.

Treatment.—Patient was put upon milk diet, an antiseptic mouth wash, liq. hydrarg. perchlorid., ℥xxx, thrice daily as an intestinal antiseptic; with carbonate of ammonia (gr., 3), and tincture of digitalis ℥v as a stimulant.

Daily notes of case :—

July 6th.—Patient had an attack of sickness yesterday, preceded by much pain in the usual situation, at 4 p.m., about quarter hour after taking medicine (vomit bilious in character, according to patient); after which he was all right and had a good night's rest. This morning he feels very sore in the stomach, and legs ache very much from knee to ground. The tongue has a prickly feeling which makes it feel "as if it were clinging to roof of mouth." On examination, nothing is made out except a small red patch in the middle line almost at position of hard and soft palate; patient puts his fingers on it and says it is "*raw.*"

Blood.—Examination on July 6th. Great difficulty was experienced this morning in getting away blood at all for examination. On puncturing the fingers, scarcely a drop came away; and it was only on pressure to the part, and allowing hand to hang before puncture, that any was forthcoming.

July 7th.—Blood examination this morning showed red corpuscles 1,350,000 (27 per cent.), with distinct poikilocytosis, and many nucleated reds were seen. Pain in the side (spleen) and stomach, continue as before. Feet very cold; mouth distinctly better; no sign of irritation.

July 8th.—Better this morning; pain in stomach and side easier but still present in limbs; mouth quite easy; wash has improved it.

July 9th.—Patient feels unwell this morning; complains of pain in limbs (usual situation), stomach, and heart—described as a "feeling of wind with pains like pressure"; the mouth is causing some trouble by pains around the first premolar on left side; the local signs of condition are nil. The stomach is dilated slightly. Temperature 99°·4. First injection of antistreptococcic serum made, 10 c.c., at 6 p.m.

July 10th.—Patient feels tired and worn out this morning; has passed a sleepless night. Temperature 99°. Pains are complained of all over body, particularly over right side, and stomach and legs. He looks flushed. Pulse 98. Mouth "*dry taste*"—nothing obvious on examination.

July 11th.—Patient feels distinctly unwell to-day. Temperature 101°·6; complains of pains in right side of stomach (hot burning), and slightly on left side. Pulse 120. Headache severe.

July 12th.—Temperature 102°·6; pulse 120. Although temperature and pulse are still high, the patient does not feel anything like as unwell to-day as yesterday. The principal complaint is headache, felt principally at vertex; pains in stomach and side as before; complains also of flatulence and retching, although food is still peptonized; mouth is very dry (lemon drink given); great thirst. Legs remain the same, and arms also ache badly. Throbbing pains, lightning like. Blood examination, corpuscles 1,580,000 (31 per cent.). Hæmoglobin 53 per cent.

July 13th.—Temperature 99°; pulse 100. Patient feels more himself to-day. Headache has passed to occiput, and is not so severe. The pain in stomach, side, and limbs is better. Motions are liquid. Mouth better.

July 14th.—Injection of serum last night at 8 p.m. Rigor for quarter hour at 1 a.m.; sleepless and restless night. Feels better this morning—very little pain complained of. The rigor started in left shoulder, and passed down whole left side. Right side unaffected.

July 15th.—Temperature 100°·2. Complains of severe pains in head. Otherwise as before; slept well; appetite good.

July 16th.—Temperature 100°·8; pulse 96. Blood 1,800,000 (36 per cent.). Hæmoglobin not estimated. Great difficulty experienced in getting blood for ordinary numerical estimation. Pains and discomfort are complained of. Motions are more solid; liq. hydrarg. perchlor. is reduced.

July 17th.—Temperature 99°·2; pulse 88. Headache not so violent, but with sharp pains; soreness on left side from point of last injection down left groin and leg. Mouth and tongue not sore to-day. Patient has difficulty of passing water lying on his back.

July 20th.—Patient feels much better. His head feels better, but complains of sweating on his head. Soreness in side is better, and no difficulty in passing water. Temperature (10 a.m.) 98°·4; pulse 76. Corpuscles 2,530,000 (50 per cent.).

July 21st.—Patient describes himself as better altogether. (Have not seen him since Monday.)

July 23rd.—Blood count, 2,635,000 (52 per cent.). Blood flowing much more easily than formerly. The corpuscles were noticed to be more even in shape, approaching more nearly the normal cells. Hæmoglobin obviously more abundant, but not estimated. Patient describes himself as improving. Sleeps well. Temperature normal.

July 25th.—Patient improving daily. Yesterday food changed; more solid nature; fish, etc. Patient relishes the change. All aches, pains, etc., have disappeared of late.

July 31st.—Patient has not felt so well since Saturday, 28th. Complains of pains in head, feeling of thickness or dulness. Stiffness in shoulders and neck, soreness under ribs. Some palpitation on movement. Skin all over body is clearer. There is a certain amount of rawness in the perineal region—an old complaint which patient suffers from periodically.

Blood count, 2,845,000 (56 per cent.).

August 1st.—Blood (W.H.). R.B.C. 3,290,000; 65 per cent. W.B.C. 17,000. Hæmoglobin 75 per cent.

August 2nd, 11 a.m.—Last night 5 c.c. serum injected. Afterwards no sleep until 4 a.m., when he had an hour's sleep. (Trional grs. 20

given, before 10 grs. with no effect)—slept again this morning—appetite fairly good—complains chiefly of pain in the left side, near seat of injection, and passing into flank—looks flushed. Temperature practically normal (98°·6). Pulse 120. Headache improved.

3.30 p.m.—Patient feels much better this afternoon.

August 3rd.—Temperature 99° this morning—slight reaction has set in after the injection on the 1st. Pulse 120. Patient feels better to-day.

August 4th.—Pulse 120. Temperature last night rose to 99·8°. Now 99°, slept well. Troubled with headache. Complains of flatulence after food.

Locally, still some brawny œdema left flank close to site of injection.

Urine.—High colour, heavy deposit of red urates.

August 7th.—Feeling better—up each day from 12 to 6 p.m. Pulse 84. Looking well. Urine normal in colour. Much lighter than any time since admission. Blood 2,750,000. Hæmoglobin 70 per cent. Slight looseness of bowels to-day (twice) (55 per cent.).

August 8th.—Two lower incisors, formerly described, edges red and inflamed, and covered with pus. Swabbed out with 1–20 carbolic acid. Edges bleed freely. Tartar removed. Gums to be swabbed daily with 1–20.

Slight desquamation of skin over face. No local tenderness over abdomen.

Pulse 78. Temperature 97°·8.

Urine.—Straw colour. Sp.G. 1018. No albumen.

August 10th.—Blood examined. Corpuscles 3,360,000 (67 per cent.). Hæmoglobin 72 per cent.

Corpuscles normal in appearance. *Feeling very well.*

August 15th.—Three teeth drawn. Back wisdom upper jaw; lower jaw left wisdom; upper canine. *Lower incisors.*—Gums previously receded, now grown up around tooth and looking healthy. They have not been right, he says, for 10 years.

August 16th.—Patient goes out to-day. Pulse 84. Appetite good. Temperature 99°. Urine darker, 1025. No albumen. No indican.

Sep. 26th, 1900.—Returned. Looking stout. He has put on 7lbs. in weight. Weight is now 10 stone. Good colour. Complains still of numbness and dead feeling of finger-ends. Mouth and teeth very clean.

Blood.—Red corpuscles 3,200,000 (64 per cent.). Hæmoglobin 80 per cent.

Treatment since he went out has been: Mouth wash. Mercury as before, and ℥1 of Fellow's Syrup thrice daily. Now put upon Liquor Arsenicalis ♏ 3 *ter die.*

Oct. 4, 1900.—Looking still better, and feeling very well. Weight

10 stone 2 lbs. Appetite good; stomach comfortable. Bowels regular, generally once and sometimes thrice daily. Urine pale straw colour. He notes himself "it is much better"; that sometimes it is very dark, *e.g.*, last week; and that it is always darker when he is not feeling very well.

His tongue looks red. He states it has been very sore last four days. "Feels cracked all over" when he takes anything to eat or drink. Last attack of the kind was four weeks ago, lasting about a week.

His chief trouble now is that his fingers feel perfectly numb, so much so that he can't button his clothes, owing to want of feeling in fingers. This affects both hands, and extends up to elbows. Calves of legs feel weak, but there is no numbness in them.

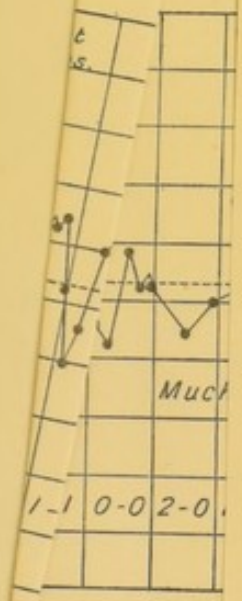
Remarks.—The chief interest of this case is, that the treatment employed throughout was oral and intestinal antisepsis, with injection of antistreptococcic serum, as recommended by me (see TREATMENT). Under this treatment the blood improved in the short space of 24 days—*Red corpuscles*, from 27 to 65 per cent.; *hæmoglobin*, from 35 to 75 per cent. The injections caused reaction both locally and generally (see Chart), this latter being a feature also noticed in Case 10. The improvement continued, although much more slowly, for six weeks after he went out—viz., corpuscles, 64 per cent.; hæmoglobin, 80 per cent.; and it is still going on.

Nov. 8.—Improvement still continues. Weight 11 stone 2 lbs. (an increase of 1½ stones); R.B.C. 4,040,000 (80 per cent.); hæmoglobin 90 per cent.

CASE 12.—A case of pernicious anæmia following on traumatic stricture of the small intestine; reported by Mr. Arthur W. Barker, with "Pathological Report" by myself, *Lancet*, July 1900.

A man, aged 28 years, a sawyer, was admitted into University College Hospital on Feb. 5th, 1900. He had always enjoyed good health until seven years ago, when he was run over by a loaded wagon. The two near wheels, which were broad, passed over the lower part of the thorax, breaking, it is stated, five ribs and splintering another. This was followed by "pleurisy and inflammation." He was ill for 14 weeks, and after this began to have the attacks now complained of. There was no history of syphilis, rheumatic fever, or tumours, but the patient had always suffered from "heartburn," which had been worse since the accident. The patient had always been quite temperate. He had been well fed, and had lived among healthy surroundings.

On admission he was noted as being very well nourished, inclining to fat, but extremely anæmic. This was most marked in the conjunctivæ, lips, and finger-nails. An examination of the abdomen revealed no abnormality of the internal organs, and only a slight tenderness and increased resistance midway between the right iliac spine and the navel.


Much
1-1
0-0
2-0

Nothing unusual could be felt from or in the rectum. His reason for seeking treatment now was extreme weakness and anæmia, with periodic attacks of pain and vomiting, which set in soon after the accident seven years ago. These had occurred at intervals of from a week to a month, and lasted from a week to a fortnight. During these attacks pain and swelling began about two inches to the right and below the umbilicus, and spread from there all over the abdomen. At the same time the patient had vomiting and diarrhœa. The vomit consisted of food and green fluid which tasted bitter and sour. The motions during these attacks were much lighter in colour than usual, and sometimes very pale indeed. The pain was much relieved by change of posture in any direction. The great pallor was first noticed in the summer of 1899, and, since September 1899, the patient had suffered from shortness of breath on exertion accompanied by palpitations. During and after September 1899, the patient was prevented from working for about 10 weeks by vomiting and diarrhœa. On admission the temperature was 99°·4 F. and the pulse was 112. This was about the average for nearly a week, when the fever slightly increased to about 100° or a little over this. He then (Feb. 17th) had the first attack of pain since admission. It began at the point described and spread all over the abdomen, lasting about one and a half hours. He vomited at this time both food and bile, and had a loose stool without any undigested food or fat and not offensive. Dr. Thiele's analysis of the blood showed red corpuscles 2,000,000, white 54,000, and hæmoglobin 30 per cent. The optic discs were now examined and were found to be normal. On Feb. 16th the stomach was washed out, but showed nothing abnormal. On the 17th a hæmorrhage was noticed in the left eye above and to the outer side of the optic disc. Pain and vomiting occurred on the previous night. The vomited matter was bile-stained with very little undigested food. It contained free hydrochloric acid. Reduced iron was now given. The diet was full and was eaten with appetite except in the morning. The patient was growing paler. On the 21st he vomited twice with but little pain. The urine had been free from albumen since admission. It was acid and of normal colour with an excess of indican. Urea 2·5 per cent. There had been no loss of flesh, but the pallor was increasing very much and severe headache had been complained of for some days. On the same day (the 21st) an examination of the blood showed red corpuscles 1,000,000, hæmoglobin 20 per cent., and white corpuscles 1 : 450. The blood itself to the naked eye was very thin and watery; megalocytes and microcytes, but no nucleated red corpuscles, were seen. Feeling now satisfied that there was some serious lesion high up in the small bowel, probably of the nature of a stricture, Mr. Barker decided to explore the abdomen.

Operation was performed on Feb. 22nd. The abdomen was

opened in the mid-line above the umbilicus. The first thing noticed was a coil of enormously distended and thickened small intestine of white colour, which for the moment was taken to be the stomach. It was seen, however, on nearer inspection to lie below the colon, but to overlap it above. The distention terminated to the right of the spine in a sharp kink among many old smooth adhesions, and below this the intestine was normal and empty. On pushing the finger into the distended coil so as to invaginate it a narrow stricture could be felt at the kinked spot. To the left the dilated coil was held down to the spine by adhesions which led me to the conclusion that I was dealing with the first part of the jejunum as it emerged from under the plica. These adhesions, too, were all smooth and evidently old. I now anastomosed the distended loop with the empty portion below the kink and stricture. This was done by a double row of silk sutures in the usual way. In making the openings in the contiguous loops the contrast between the thick-walled upper portion and the thin-walled normal viscus below was very striking. The abdomen was now closed in with silk sutures. The operation lasted 50 minutes, and towards the end the condition of the patient was not very good. On this account a pint of normal saline solution was injected hypodermically during its concluding stages. After the operation there was a good deal of pain which was relieved by morphia, after which the patient fell asleep. The pulse was 116, the temperature 102°·2, and the respiration was 38. The next morning he was not so well. The temperature was 102°·8 and the pulse was 136. Death took place at 5.15 on the 24th.

Post-mortem.—For the points of surgical interest connected with this case, reference should be made to Mr. Barker's report.

On opening the distended bowel the stricture was found to be due to the contraction of an ulcer produced by the crushing of the mucous membrane where the cart-wheel caught it against the spine. It was annular, and the lumen was only about the size of a cedar pencil. Other healed ulcers were seen above it and some partially healed. The seven feet of bowel between the stricture and the duodenum were enormously dilated and full of pale yellow fluid like thin custard. For *post-mortem* notes and pathological report, see Chaps. XIX. and XX.

PART VII.—TREATMENT.

CHAPTER XXXII.

TREATMENT.

THE investigations detailed in the foregoing pages, by throwing light on the true nature of the disease, serve to establish a basis for its systematic treatment—preventive and curative.

The objects to be aimed at I conceive to be three:

1. Prevention and removal of the infective cause.
2. Removal of the gastro-intestinal conditions, favouring its operation.
3. To combat the chief symptoms.

Removal of the Cause—Antiseptic Treatment.

The result of the foregoing observations has been to prove the infective nature of the disease; to trace the infection either to the mouth itself, or to outside sources; and to localize the resulting infection to the mouth, stomach, or intestine.

1. *The Hygiene of the Teeth and Mouth.*

I consider it, then, all-important in all cases of commencing anæmia that special attention should be directed to the condition of the teeth; and that even more than ordinary care should be taken with regard to their health, by removal not only of old stumps, but also of all black teeth, and of teeth showing commencing cario-necrosis. Moreover, I consider these precautionary measures necessary, irrespectively of any statements made by the patient as to the degree of discomfort which his teeth are

causing. As a matter of fact, in no single case above recorded, however bad I found the teeth to be, was my attention drawn to them by the patient, or was any complaint made of them by him. Discomfort and pain in the teeth are the results of local inflammatory reaction—periostitis and gingivitis. To a certain extent they may be regarded as relatively healthy conditions, inasmuch as they denote that the local tissues still have the power to react more or less actively to irritation. There is a stage, however, in pyogenic conditions, as, indeed, in other forms of infections, when local reaction is absent, or at most insignificant, at the very time when the general septic effects are most marked. This combination I consider to be characteristic of the septic condition in pernicious anæmia.

The hygiene of the mouth demands, therefore, in this disease the most scrupulous attention, irrespective of the statements or opinions of the patient. Absence of local pain and discomfort in the teeth is no criterion of absence of general septic effects, if their condition be recognizably bad.

As I have pointed out elsewhere, with regard to oral sepsis generally and its treatment, what we want recognized on the part of all physicians, surgeons, dental surgeons, and patients, is the *septic nature* of this condition of dental *caries* itself. The gastric trouble is not the result of any dyspeptic trouble, or of ill health, or of insufficient mastication ; it is the result of sepsis caused by the carious teeth.

The matter, moreover, is important from the point of view not only of the gastric trouble, but of the infections in the body caused by pathogenic organisms generally : *locally*—acute and chronic tonsillitis, pharyngitis, otitis, follicular abscesses, glandular swellings in the neck in connection with diseased teeth ; or more *remotely*—ulcerative endocarditis, meningitis, obscure septicæmia complicated by purpuric hæmorrhages, pyæmia, osteomyelitis—in fact, the whole series of conditions, including pernicious anæmia, in which sepsis plays a part.

The chief problem with regard to these conditions is to find out where the pus organisms have gained entrance. They are not ubiquitous, but are definite organisms causing pus formation. We take most elaborate precautions to ensure ourselves against typhoid infection, either from drains or from water ; and

we take great precautions to protect ourselves from tubercle; and there is no reason why, when we are doing all this, we should allow the most accessible part of the body to remain a favourable seat not only for the propagation, but for the actual production of organisms no less pathogenic—pus organisms. Therefore I consider that in regard to oral sepsis there is a wide field open for preventive medicine in the practice of oral antisepsis.

2. *Local Treatment of the Stomach.*

As I have shewn, whether the infection arises from the mouth or outside, its chief seat is invariably the stomach. The first effect is a septic catarrh, followed later, if the patient live long enough, by deeper seated changes of the nature of glandular atrophy and gastritis. The indications here, then, are to remove or lessen this sepsis in the stomach. *The most important part of this indication is fulfilled by carrying out measures of oral antisepsis.* The local conditions in the stomach can be treated in two ways, either by washing out the stomach, as suggested by Sandoz; or still better, as I conceive, by administering local antiseptics with a view to diminish or destroy the infection underlying the gastric catarrh.

Washing out the Stomach.—This treatment was first suggested by Sandoz on the view that certain of the symptoms were those of indigestion, and that the products of indigestion might in this way be advantageously removed. In my judgment, the products are of an entirely different character from those of indigestion; they are really products of infection formed in the walls of the stomach itself. How far under these circumstances this plan of treatment can be successful may be open to doubt. We are not likely to remove an infection of the gastric mucosa by washing out the stomach, any more than we can hope to cure a stomatitis or glossitis by rinsing the mouth. In the later stages of the disease, the gastric conditions are of a too deep-seated character to be affected by such local measures as washing out the stomach. But in the earlier stages of the disease the case is different, and the measure is one which I conceive might be adopted with advantage.

Fortunately for this purpose, an early diagnosis of the disease is now in my judgment rendered possible by the fore-

going researches. In diagnosing the disease regard must be had, not to any single feature, but to

(1) The *whole group of blood changes* (Chap. V.);

(2) *The combination of clinical features*, associated with these changes as part effects of the infection (Chap. XXIV.);

(3) The *more or less sudden onset* of the anæmia out of all proportion to any ordinary cause of anæmia (Chap. XX.); and lastly

(4) The *antecedent history of gastric and oral sepsis* (Chap. XVIII.).

Antiseptic Treatment.—The chief advantages to be got from washing out the stomach can in most cases be got in other ways, namely, by administration of local antiseptics. The case which appeared to me the most suitable for washing out the stomach was Case 8, in which there was intense salivation with gastrorrhœa. Before carrying it out, I determined to try the effect of local antiseptic treatment. The antiseptic selected was the one that had proved successful against ordinary septic gastritis in Case 7, namely, salicylic acid. I had selected this drug on general grounds, as the antiseptic which appeared to be at once the most powerful and the least harmful. The result in Case 8, as in Case 7, was eminently satisfactory. Improvement was noticed from the first day; salivation and sickness, which had been persistent for several months, ceased by the fourth day; and their cessation was followed by a remarkable improvement in the blood, namely, an increase of 20 per cent. of corpuscles in the course of the next two weeks.

There are many other antiseptics of the same character which may prove equally efficacious. One which I have been in the habit of using constantly is salicylate of bismuth.

3. *Local Treatment of the Intestine.*

In the cases where the symptoms point to intestinal rather than to gastric irritation, a similar treatment should be adopted —use of intestinal antiseptics, as I before recommended—*e.g.*, salol, naphthol, calomel, or mercuric chloride (Case 2). In cases where the symptoms point to the colon or the rectum this may be supplemented, as I now recommend, by enemata containing salicylic acid.

Medicinal Treatment.

Arsenic.—The above measures should not replace, but should be supplemented by, the use of arsenic. The great value of this drug, first introduced by Dr. Byrom Bramwell, has now been fully established. Its use has, indeed, in my judgment, modified the character of the disease. Instead of being a disease of a few months' duration, rarely if ever exceeding twelve months, as was the case in the experience of the early observers (Addison, Biermer, Eichhorst), a duration of two, three, and even four years from the time of onset, is now, in my experience, not uncommon. For this result, the use of arsenic, more than any other individual factor, deserves, in my judgment, the credit.

The good effect of arsenic is here brought out by Dr Byrom Bramwell's careful analysis of 45 cases, which have come under his observation. The patient's ability to take arsenic is, in his opinion, the most important point in determining the prognosis of the case. He even expresses the hope—one which, unfortunately, is not fulfilled in actual experience—that if arsenic was steadily given for long periods of time after temporary recovery, the tendency to relapse, which is so striking a feature of the disease, might perhaps be prevented. So far as his own experience is concerned, and he thinks this is the experience of most other observers, it is the only remedy with which we are at present acquainted which is likely to produce benefit in any considerable proportion of cases of the disease.

He was led to try the administration of arsenic by the observation, that in cases of pernicious anæmia, the most striking morbid change was the extreme fatty degeneration of the heart; and his experience had taught him that arsenic was a remedy of undoubted value in many cases of fatty heart. In three of the first cases in which he tried it, rapid and immediate improvement took place; and the result of his whole experience, now extending over twenty-three years, is to show that the arsenical treatment is in many cases attended, for a time at least, with marked benefit—unfortunately in the vast majority of cases only temporary in its character.

In his recent work, he appends a valuable analysis of the result of arsenical treatment in 45 cases which have come under

his own notice. Of these 45 cases 35 had died, 3 cases were still alive, and in 7 the result was not known.

In 38 of the 45 cases arsenic was given with the following results:

10	Cases	Complete (temporary) recovery.
8	„	Marked (temporary) improvement.
7	„	Slight („) „
12	„	No improvement.
1	„	Result not known.

In 7 of the 10 cases in which complete (temporary) recovery resulted, a relapse subsequently occurred; and in one of these cases, the patient remained well for twelve years and died at the end of thirteen years.

An analysis of the immediate results of the treatment in those cases in which arsenic was well and badly borne shows very clearly, he considers, that the immediate improvement under this treatment largely depends upon the patient's ability to take full doses of the drug. Out of the total number of 38 cases in which arsenic was given, the remedy was well borne in 24 cases. In these 24 cases, improvement more or less marked occurred in 20, whereas in nine cases in which arsenic was badly borne, improvement only occurred in one.

Mode of administration.—It is best begun in small doses—two drops of Fowler's solution in water thrice daily after food; afterwards increased gradually up to 10 and 15 or even 20 drops thrice daily.

My own experience may be exceptional, but personally I have not been able to satisfy myself that the benefit to be got from this drug is dependent on the largeness of the dose given. When benefit results, it is, in my experience, as marked with the smaller doses as with the larger; and in such cases I prefer to hold the larger doses in reserve for the subsequent relapses which inevitably occur, rather than push the arsenic to its utmost limits of toleration in the first instance.

For the chief feature about arsenical treatment is this, that however marked the improvement under it may be, it does not prevent the recurrence of the disease. How far this feature of the disease will be altered by the adoption of the strict measures of oral and dental antisepsis which I have now recommended,

will remain an interesting point for future experience to determine.

In the absence of any such measures hitherto, the patient, however much relieved, has always been left exposed to reinfection from the original source of his trouble.

Dietetic Treatment.

The most important symptom of the disease is the excessive destruction of blood, induced by the absorption of the poisons. It is the continual drain on the blood thus brought about that causes the intense anæmia and excessive weakness.

The best way of combating this—apart from the removal of the cause—I conceive to be by regulation of the diet, with a view to diminish blood destruction so far as possible. The most important factor regulating the amount of blood destruction in health I find to be the nature of the diet, a nitrogenous diet causing a much greater destruction than a farinaceous or fatty one. The blood destruction which occurs in this disease so greatly exceeds, however, that of health, and depends upon the operation of such different factors — the formation and absorption of specific poisons of the nature of ptomaines— that the difference between a nitrogenous and a non-nitrogenous diet may be of comparatively little moment. Nevertheless, the results obtained in various cases appear to suggest that great benefit is to be got from a most careful regulation of diet. The object to be aimed at is to ascertain for each patient the particular kind of diet which in his case gives least work to the stomach, but at the same time is sufficient in quantity to maintain his strength. This is a matter not so easy as may appear. For the sense of weakness which the patient experiences is oftentimes so great—and is so often accompanied by an intense feeling of emptiness or sinking referred to the stomach, only relieved by food—that the patient craves for food, although he may be actually taking a more than average amount of food. The result is naturally to overburden the stomach, with further grievous discomfort.

Until, then, the digestion has been got into a fairly satisfactory condition, I am no advocate for "feeding up" in this disease.

If the disease could be controlled or arrested by feeding up, it would long ere this have lost the *perniciousness* which characteristically distinguishes it.

In Case 1, in which I was led by the foregoing considerations regarding hæmolysis to adopt a milk diet, the result seemed in the first instance satisfactory.

The patient was placed on a more farinaceous diet on March 10th, his previous diet having been made up of beef-tea, extracts of meat, etc. The effect of this treatment was at once noticeable, being evidenced by an entire disappearance of blood-pigment granules from the urine, and by the subsequent improvement in the patient's general condition.

After his attack on April 20th, I placed him on a purely milk diet. The disease was, however, too far advanced to permit of successful treatment. Under the milk diet the amount of blood destruction, as evidenced by the high colour of the urine, continued to be increased. I should be inclined, however, to give a purely milk diet another and a fairer trial than the advanced nature of this particular case admitted of. This line of treatment was in part suggested by the investigations I was at the time (1889) making on this very case, with regard to the putrefactive changes in the intestinal canal (see "Excretion of aromatic sulphates," Chap. XVII.).

I deemed the matter sufficiently important to be submitted to experimental test.

Influence of Diet on Intestinal Putrefactive Changes.

I therefore instituted a series of observations in order to obtain some further data as to the effect of a more exclusively farinaceous diet on the change occurring within the intestine. The observations undertaken to this end were kindly carried out for me by Dr. F. W. Burton-Fanning (now of Norwich). The results obtained are of great interest in this connexion. The method adopted was to determine the relative excretion of free and aromatic sulphates in the urine of a dog, on (1) a mixed diet, and (2) on a more farinaceous one.

Table shewing Influence of Diet on Excretion of Aromatic Sulphates.
(*Dog.*)

Date.	Quantity of Urine in c.c.	Free Sulphates, as $BASO_4$ (A).	Aromatic Sulphates, as $BASO_4$ (B).	Ratio of A to B.	Diet.
1889.		Gramme.	Gramme.		
Feb. 8	434	0·978	0·106	9 to 1	Meat biscuits.
,, 13	420	1·386	0·105	13 ,, 1	,,
,, 18	470	0·639	0·0775	8 ,, 1	,,
,, 20	340	0·720	0·1258	5½ ,, 1	,,
,, 22	...	...	...	...	Milk, bread, and oatmeal.
,, 24	440	0·673	0·0396	17 ,, 1	,,
,, 25	440	0·776	0·0484	16 ,, 1	,,
,, 27	300	0·757	0·0540	14 ,, 1	,,
,, 28	260	0·824	0·0572	14 ,, 1	,,

Results.—From the foregoing table it will be seen, that while on a mixed diet the ratio of the free to the aromatic sulphates was on the average 9 to 1—the normal ratio (see p. 190)—the effect of the more farinaceous diet was to reduce the excretion of aromatic sulphates (*i.e.*, to lessen the amount of putrefactive loss occurring in the food within the intestinal canal) by more than one-half, with an average ratio of 15 to 1.

The result may be expressed in this way—that with an almost equal quantity of food of both kinds, the amount of loss due to putrefactive changes within the intestinal tract was diminished by more than one-half by the use of a more farinaceous diet; at the same time there was an increase in body weight. It is on these grounds that I believe good results may be expected from a more exclusively farinaceous diet in cases of pernicious anæmia.

But, as I have stated, no general rule can be laid down applicable to all cases alike.

I am satisfied, however, of the great importance of determining in each case the particular diet most suitable; and it is in this respect that hospital patients, in my experience, appear to be far better off than private patients, since they remain a longer time under daily observation, and their individual peculiarities can be better ascertained.

Serum Treatment.

It is obvious, however, that if once the infection gets firmly rooted in the mucosa, mere local antiseptic treatment—however much it may benefit by diminishing or removing catarrh and thus arresting the disease temporarily—may fail to arrest it permanently, even when aided, as when possible it ought to be, by the use of arsenic, and by every possible dietetic measure; and experience proves only too fully that such is the case.

The only indication for treatment, then, is to combat the action of the poison on the blood after its absorption.

To this end I propose in future to give a sustained and systematic trial to a serum treatment based on the results above stated.

There is no disease in which we have such conclusive evidence of a local action on the blood as we possess in the case of pernicious anæmia. The chief ill-effects of the disease are due to the progressive blood destruction, and its consequent anæmia. If we could eliminate this local action on the blood, or counteract it, the disease as a disease would lose its characters. Its infection would be interesting as a cause of septic stomatitis, gastritis, or possibly some form of enteritis, with their attendant symptoms; but it would not cause the anæmia which it now does.

I propose, then, to try the effect of systematic serum treatment. The nature of the serum I shall reserve for later investigations accurately to determine. For the present I propose to try the effect of antistreptococcic serum, inasmuch as my observations point to pyogenic organisms as always being concerned in the infection.

In suggesting this treatment I desire to make clear that its trial is based, not on any hypothetical considerations as to the nature of the anæmia, but on a series of observations, extending now over fifteen years, which slowly, step by step, have served to trace the anæmia back to an infection arising in connection with the alimentary canal. I have purposely refrained from suggesting such treatment, or from trying it, till I was in possession of facts which appeared to me conclusive as to the infective nature of the disease; and till I had definitely formulated, as I have now done, the grounds of my conclusions.[1]

[1] Hunter, *Lancet*, Jan. and Feb. 1900.

The first case of the disease treated on the lines recommended above—oral and intestinal antisepsis combined with anti-streptococcic serum—is that recorded by Dr. William Elder of Leith.[1]

The case is very fully recorded, and is of special interest, apart from the remarkably beneficial effects of serum treatment, as being the first case published subsequent to my drawing attention to the importance and prevalence of oral sepsis in this disease.

As regards the possible benefit to be got from serum treatment, Dr. Elder's conclusion appears to me to put the matter so clearly, that it may fitly be reproduced here, in connexion with a summary of the case.

The case, I agree with him, was one of pernicious anæmia, and, moreover, a severe case. The treatment was oral and intestinal antisepsis with injection of antistreptococcic serum. None of the usual remedies for anæmia were given. The result was, that in forty-five days after the commencement of the treatment, the blood condition, which at the outset was 18 per cent. of corpuscles with 24 per cent. of hæmoglobin, was normal: namely, 96 per cent. of corpuscles and 104 per cent. of hæmoglobin. A month later "he reported himself as feeling fit and well, and looked in very good health."

In all, no fewer than eighteen injections were given in the course of six weeks without any ill-effects, either local or general.

The only systematic trial I have made of the treatment has been in Case 11. [In Case 10 it was used alternately with arsenic, so that no therapeutic inference can be drawn.] The case was a very typical one in its mode of onset, character of its gastric symptoms, its urinary changes, its nervous symptoms, and in its oral symptoms, and it was in a comparatively early stage. It had not been recognized before as one of pernicious anæmia: consequently had had no arsenical or other special treatment.

The blood condition was 30 per cent. of corpuscles and 35 per cent. of hæmoglobin.

[1] *Lancet*, April 28, 1900, "A Case of Pernicious Anæmia treated by Antistreptococcic Serum," by William Elder, M.D., F.R.C.P. Edin., Physician to Leith Hospital.

The treatment was milk diet, oral and intestinal antisepsis, ammonium carbonate and tincture of digitalis as a cardiac tonic, and injection of antistreptococcic serum.

In all, four injections of the latter were given—viz., 10 c.c. on the 9th and 13th July, followed later by two injections of 5 c.c. Before treatment was commenced the blood condition had further deteriorated, the red corpuscles being reduced to 27 per cent. This was on the 7th July.

Between the 9th July, when he got the first injection, and the 1st August (*i.e.*, three weeks), the corpuscles had risen from 27 per cent. to 65 per cent., and the hæmoglobin from 35 per cent. to 75 per cent., and one notable feature of the blood at this time was the marked leucocytosis—leucocytes 17,000 per c.mm. (instead of the normal 5000 to 7000).

He received a fourth and last injection (5 c.c.) on August 1, and the treatment was discontinued mainly on account of the local reaction caused by the serum. It excited a brawny œdema which extended over the flank.

The patient continued to improve for the next ten days, although his actual blood condition showed some relapse; and he then went to the country (Aug. 16). The treatment was as before, namely:—strict oral and intestinal antisepsis, with in addition ʒi. of the syrup of the hypophosphites thrice daily as a tonic. Arsenic was still withheld. He returned in six weeks' time (Sept. 26) greatly improved in looks; and his blood shewed red corpuscles 3,200,000 (64 per cent.), and hæmoglobin 80 per cent.

He was now given liquor arsenicalis in three minim doses thrice daily, increased to five minims three weeks later.

The result up to the present is that when he reported himself on Nov. 8th, 1900, his blood shewed: red corpuscles 4,040,000 (80 per cent.), hæmoglobin 90 per cent., and leucocytes 7500 per c.mm.; his weight was 11 stone 3 lbs. (157 lbs.), an increase from the time he came under observation of two stones (24 lbs.); and his gastric and intestinal functions were in all respects normal.[1]

	Red Corpuscles.	Hæmoglobin.	Leucocytes.
[1] Dec. 6, 1900.	4,320,000 (86 per cent.)	90 per cent.	——
,, 20, ,,	4,640,000 (92 ,,)	92 ,,	5000 per c.mm.

Patient looks in robust health.

He still retained the feeling of numbness in his fingers, although this had recently greatly lessened.

As regards the effects of the serum treatment, it was observed in this case, as also in Case 10, that the injection usually caused a distinct general reaction, lasting usually for forty-eight or sixty-four hours; and several times, as already stated, there was a local reaction as well; this latter, possibly, due to the fact, ascertained on enquiry, that the serum contained double the usual strength of carbolic acid.

There was no general reaction in Dr. Elder's case with any of the injections.

Whether its presence was connected with the character of the disease, or of the special serum used, it is impossible to state. But in view of its possible occurrence, it is, I consider, advisable to begin with small doses (5 c.c.).

As regards the probable scope of usefulness of this treatment, it is at present quite impossible to speak. As I have said, the object of it is not to replace the line of treatment hitherto employed—and up to a certain point successfuly employed—namely, by arsenic; nor is it to replace the new line of treatment by combined oral and intestinal antisepsis which I have recommended, and to which I attach an even greater importance than to arsenical treatment, inasmuch as it aims at *the removal of the cause* and not merely *the combating of the results*.

It is intended to supplement both these lines of treatment if they fail to arrest the disease.

It is, in my experience, certain that the disease cannot be permanently checked by the use of arsenic alone. But that may possibly be due to the fact that up till now—the septic nature of the disease and the importance of oral sepsis not having been recognized—the source of infection has remained undisturbed, and hence the patient, cured once by arsenic, has remained continuously exposed to fresh infection.

The prime object of the combined oral and intestinal antiseptic treatment is to remove both the original source of the infection and the conditions which favour infection. If this succeeds, there may be no necessity for further treatment other than by arsenic.

If both together fail to arrest the disease, the serum treatment is the one which appears to me to hold out most prospect of benefit, and the cases just recorded certainly denote that it has markedly therapeutic properties.

Dr. Elder's Case.

"A man, aged 35 years, was admitted to Leith Hospital on Jan. 27th, 1900, complaining of debility and breathlessness. The history of his present illness was as follows. About six months before (in July 1899) the patient had a severe attack of sickness and diarrhœa, and since then he had felt that he was gradually getting weaker, and he had had occasional attacks of sickness. About the end of the following November he had what he called a 'chill,' which seems to have been a slight feverish attack. After this left him he felt more debilitated than ever. It tired him to walk short distances, and he began to be very breathless. About the first week in December he first noticed that his skin was of a pale yellow tinge and he became troubled with constipation. For a month or two before he came under treatment he had had very slight bleeding piles, but he had never lost much blood, only a streak having been detected very occasionally. He continued to work till three weeks before admission, and was then forced to stop owing to his weakness. He attended at the hospital as an out-patient for ten days before his admission. He had not previously had any definite illness, but he occasionally suffered from pain along the costal margin on both sides, which was, he said, very slight, and he sometimes had 'bilious attacks.' About seventeen years ago he was troubled very much with bad teeth, had many gumboils, and had to get several teeth extracted. Since then his teeth had been bad and had troubled him much, but gumboils had not been so frequent. His mother, father, and the other members of the family were strong and healthy.

"*State on Admission.*—The patient was found to be a markedly anæmic man. His skin was of a lemon-yellow colour. The palpebral conjunctiva and the mucous membrane of the mouth were very pale, and the ocular conjunctiva was slightly yellow. He had a rigor shortly after admission, was breathing very rapidly, and was almost pulseless. The temperature was 100°·8 F. The pulse improved after he was given an ounce of whisky and five minims of digitalis, and it was 124 about half-an-hour after admission. *The Spleen* was not enlarged. *The Blood* was examined on Jan. 29th, two days after admission, and shewed hæmoglobin 24 per cent., red corpuscles 797,500, and white corpuscles 4520. *Integumentary System.*—The skin had a soft velvety feel and was of a yellow lemon tint, except over

the lower part of the back, where it was brownish in colour, the discoloration being diffused and not in circumscribed patches. *Circulatory System.*—He had palpitation and shortness of breath on exertion. If working with his head low, he felt very giddy. He was occasionally troubled with tinnitus aurium. The cardiac impulse was neither visible nor palpable. On percussion the base was at the upper border of the third rib and the right border reached to the right edge of the sternum. The left border was $3\frac{1}{2}$ inches from the mid-sternum. Auscultation detected nothing abnormal about the sounds. The pulse was 124 per minute; it was large, soft, and easily compressible. *Alimentary System.*—The tongue was pale, flabby, and indented by the teeth. The lips and the mucous membrane of the mouth were pale. Many of the teeth were in a state of decay, and there were a number of carious stumps. The appetite was fairly good and the thirst was not increased. The patient sometimes suffered from pain along the left costal margin and a burning sensation in the stomach. These sensations had no reference to food. The bowels were very constipated. The stomach was not enlarged. Liver dulness extended to about an inch above the costal margin. *Nervous System.*—On rising after sitting for any length of time he felt giddy and his limbs were very tremulous when he walked. He complained of seeing dark specks before his eyes, and occasionally he saw yellow and red lights floating in the air, the red being close before his eyes and the yellow at a distance. His temper was rather irritable. He had not been sleeping very well for some time. On ophthalmoscopic examination nothing abnormal could be seen in the retina. *Respiratory System* shewed nothing abnormal. *Urine.*—The specific gravity of the urine was 1020. The reaction was acid. There were no abnormal constituents and no indican.

"*Treatment and Progress.*—The patient was put on milk diet and was given a febrifuge mixture and half an ounce of whisky every six hours as a stimulant. On the evening of Jan. 27th the temperature reached 103°·6 and the pulse was 120. On the 28th the temperature was 101° in the morning and 101°·4 in the evening, and the pulse was 120. On the 29th the temperature was 100°·8 and the pulse was 110. On the 30th he was very suspicious, and it was very difficult to get him to take his medicines, as he thought that the medical attendants and the nurses were trying to poison him. The temperature on this day was 100° and the pulse was 108, and on the 31st the temperature was 99° and the pulse was 100. On Feb. 1st the temperature was down to normal and the pulse was 100. When the lights were turned down he became very excited; he jumped out of bed and was brought back after a great deal of persuasion. An attempt was made to give him bromide, but he absolutely refused to take any drugs. He complained of being hungry,

so he was given hot milk with 15 grains of sulphonal dissolved in it. He quieted down after a while and slept better than he had done for several nights. On the 3rd he was quieter, and talked more sensibly. He was put on a convalescent diet. *Special Treatment.*—The following treatment was then begun.

"*Special Treatment.*—As regards the treatment of the case, the details are sufficiently noted in the notes which I have already given. The treatment was begun on Feb. 3rd, exactly a week after the patient's admission into the hospital. His mouth was thoroughly washed, and brushed with an antiseptic mouth-wash, and he was given 5 grains of salol and 15 grains of salicylate of bismuth internally every six hours. Ten c.c. of antistreptococcic serum were at first injected into the subcutaneous tissue over the dorsum ilii every second day. At the first two injections, on account of a fault in the syringe, he received only about eight cubic centimetres, but afterwards ten cubic centimetres were given on each occasion except on Feb. 9th, when he got only five cubic centimetres. From Feb. 3rd till March 19th he received in all eighteen injections of the serum, and the antiseptic treatment was continued all through. With the exception of a hypnotic occasionally when his nervous symptoms required it and a dose of castor oil or cascara sagrada for his constipation, this was the only medicinal treatment. He got none of the usual remedies for anæmia—neither iron nor arsenic nor bone-marrow. His blood was examined at intervals of about a week and the result is noted in the following table. The treatment, it should be said, began on Feb. 3rd."

Date.	Red Corpuscles.	Hæmoglobin.	Leucocytes.
January 29, . .	797,500	24 per cent.	4520
February 7, . .	1,962,500	44 ,,	4700
,, 13, . .	2,340,000	66 ,,	4500
,, 23, . .	3,355,000	66 ,,	5100
,, 28, . .	3,700,000	90 ,,	5100
March 10, . .	4,360,000	88 ,,	4500
,, 20, . .	4,800,000	104 ,,	...

On March 20th (fifty-two days after his admission and forty-five days after the commencement of treatment) his blood had practically reached the normal.[1]

"It would be a mistake to draw very decided conclusions from the results obtained by the serum treatment of one case, the more

[1] On April 3rd an examination of his blood was made. The red corpuscles were found to be 4,325,000, hæmoglobin 104 per cent., and leucocytes 5600. On April 16th he was discharged from hospital, and on April 22nd he reported himself as feeling fit and well, and looked in very good health.

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especially as cases of pernicious anæmia are so apt to be intermittent—a fact which almost every practitioner who has had experience of such cases must soon have noted. If a new method of treatment is adopted in those cases, we are apt to think that the particular treatment has been the cause of the improvement. The hopes of the profession have been raised again and again with regard to this disease by the announcement of good results from particular forms of treatment. Arsenic and bone-marrow have probably hitherto given the best results, but although improvement has been derived from both forms of treatment, in many cases such improvement has generally been only temporary, and the disease, as regards its ultimate result, has been one of the most hopeless. Whether further experience of antistreptococcic serum will confirm the result I have obtained in this case or not time alone will enable us to judge. That every case will be benefited by this treatment I can scarcely venture to hope, because the chances are that the disease, even if due to a specific infective affection of the gastric mucosa, may not always be due to the same species of organism and may, as suggested by Dr. Hunter, be owing to 'mixed' infection. Judging from the results which have been obtained from the use of the antistreptococcic serum in other conditions of blood infection, and from what is recorded in the medical journals, it must be concluded that this serum is not at all certain in its curative action. Whether this result is due to faulty serum placed upon the market, or, as is more probable, to some cases of blood-poisoning being due to 'mixed infection,' or to there being several species of streptococci producing a poison, giving rise to similar symptoms but not counteracted by the administration of the antistreptococcic serum in the market, further experience will show. The case recorded above is suggestive, and I believe this form of treatment is worthy of a further careful trial by those who have cases of pernicious anæmia under their care."

Remarks.—When one considers how unsatisfactory the treatment of cases of pernicious anæmia has been in the past, I make no apology for thus early recording the results obtained in this interesting case. Dr. Hunter, who has done so much in his investigations on this disease carried on for many years, has arrived at the conclusion that the anæmia which is such a characteristic symptom is *only* a symptom, and is a result of an infection of the alimentary tract. I do not at this time intend entering into a full discussion of the evidence which he has so ably brought forward in support of his conclusions, but this case is one which, apart altogether from the result of the treatment, might be used by him to further support his views.

"As regards the primary cause of the disease this case supports Hunter's views. The mouth and teeth could be described as in a state of neglect. A large number of teeth were carious and many were

reduced to mere stumps, and he gave a distinct history of having had frequent gumboils. The history of discharge of pus into the mouth extended back for many years. He had a history of occasional bilious attacks during the previous six months, with pains referred to the costal margin, pointing to gastric disturbance, for some time before the onset of his anæmia, and he gave a history of having suffered from an attack of diarrhœa at the onset of his gastric symptoms. These gastric and intestinal disturbances are therefore also in accordance with Hunter's theory of the cause of the disease."

PART VIII.—THE PHYSIOLOGY OF BLOOD DESTRUCTION (HÆMOLYSIS).

CHAPTER XXXIII.

EVIDENCES OF HÆMOLYSIS.

Introductory.

What evidence do we possess that a destruction of blood is a normal physiological process?—There is every reason, if only from analogy with the case of all tissues, to believe that the blood is subject to changes both in its corpuscles and plasma, necessitating their renewal from time to time.

To what extent is this the case? Where—in the blood, or in certain organs—is it most exposed to such changes; by what agencies is its destruction effected; and what are the conditions that determine its amount?

These constitute the problems comprised under the title 'Hæmolysis,' which formed the subject of the following histological, experimental, and chemical investigations.

The evidence as to the existence of a regulated hæmolysis, carried on by certain agencies, in certain situations, and under certain conditions, precisely as is the converse process of blood formation, proves, I find, to be very considerable in amount. It necessarily varies, however, according to the portion of the blood to which we have regard, whether *Plasma*, *Leucocytes*, or *Red Corpuscles*. It is greatest in the case of the red corpuscle—not at all on account of the intrinsic importance of the changes affecting red corpuscles as distinguished from those affecting the leucocytes and plasma, but solely on account of the

prominence of their chief constituent, hæmoglobin, and of the pigments derived from them.

1. *Pigments.*

Hence it is, that what at first sight may seem an altogether disproportionate amount of attention has to be given to the red corpuscles—to the fate of hæmoglobin, and to the fate of pigments derived from hæmoglobin. Important evidence as to the occurrence of hæmolysis as a normal process is derivable from a study of these *Pigments*—whether excreted in the form of *Bile* or *Urinary Pigment*, or stored up as *Blood Pigment*.

If, then, in the course of these studies much space is devoted to pigments, and particularly to blood pigment—its character, distribution, mode of formation, and ultimate disposal—it is not on account of the importance of blood pigment as such, or of any lesser prominence of the products of leucocytolysis or plasmolysis. It is solely because I found the points necessary to elucidate regarding hæmolysis could best be elucidated by a detailed study of the fate of the red corpuscles and their constituent—hæmoglobin, rather than by any similar study regarding the other constituents of the blood—leucocytes, or the plasma.

As it has turned out, this greater attention bestowed on the red corpuscles and their fate has not tended to eclipse in any way the importance of the leucocytes or of the plasma—quite the contrary. For one of the chief results of these detailed studies regarding the mode of origin of blood pigment from hæmoglobin has been, to shew that in the process of hæmolysis all parts of the blood are involved; that the changes which affect the red corpuscles injuriously are referable to changes in the plasma; these, in turn, to the activity of the leucocytes; and these again to the activity of the mass of lymph follicular tissue of the blood glands, notably of the gastro-intestinal mucosa, of the spleen, and of the lymph glands.

2. *Morphological Changes in the Corpuscles.*

The evidences of hæmolysis are, however, not confined to pigments, either biliary, urinary, or blood. They include also

certain well-marked *morphological changes* in the blood itself. These changes are often little marked, and might be of doubtful significance in health; but they become very prominent and significant in disease when the amount of hæmolysis is increased. They affect chiefly the red corpuscles—viz., changes in shape, size, and consistence; but they also affect the plasma, which throws down precipitates of nucleo-proteid matter in the form of small granules, spheres, etc.

The chief changes referred to above, and which, as stated, involve the plasma, the red corpuscles, and the leucocytes, are as follows:—

1. The formation of *colourless albuminous granules and spherules* of varying size, the products of the disintegration of plasma and of red corpuscles, the smallest of them closely resembling the bodies variously termed by observers 'hæmatoblasts' (Hayem), 'blood plates' (Bizzozero), 'granule bodies' (*Körnchenbildungen*, Max Schultze), 'elementary bodies' (*Elementarkörperchen*, Zimmermann).

They are derived, according to my observations, *partly from the red corpuscles*, the protoplasmic stroma of which can be seen oozing out in droplets and floating away free in the form of small spherules;[1] *but far more largely as precipitates from the plasma itself.* A large number of them I therefore regard as nucleo-proteid precipitates (granules) thrown down from the plasma. The leucocytes, so far as my observations go, are an altogether secondary and unimportant source of such granules.

The relation between these products of hæmolysis on the one hand, and the "hæmatoblasts" (Hayem), and "blood plates" (Bizzozero), regarded as normal elements of the blood, and, by the former, as the precursors of the red corpuscles, has been to me a subject of much interest throughout these investigations. Without dealing with it in detail, I may say that I have not been able to detect any essential or constant difference between the granules described above and the blood-plates. Hence the question as to the relation of these blood-plates to blood formation, a subject on which Hayem expresses himself with much assurance, I regard as still an entirely open one. I have totally failed to satisfy myself of the existence of

[1] See Plate I.

any such relationship. I regard them rather as precipitates from the plasma.

2. Small *coloured microcytes* derived from the red corpuscles, partly by a process of oozing in the way just described, but more frequently and characteristically by what I have for convenience termed a process of '*budding*' (Plate I.). The red corpuscle is seen to become constricted at some part, forming a small bud identical in depth of colour and appearance with the main mass of the corpuscle, and the two portions may frequently be seen united for a time by a delicate colourless process. This change in the red corpuscle I regard as very characteristic of blood undergoing destructive change. I never observed it in healthy blood, but I have found it to be a characteristic and notable feature of the blood in pernicious anæmia. In no way can it be better studied than by gradually warming blood to a temperature of 45° or 50° C., as Max Schultze first shewed. Under these circumstances the whole of the red corpuscle may be seen thus to break up, forming a number of highly-coloured spheres.

3. *Stromata*, decolorized red corpuscles, the framework of the red corpuscles freed from hæmoglobin; best studied after injection of distilled water into the blood; albuminous spheres, usually colourless, sometimes retaining a little of their hæmoglobin, homogeneous throughout, and without obvious envelope.

4. The stromata are to be sharply distinguished from *schatten*. These are small vesicles consisting of an outer envelope enclosing a fluid, and usually two or three exceedingly minute particles of indistinct character. They are derived from red corpuscles, freed from hæmoglobin, the envelope being, I consider, an artificial product, resulting from a chemical change in the extreme outer portion of the stroma. I have *never found this change in the blood in health; it is not a product of normal hæmolysis*. It denotes a degree of change in the blood such as is never found as the result of disease, and can only be induced by the action of certain chemical agents. The bodies described are not to be found in the blood after injection of distilled water, while stromata and colourless spherules are in abundance. They are frequently found, however, in great numbers after the injection of strong chemical agents, such as pyrogallic acid or toluylendiamin, more especially the former.

It was from a study of the distribution of these changes in different organs and portions of the circulation during active hæmolysis induced in various ways that I obtained most information regarding both the nature and the seats of hæmolysis.

These are the chief evidences of hæmolysis in health. In disease, however, additional evidences of an even more marked character are forthcoming.

They include:—

3. *Increased Excretion of Biliary and Urinary Pigment*—viz., *Polycholia* and *Urobilinuria.*
4. *Hæmoglobinuria.*
5. *Jaundice*, or icteric conditions allied thereto.
6. *Anæmia*, including *Oligocythæmia*; marked variations in size and shape of the red corpuscles—*Poikilocytosis*; *Reduction in Hæmoglobin.*
7. *Deposition of Pigment* in the liver, spleen, and kidney.

The significance of these conditions in relation to hæmolysis has already received ample illustration in the course of the studies already recorded regarding the changes in disease. In health the evidence of most importance is that connected with blood pigment and bile pigment, and that evidence will therefore now be considered.

A.—Blood Pigment as an Evidence of Hæmolysis.

This is the pigment so frequently met with around old extravasations, and its characters and the appearance it presents have long been familiar to every one. It differs from the bile and urinary pigments in two respects—first, that it is usually found in an amorphous or granular form; and secondly, that it retains all the iron of the original hæmoglobin molecule.

The first circumstance enables it to be recognized by means of the microscope. The second also conduces to its easy recognition and detection, since by suitable micro-chemical methods the iron it contains can be made to yield characteristic colour reactions. In the original hæmoglobin the iron is so combined as to be unrecognizable by the ordinary tests. In blood pigment, on the other hand, it is in a more or less free condition, existing as a ferrous or ferric salt, probably as an albuminate of

iron. As such it gives the usual reactions of iron salts, being blackened by sulphide of ammonium, and giving the Prussian-blue reaction with ferrocyanide of potassium and dilute hydrochloric acid, etc.

Although the origin of blood pigment from hæmoglobin is so obvious as to be beyond all dispute, the interest connected with its genesis is by no means thereby exhausted. On the contrary, around the apparently simple question of the mode of origin of blood pigment from hæmoglobin, there raged nearly half a century ago a sharp controversy, taken part in by three of the most distinguished pathologists of the century—*i.e.* Henle, Virchow, and Kölliker; and the controversy cannot even yet be said to have terminated.

It was with regard, then, to the above pigment that in the course of enquiry I found it necessary to study in detail many points which at first sight appear of relatively little importance —*e.g.* in the case of the liver the situation of the pigment within the capillaries, or within the liver cells; the differences in the size of the pigment and granules under different circumstances; the conditions under which it appears in one or other situation; the conditions determining the distribution of pigment amongst the various organs—sometimes more in one, sometimes more in another.

It was a study of these various points that led me to certain conclusions of importance regarding the significance to be attached to blood pigment as an indication of a destruction of blood.

Situations in which Blood Pigment is found.—There are three chief situations in which, according to my observations, blood pigment is to be found, independently of extravasation or congestion—viz. (1) *Liver* (capillaries and liver cells), (2) *Spleen*, and (3) *Bone marrow*; occasionally also the *Kidney* (cells of convoluted tubules).

It has been usual to hold that the presence of blood pigment (always, of course, apart from extravasation or congestion) in such organs as the liver or spleen is not only an indication of some previous destruction of blood, but also that its amount indicates the extent of that destruction. Other things being equal, so it has been held, the larger the amount the greater

necessarily the previous destruction. Such was the view I also held at the outset of my investigation.

I find, however, that this is very far from being the case. On the contrary, the significance attachable to blood pigment as an index of hæmolysis varies very much under different circumstances. Its presence may denote not a larger, but, on the contrary, a lessened hæmolysis; while conversely its absence is not only compatible with, but may indeed indicate increased hæmolysis.

In the case of mammals, *in health*, it may almost be said that the amount of blood destruction has been inversely proportional to the amount of blood pigment present in the spleen and the capillaries of the liver.

Consideration of mere quantities alone, apart from that of its character and situation, may thus lead to entirely erroneous conclusions regarding the extent of the destructive changes.

Two different processes may, I find, be distinguished in the blood, each of which may lead to a formation of blood pigment —one of them denoting active hæmolysis, the other the absence of such hæmolysis. These may be designated (1) *Acute Hæmocytolysis* and (2) *Chronic Hæmocytolysis.*

Curiously enough it is the latter process that leads to the formation of most blood pigment.

The changes in the red corpuscles that precede a formation of blood pigment in the two cases are different.

(1) **Chronic Hæmocytolysis.**—This process is marked by a gradual decay of the red corpuscles. They become spherical, deepen in colour, and retain their hæmoglobin to the last. In this form they continue to circulate until finally they are enclosed within the active cells of the spleen, or leucocytes of the blood, and are stored up within the *spleen* or in the *capillaries of the liver.*

Within these cells their hæmoglobin becomes transformed into blood pigment; and the pigment so formed is characterized generally by the varying size of its granules, and by the largeness of at least some of them, corresponding as they do in size to that of the original red corpuscle. The large size of such pigment granules is best seen in animals possessing large corpuscles—*e.g.* birds, frogs. It is this process that leads to the formation of the larger particles and clumps of pigment in the

capillaries of the liver in frogs, birds and mammals; and also in the spleen of old mammals and after transfusion. (See figs. 12, 13, p. 133; fig. 1, Plate V,; and fig. 1, Plate VII.)

The particular points to be noted about this process are:—(1) That *the whole of the hæmoglobin of the corpuscle is converted into blood pigment*; and (2) that, as regards the liver, *the pigment so formed is found within the capillaries, and never within the liver cell.*

The conditions favourable to such a mode of death of the red corpuscle are for the most part negative. They are such as *old age, abstinence from food, want of exercise*—in short, conditions implying a relative inactivity of the cells of the body. The red corpuscle, it may be said, dies a slow natural death.

(2) **Acute Hæmocytolysis.**—The second process is marked by a different series of phenomena. The first of these is a liberation of hæmoglobin from the corpuscle. It escapes from the corpuscle, either alone, or in combination with the albuminous stroma. Its fate is not, as in the former case, to be taken up by splenic cells or leucocytes within the blood; but it is carried to the liver in the portal blood, whence it is taken and broken up by the liver cells. The chief result is a formation of bile pigments, not of blood pigment. A formation of blood pigment does not necessarily, in my opinion, attend the breaking up of hæmoglobin by the liver cell in mammals.

It is in this respect that the above process differs most materially from the one first described. In that, the whole or greater part of the hæmoglobin is transformed into blood pigment; in this process, on the other hand, little or no blood pigment may be formed, the chief result being bile pigment. Although the splitting up of hæmoglobin within the liver cell is not *necessarily* attended by a formation of blood pigment, such a formation may, and in many cases does, take place: sometimes to a very large extent, both in health (birds and mammals), and still more markedly in disease (pernicious anæmia, action of certain poisons). In that case, however, only a part of the hæmoglobin molecule is converted into blood pigment; and the pigment so arising may be distinguished by certain features—namely, the small and more or less uniform size of its granules. It is only pigment of this kind that is

found *within* the liver cell. (Fig. 2, Plate V.; and Plates III., VI., VIII., IX., and X.)

A liberation of hæmoglobin from the red corpuscles implies the existence of conditions of the plasma to a certain degree unfavourable to the red corpuscles. These conditions are such as are induced during the absorption of the products of digestion, when the activity of cells within the blood and within the blood tissues (lymphoid tissues) is at its greatest. The death of the red corpuscle is thus an acute process, as compared with the slow decay characterizing the first-mentioned process.

Summary.—I am thus led to recognize that two diametrically opposed processes in the blood may lead to the formation of blood pigment, one of them marking the absence of changes in the blood—an absence of hæmolysis; the other as definitely marking great activity within the blood—*e.g.* active hæmolysis.

Since the object of our study is to ascertain what it is that affects the blood as a whole, and not any one particular element of it, it will, I think, be clear that it is only the latter process which invites attention. It alone affects the blood as a whole, the former being unattended by general changes in the blood, but rather marking the absence of such changes. It is the changes in the red corpuscles connected, then, with acute hæmocytolysis that especially deserve our consideration.

I consider then that the mere amount of blood pigment, apart from its character and situation, is no reliable index of the amount of hæmolysis. The slow death of the corpuscles, by favouring, in the way above described, the conversion of the whole of the hæmoglobin into blood pigment, may lead to the formation of much blood pigment in spleen, capillaries of liver and marrow. Anything, on the other hand, that favours the liberation of hæmoglobin favours the destruction of the hæmoglobin by conversion into bile pigment, and its removal from the body without necessarily any formation of blood pigment at all. The increase of blood pigment in the spleen and *capillaries* of the liver commonly met with as age advances is not, then, in my judgment, an evidence of *increased* hæmolysis, but rather an evidence of *lessened* hæmolysis. Conversely, the absence of such pigment (*e.g.* in health, in young mammals) is, on the other hand, not only quite compatible with a very considerable

hæmolysis, but, properly regarded, may be considered to be important evidence of such hæmolysis, since it denotes that the red corpuscles have not been allowed time to undergo a process of natural decay.

B.—Bile Pigment as an Evidence of Hæmolysis.

Origin from Hæmoglobin.—As regards the *Bile pigment*, all evidence points to (*a*) *Hæmoglobin* as its source; and (*b*) the *Liver* as the seat of its formation.

(1) It has been fully established by Virchow, Jaffe, Langhans, Hoppe-Seyler, Cordua, and Quincke, that the crystalline pigment—hæmatoidin—so frequently found in old blood extravasations is chemically identical with bilirubin, the chief pigment of the bile. Some of the pigments causing the characteristic discolorations of bruises are indistinguishable in character and reactions from bilirubin and biliverdin (Langhans, Cordua, and Quincke).

Under certain conditions, therefore, such as those above referred to, the hæmoglobin of the blood undergoes changes leading to the formation of pigments closely resembling, if not identical with, the chief pigments of the bile.

(2) The close relation between hæmoglobin and the bile pigments becomes still more clear when we consider the close connexion (Hermann, Nothnagel, Kuhne, Tarchanoff, Stadelmann, and Afanassiew) between an increased destruction of hæmoglobin on the one hand, and an increased formation of bile pigments on the other. When hæmoglobin is injected into or set free in the blood, it is followed by an increased excretion of bile pigments (Stadelmann, Tarchanoff). So immediate and close is this relation, that an attempt has even been made (Stadelmann)—hitherto, it is true, with but partial success—to prove that it is quantitative as well as qualitative, and that the increase in the excretion of bile pigments is proportional to the quantity of hæmoglobin set free. Hæmoglobin is thus the source of the bile pigments daily excreted in health.

To what extent is this an evidence of a daily hæmolysis? The daily formation of bile pigments derived from hæmoglobin affords presumptive evidence of a certain amount of wear and tear of the hæmoglobin of the blood. This, however, does not

necessarily point to a *daily* destruction of blood. For, as I have just shewn, a certain amount of hæmoglobin may become effete—in the process of slow decay of red corpuscles—without the plasma or leucocytes participating, that is to say, without the occurrence of any destructive change in the blood as a whole (hæmolysis). If bile pigments can be formed in this process—if the hæmoglobin thus rendered effete is sufficient to give rise to all the bile pigment daily excreted—it is clear that bile pigment need not necessarily be an indication of a daily destruction of blood. It may be only an evidence of a certain slow decay of red corpuscles (chronic hæmocytolysis).

According to Quincke this is precisely what occurs. The normal fate of red corpuscles according to him is that, after a life duration extending for a period of from two to three weeks, they are taken up by the white cells of the blood and deposited in the capillaries of the liver, spleen, and bone marrow. Within these cells their hæmoglobin is transformed into various products of an albuminate nature, partly coloured, partly colourless; and these are afterwards used up in forming new red corpuscles, or got rid of by being excreted through the liver cells. Presumably during these changes—although as to this Quincke says nothing—the bile pigments are also formed.

It thus becomes a matter of importance to ascertain by which of the two processes in the red corpuscles above described—the slow decay or the active destruction—the formation of bile pigment is subserved.

A large weight of evidence—more particularly that adduced by Minkowski and Naunyn—points to the liver as the seat of formation of bile pigment from hæmoglobin. Within the liver, however, there are two possible seats of this transformation—*the blood capillaries* and *the liver cells*.

This being the case, the question now before us resolves itself into one as to the relative importance of the *capillaries* and the *liver cells* themselves as seats of formation of bile pigment.

Capillaries of Liver, or Liver Cells, as seats of Origin of Bile Pigment.—It may appear at first sight a matter of indifference, precisely where within the liver the transformation

of hæmoglobin into bile pigment takes place—whether within the capillaries, through the agency of leucocytes or endothelial cells, or within the liver cells themselves. I have not found it so.

On the contrary, I have found it necessary, in the course of these studies to distinguish, as clearly as possible, between processes carried on within the liver cells, and those occurring within the capillaries through the agency of the large mass of leucocytes contained within them.

In illustration two experiments (33 and 34, p. 375), in which a large quantity of ultramarine blue in suspension was injected directly into the circulation of rabbits duly anæsthetized, may be cited. The pigment was very abundant in the liver—more abundant, indeed, than in any other organ, excepting the lungs. Even during the injection, the liver, on being exposed, could be seen to become markedly blue. On examination, most of the pigment was found within leucocytes; not a single particle could be found within the liver cells.

The arrest of this pigment and its accumulation within the liver was, therefore, due entirely to the activity of leucocytes and kindred cells, endothelial and otherwise—not to the action of the liver cells themselves. We are not justified in speaking of such a function of the liver as on a parallel with hepatic functions proper—*e.g.* the glycogenic. The two are not even comparable with one another in importance. The one is carried out exclusively by cells of leucocyte and endothelial nature; the other by the liver cells proper. The only circumstance common to both is that they are carried out within one organ.

So with this conversion of hæmoglobin into bile pigment. If it can be effected equally well by leucocyte or liver cell—if, as Quincke, Minkowski and Naunyn seem to maintain, from the importance they attach to the pigment cells within the capillaries, these cells play the *chief* rôle in the formation of bile pigment—then the formation of bile pigment would cease to be exclusively a hepatic function. There would be no reason why it might not be carried out in other organs of the body equally rich in such cells—for example, the spleen, where such pigment cells, as will be afterwards seen, are very common.

Pigment Cells as the Seat of Origin of Bile Pigment.—When, passing from these more general considerations, we come to

the facts themselves, we find as follows: First of all, I consider it undoubted that cells of leucocyte and connective tissue nature do possess a certain power of forming pigments from hæmoglobin, apparently identical with those of the bile.

The observations, already referred to, of Langhans, Cordua, and Quincke are conclusive on this point. Langhans clearly shewed that the pigments causing the well-known colours of bruises—subcutaneous extravasations—are of the same nature as those of the bile. Even more clearly, if possible, has this been demonstrated by Minkowski and Naunyn. They have shewn that a green pigment, giving the reactions of biliverdin, may be found in the pigment cells within the liver capillaries in the goose. They found, moreover, that when they induced an increased destruction of blood, by exposing these animals to the fumes of arseniuretted hydrogen, the consequent increased formation of bile pigments went hand in hand with the appearance of large numbers of these cells in this situation. Sometimes only a single particle amidst the blood pigment within these cells gave the green reaction of biliverdin; at other times the whole cell substance appeared green. They conclude, then, that these pigment cells take a part, if not indeed, the major part, in the formation of bile pigments from effete hæmoglobin, a conclusion that would seem, under the circumstances, to be amply justified.

Such a view as to the mode and seat of formation of bile pigment agrees, in all points, with the view held by Quincke as to the ordinary mode of death of the red corpuscles (*v.* p. 367).

Liver Cells as the Seat of Formation of Bile Pigment.—My observations, however, lend no support to the view that such a method of formation of bile pigment is even a common one; still less, the usual one in health. On the contrary, they point to the liver cell itself as the seat of formation of bile pigment.

First of all, I consider that mistake has arisen from directing attention too exclusively to one group of animals, and applying the results thus obtained to animals of another group. This mistake has been made, in some degree at least, both by Naunyn and Minkowski, and by Quincke. The former based their conclusions too exclusively on their observations on the goose; the latter on his observations on the dog.

Now in both these animals the presence of a certain number of pigment cells in the capillaries of the liver is, in my experience, the rule; while, according to my observations, in most classes of animals—in the rabbit, cat, guinea-pig, pig, and in man—the presence of such cells is the exception, this being also the case in all *young* mammals, including even the dog. Individual differences exist in different animals in this respect, dependent mainly upon different conditions of life and individual differences in the resisting power of the red corpuscles—a resistance which also admittedly varies in different animals.

In the rabbit, for example, I have time after time examined the liver without finding a single pigment cell in its capillaries. Their presence is indeed the exception. Nevertheless, the excretion of bile pigment in the rabbit—as, indeed, in all herbivora—is, to say the least, fairly abundant. The daily excretion of bile is, indeed, greater in the herbivora than in the carnivora. According to Bidder and Schmidt, in the cat and dog it is approximately 15 c.c. and 19 c.c. per kilo of weight respectively, in the rabbit and guinea-pig it is 136 c.c. and 175 c.c. per kilo respectively. With such an abundant excretion of bile, containing a considerable percentage of bile pigments, one might reasonably expect to find, at least, some pigment cells in the capillaries of the liver, if pigment cells are the seat of formation of bile pigment. Still more might this be expected when it is borne in mind how permanent such blood pigment is, lasting, as it frequently does, for weeks, months, and even years. Yet none is present.

Conclusion.—I am compelled, therefore, to conclude either that the mode of formation of bile pigments may vary in different animals, being effected sometimes through the agency of pigment cells (leucocytes and cells generally), sometimes through the agency of the liver cells; or that its formation by the former, when it does occur, is altogether unimportant and insignificant, the constant seat of this process being within the liver cell itself. The first conclusion seems to me altogether untenable, if only on general grounds. It appears altogether improbable that a function, so characteristic of the liver as the formation of bile pigments, should be discharged, not by the special glandular structure—the liver cell—but by ordinary cells of leucocyte and endothelial nature lying adjacent to it. On such a view, one

would expect the spleen to be as much the seat of formation of bile pigment; since not only are its cells in closer relation to the blood than those of the liver, but the spleen is generally a repository of blood pigment to a far greater extent than the liver. Even Minkowski and Naunyn, however, have failed to find any trace of biliverdin in the pigment cells of the spleen. So far as pigment cells are concerned, the evidence is thus negative or inconclusive.

My own observations point on the contrary to the liver cells as the seat of this transformation, and to free hæmoglobin as the immediate source of the bile pigment—and that, too, not only in mammals, but also in birds.

In my experience, nothing more clearly indicates an acute hæmocytolysis with liberation of hæmoglobin than the presence of minute granules of blood pigment in the liver cells, more especially in those of the portal zone of the hepatic lobule. I find,

(1) That an increased formation of bile pigments is more frequently associated with an increased deposit of blood pigment *within the liver cells* than it is with an increase of pigment cells *within the capillaries.*

(2) Further, such an increased formation is frequently attended by an increase of blood pigment in the liver cells, without a particle of pigment or a single pigment cell being discoverable within the capillaries.

(3) Lastly, as already seen, the presence of pigment cells within the capillaries of the liver is the exception in certain classes of animals.

From these observations I therefore conclude that it is within the liver cells, and not in the capillaries, that bile pigment is formed from hæmoglobin. And inasmuch as in my experience the red corpuscles never pass bodily into the liver cell, the hæmoglobin thus transformed must have escaped from the red corpuscles before passing into the liver cells. In short, the immediate source of the bile pigment is not blood pigment, but free hæmoglobin; and *hence the daily formation of bile pigment must be regarded as implying a certain daily acute hæmocytolysis.*

Although, then, I do not absolutely deny to pigment cells of leucocyte and connective-tissue nature the power, under certain circumstances, of forming pigments similar to the bile pigments

from hæmoglobin, I am of opinion, for the reasons above stated, that such a mode of origin of the bile pigments is altogether of secondary importance. *The chief seat of their formation is the liver cell.* Not only are such pigment cells frequently absent from the tissues of animals in which an undoubted and even a largely increased formation of bile pigments is taking place ; but also, what is even more significant, a largely increased formation is frequently marked by an increase of the blood pigment in a situation where it can only be derived from free hæmoglobin, namely, within the liver cell. Such an escape of hæmoglobin from the red corpuscle into the plasma of the blood denotes some process at work in the blood, leading to the disintegration of a certain number of red corpuscles daily—an acute hæmocytolysis—and, inasmuch as the formation of bile pigments is a constant daily process, it follows that the hæmocytolysis which supplies the necessary hæmoglobin must be of no less constant daily occurrence.

CHAPTER XXXIV.

THE SPLEEN AS A SEAT OF HÆMOLYSIS.

Introductory.— Hæmolysis is thus, according to the preceding studies, not the slow chronic process we had hitherto supposed, but an altogether more acute process, of daily occurrence, involving the liberation of a certain quantity (however small) of free hæmoglobin.

I have now to consider where this change occurs—whether in the blood generally, or in some particular organ.

In this relation the first organ which naturally suggests itself as the probable seat of hæmolysis is the *Liver*. The bile pigments are formed by the liver, being derived within that organ from hæmoglobin. The liver is the chief seat of deposition of blood pigment in certain diseases—*e.g.* pernicious anæmia. It is also, in certain cases (see Plates IX. and X.), the seat of deposit of pigment when an increased destruction of blood has been brought about experimentally. Where more likely than within the liver does this destruction take place? And so, hitherto, the liver has been regarded as probably the chief seat of hæmolytic changes.

Next to the liver the *Spleen* suggests itself, and, if anything, with claims which appear to rival those of the liver. Blood pigment in greater or less amount is an almost constant constituent of splenic tissue; and the structure of this organ, along with the peculiarities of its circulation, seems specially favourable to the action of its cells on the blood circulating through its meshes, and possibly therefore to the destruction of some of the blood elements. (See p. 146.)

The determination of the exact rôle of the Liver and Spleen in hæmolysis I found to be one of the most difficult portions

of my investigation. The requisite data for deciding the matter one way or another were wanting.

The questions raised were of the following nature:

With regard to the significance of the simplest and commonest evidence of hæmocytolysis—namely, *Blood Pigment*—

(1) How far did its presence—*e.g.* within the liver, spleen, or other organ—denote that particular organ as the site of the antecedent hæmolysis?

(2) How far did its distribution between such organs—its greater abundance in one or other—denote the relative activity of these organs in the hæmolysis?

(3) How far indeed did its presence denote any hæmolysis at all? Might it not—*e.g.* in the case of the spleen—be merely an evidence of a 'scavenging' function on the part of that organ, as distinguished from any hæmolytic function; might it not even be, as suggested by Von Wittich, the result of capillary extravasations of blood in the delicate splenic tissue itself?

To these various questions, some very definite answers have been supplied by the studies here recorded.

1. Blood Pigment of Spleen not the result of Congestion or Extravasation.

The pigment within the splenic pulp is, I find, in no way due to the occurrence of capillary extravasations of blood, as suggested by Von Wittich. If such were the case it ought to be specially abundant in the chronically congested spleen of cardiac or hepatic disease. I have found, on the contrary, that such spleens are often singularly free from blood pigment.

2. Hæmolytic Function of Spleen no mere Scavenging One.

The blood pigment so often found has not accumulated in the spleen merely as the result of the scavenging function of the cells of that organ.

If such were the case, the liver ought invariably to contain an equal, or even greater, amount of pigment; whereas what one finds is that the spleen may be loaded with pigment while the liver contains none. So far as a mere scavenging function towards inert particles is concerned, the liver is a far more important organ than the spleen.

Thus after injection of carmine or ultramarine blue into the blood, the pigment particles are to be found in large masses within the capillaries of the liver, chiefly in the portal capillaries, while not a twentieth or even a fiftieth part of the quantity is to be found in the spleen.

Exp. 33: Rabbit: 2 grammes of ultramarine blue suspended in 10 c.c. of a $\frac{3}{4}$ per cent. saline solution, injected into jugular vein. Death half an hour later.

Blood.—Shewed no pigment.

Spleen.—Looks normal: no naked eye change. Microscopically shews only a few pigment particles.

Liver.—Markedly blue from pigment: contains a very large quantity of blue pigment lying within leucocytes in capillaries; none in the liver cells.

Lungs.—Much pigment.

Exp. 34: Small quantity of ultramarine blue, suspended in saline solution, injected into jugular vein. Twenty-four hours later, animal killed.

Spleen.—Shrunken and contracted. Examination shews a very few blue granules lying in pulp.

Liver.—Considerable quantity of blue particles, lying not in liver cells, but within leucocytes and endothelial cells.

Bone Marrow.—Very few blue particles.

The same applies, I find, not only to inert particles introduced into the blood, but also to stromata and other morphological remains of red corpuscles formed during active hæmolysis. After injection of distilled water in large quantity, colourless granules and spherules (stromata) in the spleen are absolutely and relatively few; while in the capillaries of the liver they are in extraordinary abundance. The conditions are more favourable to their arrest in the capillaries of the liver than in the spleen.

Exp. 88: Rabbit: 24th Feb. 1888: 70 c.c. of distilled water injected into jugular vein. Two hours later contents of bladder almost pure hæmoglobin.

Portal Vein.—Red corpuscles look pale, but no granules.

Splenic Vein.—Red corpuscles look pale, but no granules; a few red corpuscles seen budding.

Spleen.—Shews a few red corpuscles budding.

Liver.—Marked polycholia; whole of upper intestine filled with yellow bile. *Liver shews most evidence of blood destruction*—

viz., great number of decolorized spherules, some of them the size of red corpuscles, others smaller; some still shewing a yellowish tinge. In addition, smaller yellow spherules in extraordinary number.

In the spleen, on the other hand, the red corpuscles are almost all normal, only a few shewing buds; there is very little granular débris, and only a few pale spherules.

How, then, is the large excess of pigment of the spleen in certain cases (*e.g.* after transfusion), without any increase in the liver, to be explained? (Plate VII. fig. 1.)

According to Quincke the manner of death of red corpuscles after transfusion is—that they gradually lose their elasticity, become effete, are taken up by leucocytes, and ultimately deposited within the capillaries of the liver and in the spleen.

If such a description were the whole truth, the rôle of the spleen would be a comparatively passive one. The spleen would merely be the repository of the pigment conveyed to it; and a proportional—or even larger—amount of pigment should always be found in *the capillaries of the liver*. According to my experiments, however, after transfusion large quantities may be found within the spleen, while little or none is present within the liver. Even the little that is present may be solely confined to the liver cells, and absent from the capillaries—a distribution denoting, for reasons I have already given, that the death of the corpuscles has not been a slow decay; for in that case pigment would, like the ultramarine particles, be found in the liver capillaries. The rôle of the spleen is by no means the passive one thus ascribed to it.

I conclude, then, from the presence of much pigment in the spleen, when none is to be found in the capillaries of the liver, that the slow mode of death above described by Quincke does not represent what actually takes place.

The rôle of the spleen in removing red corpuscles from the circulation is not the relatively subordinate scavenging one ascribed to it.

3. Active Hæmolytic Functions of the Spleen.

It is more active, as shewn in other ways. Thus I find that the cells of the spleen have the power of arresting red corpuscles *before* these latter have undergone sufficient change to allow their enclosure within ordinary leucocytes (Exps. 93 and 94).

Nature of Experiments.

The experiments were of this kind: blood from the ear was examined and compared with that obtained by puncture of the exposed spleen. For this purpose an incision was made directly over the spleen, and blood obtained from it by puncture. Control observations shewed, that mere exposure of the organ in this way for several hours did not appreciably affect either its size, or the character of the blood obtainable by puncture from it.

If pyrogallic acid were injected into the blood, then either immediately (Exp. 94) or within three minutes (Exp. 93), according to the largeness of the dose, a great enlargement of the spleen occurred, amounting, it might be, to a fourfold or fivefold increase. The organ, at the same time, became excessively turgid; and its former red colour was replaced by a dark venous one, the position of the Malpighian bodies being, however, still marked out as red points.

As early as fifteen minutes after such an injection, well-marked changes were observable in blood withdrawn from the spleen, especially in the red corpuscles, while the blood of the ear at the same time shewed nothing abnormal; and fifteen minutes later these altered red corpuscles were found enclosed within large splenic cells of pulp. After death, in four or five hours, *numerous hæmolytic changes*, including many large cells filled with red corpuscles only slightly altered, were found *in the spleen*; while *absent from the liver*, or *from the blood elsewhere*.

Exp. 93: Rabbit: 11th May 1888: etherized. Spleen exposed by small incision over it: found small and red.

Comparison of Blood from Spleen and Ear.

Spleen.	Ear.
10.30 A.M. On puncture: blood corpuscles normal, only a few granules, plasma colourless.	10.45 A.M. Corpuscles normal. A few blood plates.
10.50 A.M. As before: one large splenic cell seen.	
[11.15 A.M. Pyrogallic acid injected into jugular vein.]	

Comparison of Blood from Ear and Spleen—continued.

Spleen.	Ear.
11.18 A.M. Spleen greatly enlarged, swollen; turgid; fallen away from opening in abdominal wall; dark in colour.	11.20 A.M. Blood not dark. Same as before.
11.20 A.M. Blood obtained by puncture. No obvious change in corpuscles, no increase of granules. One red corpuscle with hæmoglobin, withdrawn to centre and of a darker colour.	11.25 A.M. Blood unchanged.
11.35 A.M. Spleen presents same (swollen dark) appearance. No change in red corpuscles, except that the number of darkened forms increased. It is doubtful whether these latter are of any significance. They seem to be changed.	11.35 A.M. One or two of the darker corpuscles seen, but fewer in number than in the blood of the spleen.
12 noon. Now no doubt that some of the red corpuscles are changed in colour—of a deeper tint. One of them also budding. Some colourless granules and spherules. Large splenic cell with large vesicular nucleus and clear protoplasm. Also some lymph corpuscles.	12 noon. Distinct increase of granular material, but no changes in red corpuscles.
12.30 P.M. Spleen contracted up to half its former size. Now uniformly red in colour, dark colour being lost.	12.30 P.M. No changes in blood.
1 P.M. A few red corpuscles seen of deeper colour: otherwise blood normal, plasma free from granules.	1 P.M. Blood normal. No excess of granules.
2 P.M. Spleen slightly larger again. No obvious changes in blood.	2 P.M. Blood corpuscles perfectly normal, have seldom seen corpuscles so well preserved.
3 P.M. Spleen still contracted. Plasma normal. Red corpuscles normal. Some decolorized discs (spherules) somewhat smaller than red corpuscles.	
4.40 P.M. No changes. Killed with chloroform.	

Renal Vein.—Blood very dark chocolate colour. Corpuscles normal: no granules, no *schatten*.

Mesenteric Vein.—Blood same appearance. No changes.

Portal Vein.—No changes.

Spleen.—Still small and contracted; contains little blood. Shews numerous spherules: colourless and coloured. Many of the red corpuscles throwing off colourless spherules. No *schatten*.

Liver.—Shews nothing. No granules or spherules such as are so numerous in the spleen. No *schatten*.

[In this experiment the destruction was very slight; what little evidence of it was to be found, was confined to the spleen. No changes in the liver.]

Exp. 94: Rabbit: 15th May 1888: etherized. Spleen exposed by an incision directly over it.

Spleen.	Ear.
11.30 A.M. Of a bright red colour. Blood (obtained by puncture) quite normal: plasma colourless.	11.45 A.M. Blood perfectly normal.
12 noon. (1·2 gramme pyrogallic acid in 25 c.c. saline solution injected into jugular.)	
12.1 P.M. *Immediately after, spleen much larger, dark and swollen.* Now bleeds freely from a puncture. Blood corpuscles normal. No granules or *schatten*.	12.1 P.M. Vessels of ear contracted. Blood very dark chocolate colour. Corpuscles normal. No granules in plasma.
12.15 P.M. Spleen still more turgid. Three or four times its normal size; very dark in colour; rigid in consistence; bleeds profusely from a slight puncture. *Corpuscles* shew some changes. Crenated; some of them of darker colour, many of these latter floating about do not fall as before: slight excess of granules.	12.15 P.M. Vessels relaxed. Corpuscles contrast greatly with those in spleen, are perfectly normal: biconcave, no crenation; plasma quite free from granules.
12.30 P.M. Spleen as before. Corpuscles as before. Several large splenic cells, six or seven the size of leucocytes, containing red corpuscles, and yellow remains of red corpuscles.	12.30 P.M. Corpuscles normal. No granules or *schatten*.

Exp. 94—continued.

Spleen.	Ear.
12.45 P.M. Spleen still enlarged, bleeds profusely when pricked. A few red corpuscles seen throwing off yellow buds. Some of these seen free. Granules increased. No *schatten*. Plasma presents a doubtful hæmoglobin tint.	12.45 P.M. Corpuscles normal. Plasma presents a doubtful hæmoglobin tint.
1 P.M. Spleen as before. Plasma (?) hæmoglobin tinted. Small decolorized spherules seen: also some large leucocytes containing yellow pigment granules.	1 P.M. Plasma (?) tinted. Granules slightly more numerous. One partially decolorized, red corpuscle seen.
1.30 P.M. Plasma tinted. Some of the red corpuscles budding.	1.30 P.M. Corpuscles much more normal in appearance than in spleen. Plasma less tinted. One corpuscle budding.
2.30 P.M. Spleen enlarged as before. Slight increase of granules. No *schatten*.	2.30 P.M. Slight increase of granules. Corpuscles normal.
3.30 P.M. Killed with chloroform.	3.30 P.M. Corpuscles normal.

Splenic Vein.—Red corpuscles normal for the most part. Some of them looking pale; also some colourless spherules.

Mesenteric Vein.—A few colourless granules and spherules. Otherwise corpuscles normal.

Spleen much diminished in size since death. (Hence size of spleen during life cannot necessarily be judged by its size after death.)

Splenic tissue shews a large number of partially decolorized and completely decolorized spherules; some of the former exactly resembling 'microcytes.' Some of these decolorized bodies are the same size as the red corpuscles, most of them are smaller. A few *schatten* seen.

A considerable number of small yellow 'microcytes.' Some of them in act of becoming detached from the red corpuscles (by 'budding').

Large splenic cells seen filled with red corpuscles, so little changed that they appear to differ in no way (except their inclusion within these cells) from the red corpuscles around.

(The corpuscles seem as if they had been 'killed' by the poison.)

Liver.—Cells very fatty, without pigment. Red corpuscles normal. No budding: a few colourless spherules seen.

Exp. 54: Rabbit.

Date.	No. of Red Corpuscles.	Changes in Blood.	Remarks.
Nov. 4, 1887, 11.20 A.M.	5,350,000	Normal.	·5 gramme pyrogallic acid in 10 c.c. saline.
12.20 P.M.	5,090,000	No changes.	Injected subcutaneously.
3.20 P.M.	5,150,000	,,	
,, 5,	4,240,000	,,	
,, 7,	4,400,000		Animal apparently in good health; killed with ether.

Liver.—Very rich in blood; no iron reaction (with NH_4HS), no pigment in cells.

Spleen.—Intense iron reaction (becomes coal-black in NH_4HS). Large heaps of pigment, all blackened by NH_4HS.

[In this experiment the injury inflicted on the red corpuscles by the poison allowed them to be taken up by the splenic cells in great numbers, *before* the leucocytes of the blood could seize on them; otherwise pigment ought to have been found within the liver capillaries, just as the particles of ultramarine blue were.]

Conclusions.

I consider, then, that the behaviour of the splenic cells towards the injured red corpuscles is not merely that of a scavenging organ. If it were, the red corpuscles ought to have been taken up in still larger number by leucocytes and deposited in the liver. This was not the case. The rôle of the spleen is thus more active, a fact which becomes most manifest when through any cause—*e.g.* transfusion, or action of certain poisons—the red corpuscles have received injury short of their complete disintegration. The injured corpuscles are seized in great numbers by the cells of the spleen, long before a single one can be found within the leucocytes. After death, the chief and sometimes the exclusive seat of such cells is the spleen, few or none being found within the liver (Exps. 86, 87). The activity of the spleen in

withdrawing red corpuscles from the circulation is thus decidedly greater than that of the whole body of leucocytes, including those within the liver. *Were the spleen not present, red corpuscles in process of becoming effete would remain longer in the circulation than they actually do.*

It is in virtue of this function that the spleen is often the seat of much pigment, *e.g.* after transfusion, when the liver may be free. To a certain extent, therefore, the presence of blood pigment within the spleen, when absent from the capillaries of the liver, is an indication of active hæmolytic function on the part of that organ (Exp. 54).

CHAPTER XXXV.

THE SPLEEN AS A SEAT OF HÆMOLYSIS—(*continued*).

4. The Spleen the Chief Seat of Active Hæmolysis.

Introductory.—The function of the spleen in hæmolysis is, however, not confined to the relatively humble one of withdrawing from the blood red corpuscles already injured or effete. The hæmolysis which occurs in it is of a much more active character.

This appears best from the remarkable influence the organ exerts on the hæmolytic action of certain agents, *e.g.* pyrogallic acid or toluylendiamin.

Action of Toluylendiamin.—The substance whose action proved most interesting in this relation was *Toluylendiamin.* This drug, like pyrogallic acid, exercises a well-marked destructive action on the blood. The chief point of interest connected with it is that, unlike pyrogallic acid, its action differs greatly in different animals. It is exceedingly destructive and poisonous in the cat—even small doses, *e.g.* 0·15 gramme—killing a cat in the course of a few hours with intense hæmoglobinuria. It is less so in the dog, such a dose causing jaundice without hæmoglobinuria. It is least of all destructive in the rabbit, causing no jaundice and rarely hæmoglobinuria even in large doses. In many of my experiments, doses as large as one gramme were injected directly into the blood of rabbits with comparatively little effect. The action of this substance in the rabbit differs indeed so strikingly from its action in the dog and cat, that Stadelmann, who first studied it, confessed himself utterly unable to account for it, and his observations were therefore exclusively confined to the latter animals.

The reason that induced him to reject rabbits was the reason that induced me to make use of them; for the object of my experiments was not to induce a marked destruction of blood, such as even small doses produce in the dog and cat, but a more moderate destruction more closely approximating to the degree of destruction in health. My purpose was not to cause a degree of change in the blood capable of inducing hæmoglobinuria or jaundice; but rather to induce, without affecting the health of the animal, an exaggeration of the process of hæmolysis which would render more prominent the ordinary evidences of hæmolysis. This object I could not attain with destructive agents like pyrogallic acid, glycerine, or distilled water, their action on the blood being directly chemical and physical, differing totally in its character, as I afterwards found, from anything that takes place in health. With toluylendiamin, on the other hand, I found it possible to produce all the evidences of an increased hæmolysis without the slightest disturbance of the animal's health, and without the occurrence of abnormal changes (*e.g.* jaundice or hæmoglobinuria), likely to affect the animal's health injuriously.

When the dose was small, these evidences included (1) increased morphological changes in the blood similar to those found in health; (2) increased formation of bile pigments; and (3) increased deposit of blood pigment either in the liver, spleen, or bone marrow, with poikilocytosis.

With larger doses, still more marked changes were induced, including, in addition to the foregoing, not only (1) a marked oligocythæmia; but also (2) changes never found in health — namely, the appearance of large numbers of stromata and *schatten* in the blood, and of remains of hæmoglobin in the urine (not hæmoglobinuria).

By varying the dose it was thus possible in the rabbit to induce the most varying degree of blood destruction, in a manner quite impossible in the dog or cat, where the substance has a poisonous action independent of its destructive action on the blood.

The most important information regarding the seats as well as the probable nature of hæmolysis in health was thus obtained from experiments with this drug.

Action of Pyrogallic Acid. — The other hæmolytic agents whose actions I studied were *pyrogallic acid*, *distilled water*, and

glycerine. In some notable respects the action of pyrogallic acid contrasted markedly with that of toluylendiamin.

The study of the mode of action of these two yielded much information regarding not only the seats, but also regarding the nature of the hæmolytic process.

The conclusion pointed to by these experiments is that the spleen is the chief seat of active hæmolysis.

Results of Experiments with Toluylendiamin.

1. After small doses, hæmolytic changes are confined solely to the spleen, and are absent from the blood elsewhere, even from that of the liver.

Exp. 80: Rabbit: 0·25 gramme of toluylendiamin per kilo of weight injected intravenously; killed two days later.

Spleen and Splenic Vein.—Numerous changes; colourless granules and spherules in great numbers, and budding of red corpuscles.

Blood of Portal System elsewhere perfectly normal.

Exp. 80: Rabbit. Date, 25th Feb. 1888.—0·5 gramme (=0·25 gramme per kilo.) of toluylendiamin injected. Killed two days later.

Splenic Vein.—Most of the red corpuscles normal; a few throwing off buds; some colourless granules.

Mesenteric Vein.—No changes.

Portal Vein.—Corpuscles perfectly normal; no granules.

Hepatic Vein.—Corpuscles perfectly normal; plasma remarkably free from granules, even after standing.

Spleen.—Shews numerous red corpuscles throwing off buds; and numerous yellow microcytes of all sizes.

Colourless granules and stromata in great number; here and there group of red corpuscles looking dead; some cells enclosing red corpuscles.

The chief change, however, is the enormous number of colourless stromata; some yellow microcytes; also an enormous number of highly refractile granules.

On comparing the appearances presented by this spleen with those presented by a spleen three days old (from another experiment), which had already commenced to soften, the latter shews very few granules.

Liver.—Gall-bladder distended with extremely dark green bile. Cells fatty; free from pigment; red corpuscles normal; almost no granules seen; a few colourless spherules; no blood corpuscles holding cells.

Neither liver or spleen gives any reaction of iron.

Exp. 86: Rabbit: weight, 2000 grammes.

21st Feb. 1888.—Animal etherized. Hepatic artery ligatured; 1 gramme of toluylendiamin given by mouth.

22nd Feb.—Killed with chloroform.

Mesenteric Vein.—Blood particularly free from granular débris of any sort. A few small yellow microcytes, spherical in shape, seen in process of being thrown off as 'buds' from red corpuscles.

Splenic Vein.—Blood contains a large number of stromata and a considerable number of *schatten*; also colourless granules.

Portal Vein below liver.—Red corpuscles perfectly normal; no stromata; no budding; no granules (even after lapse of some time).

(*Note.*—The contrast between blood of portal vein and blood of splenic vein is so striking as to leave no doubt as to the importance of the spleen in hæmolysis.)

Portal Vein, close to liver above stomach; two or three distinct *schatten*, otherwise corpuscles normal and granules few.

Systemic Vein.—Corpuscles perfectly normal; absolutely free from granules.

Spleen very dark in colour; vessels contracted; little blood in them.

Changes in spleen very marked; numerous *schatten* and stromata: splenic cells large and numerous, and contain a large quantity of fine yellow granules, most of them in addition containing red corpuscles apparently normal, but, from the fact of their enclosure, obviously dead.

Some of the cells are packed with red corpuscles, as many as eight or ten in one cell. Groups of red corpuscles, similar in appearance to those enclosed, also seen lying free.

There is a considerable but by no means excessive amount of colourless granules and colourless microcytes, the latter small and round like small red corpuscles, without colour. Many of the red corpuscles are seen throwing off 'buds.'

Liver.—Right lobe of a pale yellowish colour; soft and friable; contains little blood.

Left lobe, normal red appearance. (Obviously only the Eight branch of hepatic artery ligatured.)

Left Lobe.—Red corpuscles normal: granular débris not abundant; one or two large cells enclosing red corpuscles, similar to those in spleen—a decided increase in the number of leucocytes, some of them containing fine yellow granules.

After hardening (part close to portal trunk), liver cells normal; nuclei distinct; a few small fat particles; no trace of pigment.

Right Lobe.—Cells in a state of fatty degeneration. Nuclei in many invisible, in others still present, the protoplasm presenting a faint yellow granular appearance. After hardening, cells preserve shape; nuclei in

most gone; protoplasm in a state of fine fatty degeneration. No trace of pigment to be seen.

Branch of portal vein going to right lobe, blocked with decolorized thrombus.

Spleen gives slight reaction (iron) with NH_4HS. A more or less diffuse greenish staining limited to the protoplasm of the large splenic cells. The number of pigment granules is by no means great; not greater than usual.

[The number of *schatten* leaves no doubt in this case that a marked hæmolysis had occurred and much hæmoglobin set free, especially in the spleen.

The small quantity of pigment in the spleen, as also in the liver, shews that mere excess of hæmoglobin alone does not lead to accumulation of pigment.]

The Urine contains tube casts of yellow granules (of hæmoglobin).

Gall Bladder contains an almost pure solution of hæmoglobin (spectroscopic examination).

(The liver cells, degenerated and thrown out of action by having their blood supply cut off, have proved unable to break up the hæmoglobin supplied to it. The hæmoglobin has passed through them unchanged into the bile capillaries.)

Bone Marrow normal, fatty. Red corpuscles normal; entire absence of granules; a few nucleated red corpuscles; a few stromata.

Exp. 87: Rabbit: 2000 grammes.

Feb. 21. 1 gramme toluylendiamin by mouth (=0·5 per kilo).
,, 22. Urine, deep saffron tint; marked reaction of with toluylendiamin. (Very deep fluorescence with methylated spirit.)
,, 23. Blood remarkably normal; no granules.
,, 25. 0·5 gramme by mouth (0·25 per kilo).
,, 26. Urine extremely dark.
,, 27. Urine still dark.
,, 28. Urine clear again.
,, 29. Animal apparently well.
Mar. 3. Animal's weight, 1830. 0·8 gramme of toluylendiamin by mouth (=0·4 gramme per kilo).
,, 5. Urine very dark in colour. No changes in blood.
,, 7. Weight, 1800. Urine normal. Animal well. 1 gramme of toluylendamin by mouth (=0·6 gramme per kilo).
,, 8. Urine of a most intensely deep saffron colour. No hæmoglobin; no albumen. Blood corpuscles normal; no *schatten*; a few small pale spherules; granules slightly increased.

Mar. 12. Weight, 1750.

,, 17. 0·9 gramme of toluylendiamin by mouth.

,, 19. Died this morning.

Splenic Vein.—Corpuscles normal; no *schatten*; very few granules; few colourless discs.

Portal Vein.—Corpuscles perfectly normal; a very few granules; no *schatten*; no microcytes.

Spleen.—Much enlarged and very dark in colour. Numerous hæmolytic changes. A large number of red corpuscles in all stages of decolorization; stromata; *schatten*; colourless granules very abundant. A number of the splenic cells enclose red corpuscles (evidently from their appearance recently taken up, as their colour is the same as many lying free).

Great excess of blood pigment; darkens in NH_4HS; also a number of spheres of shape of red corpuscles, resembling decolorized red corpuscles, which become dark in NH_4HS.

(The appearances are not those usually seen after toluylendiamin poisoning, but resemble more those after pyrogallic acid poisoning.)

Liver.—Cirrhosed (echinococcus).

Bile.—Small quantity; dark yellow. Shewing microscopically a large number of pigment-granules (? derived from hæmoglobin).

Liver cells very fatty; no darkening in NH_4HS. Leucocytes increased; larger in size, containing fine granular pigment.

Kidney.—Urine of yesterday and to-day contained a very large quantity of yellow granular débris and tubecasts.

Bone Marrow.—Cells contain excess of fine granules; no nucleated red corpuscles; no *schatten*; a considerable number of colourless discs.

2. After a medium dose of toluylendiamin, hæmolytic changes are most marked in the spleen, but extend also to the portal blood within the liver; they are still absent from the general circulation, both during life and after death.

Exp. 61: Rabbit: 0·66 gramme toluylendiamin per kilo injected intravenously. Killed two days later.

Blood of ear.—No change during life, either in plasma or in corpuscles.

Spleen and *Splenic Vein.*—Well-marked changes in plasma and red corpuscles.

Liver.—Changes much less marked, but none in *hepatic veins* issuing from liver, or in blood of inferior vena cava. Large amount of iron in spleen, none in liver.

Similar distribution of changes in Exp. 75 (after pyrogallic acid poisoning).

Exp. 61: Rabbit: weight, 1500 grammes. R.B.C. 6,060,000 per c.mm.

1887.

Nov. 21. 1 gramme toluylendiamin (0·66 gramme per kilo) in 20 c.c. saline ($\frac{3}{4}$ NaCl), injected into jugular.

„ 22. Blood examined fresh, shews no obvious change, except one or two corpuscles throwing off 'buds.' R.B.C. 6,130,000, weight 1450.

„ 23. No changes in general blood. R.B.C. 6,370,000, weight 1350. Killed.

Portal Vein.—Blood corpuscles, normal in shape and appearance. Leucocytes normal, free from pigment.

A few large (splenic) cells containing a mere trace of yellow pigment, just sufficient to tinge them.

Splenic Vein.—Most of the corpuscles normal; but a number are throwing off 'buds.' Also large cells (splenic) presenting a yellowish tinge.

Inferior Vena Cava (above liver).—Corpuscles and leucocytes normal; no appearance of budding; no *schatten*; no pigment cells such as are seen in portal vein.

Spleen neither enlarged, swollen, nor dark in colour. Pigment *apparently* only slight in amount. Red corpuscles budding; yellow microcytes; increase of colourless granules.

Iron Reaction.—Distinct darkening, with NH_4HS. On microscopic examination, protoplasm of large splenic cell stained greenish, and large number of small pigment granules of varying size (coal-black) throughout cell.

Some larger bodies of size and shape of red corpuscles present a similar green coloration.

Liver.—Gall-bladder moderately distended with dark bile; liver not enlarged; cells slightly fatty; free from pigment; no pigment in capillaries; no iron reaction (with NH_4HS).

Bone Marrow.—No darkening in ammonium sulphide.

(Compare with Exp. 60, *postea*, p. 395.)

Exp. 75: Rabbit: weight, 1650 grammes.

1888.

Jan. 19. 0·75 gramme pyrogallic acid (=0·45 gramme per kilo) in 20 c.c. $\frac{3}{4}$ NaCl, injected into jugular vein.

„ 20. 25 c.c. of smoky-looking urine; no guaiac reaction; no albumen; deep colour reaction with HNO_3; blood of ear bright red; corpuscles perfectly normal; no *schatten* or granules.

„ 21. Blood from ear looks thin and watery. Killed with chloroform.

Splenic Vein.—Some red corpuscles budding; no *schatten*.

Portal Vein.—Corpuscles all normal.

Inferior Vena Cava (above liver).—Corpuscles normal.

Spleen of a very dark colour; numerous corpuscles throwing off 'buds'; number of pale granules, and a number of *schatten*. The appearances presented by red corpuscles in spleen are exceedingly striking, nearly every one of them shewing their stroma oozing from them in colourless granules.

Some splenic cells shew pigment particles and remains of red corpuscles.

Marked excess of iron (with NH_4HS); the pigment mostly in diffuse form in splenic cells, although also in small granules; also numerous dark green bodies resembling in size and appearance decolorized red corpuscles.

After hardening, spleen gives excessive iron reaction, the pigment mostly confined to large pigment-holding cells in sinuses of pulp.

Liver.—Cells fatty; no iron reaction.

In capillaries, excessive amount of colourless granules; but most of the red corpuscles are normal, only a few shew budding (*cf. antea*, spleen).

Bone Marrow.—Marrow cells contain excess of granules, very slight iron reaction.

3. After large doses of toluylendiamin, hæmolytic changes still continue most marked in spleen and portal blood, but extend to the general circulation, although much less marked there.

Exp. 82: Rabbit: 0·8 gramme toluylendiamin per kilo. Death in sixteen hours.

Spleen and Splenic Vein.—Great majority of red corpuscles converted into *schatten*; only a few normal corpuscles left.

In *Blood of Mesenteric Veins*, only a few *schatten*; majority of corpuscles normal.

In *Hepatic Vein*, *schatten* still fewer in number.

Inferior Vena Cava (below the liver), *schatten* exceedingly few in number.

Spleen gives an excessively deep iron reaction.

Liver a very slight reaction.

Exp. 82: Rabbit: weight, 2500 grammes.

1888.

Feb. 6. 2 grammes of toluylendiamin (=0·8 gramme per kilo) given by mouth.

Feb. 7. Corpuscles normal; no granules in excess; no *schatten*; no budding. Animal purged. Death during night.

„ 8. *Splenic Vein.*—Blood contains enormous number of *schatten* (decolorized red corpuscles). They are more numerous than red corpuscles; also large splenic cells containing pigment.

Portal Vein and Branches.—Majority of red corpuscles normal; only a few *schatten.*

Hepatic Vein.—Only a few *schatten.*

Inferior Vena Cava.—*Schatten* still fewer in number. Blood coagulated.

Spleen excessively small and shrunken.—About $\frac{1}{3}$ or $\frac{1}{4}$ its normal size; of a dark red colour; contains *very large* quantity of pigment in form of minute yellow globules of varying size, contained for the most part within large splenic cells. (These bodies have all the appearance of the similar globules resulting from the action of toluylendiamin on the blood outside the body.) A considerable number of *schatten.* Most excessive iron reaction, the spleen containing an enormous excess of pigment, chiefly within large splenic cells.

The excess is very striking, especially when contrasted with trace of pigment in liver, and the entire absence of such cells from the liver capillaries.

Liver.—Cells vacuolated. Slight trace of fine pigment in liver cells; none in capillaries.

Exp. 90: Cat: 29th Feb. 1888, 12.30 P.M. 0·16 gramme toluylendiamin given by mouth. 5 P.M. Urine albuminous. Death in eighteen hours.

Mesenteric Vein.—Plasma appears slightly hæmoglobin tinted, but red corpuscles all normal; no granules, and only two or three colourless spheres, $\frac{1}{2}$ to $\frac{1}{3}$ size of red corpuscles.

Splenic Vein.—The blood is of a chocolate colour; shews a number of *schatten*; plasma has a rosy tint; no granules, but decolorized spheres size of red corpuscles; red corpuscles shew no buddings.

Portal Vein.—A few *schatten* here, and also some pale spherules, but no granular débris; red corpuscles all normal.

Inferior Vena Cava.—Plasma tinted; corpuscles normal; a few *schatten*; no granular débris.

Spleen very dark in colour; blood contains *a large number of schatten*, and other evidences of blood-destruction; large numbers of stromata and broken-up red corpuscles; no pigment, and no cells enclosing red corpuscles.

Liver.—Cells very fatty; numerous evidences of blood destruction; both *schatten* and colourless stromata, the latter in greater number than in spleen or elsewhere.

Exp. 91 : Cat : weight, 2350 grammes.

1900.

Mar. 22. 0·1 gramme of toluylendiamin by mouth.

„ 23. Urine normal ; contains no blood.

„ 24. Large quantity of dark bloody urine passed containing much granular débris of hæmoglobin, and giving distinct spectrum of hæmoglobin.

„ 25. Animal apparently well.

„ 26. 0·15 gramme of toluylendiamin given in milk.

„ 27. Killed with chloroform.

Mesenteric Vein.—Schatten very numerous, also a few colourless granules ; red corpuscles normal ; no budding.

Splenic Vein.—Normal red corpuscles much fewer in number than *schatten* ; *schatten and granules exceedingly numerous* ; also a considerable number of large pigment cells filled with particles of bright yellow pigment, also colourless stromata ; leucocytes increased in groups.

Spleen very dark in colour, swollen, rich in blood ; evidences of hæmolysis very numerous — the whole field filled with *schatten* granules, fragments of red corpuscles, yellow in colour, and excessive amount of yellow granular material ; also colourless stromata and yellow microcytes ; large pigment cells and blood corpuscle-holding cells, the red corpuscles enclosed, perfectly preserved, resembling those outside, only of a deeper colour. In NH_4HS considerable but not excessive darkening (iron reaction), the large pigment cells being mainly affected.

Liver very fatty ; cells contain some pigment granules, but no darkening, in NH_4HS ; bile very dark yellow in colour ; intestine contains excess of bile ; no congestion of duodenum.

Bone Marrow.—Cells normal ; no excess of pigment. A considerable number of nucleated red blood corpuscles ; *schatten* much less numerous than elsewhere.

Summary.

In all cases, then, the greatest degree of change was found in (1) the spleen and the blood issuing from it ; (2) next, in the blood of the portal tract ; and only when extreme, (3) in the blood of the general circulation. Had the changes been always found in the liver as well as within the spleen, one might have referred their presence in these situations to the scavenging functions which we have seen is performed by these two organs. Thus, after injection of distilled water, the stromata and other remains of red corpuscles are found in greatest abundance in the liver (see Exp. 88, p. 375).

In the foregoing cases, on the contrary, the chief and

sometimes the exclusive seat of the various products of disintegration was the spleen. It was only when the dose was large, that changes could be found outside the spleen and the blood of splenic vein—*e.g.* in the liver and mesenteric veins; and it was only when still larger (toxic) doses were given, that the changes could be found outside the portal circulation—*e.g.* in the general circulation.

The greater number and variety of the evidences of hæmolysis found in the spleen, as compared with those found in the liver or in the blood elsewhere, all pointed to the spleen as the special seat of an active hæmolysis.

CHAPTER XXXVI.

THE SPLEEN AS A SEAT OF HÆMOLYSIS—(*continued*).

Effect of Splenectomy.

To test still further to what extent the spleen was the seat of an active hæmolysis, or how far, on the other hand, it had merely acted as a scavenging organ in collecting from the blood the various débris circulating in it, I made a parallel series of experiments in animals after *removal of the spleen.*

Nature of Experiments.

This operation was exceedingly well borne by the animals; it appeared, indeed, to affect them but little. In the earlier experiments I waited for a day or two after the excision, before injecting the drug. Later on, when I found that the operation itself was without any ill effect, I injected the drug immediately after the spleen was excised. The drug was always injected directly into the general circulation through the jugular vein. The results of the experiments under these circumstances appear all the more remarkable, the animal not only having to recover from the effect of the operation, but having also at the same time to combat the action of a powerful poison.

The action of toluylendiamin in the healthy animal was illustrated chiefly by three experiments, in which the doses were respectively 0·25, 0·66, and 0·8 gramme per kilo of weight—doses which may for convenience be termed *small*, *medium*, and *large*. In the healthy animal these doses caused an appreciable destruction — varying in degree; evidenced not only by changes in the blood, but by pigment changes in the liver or the spleen.

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1. Effect on Hæmolysis. — Removal of the spleen greatly lessens the hæmolytic action of toluylendiamin. In small and medium doses its destructive action is practically abolished; in large doses it is much diminished. Thus, whereas doses of 0·25 gramme per kilo in the healthy animal caused appreciable hæmolysis, doses three and even four times as large, (0·75 to 1 gramme per kilo) in the spleenless animal were without effect.

Exp. 68: Rabbit: Dec. 12, 1887.

Spleen excised; 1 gramme toluylendiamin (0·6 gramme per kilo) injected into blood; killed three days later. Absolutely unaffected during life.

Blood.—No changes found either during life or after death.

Urine.—No remains of hæmoglobin.

Liver or *Bone Marrow.*—No reaction of iron.

Exp. 69: Rabbit: Dec. 16, 1887.

Spleen excised; 1·5 gramme toluylendiamin (0·75 gramme per kilo) injected into blood. Killed on following day.

Portal and *General Circulation.*—Absolutely no change of any kind in blood or in liver.

Liver gives no iron reaction. Cells very fatty, but contains no pigment. Gall-bladder empty.

Urine free from hæmoglobin or its pigment remains.

The effect of removal of the spleen was in these cases very striking. The test was a severe one: the animal had its spleen removed, and the drug was injected immediately afterwards directly into the circulation.

Exp. 60: Small Rabbit: weight, 1600 grammes.

1887.

Nov. 18. Etherized; spleen excised with antiseptic precautions.
2 P.M. 1 gramme of toluylendiamin in 20 c.c. ¾% NaCl injected into jugular vein (= ·62 gramme per kilo).
3 P.M. Animal recovered. Blood normal.
4 P.M. Blood normal.

„ 19. Animal completely recovered; moving about freely. Sitting up on hind legs (shewing absence of peritonitis).
Blood perfectly normal: no granules; no *schatten.*

„ 21. Blood shews no sign of change. Weight, 1400. R.B.C. 5,850,000.

Nov. 22. No change. Weight, 1350. R.B.C. 6,560,000. Urine shews yellow granular and globular remains of hæmoglobin in small quantity.

„ 23. In good health. Weight, 1450. R.B.C. 5,460,000.

„ 24. In good health. R.B.C. 5,140,000.

„ 25. A few yellow microcytes seen. Also a few red corpuscles apparently budding. R.B.C. 5,780,000.

1·5 gramme of toluylendiamin in 25 c.c. ¾ % NaCl injected (= 1 gramme per kilo).

„ 26. Weight, 1350. Animal eating as usual.

Blood shews not a trace of *schatten*, granules, or other sign of blood destruction. Red corpuscles beautifully preserved. R.B.C. 5,510,000.

100 c.c. of an extremely dark bilious-looking urine.

No albumen or blood; no bile pigment. A few fine yellow granules (? hæmoglobin) seen.

„ 28. Weight, 1400. Animal apparently well. Blood shews no change. R.B.C. 5,520,000.

Killed.

Portal Vein (close to liver).—Red corpuscles perfectly normal. No granular débris; leucocytes normal size and appearance, no pigment-holding cells.

Hepatic Vein.—No changes of any sort.

Liver healthy; cells small; faintly granular. Contain little fat, and no pigment, no darkening in NH_4HS (iron reaction).

Bone Marrow.—Quite unaffected by NH_4HS. Entire absence of pigment.

Control Experiment (Exp. 61) in animal of same brood and weight (*vide antea*, p. 389).

Result.—A dose of 0·66 gramme of toluylendiamin per kilo in healthy animal caused distinct hæmolysis; while a dose of 0·62 gramme per kilo followed by the very large one of 1 gramme per kilo in spleenless animal, same size and brood, had no effect. Contrast, also, result in Exp. 80, (p. 385), where a dose of 0·25 gramme per kilo caused marked hæmolysis in healthy animal.

2. Effect on Body Weight.—The effect of splenectomy was evidenced in other ways than by the absence of hæmolysis—viz., by the effect on body weight.

Thus while in the healthy animal a dose of 0·66 gramme per kilo caused a loss of weight of 150 grammes in the course of two days, a similar dose, followed five days later by the

enormous dose of 1 gramme per kilo, caused in the spleenless animal a loss of only 50 grammes in weight.

3. Difference of Dosage.—The difference of effect may be brought out in another way. In seventeen observations on the healthy animal the doses found sufficient to produce hæmolysis from the slightest to the most extreme degree varied from 0·13 to 0·8 gramme per kilo of body weight—average 0·36 gramme whereas in eight observations on spleenless animals the dose ranged from 0·28 to as much as 1 gramme per kilo—average 0·64.

In both cases the conditions as to food and drink were alike.

All the characteristic effects of toluylendiamin as a hæmolytic agent—whether as regards changes in blood, in urine, in organs, or in body weight and nutrition—were nevertheless much more frequently and more strikingly manifested in the healthy than in the spleenless animal. In the latter, as has been seen, it was only when the dose was a very large one that they were manifest at all.

4. Effect on Formation of Bile Pigment.—The effect was not confined to the blood, but extended to other processes related to hæmolysis. Doses which, in the healthy animal, caused an increased formation of bile pigments, seemed, in the spleenless animal, to be without effect.

Thus in the *Healthy Animal:*

Exp. 61: After dose of 0·66 gramme per kilo of weight, 48 hours later a large quantity of dark green bile found.

Exp. 80: After dose of 0·25 gramme per kilo, 48 hours later gall-bladder filled with extremely dark green bile.

Spleenless Animal:

Exp. 69: After dose of 0·75 gramme per kilo, 24 hours later gall-bladder empty.

5. Effect on Character of Hæmolysis.—Removal of the spleen seemed not only to lessen the amount of hæmolysis, but to make it of a more chronic character. As I have already shewn, there is no more characteristic evidence of a chronic gradual hæmocytolysis than the presence of *large* pigment particles within the *capillaries of* the liver; while there is no more striking evidence of acute hæmolysis with liberation of hæmoglobin than this presence of *small* pigment granules within the *liver cells.*

After frequent administration of toluylendiamin in spleenless rabbits, pigment cells were found in the capillaries of the liver in number and variety such as I never met with in the healthy animal, or ever otherwise found after toluylendiamin poisoning (Exp. 89).

Exp. 89: Rabbit: weight 2100 grammes.

1888.

Feb. 29. Spleen excised (under ether).

Mar. 3. Recovered. Weight, 1800 grammes; 0·5 gramme toluylendiamin by the mouth.

„ 4. Urine very dark in colour; no reaction with HNO_3; no hæmoglobin. Gives marked colour reaction (of toluylendiamin) with nitrite of sodium; green fluorescence with methylated spirit.

„ 5. Urine 115 c.c.; slightly darker than normal, but much clearer than yesterday; does not give reaction with nitrate. Animal apparently well.

„ 7. Weight, 1800; animal well; urine normal; 1 gramme toluylendiamin by mouth.

„ 8. Urine bilious-looking; no albumen; no hæmoglobin; marked colour reaction with sodium nitrite. Contains a large quantity of yellow granular and globular remains of red corpuscles. Animal well; fæces normal, not soft.

Blood.—Red corpuscles adhering to one another; a very large amount of granular material partly run together, partly free.

„ 9. Weight, 1800; blood as yesterday.

„ 12. Weight, 1850.

„ 17. Weight, 2000; in good health; 1 gramme toluylendiamin by mouth.

„ 18. Urine again very dark; blood contains a very large number of blood plates, small colourless spherules; no *schatten*.

„ 26. Weight, 1900; in good health; killed with chloroform.

Mesenteric Vein.—Red corpuscles normal; granules in excess; also of larger size than usual; also a few small yellow microcytes.

Portal Vein.—Colourless granules even more abundant, and a few yellow microcytes; no pigment cells.

Liver.—Gall-bladder contains pale yellow bile cells finely granular; leucocytes numerous, some of them containing granules of pigment; also a number of large cells absolutely packed with yellow pigment granules to such an extent as to obscure the nucleus. So far as can be seen these are of leucocyte nature, and lie within the capillaries.

Liver tissue becomes coal-black in NH_4HS (iron reaction), the

granules within cells becoming coal-black. They are of *varying* size, an appearance not hitherto seen.

The heaps of pigment within the capillaries also become coal-black.

The liver contains an extraordinary amount of pigment.

Bone Marrow.—Extraordinary increase in the number of marrow cells, all of them richly granular. Great excess of pigment; mostly in heaps resembling those in capillaries in liver; also nucleated red corpuscles, most of them with double nuclei; many of the nuclei seen in process of division.

A very considerable number of small colourless spherules. (The bone marrow appears to have taken on the functions of the removed spleen. Under normal circumstances its function as a blood-destroying organ are mainly passive, retaining effete corpuscles.)

[The chief feature in this experiment was the number of large pigment cells *within the capillaries*, and their extraordinary richness in pigment, in the form of *large pigment particles of varying size*—evidence of chronic hæmocytolysis (*v.* p. 133). Contrast this with situation and character of pigment in Plate IX., 182.]

Summary.

As evidenced in all these various ways—lessened hæmolysis in the blood, lessened formation of bile pigment, alteration of the character of the subsequent hæmolysis, and effect on nutrition—removal of the spleen undoubtedly influenced in a remarkable manner the amount of hæmolysis caused by toluylendiamin. The result, therefore, seems to me conclusive as to the importance of the spleen as the seat of hæmolysis.

There were no fallacies connected with the experiments themselves—*e.g.* as to the amount of the drug actually entering the system; for in both cases alike the drug was injected directly into the blood itself.

Moreover, in the spleenless animals the conditions were distinctly more unfavourable than in the healthy, inasmuch as these animals had to recover from the operation. Even under these circumstances, their blood was able to resist double the dose of poison.

Contrast betwixt Toluylendiamin and Pyrogallic Acid in regard to the Effect of Splenectomy.—This remarkable result became more interesting, when it appeared, as it subsequently did, that *Pyrogallic acid*, the other destructive agent chiefly experimented

with, had no such influence, its destructive action being practically unaffected by the removal of the spleen.

(1) Thus in the following experiments the removal of the spleen was without the slightest effect on the action of that drug.

Exp. 78: Normal Rabbit: 0·5 gramme of pyrogallic acid per kilo injected intravenously. The following day *schatten* found in the blood. Two days later the animal looking ill; number of red corpuscles fallen to 3,410,000 per cubic millimetre. From this time gradual recovery.

Exp. 79: Rabbit: spleen excised; 0·55 gramme of pyrogallic acid per kilo injected intravenously. Following two days numerous *schatten* in blood, and on the third day the number of red corpuscles had fallen to 1,360,000 per cubic millimetre. From this time onward the recovery was rapid.

(2) When smaller doses were given, some slight difference was observable, in the direction of a lessened effect after removal of the spleen; but this was in no way so marked as was the case with toluylendiamin. The removal of the spleen slightly lessened the destructive action; but it failed to do what was so striking in the case of toluylendiamin—abolish it altogether (Exps. 75 and 76).

Exp. 75: Rabbit: 0·45 gramme per kilo of pyrogallic acid in 20 c.c. saline solution injected into jugular vein. Weight, 1650 grammes.

No albumen, or hæmoglobin in urine.

A few *schatten* in blood of ear. Killed two days later. Weight, 1650. Numerous evidences of blood destruction in spleen, and in capillaries of liver; absent from inferior vena cava above liver.

Exp. 76: Rabbit: spleen excised. 0·46 gramme per kilo of pyrogallic acid in 25 c.c. saline solution injected into jugular vein. Weight, 2150 grammes. No changes in blood during life. Animal appears quite well. Killed two days later. Weight, 1950 grammes.

[*Query.*—Although no change in general blood, question arises whether some hæmolysis may not have occurred, limited possibly to portal blood. If the destruction were slight and limited—*e.g.* to the portal system—possibly the liver had been able to prevent *schatten* or other morphological remains passing into the general circulation.]

Mesenteric Vein.—Red corpuscles perfectly normal. No tinting of plasma with hæmoglobin.

Portal Vein.—Corpuscles mostly normal: a few shewing buds.

Inferior Vena Cava (above liver).—Corpuscles mostly normal. A few *schatten* seen.

Liver cells excessively fatty, but shew no trace of pigment. No

schatten: a few corpuscles seen throwing off buds; almost no granular débris.

Bone Marrow.—A few *schatten* seen: otherwise red corpuscles normal.

In this experiment, therefore, despite absence of changes from the general blood, hæmolysis had occurred, and evidences of it, although few, were nevertheless found in the liver, and even outside the confines of the portal circulation, viz. in the bone marrow.

The difference in result, surprising as it appeared at first to be, proved subsequently to be of special importance. If, indeed, it had been otherwise—if splenectomy had materially affected the hæmolytic action of pyrogallic acid—the fact would have involved the conclusion that some fallacy underlay the observations, both in its case, and probably also with regard to the action of toluylendiamin.

For, as has been seen, pyrogallic acid has undoubtedly a *direct* poisonous action on the red corpuscles, evidenced as early as a few minutes after it comes into contact with them (see Exp. 93, p. 377), and such an action could obviously be in no way affected by removal of any organ. It was obviously a matter that lay between the red corpuscle and the drug in contact with it. Precisely the same changes in the corpuscles as those observable in the blood can be seen to take place when the corpuscles are exposed to the action of pyrogallic acid *outside the body*. The action is a *direct* one.

On the other hand, the action of toluylendiamin on the blood outside the body differs markedly from its action within the body. In the latter case, as seen, it causes distinct hæmolysis; while on the other hand outside the body in certain strengths it actually preserves the red corpuscles. Its hæmolytic action within the body is thus an *indirect* one—effected through cell-activity.

On the nature of these agencies the above experiments regarding the remarkable effect of splenectomy threw considerable light. They shewed, namely, that the hæmolytic action of so powerful an agent as toluylendiamin could be materially lessened by the removal of a mass of cells—the spleen. If cells had such an influence on the action of so powerful a poison as this drug, *a fortiori*, how much more were they likely to influence the

action of any of the products formed in health capable of inducing any degree of hæmolysis?

The action of such products was much more likely to be *indirect*, as in the case of toluylendiamin—than *direct*, as in the case of pyrogallic acid.

Hence the striking contrast betwixt the action of these two poisons, as regards the effect of splenectomy, not only served to establish a conclusion of great importance—namely, that the spleen possesses a remarkable hæmolytic power, but also led up indirectly to a conclusion of even more importance—namely, the influence of cells in determining hæmolysis (see Chapter XXXVIII.).

CHAPTER XXXVII.

GASTRO-INTESTINAL CAPILLARIES AS A SEAT OF HÆMOLYSIS.

THE spleen being thus apparently the chief seat of hæmolysis, my next enquiry was — where hæmolysis occurred after its removal.

(1) As regards accumulation of blood pigment, the place of the spleen is then taken, partly by red bone marrow, and partly by the capillaries of the liver (Exps. 64, dog, and 89, rabbit), the amount of pigment within the capillaries of the liver being greater than ever observed under any other circumstances (Exp. 89, p. 398).

Exp. 64: Dog (Fox Terrier): weight, 7150 grammes. Animal old. 1888.

Dec. 2. Animal etherized. Spleen removed with strict antiseptic precautions; wound closed with catgut and silk.

„ 5. Recovered. 0·5 gramme toluylendiamin in solution injected subcutaneously.

„ 6. Slight conjunctival jaundice.

„ 7. Jaundice well developed all over body. General health seems good.

Blood.—Plasma shews a distinct rosy appearance as if from hæmoglobin. No *schatten*; no granules; a few red corpuscles seen 'budding.'

Dec. 8. Jaundice still more marked. Killed with chloroform.

Portal Vein.—Most of the red corpuscles perfectly normal; a few *schatten* seen, and a considerable number of the red corpuscles shew 'buds'; some shew peculiar appearances as if the hæmoglobin were withdrawn to one side of the corpuscle.

Leucocytes greatly increased in number (30 in a field), but unchanged in appearance. No pigment cells.

Inferior Vena Cava. — Corpuscles all normal; no *schatten*, no budding.

Liver.—Dark, and rich in blood.

Gall Bladder.—A small quantity of intensely dark bile. Central part of lobule shews a most beautiful natural injection of the bile capillaries with bile. The liver cells fatty. The liver tissue is intensely darkened by NH_4HS (iron reaction), limited almost exclusively to the portal zone; the pigment mostly in form of large pieces, made up of globules and particles of varying size, lying within the capillaries. At parts, the capillaries seem partly blocked by the large pigment heaps.

Some of the pigment globules are exactly the size and shape of red corpuscles. The general character of the pigment resembles closely that usually found in the spleen, not that usually met with in the liver.

Bone Marrow of Shaft.—Much less fat than usual; its tissue almost entirely made up of cells smaller than marrow cells, and resembling in size and appearance the cells of spleen; is extraordinarily rich in iron pigment, more so than in any case yet observed; most of it in large conglomerate heaps; also great numbers of finer granules of pigment within cells, with diffuse staining of the protoplasm of the cells.

(Probability is that the animal, being an old one, a large excess of pigment had accumulated in the spleen, in pigment cells within the capillaries of the liver, and in the bone marrow.

Spleen (excised).—Contains a very large amount of pigment in the form of large irregular masses and globules; extraordinarily abundant. The larger pigment heaps were doubtless the result of slow, chronic hæmocytolysis; the finer particles and diffuse pigment probably represented a more active and recent hæmolysis.)

Duodenum contains a large quantity of deeply bile-stained *viscid mucus*. Mucosa greatly swollen, œdematous, congested, with punctiform hæmorrhages; most intense at upper part of duodenum, at the point where bile duct opens, and diminishing gradually from that point downwards, till at a distance of a foot from pylorus the mucosa presents a perfectly normal, healthy appearance.

The mucosa of stomach is perfectly smooth, and normal in appearance; bile stained at pyloric end.

(2) Pigment alone has, however, as I have shewn (p. 138), but a limited significance as an index of the seat of hæmolysis; and this is again found to hold good. For my observations shew that after removal of the spleen, it is not the capillaries of the liver, but those lying at the other end of the portal area—namely, within the gastro-intestinal mucosa—that constitute the chief seats of hæmolytic change.

The evidence to be adduced in support of this is naturally much less conclusive than it was in the case of the spleen, on account of the widespread area over which these capillaries extend. The evidence is of the following nature:—

When destruction was moderate in amount, the blood of the mesenteric veins shewed no changes, while that of the splenic vein shewed, it might be, extremely marked changes (Exps. 78, 80, 86, and 87, pp. 400, 385, 386, 387).

If the degree of destruction were greater, slight changes were found, but much less pronounced in character than those in the splenic vein (Exp. 82, p. 390).

It was thus exceptional, when the spleen was present, to find changes in the blood issuing from the gastro-intestinal tract, even when a considerable hæmolysis had been experimentally induced; after removal of the spleen, on the other hand, this was the rule even with a considerably less hæmolysis.

Moreover, not only were changes more frequently met with; they were more various and extensive in their character.

In the normal animal, they comprised at most the presence of an excess of albuminous granules. In the spleenless animal, they included not only a much larger number of both granules and spherules, but also—what formerly had never been found—large pigment cells enclosing red corpuscles, and red corpuscles in process of active disintegration, their stroma oozing out and breaking up into coloured spherical bodies. Such changes had previously been entirely confined to the blood of the spleen and the splenic vein (Exps. 62, 64, and 77, pp. 176, 403, 177).

They comprised, further, a still more significant change—one to which as yet no reference has been made—namely, a very large increase in the number of leucocytes, fourfold or fivefold increase (Exp. 64, dog)—a change never observed to the same degree even in the splenic vein, to which it formerly was mainly confined (Exp. 121, p. 418).

Obviously, therefore, some of the changes normally confined to the spleen were after its removal carried out within the much wider area of the gastro-intestinal capillary tract.

Surprising as this result at first seemed, it ceased to be so in the light of the facts afterwards ascertained. With regard both to their mass and activity, the cells (epithelial and lymphoid) in relation to the capillary area of the gastro-intestinal mucosa constitute in themselves an organ second in size and functional activity to none in the body, not even excepting the liver. And although it seemed difficult at first to explain why the destructive action of a drug like toluylendiamin should apparently be more marked in this area than in another, this difficulty was cleared up when, in the experiments presently to be recorded, it was found how important was the rôle of cells in *determining the hæmolytic action* of certain poisons, even of one so destructive as toluylendiamin.

Conclusion.—I conclude, then, that—second only in importance to the spleen—the gastro-intestinal capillary area is the chief seat of hæmolysis. I place it second to the spleen for the reason that when the spleen is present, the changes in the blood coming from this area are altogether less marked than those found in the splenic vein. I place it before the capillary area of the liver partly because the chief changes after removal of the spleen are presented by the blood issuing from the gastro-intestinal area, and are of the same character as those previously found in the splenic vein ; partly because as regards their mass, their character, and their activity, the cells lying in relation to the capillary area resemble more closely those within the spleen than do those in relation to the liver capillaries.

CHAPTER XXXVIII.

FUNCTION OF THE LIVER IN HÆMOLYSIS.

THE result of these observations with regard to the seats of hæmolysis has so far been to point to the portal circulation and the organs in relation to it—viz., (1) the Spleen; (2) the Gastro-intestinal capillary area; (3) the Capillaries of the liver.

These organs have two features in common of capital importance—namely, comparative slowness of the circulation, and a large mass of active cells lying in close relation with the blood.

All the seats are in connexion with the portal circulation, and pour their blood into it. In all cases, therefore, the products of hæmolysis, whatever be their nature, have to pass through the liver before they reach the general circulation. It is then that the chief function of the liver in relation to hæmolysis becomes manifest. A certain amount of hæmolysis doubtless takes place in its capillary area as the result of the activity of its mass of *leucocytes* and *endothelial* cells, and of the changes in the plasma induced by the activity of the liver cells adjacent. Still, the chief function of the liver in relation to hæmolysis is, I conclude, in getting rid by excretion or destruction of the products of hæmolysis.

Amongst the most abundant of these is *hæmoglobin*. Set free within the spleen and in the gastro-intestinal capillary area (by the activity of the cells lying in these areas), it is carried to the liver, passed through the endothelial cells of the walls of the capillaries, and taken up by the liver cells. It is here broken up, the usual products of this destruction being the bile pigments, and a small trace of iron daily excreted in the bile (Young, Kunkel, Hoppe-Seyler, Baserin, and Novi). Sometimes, but not necessarily constantly, a trace of blood pigment remains behind within the liver cell. Under certain conditions of increased

hæmolysis, of which the chief example is pernicious anæmia, this trace becomes very excessive.

With regard to the significance of such an increase, these experiments shew very clearly how little value can be attached to blood pigment within the liver cells as an evidence that hæmolysis has occurred in that organ. For, as has been seen, it is precisely in this situation that a large excess of pigment is occasionally found as the result of the action of toluylendiamin ; and yet the liver cells, or even the capillaries of the liver, have not been the seat of the actual destruction thus occasioned, since in certain cases the removal of the spleen can arrest it altogether.

I conclude, then, that the pigment found in the liver cells in such cases has been formed from hæmoglobin set free within the portal area. I can see no other way of interpreting these facts. The liver, instead of being the actual seat of hæmolysis, has been merely concerned in disposing of some of its products, notably of hæmoglobin.

The *morphological products* of destruction—the granules and spherules, etc.—are likewise arrested in passing through the liver, and prevented from passing into the general circulation—not, however, through the agency of the liver cells, but through that of the leucocytes and endothelial cells of the capillaries. From the frequency with which I have found elements of this kind, and pigment cells, in the capillaries of the liver and in the portal area, while none are to be found in the general circulation during life or in the systemic veins after death, I am led to conclude that the power thus possessed by the leucocytes and endothelial cells of the liver is a very considerable and important one.

The importance of the liver *as a seat of hæmolysis* is thus quite subordinate to that of the spleen. Its rôle still remains sufficiently important, since it has the function of getting rid of the hæmoglobin (and doubtless many other products) thus set free, and of preventing their passage into the general circulation.

It is, in short, the excretory organ of the portal system.

It was of interest to me to ascertain whether hæmoglobin could ever pass through the liver cell unchanged.

To this end the hepatic artery was ligatured (branch going to the right lobe) and a large dose of toluylendiamin injected immediately afterwards (see Exp. 86, p. 386).

On the animal being killed the following day, the right lobe was found to be pale and bloodless—its cells degenerated—and the contents of the gall-bladder consisted of almost pure hæmoglobin. Hæmoglobin had thus passed through the liver cells unchanged.

Summary Regarding Seats of Hæmolysis.

The conclusions arrived at regarding the seats of hæmolysis differ thus in many respects from the conceptions regarding this process with which I started.

(1) In no respect, perhaps, more so than with regard to the part taken by the liver in hæmolysis. At the outset one was disposed, in accordance with current teaching, to assign to it the first place in this relation. The function of the spleen (and other organs) might be called in question, either on the ground that no diminution was discoverable in the number of red corpuscles issuing from it, or that no free hæmoglobin could be detected in the blood of the splenic vein (Schäfer). But as regards the liver, if any organ were specially concerned in hæmolysis more than another, that organ was presumably the liver; and the destruction was, moreover, effected in some way or other through the agency of the liver cells (see p. 74).

In the light of the results of this investigation, I can no longer assign to the liver this position of supremacy. As a seat of hæmolysis, it is much less important than the spleen. Its rôle in hæmolysis still remains important enough—namely, that of an excretory organ.

(2) Further, hæmolysis does not occur in all portions of the blood equally. On the contrary, I find that it is confined almost exclusively to the *Portal* as distinguished from the *General* circulation, and, moreover, that its two chief seats within this area are first the *Spleen*, and secondly the *Gastro-intestinal capillary area.*

(3) Lastly, instead of it being (1) an occasional process, caused, *e.g.*, by accidental presence of injurious products, or (2) a slow chronic change in the blood, evidenced in the case of the red corpuscles by their gradual loss of elasticity and loss of function—I find that hæmolysis is a daily process, conditioned by the activity of the cells in relation to the portal area, and by changes in the plasma secondary to that activity; these changes in the case of the red corpuscles involving what is the most obvious sign of hæmolysis—viz. a daily liberation of hæmoglobin and a daily conversion of a certain amount of hæmoglobin into bile pigments.

CHAPTER XXXIX.

CELLULAR NATURE OF HÆMOLYSIS.

Nature of Investigation.—The next object of my investigations was to ascertain why hæmolysis should be confined to the *Portal* as distinguished from the *General* circulation; and more especially why the removal of the spleen should affect so materially the hæmolytic action of particular poisons, even when injected directly into the general blood.

In arriving at a solution of this problem I encountered at the outset considerable difficulties, which at first could hardly be surmounted. The hæmolytic action of a poison like toluylendiamin was so obviously intensified within the spleen—sometimes, indeed, confined to that organ—that my first surmise was, that the poison had accumulated in the spleen in greater quantity than elsewhere.

I therefore sought for a method by which the presence of toluylendiamin even in the smallest quantity could be detected. I thought at one time this had been found in the use of benzoyl-chloride—an agent which, I found, forms a bulky compound with toluylendiamin. On being put to the proof, however, the method failed—doubtless, as afterwards appeared, from the small quantity of the poison present.

Colorimetric Test for Toluylendiamin.—Some other method, preferably a colorimetric one, was then sought, and eventually found—a reversal of that usually employed for the detection of nitrites in drinking water.[1] Phenylendiamin gives with nitrites, on addition of dilute hydrochloric acid, a deep characteristic colour reaction. If phenylendiamin could be thus used to detect

[1] To Dr. Rühemann of the Cambridge Chemical Laboratory I was indebted for this suggestion.

the presence of nitrites, it suggested itself that the process might be reversed, and that nitrites might be used to detect the presence of phenylendiamin, or also of toluylendiamin.

After a number of trials and failures I succeeded in working out a method based on this principle for the detection and estimation of toluylendiamin even in minute traces in the blood and other tissues. The delicacy of the colour reaction was such, that it was possible to estimate the substance even to a hundredth of a milligramme. Thus, out of 10 milligrammes of the substance added to blood, there were found on estimation 9·95 milligrammes—viz. 9·75 in the plasma, and 0·2 milligrammes in the corpuscles (Exp. 132).

Examination for Toluylendiamin.

Toluylendiamin, even in extremely dilute solution, gives a very well-marked reddish-brown colour reaction on adding to the solution a drop of dilute hydrochloric acid, and subsequently a drop or two of a solution of nitrite of sodium.

There was at first some difficulty in applying the test in the case of coloured fluids—like bile, urine, blood.

After a number of experiments, with the object of decolorization, *e.g.* by charcoal, heating, etc.; the best method, I eventually found, was to dilute the urine and bile greatly, and to use as the comparison solution one of normal bile and urine diluted to the same colour. Thus, in the case of bile, the method was as follows:—

1. A few drops of the bile were placed in a test tube and diluted up to a certain point.

2. In another test tube a small quantity of normal bile was diluted till the colour was the same as in 1.

On applying the test to the latter, the yellow colour entirely disappeared, and solution remained colourless.

If toluylendiamin were present, even in minute trace, a faint brownish coloration was seen on looking through a deep layer of the fluid; and this became quite marked when more was present.

The solutions were placed in cylindrical, flat-bottomed glasses of uniform diameter, and the degree of coloration was judged by looking down through the fluids against a layer of white paper on which the glasses stood.

The method employed for the *Quantitative Estimation* was to ascertain the amount of toluylendiamin it was necessary to add to normal bile to produce the same degree of colour reaction as the bile under examination.

The following was the standard solution :—

Either 0·3 mgrm. of toluylendiamin in 100 c.c. water, or 1 mgrm. in 100 c.c.

Delicacy of Test. The following experiments shew the delicacy of the test employed :—

Exp. 131 : Rabbit bled into 50 c.c. $\frac{3}{4}$% NaCl solution, to which 10 mgrms. of toluylendiamin had been added.

Serum pipetted off; quantity, 100 c.c.

2 c.c. gave colour reaction equivalent to 0·19 mgrm.

100 c.c. = 9·5 mgrms.

Blood clot gave no reaction.

Total accounted for, 9·5 mgrms (= 95 per cent.).

Exp. 132 : Rabbit bled into 50 c.c. 10 per cent. NaCl solution, to which 10 mgrms. of toluylendiamin had been added.

Serum carefully pipetted off; gives marked reaction of toluylendiamin.

Total quantity, 100 c.c.

2 c.c. gave colour reaction equal to 0·195 mgrm.

100 c.c. gave colour reaction equal to 9·75 mgrms.

Total accounted for 9·75 out of 10 mgrms. injected = 97·5 per cent.

I made use, then, of this method in another series of experiments both on rabbits and dogs; estimating the amount of toluylendiamin in the various organs — *Liver, Spleen, and Kidney*, and excretions— *Urine, and Bile*, at intervals of time, varying from one hour up to eighteen after its injection.

Results.

(1) The drug does not accumulate in the spleen in greater amount than elsewhere. On the contrary, even three hours after the injection of half a gramme of toluylendiamin, the amount found in the spleen is too small to be estimable—less even than in the Blood, Liver or Kidneys (Exp. 126).

Exp. 126 : Rabbit : 5th Dec. 1889.

Animal etherized. 11.40 A.M. 0·5 gramme toluylendiamin in 25 c.c. NaCl solution injected into jugular vein. (Object of experiment to kill animal after two hours, and determine amount of toluylendiamin in the blood.)

Killed 2.30 P.M.—viz. nearly three hours after.

Bled into 75 c.c. normal NaCl solution.

Blood set aside in cool place.

Urine.—A small quantity in bladder, clear, limpid, gives an extremely marked reaction of toluylendiamin.

Bile.—Small quantity in gall bladder; withdrawn by pipette; gives a faint but very distinct reaction of toluylendiamin.

Liver, Spleen, Kidneys.—Cut up and ground severally in cold water: allowed to stand over night.

Result of Examination:—

Urine.—Gives colour reaction equivalent to 2·4 milligrammes of toluylendiamin.

Blood.—(1) *Serum* drawn off, colourless; free from hæmoglobin. Total quantity gives colour reaction equivalent to 0·6 milligrammes of toluylendiamin. (2) *Clot.*—Very faint reaction; much less than serum.

Spleen.—Very faint reaction.

Liver.—Distinct reaction of toluylendiamin; about twice as strong as similar degree dilution of serum.

Kidneys.—Distinct reaction of toluylendiamin; twice as marked as that of serum; diluted to equal quantity.

(2) Even within the short space of one hour after its injection, the total amount of the substance present in the blood rarely exceeds one milligramme, and is generally less—this, too, after injection of quantities of half a gramme (Exps. 119 and 125, Dog; 126, 128 and 135, Rabbit.

Exp. 119: Nov. 19, 1889. Dog: weight, 10·15 kilogs.

Narcotized with morphia.

Right ureter exposed, and a cannula introduced.

Common bile duct exposed, and a glass cannula introduced.

Gall-bladder found distended with richly-coloured *bile* (bilirubin colour).

11.45 A.M. Operation completed.

12 noon. Bile flowing fairly well; some hindrance to flow of urine.

12.7 „ Still no flow of urine; 20 c.c. warm normal saline solution injected into vein.

1 P.M. 3·5 c.c. of urine, 3 c.c. of bile } = Sample A.
10 c.c. blood withdrawn from femoral artery = I.

1.30 „ 1·6 c.c. urine, 2·3 c.c. bile } = Sample B.

1.35 „ 0·5 gramme toluylendiamin in 20 c.c. normal saline injected into jugular vein.

2 P.M. Secretion of urine has been very slow.
1·9 c.c. urine } = Sample C.
2·2 c.c. bile }
2.33 „ 2 c.c. bile = Sample D.
3 „ 1·4 c.c. bile = Sample E.
2·2 c.c urine = Sample D and E.
The latter muddier and distinctly darker in colour than first specimen.
5 c.c. of blood withdrawn into saline solution = Sample II.
3·30 „ 2 c.c. bile = Sample F.
Bile secretion during last half-hour has been greater in quantity; colour of bile is less than in Sample E.
No flow of urine.
3·55 „ 20 c.c. of ¾ per cent. NaCl solution injected into vein.
3·56 „ Urine again flowing.
4 „ 1·1 c.c. bile = Sample G.
0·6 c.c. urine.
4·35 „ 5 c.c. blood withdrawn = III.
5·30 „ 2·7 c.c. bile.
1·4 c.c. urine.
5·35 „ 5 c.c. blood withdrawn = IV.
5·45 „ 4 c.c. bile = Sample H.
1·4 c.c. urine = Sample H.
Urine from bladder obtained by squeezing.
Experiment stopped.
Animal killed by bleeding from femoral artery.

Blood of a dark chocolate colour.

(1) Greater portion withdrawn into a beaker containing ¾ per cent. NaCl solution.

(2) Remainder into 8 per cent. NaCl solution.

Placed below in cold cellar.

Weather at the time cold.

Nov. 20, 10 A.M. (1) Has firmly coagulated. A large quantity of serum expressed.

A portion of this serum carefully drawn off with a pipette. No trace of blood-colouring matter either to naked eye or on spectroscopic examination. No hæmoglobin.

(2) Supernatant serum quite colourless. No trace of hæmoglobin on spectroscopic examination.

Examination of Bile.

Samples A and B. Taken before the injection of toluylendiamin. No reaction.

Sample C. Twenty-five minutes after the injection. No reaction.

„ D. One hour after injection. Merest trace of characteristic colour reaction.

„ E. One and a half hours. Still very faint, but more marked than before.

„ F. Two hours. Reaction easily appreciable, even in thin layers.

„ G. Two and a half hours. Still more marked.

„ H. Four hours. Diluted up to 28 c.c. Of this, $2\frac{1}{2}$ c.c. taken and diluted, and tested. Its yellow colour gives place to a distinct brownish colour. A control solution of normal dogs' bile similarly diluted and tested, yellow colour completely disappears. No trace of reaction in this latter.

Examination of Blood withdrawn during Experiment.

1. Withdrawn before the injection.
   Gives no reaction of toluylendiamin.
2. Three hours after injection.
   Gives a trace of reaction.

Examination of Blood after Death.

Portion I. Withdrawn into $\frac{3}{4}$ per cent. NaCl solution.

Both serum and clot give distinct reaction of toluylendiamin.

The method employed was as follows:—

Clot beaten up in water, raised to boiling-point, and filtered. The filtrate treated with equal parts of methylated spirit, and again filtered.

A colourless solution then obtained.

Serum raised to boiling-point and filtered.[1]

Treated in this way, the serum contained an estimated quantity of 0·6 mgrm.

Serum.—Total quantity, 60 c.c.

2 c.c. gave distinct colour reaction, equivalent to colour reaction in water of 0·02 mgrm.

60 c.c. = 0·6 mgrm.

Clot.—Total quantity of fluid, 70 c.c.

2 c.c. = Distinct reaction.

70 c.c. = 0·7 mgrm.

Total quantity of toluylendiamin in blood, 1·3 mgrms.

[1] I subsequently found it better not to heat the serum, but to test it pure, using healthy serum as the control solution.

Examination of Urine.

Samples D and E (2·2 c.c.).—One and a half hours after injection.

Distinct reaction of toluylendiamin.

Diluted to 30 c.c.

2 c.c. contains 0·05 mgrm.

30 c.c. „ 0·75 „

Sample H (1·4 c.c.).—Four hours after injection.

Diluted to 60 c.c.

2 c.c. requires 7 c.c. of standard solution.

(1 mgrm. in 100 c.c.) of toluylendiamin = 0·07 mgrm.

60 c.c. = 2·10 mgrm.

Urine of bladder diluted up to 50 c.c.

2 c.c. required 1·3 c.c. of standard solution = 0·13 mgrm.

50 c.c. = 3·25 mgrms.

Total found in urine = 6·10 mgrms., giving an excretion of 2·85 mgrms. from left kidney, and 3·25 mgrms. from right kidney.

In this experiment there was definite evidence of an excretion of the poison through the bile as early as one hour after its injection, and by the fourth it was in appreciable quantity (0·47 *mgrm.*).

At the same time it was being excreted in the urine—the total quantity excreted in four hours being 6·10 mgrms.

Exp. 125: Dog.

1889. Dec. 2: 0·4 gramme injected.

Killed by bleeding 1¼ hours later; the blood withdrawn into 200 c.c. ¾ per cent. NaCl solution.

Blood.—Twenty-four hours later firmly coagulated; the serum colourless, shewing no trace of hæmoglobin bands.

Both serum and clot (the latter after being treated with distilled water and boiled) gave a slight reaction of toluylendiamin; the total being estimated as not more than 1 mgrm.

Duodenum.—Mucous membrane covered with thick dark bile for a distance of six inches, and slightly congested. Mucus and bile scraped off, diluted with water, heated, and filtered. Filtrate gave faintest reaction.

Exp. 128: Rabbit: 7th Dec. 1889.

12 A.M. 0·5 gramme toluylendiamin in 20 c.c. NaCl solution injected intravenously.

5.30 P.M. Killed by bleeding. Blood set aside to coagulate.

9th Dec. Blood clot firmly contracted; serum thoroughly expressed; of a brownish tinge; no bands of hæmoglobin; but faint darkening over whole field of spectrum.

Serum.—Bulk made up to 150 c.c.; shews faint reaction.

Blood clot.—Well washed; bulk made up to 150 c.c.; shews faint reaction.

In both cases reaction so faint that it cannot be estimated; the reaction of whole of blood not exceeding that of 0·6 milligramme of toluylendiamin.

Liver.—Extracted with water; bulk 150 c.c.; reaction not, however, so distinct as in Exp. 126 (3 hours after injection).

Kidneys.—Bulk of washings 150 c.c.; very faint reaction.

Urine.—Gives a very deep reaction of toluylendiamin.

Exp. 135: Rabbit: 11th Dec. 1889.

4 P.M. 0·5 gramme toluylendiamin in 16 c.c. solution of salt injected into vein.

9 P.M. (5 hours). Killed by bleeding into 60 c.c. of 10 per cent. NaCl.

Spleen contracted and of a red colour; almost bloodless. Shews numerous evidences of hæmolysis—granules, stromata, yellow buds in process of detachment and detached.

12th Dec. *Serum.*—Merest trace of reaction, not estimable.

Corpuscles.—Merest trace of reaction, not estimable.

Urine contains 0·025 gramme of toluylendiamin ($= \frac{1}{20}$th of amount injected).[1]

Excretion of Toluylendiamin through the Urine.

Exp. 121: Dog: 4·75 kilogs. in weight.

1889.

Nov. 25. 0·3 gramme toluylendiamin subcutaneously.

„ 26. 100 c.c. dark bilious urine.

Whole carefully collected, amounting with washings to 150 c.c.

3 c.c. when diluted gave colour reaction equal to 3·4 c.c. of standard solution of toluylendiamin. (10 mgrms. in 100 c.c.)

3 c.c. = 0·34 mgrms.

150 c.c. = 17 mgrms. (0·017 gramme).

„ 27. Urine dark bilious. With washings, 230 c.c.

No trace of toluylendiamin reaction.

Only one-eighteenth part of the amount injected accounted for in the urine; the remainder broken up within the body.

[1] The urine of the rabbit gives naturally a faint colour reaction with sodium nitrite and dilute HCl, so that the figures here given are really in excess of the amount of toluylendiamin actually present. This does not affect the argument here being considered.

Summary.—It will thus be seen that the organs containing most of the substance were those concerned in excretion—namely, the liver and kidneys (Exp. 126). Further, and still more important, in passing through the body almost the whole of the toluylendiamin was broken up, only an eighteenth or twentieth part of it being accounted for in the urine and bile excreted subsequently to its injection (Exps. 121, dog, and 135, rabbit).

This last result I was quite unprepared for. Toluylendiamin is a remarkably stable body, and it had never occurred to me as possible, still less probable, that it could be thus broken up. The fact, however, that it is so, supplies, I consider, the key to the explanation of the remarkable effect of removal of the spleen on its action.

That explanation I consider to be: that *cell activity plays an important part in determining the fate—and with this the hæmolytic action—of toluylendiamin.*

The differences between it and other destructive agents in this respect are brought out in the following table:

Comparison of Hæmolytic Action of (1) Distilled Water, Glycerine, or Pyrogallic Acid—and (2) Toluylendiamin.

Action of Distilled Water, Glycerine, or Pyrogallic Acid.	*Action of Toluylendiamin.*
1. Their action on the corpuscles same within the circulation as outside the body.	1. Action on the corpuscles *within the body* destructive: *outside the body* rather preservative; even when in strength of $\frac{1}{4}$ or $\frac{1}{2}$ per cent.
2. Their injection followed by hæmoglobinuria.	2. Injection not followed by hæmoglobinuria.
3. Amount of destruction is proportional to amount injected.	3. Amount of destruction is not proportional to amount injected: for it may be great within a small dose (*in the normal animal*) and absent altogether with double the dose (*in the spleenless animal*).
4. Destruction is greatest at the time of injection or immediately afterwards—*i.e.* is proportioned to the amount within the blood.	4. Destructive action is delayed, and is not proportioned to amount within the blood; for it is often greatest when the total amount of poison in the blood is less than a milligramme (out of a total, *e.g.* of ·5 gramme injected).

In all these respects, then, the destructive action of toluy-

lendiamin presents a striking contrast to that of such agents as glycerine or distilled water. It is apparently *indirect*, while that of the latter is *direct*.

In this respect, although to a less marked degree, a similar contrast is also presented by the actions of toluylendiamin and pyrogallic acid.

As already described, after the injection of pyrogallic acid into the blood, large numbers of red corpuscles are so injured that within fifteen minutes they are to be found enclosed within the cells of the spleen. Such direct poisonous action on the red corpuscles was rarely observed with toluylendiamin. The destructive action of pyrogallic acid on the blood is thus, to a considerable extent at least, a direct one.

Further confirmation of the difference in the action of these two drugs was afforded, as already seen by experiments in which the spleen was excised. It then appeared that while the hæmolytic action of toluylendiamin was materially lessened, the action of pyrogallic was not at all affected by removal of the spleen.

Toluylendiamin thus differs from hæmolytic agents such as water, glycerine, or pyrogallic acid—whose destructive action on the circulating blood appears to be exactly the same as on the blood outside the body—in the important particular, that its destructive action can be lessened or abolished altogether by the removal of a richly cellular organ—the spleen.

Conclusion.

I conclude, therefore, that the activity of cells more than any other factor determines the occurrence of hæmolysis.

This conclusion is, of course, so far as toluylendiamin is concerned, only applicable in its entirety to the particular animal on which the observations have been made. Its importance, however, is much more wide-reaching, and rests on the circumstance that it is capable of extension to all animals for the particular products normally formed in the body likely to exert any injurious action on the blood.

For if in the case of a drug so powerful as toluylendiamin the cells are the final arbiters whether or not it occasions hæmolysis, the conclusion is permissible that the same will

apply (to an even greater degree if possible) to products formed by these cells themselves.

The issue is left with the cell—a factor common to all animals alike; and, so far as hæmolysis is concerned, not with cells generally, but with the cells of the spleen, of the gastro-intestinal capillary area, and of the blood.

[For summary of conclusions regarding hæmolysis in health, see Chapter XI.]

PART IX.—HÆMOLYSIS AND JAUNDICE.

CHAPTER XL.

THE RELATION OF HÆMOLYSIS TO JAUNDICE.

1. Obstructive Nature of Hæmolytic Jaundice.

THE important observations of Stadelmann[1] shew that a number of forms of jaundice, formerly regarded as of non-obstructive and hæmatogenous nature, are really of obstructive origin, caused by changes in the character of the bile.

The result has been arrived at from a careful study of the changes undergone by the bile in forms of jaundice connected with an excessive destruction of blood caused by certain poisons.

Toluylendiamin Poisoning.—Of special interest and importance in this relation has proved to be the study of the action of toluylendiamin.

Stadelmann's Observations.—This drug has the peculiar action, first noted by Schmiedeberg, of causing intense jaundice in dogs.

Stadelmann, at Schmiedeberg's suggestion, undertook to investigate its action. He was at first quite unable to explain the jaundice. He failed to find any evidence of duodenal catarrh; and the drug appeared according to his first observations to be without any destructive action on the blood. He found, however, that it caused well-marked changes in the bile.

[1] "Das Toluylendiamin und Seine Wirkung auf den Thier körper," *Arch. f. exper. Path. u. Pharmakol.*, Leipzig, 1881, bd. xiv.; "Zur Kenntniss der Gallenfarbstoffbildung," *Ibid.*, Leipzig, 1882, bd. xv.; "Arsenwasserstoffvergiftung: Ein weiterer Beitrag zur Lehre vom Icterus," *Ibid.*, Leipzig, 1883, bd. xvi.; "Das Chronische Vergiftung mit Toluylendiamin," *Ibid.*, Leipzig, 1887; "Weitere Beiträge zur Lehre vom Icterus," *Deutsches Arch. f. klin. Med.*, Leipzig, bd. xviii.; "Ueber den Einfluss des experimentell in den Körper Engeführten Hæmoglobins auf Secretion und Zusammensetzung der Galle," *Ibid.*, Leipzig, bd. xxvii.; "Der Icterus und seine Verschiedene Formen," Stuttgart, 1891.

First stage.—The bile is increased in quantity, and is very rich in bile pigments; this stage beginning about two hours after the injection, and lasting about twelve hours.

Second stage.—It loses all the characters of bile, and is replaced by a small quantity of viscid, colourless mucus. This begins about the fourteenth hour, and lasts from sixty to seventy hours.

Third stage.—The bile gradually returns to its normal character.

The jaundice begins during the first stage, reaches its maximum during the second, and gradually disappears during the third.

Behaviour of Bile acids.—The jaundice is marked by the presence of bile acids in the urine, sometimes in abundant quantity. This increase of the bile acids does not occur contemporaneously with the increase in the bile pigments. On the contrary, they are usually diminished during the first stage, at the time when the bile pigments are increased. It is only about the twenty-second, thirty-first, or forty-eighth hour that they appear in the urine; they reach their maximum in the next twenty-four hours, diminish during the following twenty-four hours, and then disappear altogether. Their appearance in the urine, therefore, does not correspond in point of time with the development of the jaundice, for the latter is well developed fifteen to twenty hours after the injection, while the bile acids do not appear until later.

Afanassiew's Observations.—In one important particular Afanassiew[1] supplemented these observations by shewing that the drug exercises a markedly destructive action on the blood, an observation subsequently confirmed by Stadelmann himself.

Obstructive Nature of the Jaundice.—This observation seemed to supply the missing clue to the explanation of the jaundice. That explanation, according to Stadelmann, is that the drug causes a destruction of blood; the hæmoglobin set free leads to an increased formation and excretion of bile pigments; this increased excretion is attended by an altered character of the bile in the direction of increased viscidity; this, in the face of the low pressure at which the bile is excreted, causes a temporary obstruction, and leads to a re-absorption of the bile; and when the action of the drug exhausts itself, the bile gradually loses its viscid character, the flow of bile is re-established, and the jaundice disappears.

In the case of this drug, then, it will be noticed that a jaundice, possessing at first sight all the characters of a hæmatogenous jaundice, depends upon increased viscidity of the bile causing temporary arrest of its flow.

Phosphorus poisoning.—The jaundice of phosphorus poisoning, always regarded as a typical example of non-obstructive jaundice, has

[1] *Ztschr. f. klin. Med.*, Berlin, bd. vi.

been shewn by Stadelmann to be due to similar changes, differing only in one respect, that they are slower in their production.

> Ten hours after the administration of this poison, the bile begins to be darker in colour; the bile pigments are increased by one-half, the bile acids at the same time being diminished. For the next twenty-four hours these conditions persist, and no jaundice develops. Then the bile begins to change its character; it becomes clearer, more mucoid; its quantity sinks to about one-fifth; the bile pigments fall to one-half or one-third their normal amount; and the bile acids fall to a very low amount, 0·1, 0·15, or 0·7, instead of the normal 1·96.
>
> It is at this stage that jaundice develops; but it only reaches a maximum about five days after the administration of the poison. As the jaundice disappears there is again an increased excretion of bile pigments, doubtless derived by re-absorption from the tissues. The bile acids, however, remain diminished for some days longer; and it is not till the tenth or eleventh day that they again reach their normal.

Arseniuretted hydrogen.—A similar explanation applies to the jaundice produced by inhalation of arseniuretted hydrogen.

> Stadelmann's observations shew that the action of this is attended by a remarkable condition of concentration of the bile, the gall-bladder and bile ducts being filled with a thick viscid bile, which frequently contains large quantities of amorphous sediment, as well as numerous crystals of bilirubin. Hence he concludes that the jaundice is undoubtedly the result of absorption—hepatogenous and not hæmatogenous.
>
> The increase in the bile pigments in the first instance was as great as three and a half times its previous amount; and relatively still greater (twenty times), the quantity of bile being reduced five and a half times.
>
> The bile acids, on the other hand, were reduced to as much as one-tenth their normal amount.
>
> The relation of the various events to each other he conceives to be as follows:—"Without doubt the breaking down of the blood is the occasion for the icterus—but only through the agency of the liver, which produces an abnormal bile, in consequence of the abnormal blood conveyed to it."

Hæmatogenous jaundice really due to obstruction.—These observations are important, not only as serving to explain the action of the particular drugs, but still more in relation to the pathology of so-called "non-obstructive" jaundice generally.

The jaundice of phosphorus poisoning has long been held to

be a striking example of jaundice unconnected with any obstruction—of a jaundice due to suppression. So also the jaundice connected with an excessive destruction of hæmoglobin, *e.g.* in burns and scalds (Klebs, Ponfick, Lassar); following the injection of water or hæmoglobin (Kühne, Tarchanoff); or the inhalation of ether and chloroform (Nothnagel); of poisoning with pyrogallic acid or naphthol (Neisser); of paroxysmal hæmoglobinuria, malaria, pernicious anæmia—has been held to be an example of a jaundice of hæmatogenous origin.

And yet for phosphorus itself, as well as for toluylendiamin and arseniuretted hydrogen, which both exercise a markedly destructive action on the blood, these observations would appear to shew that the jaundice they severally occasion, differing though it may do in respect of its intensity, rapidity of onset, and other characters, is in all cases the result of changes in the character of the bile, and is essentially obstructive in its nature.

Significance of bile acids.—Moreover, the very feature which was held to distinguish a jaundice of *hæmatogenous* from one of *obstructive* origin, namely, the absence of bile acids from the urine in the former, receives from these observations an entirely different explanation.

It has hitherto been assumed that the formation of the bile pigments and bile acids by the liver cells must necessarily go hand in hand; and that an increase or diminution in the one must be accompanied by a corresponding increase or diminution in the other. On this assumption, the absence of bile acids from the urine at any time when bile pigments were present, was regarded as denoting that the bile pigments had been formed elsewhere than in the liver. Stadelmann's observations demonstrate for the first time that the two processes do not necessarily go hand in hand. On the contrary, a large excretion of bile pigments may be attended by a diminished excretion of bile acids, and conversely. In no respect, indeed, are his observations, in my opinion, more striking than in the demonstration they afford of this fact; and to it Stadelmann rightly attaches a special importance.

If thus, as appears, bile pigments can be formed by the liver cells without any corresponding formation of bile acids, the absence of bile acids from the urine in certain forms of jaundice need not necessarily denote, as has hitherto been supposed,

inactivity on the part of the liver. On the contrary, it is quite compatible with increased activity of the liver and increased formation of bile pigments—and with a jaundice of purely obstructive nature connected with the excretion of these bile pigments.

On this view, then, many forms of jaundice connected with disorder of the blood, hitherto regarded as of non-obstructive nature, must be grouped as varieties of obstructive jaundice—the occasion of the obstruction being intimate changes in the character and consistence of the bile, similar to those caused in phosphorus and toluylendiamin poisoning.

Cause of the Obstruction.

Stadelmann's Explanation. An important point, then, with regard to such forms of jaundice, is to understand how the blood changes cause the increased viscidity of the bile which occasions the obstruction.

According to Stadelmann, the relationship is of this kind. The blood disorder is usually marked by increased destruction of blood; the increased supply of hæmoglobin to the liver occasions an increased formation of bile pigments, which is attended at the same time by an increased concentration of the bile, caused by the specific action of the poison on the liver cells; this change in the character of the bile suffices to cause temporary obstruction to the flow of bile (with jaundice). The most constant and important change he regards as the increased formation of bile pigments (*polychromia*)—so much so, that in his opinion the jaundice might most fitly be termed "jaundice from polychromia."[1]

He takes strong exception to the term "polycholia" in this relation, as fitly describing the character of the jaundice. He contends that the term polycholia can only be rightly applied where there is an increase of all the constituents of the bile, both watery and solid. And, as he points out, this is not the case in the forms of jaundice now under consideration. So far from the quantity being increased, it is often diminished from the very first; and so far from the bile salts being increased, they are as a rule notably diminished, only regaining the normal when the jaundice is passing off.

[1] Stadelmann, *Der Icterus und seine Verschiedene Formen*, p. 247.

Author's Observations.

It is on this point—the relation between the blood changes and the bile changes—that my observations yield information.

They relate to the action of toluylendiamin. They shew that the concentration of bile, so marked a feature of its action, is due to an extensive catarrh of the bile ducts, occasioned by the excretion of the poison or its derivatives through the bile,—extending, not from the duodenum upwards, but from the intra-hepatic bile capillaries downwards.

It is the increase of the catarrhal viscid mucus thus occasioned that causes the concentration of the bile, and temporarily arrests its flow altogether.

> In all cases, where jaundice followed the injection of toluylendiamin, I found congestion, catarrh, and swelling of the mucous membrane of the duodenum, commencing on a level with the opening of the bile duct, and always most intense around the duodenal papilla. The degree of congestion varied in different cases. In only one case was it of so slight a nature that it might, perhaps, have been overlooked; and that was the only case in which there was no jaundice. In all the other cases it was very marked. In one case, so great was the swelling of mucous and submucous coats, that the lumen of the duodenum was greatly lessened, the contents being clear, colourless, viscid mucus, free from bile. In all cases a similar catarrh existed in the intra-hepatic bile ducts.

In respect of its intensity, the condition in Experiment 133 was exceptionally striking. My object was not merely to produce extreme jaundice, but to ascertain whether, by giving another large dose (0·5 gramme) while the jaundice was still very marked, the duodenal condition could be correspondingly intensified. The result was that all the essential features were intensified, especially the limitation of the congestion upwards, and its great intensity around the opening of the bile duct. In addition, however, in this case, the catarrh of the bile ducts was very manifest—the clear viscid mucus projecting from the orifice of the common bile duct being of the same character as that occupying the duodenum itself (see Plate XIII.).

Action of Toluylendiamin on Duodenum and Bile Ducts.

Exp. 63: Small Dog: weight, 4400 grammes.

1887.

Nov. 24. 0·5 gramme toluylendiamin in neutral saline solution injected subcutaneously.

,, 26. Jaundice of conjunctivæ well marked, also evident in skin of ears and mucous membrane of gums.

,, 28. Weight, 4300; jaundice very pronounced all over body, especially seen over abdomen.

,, 29. Jaundice still pronounced; weight, 4050. Animal killed with chloroform.

Liver.—Greatly jaundiced, large, soft, and somewhat fatty looking.

Gall-bladder.—Contains a quantity of extremely dark, thick, inspissated bile.

Periphery of lobule presents a bright, golden-yellow appearance, seen on microscopic examination to be due to the presence of large masses of yellow material. Many of even the larger bile ducts plugged with inspissated bile.

Great stasis of bile also in capillaries in centre of lobule.

Intralobular blood capillaries filled with coloured remains of hæmoglobin and red corpuscles.

Stomach.—Firmly contracted; empty; mucous membrane thrown into rugæ, of a pale yellow colour.

Duodenum.—Appearances very striking. From the pylorus downwards, for a distance of about twelve inches, its mucous membrane is extremely swollen and congested, shewing at parts small hæmorrhages. This is most marked at the upper part of the duodenum, especially around the opening of the common duct.

The congestion and swelling of mucous membrane diminish in intensity from this point downwards, and disappear altogether about the commencement of the jejunum.

Compared with the mucous membrane from the duodenum of a healthy dog, the mucous membrane is seen to be soft and swollen, and on section twice to three times as thick. Small hæmorrhages are seen in its substance.

Exp. 64: Fox-Terrier Dog: weight, 7·15 kilogs.

1887.

Dec. 2. Spleen excised with full antiseptic precautions; edges of abdominal incision brought together with catgut; skin edges with silk.

,, 5. Animal recovered; weight, 6450; 0·5 gramme toluylendiamin injected subcutaneously.

,, 6. Conjunctival jaundice.

1887.
Dec. 7. Pronounced jaundice all over body.
,, 8. Jaundice still more marked; weight, 6050.
Killed with chloroform.
Peritoneal wound healed.
No inflammation.

Liver.—Very dark and full of blood. Lobules not distinguishable to naked eye. Microscopically, the central part of each lobule presents the most beautiful natural injection of the bile capillaries with bile.

Gall-bladder.—Contains a small quantity of intensely dark bile.

Stomach.—Mucous membrane normal, pyloric end bile-stained.

Duodenum.—Contains a large quantity of deeply bile-stained *viscid* mucus. The mucous membrane is greatly swollen, soft, and congested, with here and there punctiform hæmorrhages. The congestion is most intense at the upper part around the opening of the common bile duct, and diminishes gradually from there downwards, till at a distance of some 10–12 inches from the pylorus the mucous membrane assumes a normal healthy appearance. The intestinal mucous membrane throughout is covered with deeply bile-stained thick viscid mucus.

The appearances are similar in character to those presented in foregoing experiment, only less marked.

Exp. 121: Nov. 27, 1889. Small Dog: weight, 4·75 kilogs.: 0·3 grammes toluylendiamin injected subcutaneously.
Nov. 26. 100 c.c. dark bilious-looking urine.
,, 27. Weight, 4·5 kilogs.; well-marked jaundice; 160 c.c. urine, deeply bile stained.
,, 28. Weight, 4·35 kilogs.
Jaundice very pronounced.
Killed with chloroform.

Stomach.—Empty; mucous membrane thrown into folds, normal in colour and appearance; towards pyloric end slightly bile-stained.

Duodenum.—The mucous membrane of duodenum is congested and ecchymosed, presenting marked injection at parts. The congestion and ecchymosis commences on a level with the papilla on which the bile duct opens; and is very marked over a tract of 3 inches in extent from this papilla downwards.

Just below the papilla the congestion has a circular arrangement around a central deeper and paler part, the appearance at first glance resembling that of an ulcer. The floor, consisting of follicular tissue, is pale; around the margins the villi are swollen, congested, and ecchymosed. At the upper part three such congested follicular patches —axis transverse to that of gut—measuring 13 mm. by 4 mm., 10 mm. by 5 mm., the third incomplete. One inch lower down another

similarly congested patch, 11 mm. by $4\frac{1}{2}$ mm.; and $1\frac{1}{2}$ inches still lower down, another, 11 mm. by 7 mm.

The congestion extends from here the whole way down to the ileo-cæcal valve, without, however, any ecchymoses; the mucous membrane swollen and œdematous. Just above the ileo-cæcal valve, over an area of $3\frac{1}{2}$ inches in extent, there is a repetition of the redness, swelling, and ecchymosis seen at the upper part of the duodenum. Near lower end of ileum, follicular patches prominent and swollen, but not reddened. At this point a considerable quantity of dark brown bile, sufficient to fill the lumen of the gut; elsewhere throughout the gut, deeply bile-stained mucus.

The whole wall of the gut is affected by the swelling, most of all, however, the mucous membrane.

A number of measurements made on a healthy dog give an average thickness of $2\frac{3}{4}$ mm. for wall of gut; the measurements here give a thickness of $4\frac{3}{4}$–5 mm., the mucous membrane alone being $3\frac{3}{4}$ mm. thick.

Exp. 129: Dec. 7, 1889. Dog: weight, 5·5 kilogs.; 0·25 gramme toluylendiamin injected subcutaneously.

Dec. 8. 80 c.c. clear straw-coloured urine.
No bile pigments.
Gives marked reaction of toluylendiamin.

„ 9. Urine slightly darker in colour.
Still no bile pigments.
Reaction of toluylendiamin distinct but less marked.

„ 10. Distinct reaction of bile pigments in urine.
No jaundice of skin or conjunctivæ.

„ 11. *Urine*—Distinct reaction of bile pigments.
No reaction of toluylendiamin.
0·34 gramme toluylendiamin subcutaneously.

„ 17. Weight, 4·55. No jaundice.
Killed with chloroform.

Duodenum and intestine.—On opening intestine from below upwards, mucous membrane is seen to be of pale colour and healthy appearance up to within 12–18 inches of pylorus. It then shews slight traces of congestion, but these are not marked, and are not such as would attract attention.

Exp. 133: Dec. 10, 1889; weight, 10·9 kilogs.; 0·5 gramme toluylendiamin injected subcutaneously.

Dec. 14. 10·1 kilogs.

„ 15. 0·5 gramme injected.

„ 16. 9·25 kilogs.

„ 17. 8·95 kilogs.
Killed with chloroform.

Extreme jaundice from second day. During whole time the animal took no food and rapidly emaciated.

Stomach.—Empty. Mucous membrane thrown into folds, pale and normal.

Duodenum.—Directly on opening abdomen, the duodenum is seen to be affected, its walls turgid, swollen, and doughy to the touch. On being opened, the most intense inflammatory congestion of its coats, especially the mucous and sub-mucous coats; the lumen of the gut narrowed, and filled with *clear, thick mucus* free from bile. The congestion and swelling have their greatest intensity around the opening of the common bile duct, from which thick mucus can be seen issuing; and for a distance of about 8 inches downwards from the point it is of the most intense character, the whole walls œdematous and thickened.

Below this it gradually fades off, but throughout the whole of the small intestine the mucous membrane is considerably swollen and congested, the follicular patches here and there being very prominent by the congestion around their margins.

The appearances are accurately represented in the accompanying Plate, from a drawing made immediately on opening the duodenum (see Plate XIII.).

Results.—As regards the relation of this duodenitis to the jaundice, it will be noted that in only one case was there little or no obvious jaundice (although bile pigments were present in the urine); and that was the only case in which the duodenal condition was so slight that it might conceivably have been overlooked (Exp. 129). In the other cases the œdematous swelling of the mucous membrane was such that it must necessarily cause obstruction if existing in the bile channels. A condition of catarrh falling far short of that here produced would amply suffice to retard, and, if continued, finally arrest the flow of bile along the bile channels. And so indeed it did. For the animals were in all cases deeply jaundiced.

The catarrh and swelling of mucosa were not confined to the duodenum. The bile duct and intra-hepatic ducts were filled with colourless mucus similar to that lying within the duodenum; a circumstance which suggested that whatever had occasioned the catarrh had reached the duodenum through the bile.

For the drug was not administered by the mouth, but hypodermically; the mucous membrane of the stomach above the pylorus was always free from the slightest trace of abnormality

or congestion, and it was precisely on a level with the opening of the bile duct that the duodenitis commenced. The irritant—using that term in its widest sense—appeared to have reached the duodenum through the bile; and its action on the mucous membrane of the bile duct, to judge from the viscid character of the colourless mucus issuing from the bile duct, had been the same as on the mucous membrane of the duodenum.

Excretion of Toluylendiamin through the Bile.

I therefore made further experiments to ascertain whether the poison was excreted through the liver, and could be found in the bile.

The results shew that the bile is one of the channels through which toluylendiamin is excreted from the body.

Results.

As early as one hour after injection, traces of it could be detected in the bile (Exps. 119 and 125); and by the fourth hour, it was present in an appreciable, albeit still very small, amount.

In the present relation, however, the actual amount excreted is a matter of comparatively little importance.

The point of importance, as it appears to me, is that it is excreted at all through this channel.

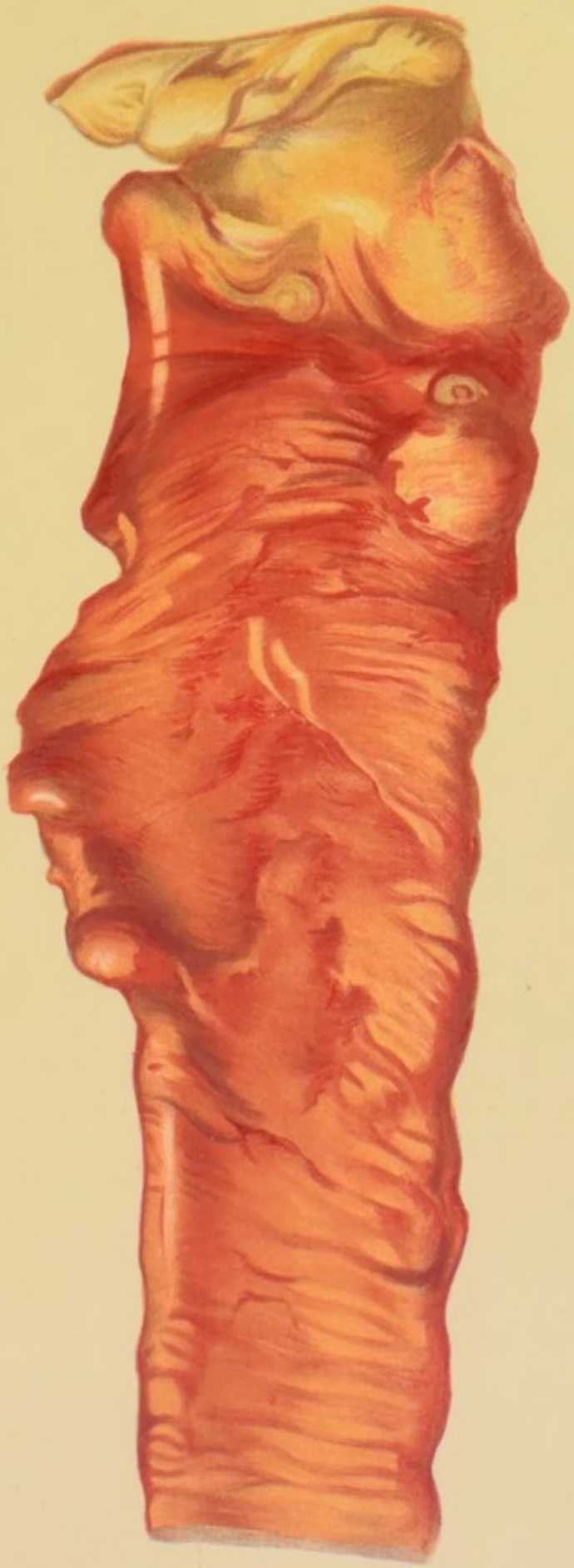
The other experiments I have recorded shew that toluylendiamin is broken up very soon after its introduction into the body; and that the greater part of it is either destroyed or leaves the body in some other form. Information on this point is afforded most clearly by Experiment 121. Of the total amount of toluylendiamin injected (0·3 gramme), only about $\frac{1}{18}$th part could be discovered in the urine (·017 gramme).

No less striking in the same relation is the small amount of the poison to be detected in the blood even one hour after its injection. Thus one and a quarter hours after injection of 0·4 gramme (Exp. 125), only a trace could be found in the whole quantity of blood.

It may be, of course, that the poison has already entered into some combination which prevents it being

PLATE XIII.

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detected. It certainly is not present in free form; for the Experiments 131 and 132 shew that the method employed for detecting it is sufficiently delicate to recognize 95 to 97 per cent. of the substance when added to blood outside the body.

Considering then, the small amount present at any time in the blood, and the small proportion ($\frac{1}{18}$) that succeeds in escaping unbroken from the body, the trace found in the bile is not inconsiderable.

Nature of the Irritant.

The question then arises—are the catarrh and congestion set up in the bile ducts and duodenum, after the injection of toluylendiamin, to be ascribed to the irritant action of this small trace of poison in the bile?

I think this is extremely improbable, and for this reason. Toluylendiamin has a slight irritant action, especially in its stronger solution ($2\frac{1}{2}$ or 5 per cent.) when injected subcutaneously, causing some inflammation, with subsequent necrosis of overlying skin and scab formation. Such an action, however, is, I consider, no criterion of what its action on the mucous surfaces of the bile ducts or duodenum may be. I think it extremely improbable that the small amount in which it is present in the bile can exert such an irritant action as that I have described.

It is, I conceive, much more likely that the irritant action of the bile after toluylendiamin poisoning is due to the presence of derivatives of the poison, and not to the poison itself. The foregoing observations shew that only a small proportion ($\frac{1}{18}$, Exp. 121) passes through the body unchanged. The remainder is either destroyed, or converted into derivatives, which, like the poison itself, are in all probability excreted through the urine and the bile.

Whatever the nature of the irritant, these observations shew that *it is contained in the excreted bile; that it reaches the duodenum through the bile; and that it must be of powerful action to induce such an inflammatory congestion as that described.*

Cause of the Jaundice.

The explanation of the jaundice produced by toluylendiamin appears to me, then, to be—that products of the poison are

excreted through the bile, and excite swelling and catarrh, with increased secretion of mucus, in its course down the bile passages into the duodenum.

The involvement of the duodenum I do not consider at all necessary for the production of the jaundice. The duodenal catarrh is secondary to that of the bile ducts. It is only in exceptionally severe cases that it occurs. The primary cause of the obstruction is, I consider, the catarrh of the intrahepatic bile ducts. Under the low pressure at which the bile is excreted, a slight degree of catarrh in this situation suffices to cause, first, increased viscidity of the bile, retardation in the flow (end of first stage); and as the catarrh spreads down the bile ducts and the viscidity increases, the flow of bile is altogether arrested (second stage).

This view, as to the relation of the catarrh to jaundice, differs essentially, it will be seen, from the one usually accepted, according to which the catarrh spreads upwards from the duodenum, the latter preceding the former.

In the present case, as I have said, I consider the duodenal condition quite unnecessary to the production of the catarrh. For the course of the catarrh is from above downwards; it commences in the bile radicles, and extends downwards; and in many cases it may not even reach the duodenum. As it is produced by substances excreted by the liver, it involves, therefore, the whole bile radicles and smaller ducts simultaneously, and to a like degree. In slight cases it may not extend beyond these; and it would be quite impossible (apart from its result, jaundice) to recognize it after death.

As a factor in causing jaundice, it derives its chief importance from the widespread character of the obstruction it produces, rather than from its high degree. The increased secretion of mucus occasions increased viscidity of bile sufficient to occasion a certain amount of obstruction and a certain degree of jaundice.

CHAPTER XLI.

OTHER VIEWS REGARDING RELATION OF BLOOD DESTRUCTION TO JAUNDICE.

OTHER views have been held regarding the relation between increased destruction of blood and jaundice.

1. Relation to Hæmoglobinæmia.

It is necessary to consider what is the influence of a hæmoglobinæmia *per se*, with increased formation of bile pigments (polychromia), on the consistence of the bile, and through the latter on jaundice.

That some relation exists between these two conditions is evident from the frequency with which some degree of jaundice is met with (both clinically and experimentally) in cases where hæmoglobin has been set free in the blood and passes into the urine.

The observation that some relation exists between the two conditions formed in Kühne's hands the very starting-point of the doctrine of a hæmatogenous jaundice independent of any destruction.

Kühne[1] considered this relation an absolute and quantitative one. An excess of free hæmoglobin in the blood was of itself sufficient, according to him, to occasion a certain degree of jaundice—such a degree, at least, as to cause bile pigments to appear in the urine.

The later experiments of Tarchanoff and Stadelmann seemed to lend additional support to this view.

Thus, according to Tarchanoff,[2] bile pigment is regularly found in the urine of dogs after injection of water or hæmoglobin into the blood.

[1] *Lehrbuch der physiol. Chemie*, 1868.

[2] *Arch. f. d. ges. Physiol.*, Bonn, bd. ix.

And, as we have seen, Stadelmann attaches quite a special importance to the increase of bile pigments (polychromia) which occurs under such circumstances, as one of the chief factors in occasioning a form of jaundice. The jaundice so caused might, he considers, be most fitly termed 'jaundice from polychromia.' After injection of large quantities of hæmoglobin, he usually found a trace of bile pigment in the urine some time or other in the course of the experiment.

Stadelmann's observations go still further; for they show in what manner an excess of free hæmoglobin may produce jaundice. The injection of free hæmoglobin into the blood, or its liberation within the circulation by use of distilled water, is followed by changes in the bile, namely, increase of bile pigments, increased viscidity of the bile, diminution of bile acids —changes, therefore, similar in character to those caused by toluylendiamin or arseniuretted hydrogen. And the explanation of the jaundice that may occur under such circumstances is, according to him, the same—namely, obstruction caused by the high concentration of the bile, and this, in turn, caused by the polychromia. Nothing at first sight seems wanting, therefore, to an understanding of the relation between hæmoglobinæmia and jaundice.

And yet other data, to which I must now direct attention, appear to me to indicate that the relation is by no means so simple and so constant as the above would appear to shew. *They justify rather the conclusion that hæmoglobinæmia, apart from the operation of other factors, is not sufficient to cause jaundice.*

Influence of Hæmoglobinæmia in producing Jaundice.

Let us first endeavour to ascertain the influence of a simple excess of free hæmoglobin in the blood in producing jaundice, apart from all other possible factors.

Hæmoglobinæmia is not of itself sufficient to cause bile pigments to appear in the urine, still less to cause jaundice.

First of all, a number of observations cast doubt on the accuracy of Kühne's statement that excess of free hæmoglobin

in the blood is sufficient of itself to cause bile pigments to appear in the urine.

Results in support of such a view have only been obtained in one class of animals (dogs), and *even in them not constantly*; whereas in rabbits the balance of experimental evidence from all sides is, I consider, decidedly against the view that hæmoglobinæmia *per se* is sufficient to cause jaundice.

Dogs.—As regards dogs, the significance to be attached to bile pigments in the urine is a little complicated by the circumstance, noted by many authors, which I can fully confirm, that it is not uncommon to find a trace of bile pigments in the urine of apparently healthy dogs. Unless this source of fallacy be kept in mind, and care be taken by suitable precautions to avoid it, erroneous conclusions may be drawn. In my experience, this is specially likely to be the case in old dogs. To avoid this source of fallacy it is, I think, necessary to employ only young healthy dogs, whose intestinal canal has been well cleared out by castor oil or calomel; the animals being kept on a milk and bread diet for some days previous to experiment. This tendency to the occurrence of a slight degree of icterus in dogs is connected, in my opinion, with their habit of eating garbage and refuse of various kinds. It is not uncommon to find in such animals some degree of catarrh of the mucous membrane of the small intestine.

The experiments of Naunyn[1] conclusively shew that if care be taken to avoid the above source of fallacy, hæmoglobinæmia, even in dogs, does not necessarily cause bile pigments to appear in the urine. In only two out of six cases in which he caused hæmoglobinuria by injecting hæmoglobin subcutaneously did the urine give any reaction to Gmelin's test for bile pigments; and in both of these cases the urine had given a slight reaction before the experiment. In the other four cases he failed to find any bile pigment in the urine, although there was marked hæmoglobinuria (and necessarily hæmoglobinæmia).

And although Stadelmann usually found a trace of bile pigment in the urine after injection of large quantities of hæmoglobin, there are, as it appears to me, certain features in his results which indicate that the presence of bile pigment was to be referred to other factors than the simple hæmoglobinæmia.

[1] "Beiträge zur Lehre vom Icterus," *Arch. f. Anat. u. Physiol.*, 1868, p. 401.

Thus the quantity was at most a trace, and in no way proportionate either to the amount of hæmoglobin set free or to the resulting increase of bile pigments. This is not what one would naturally expect, if the presence of bile pigment in the urine be directly related to the hæmoglobinæmia, as Kühne supposed, or to the resulting increased formation of bile pigments (polychromia), as Stadelmann considers.

Stadelmann's Experiments.

I have summarized the results of his experiments[1] in the following tables. It will be seen from them that the one condition to which the jaundice is constantly related is *the degree of viscidity* of the bile, *not the degree of polychromia* or hæmoglobinæmia.

> Thus in one experiment (*a*) of the latter, where there was an increase of 80 per cent. in the bilirubin secreted, with hæmoglobinuria, only a trace of bile pigment was found in the urine; while in another (Exp. 3), where the increase in bilirubin was less than 50 per cent., without hæmoglobinuria, there was a considerable quantity of bile pigment in the urine.

Exp. (*a*).—Dog; 20 grammes of hæmoglobin injected in six portions between 10 A.M. and 8 P.M.

First period of 12 hours—
- Bilirubin increased by 80 per cent.
- Hæmoglobin, but no bile pigment in urine.

Second period of 12 hours—
- Bile very dark. Viscid, diminished in quantity.
- No hæmoglobinuria, but a trace of bile pigment in urine.

Third period—
- Bile increased in quantity.
- No trace of bile pigment in urine.
- Bile acids considerably diminished at the very time the bilirubin most increased.

Exp. 1.—10·02 grammes hæmoglobin injected subcutaneously.

First period of 24 hours—
- Bilirubin increased by 56 per cent.

[1] *Op. cit.*, p. 23 *et seq.*

Bile reduced to one-third normal quantity, dark, viscid.
No bile pigment in urine.

Second period—
Bile very dark and thick.
Trace of bile pigment in urine.

Third period—
Bile normal in consistence.
No trace of bile pigments in urine.

Bile acids.—First 12 hours. Unaffected.
Second ,, Diminished by 36·8 per cent.
Third ,, ,, ,, 44·5 ,,

Exp. 2.—10·82 grammes hæmoglobin subcutaneously injected.

First period of 12 hours—
Bilirubin increased by 11·96 per cent.
Urine normal.

Second period—
Bilirubin increased by 61 per cent.
Bile thick.
Urine normal.

Third period—
Bilirubin increased by 35·8 per cent.
Bile of normal consistence.
Urine normal.
Quantity of bile fairly normal throughout.

Bile acids shewed no change.

Exp. 3.—13·94 grammes hæmoglobin injected into peritoneum.

First period of 12 hours—
Bilirubin increased by 12·3 per cent.
Bile very thick; quantity diminished.
No bile pigments in urine.

Second period—
Bilirubin increased 49·5 per cent.
Bile thick; quantity diminished.
Considerable quantity of bile pigment in urine.

Third period—
Bilirubin increased by 12·4 per cent.
Bile normal in quantity and consistence.

Bile acids. First and second periods—
Diminished by about 17 per cent.
Third period—slightly increased.

The relation, then, between hæmoglobinæmia (with polychromia), and jaundice is no mere quantitative one, even in dogs.

This is true of hæmoglobinæmia produced by injection of distilled water. It also holds true for hæmoglobinæmia induced by poisons.

Thus in one of the foregoing experiments of Stadelmann (Exp. 6), there was hæmoglobinuria after injection of 0·3 gramme toluylendiamin without any jaundice supervening; and nine days later, after a similar dose, there was jaundice without, however, any hæmoglobinuria.

Rabbits.—While, then, as regards dogs, the evidence either way is inconclusive,—hæmoglobinæmia sometimes causing jaundice, sometimes not,—in rabbits there is no such uncertainty. The great preponderance of evidence is, I consider, decidedly against the view that hæmoglobinæmia *per se* suffices to cause jaundice even in the slight degree necessary to cause bile pigments to appear in the urine.

Naunyn always failed to find bile pigments in the urine of rabbits after causing hæmoglobinuria.

Since then the list of those who have similarly failed includes the names of: Wickham Legg,[1] after the injection of bile acids; Lauder Brunton,[2] after the injection of bile acids into the circulation, or of ether or dissolved blood corpuscles into the intestine; L. Steiner,[3] after the injection of water into the circulation of rabbits.

On this latter point my observations are in entire agreement with those of Naunyn and Steiner. Both after a slight and marked degree of hæmoglobinæmia I failed to find bile pigments in the urine. (See Experiments 44 and 48 (Chap. xv.), in which intense hæmoglobinuria was produced by injection of distilled water, yet no bile pigments appeared in the urine.)

In some cases the results have varied in the hands of the same observer. Thus Graham Brown,[4] after subcutaneous injection of bile acids in rabbits, failed in most cases to find bile pigments in the urine, while in a few cases he succeeded.

[1] *Bile, Jaundice, and Bilious Diseases*, 1880, p. 235.

[2] *Handbook for Physiological Laboratory*, 1873, p. 499.

[3] "Ueber die hæmatog. Bildung des Gallenfarbstoffes," *Arch. f. Anat. u. Physiol.*, 1873.

[4] *Proc. Roy. Soc. Edin.*, 1875, p. 528.

Naunyn, who failed to discover bile pigments in the urine when he injected hæmoglobin into the circulation, found it after injecting thawed blood into the intestine[1]; an observation which Lauder Brunton[2] failed to confirm.

These varying results may perhaps be partly explained, either on the ground that the animals used were not in all cases the same, or that the conditions of the experiments were not in all cases alike—different agents being used to produce hæmoglobinuria, and different methods of administration employed. Hitherto, on the view that the positive result was the common and natural one, the chief endeavour on the part of observers has been to explain the negative results. But as I have shewn, even in dogs the result is not always positive; and when it is, it is not directly related to the quantity of hæmoglobin set free, or to the resulting formation of bile pigment. In rabbits, further, a positive result is decidedly the exception. The position of matters is thus, I consider, reversed. So long as it was held that free hæmoglobin could become transformed into bile pigment within the blood, it was natural to expect that hæmoglobinæmia should cause bile pigments to appear in the urine; and no less natural, therefore, to regard as exceptional all cases where this did not occur. Now, however, that it has been shewn by preponderance of evidence that the jaundice of blood disorder is not hæmatogenous, but hepatogenous (Stadelmann), the position of matters is, as I have said, reversed. If under the old (hæmatogenous) view the difficulty was to explain why hæmoglobinæmia should not always occasion some degree of jaundice, with our present knowledge the difficulty appears to me of another nature—to explain, namely, in what way hæmoglobinæmia, with its resulting polychromia, should cause increased viscidity of the bile and temporary arrest of its flow.

Conclusion.

For the reasons I have adduced, then, I consider that mere excess of hæmoglobin in the blood, or increase of bile pigments, however great, is not the sole factor determining the increased viscidity in the bile, which occasions the jaundice of increased hæmolysis.

[1] *Op. cit.*

[2] *Op. cit.*, p. 499.

Jaundice may be of the most intense character, with only a comparatively slight polychromia (one-half increase in toluylendiamin poisoning); or it may be slight or absent, with a threefold or fourfold increase (arsenious acid poisoning). Further, in one class of animals (dogs) we may have jaundice without hæmoglobinuria (toluylendiamin); in another (cats) we may have hæmoglobinuria without jaundice (toluylendiamin); while in a third (rabbits) we may have hæmolysis without hæmoglobinuria or jaundice. And yet in all three classes it occasions a destruction of blood. Moreover, even in the same animal its action sometimes varies. Thus in the dog it may occasionally cause hæmoglobinuria without jaundice (Stadelmann).

2. Nature of the Hæmocytolysis.

That jaundice, however, frequently occurs in conditions attended by increased destruction of blood is a fact about which there can be no dispute. The relation between the two conditions must thus be a *qualitative* one, since as just seen it is not a quantitative one.

Other explanations of these differences have been put forward. According to Afanassiew,[1] the occurrence of jaundice alone, or hæmoglobinuria alone, or both together, depends not merely on the *extent*, but also on the *nature* of the preceding blood destruction.

> He distinguishes three kinds of action of hæmolytic substances on the blood. The first is represented by the action of glycerine, which dissolves the hæmoglobin out of the corpuscles, leaving hardly any morphological remains of the latter within the blood. The free hæmoglobin escapes mostly through the kidneys, only a small portion being dealt with elsewhere (liver, spleen, or bone marrow).
>
> The second kind of action is represented by that of toluylendiamin. This acts quite differently. It breaks the red corpuscles into pieces. These circulate in the blood, and accumulate in the liver, spleen, and bone marrow, where they are disposed of, only a part escaping through the kidney. When the dose is small, no hæmoglobin

[1] "Ueber die pathologischen anatomischen Veränderungen in den Nieren und in der Leber bei einigen mit Hæmoglobinurie oder Icterus verbundenen Vergiftungen," *Virchow's Archiv*, 1884, bd. xcviii. s. 465.

passes into the plasma. Hence, in slight cases, jaundice alone occurs, produced by the increased excretion of bile; there is no hæmoglobinuria.

When the dose is larger, the remains of the red corpuscles are not sufficiently rapidly disposed of; they circulate in the blood, some of their hæmoglobin escapes into the plasma, and not only jaundice, but also hæmoglobinuria, occurs.

The third kind of action is represented by that of pyrogallic acid. It is intermediate in character betwixt the two preceding. It liberates hæmoglobin from the corpuscles, and causes hæmoglobinuria; but morphological remains (*schatten*, etc.) also soon appear, and there is usually slight icterus.

This explanation of the differences in the action of different substances on the blood is adopted by Silbermann.[1]

Stadelmann[2] hesitates to accept it, but cannot altogether reject it. It may be sufficient, he thinks, to account for the jaundice, but it is quite insufficient, in his opinion, to explain the degree of jaundice. He considers that the blood corpuscles of different species of animals have a different resisting power towards different poisons; but any essential difference in the nature of the action of different poisons on the blood he could not discover. Individual differences there undoubtedly are. Thus in dogs, arseniuretted hydrogen causes intense hæmoglobinuria and well-marked changes in the blood (altered corpuscles, *schatten*, etc.), while with toluylendiamin signs of blood destruction are infrequent. But this is not constant. Every now and again a case is met with in which the latter drug causes intense hæmoglobinuria without jaundice, although the morphological changes in the blood are the same as those which usually attend its action when it causes jaundice.

Author's Observations.

My observations on this point relate to the action of distilled water, glycerine, pyrogallic acid, and toluylendiamin,—more particularly to the last.

[1] "Ueber Hæmoglobinæmie," *Ztschr. f. klin. Med.*, Berlin, 1886, bd. xi. s. 471.
[2] *Op. cit.*, s. 237.

With regard, first of all, to the modes of action of the above agents on the blood, my observations confirm in the main those of Afanassiew regarding the differences in the blood changes in the case of individual drugs.

I do not find, however, that these differences are sufficient, either in degree or in kind, to account for the very different action of the agents qua *the production of jaundice.*

As regards *glycerine*, this agent is, in my opinion, unsuitable for comparison experiments with such agents as pyrogallic acid or toluylendiamin. When injected subcutaneously, as in Afanassiew's experiments, it produces intense inflammatory œdema; and much of the hæmoglobinæmia is due to its action on the red corpuscles at the seat of injection. The œdematous fluid is hæmoglobin-tinted.

A much more suitable agent of this class, I consider, is *distilled water* injected directly into the circulation. It likewise dissolves the hæmoglobin from the corpuscles, leaving apparently few morphological remains in the blood. At least this is the case judged by the appearances presented in the circulating blood during life.

Few or no changes are presented in the circulating blood even after the injection of large quantities of distilled water (70 c.c. Exp. 48), notwithstanding that a great destruction of blood may have taken place. Thus, in Exp. 47, the hæmoglobin was reduced in amount by one-seventh in the course of twenty-four hours.

In Exp. 48 there was intense hæmoglobinuria. If, however, the animal be killed within a few hours of the injection, numerous stromata are found, especially in the capillaries of the liver (Exps. 47, 48, p. 172, 173).

After *pyrogallic acid*, large numbers of *schatten* are to be found in the blood if the dose be large (Exp. 58, p. 180). At no time, however, are the number of schatten in the circulating blood at all proportional to the diminution of red corpuscles. Moreover, with small doses, a large destruction may, I find, take place without any *schatten* formation at all, and with as little evidence of change in the blood as is found after injection of distilled water.

After *toluylendiamin* poisoning there is less tendency to the formation of *schatten*, at least in dogs and rabbits. The red corpuscles seem rather to break up into yellow spherical particles

—these may be seen in process of being thrown off as bud-like projections from the red corpuscles.

This process goes on especially in the spleen, according to my observations. So much so, indeed, that, as I have already shewn,[1] the removal of the spleen in rabbits diminishes materially the destructive action of toluylendiamin.

In cats, however, I find *schatten* formation as marked a feature of toluylendiamin poisoning as it is of pyrogallic acid poisoning. Conversely, with pyrogallic acid, I have found in some cases, along with formation of *schatten*, the red corpuscles throwing off buds in precisely the same way as is usually found after toluylendiamin.

Certain differences are thus observable in the *mode of action* of destructive agents on the blood corpuscles. But they *are not sufficiently distinctive either as regards their character or degree to explain the remarkably different action of these drugs in the production of jaundice.* They are of some importance as serving to explain the occurrence or non-occurrence of hæmoglobinuria. But they serve in no way to explain the point at issue, namely, why in one case jaundice should occur where there is not even any hæmoglobinæmia, and is absent when the latter is pronounced.

3. Character of the Hæmoglobin.

The character of the blood changes not being sufficiently distinctive to account for the presence or absence of jaundice, we have to look elsewhere.

Another view suggests itself, namely, that the occurrence of jaundice may be influenced by the *character of the hæmoglobin.*

Or, as Lauder Brunton has suggested, the differences observable in different animals may indicate differences in the *relation of hæmoglobin to the liver cells* in different classes of animals.[2]

That individual differences exist in the character of the hæmoglobin of, *e.g.*, the dog, the cat, and the rabbit respectively, is, I think, exceedingly probable. The hæmoglobin of one has a poisonous action when injected into the other. But that these of themselves are sufficient to account for the differences as

[1] *Lancet*, 1892, ii. See also p. 394.

[2] Murchison's *Diseases of the Liver*, 3rd edition, ed. by T. Lauder Brunton.

regards liability to jaundice in these animals is, I think, extremely improbable. Much more depends, in all probability, on the natural degree of concentration of the bile in these different animals. In the rabbit, *e.g.*, the bile is normally much more watery than in the dog, and its quantity is much greater. A factor, therefore, which in a dog may occasion such a degree of concentration of the bile as to lead to a temporary arrest in its flow, and to jaundice, may quite well be without any influence in the rabbit.

As a matter of observation, I have never noticed in rabbits any condition which could rightly be termed jaundice produced by action of destructive agents on the blood. Hence, as regards jaundice, comparisons between rabbits and dogs are inapt. The latter are as naturally subject to some degree of jaundice as the former are naturally immune; and this I consider arises not so much from any difference in the *character* of the hæmoglobin in the two cases, or in its *relation* to the liver cells, as from natural differences connected with the degree of concentration of bile in the two animals.

A third alternative suggests itself, namely, that the occurrence or non-occurrence of jaundice after an increased blood destruction may be dependent on the *form* in which the hæmoglobin is supplied to the liver. Thus, after the action of distilled water the hæmoglobin is liberated from the stroma of the corpuscle, and passes freely into the urine. After toluylendiamin the red corpuscles break up into yellow globules in a manner almost identical with their behaviour under the influence of high temperatures, as described by Max Schultze.

That the hæmoglobin is supplied to the liver cells in different forms in these two cases is, I consider, certain from other evidence. It is the latter form of hæmoglobin that, according to my observation, most of all favours the formation of blood pigment both in liver cells and in spleen; and this, too, in different classes of animals alike—dog, rabbit, and pigeon; while, according to my observations, free hæmoglobin, such as is liberated by distilled water, does not lead to the formation of blood pigment, either within liver cells or spleen (*vide* Exps. Chap. xv.).

Under the action of toluylendiamin, the hæmoglobin does not, I conclude, become dissociated from the albuminous stroma of the corpuscle, as is the case with distilled water. It is found

in the form of yellow droplets or spheres within the blood, and within the spleen. In this form, also, it passes through the kidneys; not, however, as free hæmoglobin—for, notwithstanding the presence of much of this material in the urine, the urine gives none of the reactions of free hæmoglobin. There is no hæmoglobinuria in the ordinary sense of the term.

It is also in this form that the hæmoglobin reaches and passes into the liver cells.

It is, I think, important to note these physical peculiarities in the action of toluylendiamin on the blood corpuscles, and especially on the hæmoglobin of the blood. For although their bearing on the pathogeny of the jaundice caused by this drug may not be clear, they may nevertheless have some significance as denoting changes of a more obscure chemical nature in the character of the hæmoglobin supplied to the liver in such cases. This at least, in my opinion, is the only possible direction in which the occurrence of jaundice may be affected by the *character* or *form* of the hæmoglobin supplied to the liver. But while admitting this, I do not consider it at all likely that such is the case. Nor do I consider that change in the character of the hæmoglobin is sufficient to account for the changes in the bile which occasion the jaundice of toluylendiamin poisoning.

For the action of this poison on the blood is, according to my observations, identical in dogs and rabbits. Moreover, what is of more importance is—that in the rare cases in dogs in which this drug causes hæmoglobinuria without jaundice, the changes in the blood are of the same character, differing only in degree, as those found when jaundice occurs without hæmoglobinuria (Stadelmann).

I consider, then, that some other factor than mere *quantity* or *character* of the hæmoglobin must be responsible for the increased viscidity of bile produced by the drug.

Conclusion.

The observations already considered shew that the chief factor in determining the occurrence or non-occurrence of jaundice is the influence of *the poison itself*—exerted not on the liver cells, as suggested by Stadelmann, nor on the blood, as supposed by Afanassiew, but in the course of its excretion on the biliary channels.

So far as toluylendiamin itself is concerned, the jaundice is caused by its excretion and irritant action (either of itself or of its products), on the bile passages, with consequent increased viscidity of the bile. In this way I explain the differences in the behaviour of various blood-destroying agents, *qua* the production of jaundice.

As has been seen, hæmoglobinæmia (however intense) or mere increase of bile pigments (polychromia) cannot account for the increased viscidity of bile which occasions the jaundice. The latter may be intense with only a half increase in the bile pigments (toluylendiamin); or only slight, possibly absent, with a threefold or fourfold increase (arsenious acid); or may be absent altogether with the intense hæmoglobinæmia occasioned by distilled water.

It has also been seen that change in the *character* of the hæmoglobin, although a possible factor, is not sufficient of itself to bring about the essential changes in the bile necessary for the production of obstruction, namely, the increase of viscidity.

The only remaining factor, then, is the action of the poison that occasions the blood changes. According to the degree with which this is capable of exciting catarrh of the bile ducts, in course of its excretion, is there liability for the blood-destruction to be attended by jaundice.

"Toxæmic" Jaundice.

The jaundice so produced is *hepatogenous*, inasmuch as it is due to obstruction occasioned by this increased viscidity of the bile. It may also be termed "*hæmo-hepatogenous*," as suggested by Afanassiew, inasmuch as it is preceded by changes in the blood. The term "hæmatogenous" has, however, been used in connexion with jaundice in so special a sense,—implying that the bile pigment itself is formed in the blood—that its use in any other sense is apt to mislead. And hence the above term, although not inappropriate, is, in my view, open to objection on that ground.

To avoid this difficulty, Quincke has proposed the name *an-hepatogenous*, thereby denoting that while the jaundice is essentially hepatogenous, it is nevertheless closely related to, and dependent upon, other changes elsewhere (in the blood).

Stadelmann, as we have seen, regards as the essential and most constant change the increase of bile pigments; and the jaundice which results might, in his opinion, be most fitly termed "*polychromic*, or *jaundice from polychromia*."[1]

I have endeavoured to shew in the foregoing that this name is inappropriate, inasmuch as increase of bile pigments cannot be regarded as the essential change in the bile, or the chief factor in causing the obstruction.

So far as the bile pigments are concerned, identical changes, differing only in degree, are produced by agents so widely differing in their action *qua* jaundice, as normal saline (0·8 and 0·6 per cent.) solutions, salicylate of soda, distilled water, arseniuretted hydrogen, pyrogallic acid, phosphorus, and toluylendiamin. Thus normal saline solution (0·8 per cent.) may, as shown by Stadelmann, cause an increase of one-third in the bile pigments (bile acids being diminished to one-fifth or one-seventh) changes, therefore, hardly less striking than the increase of one-half in the bile pigments (with bile acids reduced at first tc one-half then to mere traces), which occurs in toluylendiamin poisoning; or the increase of one-half in the first 10 hours in phosphorus poisoning (with diminution in bile acids); or, lastly, the three-and-one-half-fold increase with arseniuretted hydrogen

Clearly, then, a condition (polychromia) which is not proportionate to the degree of obstruction cannot be regarded as the essentiate condition occasioning the obstruction. And that this is the case Stadelmann himself freely admits. While maintaining that the term polychromia best describes the jaundice, he admits that other factors must operate to bring about the change in the character of the bile itself on which the obstruction depends; and these factors are, in his view, to be sought for in a direct action of the several poisons on *the liver cells*, leading to a production of a highly concentrated bile.

It may, perhaps, seem a matter of comparatively little moment what name should be given to this form of jaundice. I cannot, however, so regard it. The terms "hæmatogenous" and "non-obstructive," formerly and still in many cases applied to it, are no longer applicable, inasmuch as the jaundice

[1] *Op. cit.*, p. 247.

is not hæmatogenous, but essentially hepatogenous and obstructive.

The term hepatogenous, therefore, fully describes its character anatomically. It is due to obstruction and to re-absorption of bile pigments, just as ordinary obstructive jaundice is. But it differs totally from the latter in its pathogeny; and some title is wanted to designate its relationship with the disorder of the blood with which it is ordinarily associated.

So far as toluylendiamin is concerned, the obstruction, as I have shewn, is essentially of catarrhal origin; and the term "*catarrhal jaundice*" might, in my opinion, quite fitly and appropriately be given to it—but for one circumstance, namely, that this designation has come to be applied to, and reserved for, a form of jaundice of essentially different origin. Ordinary "catarrhal jaundice" is, by a general consensus of opinion, supposed to arise from catarrh of the duodenum, spreading up into the bile duct secondarily. In no other sense, for example, is it spoken of by Murchison.

In the present case the course of the catarrh is, I have shown, a different one. It begins in the intrahepatic bile ducts, and extends downwards. If the duodenum is at all involved (and it is only in severe cases that it does become involved), it is only secondarily to the catarrh in the bile ducts.

It may perhaps be a question how far common catarrhal jaundice does arise in the way described, namely, secondarily to duodenal catarrh—to what extent it may not rather arise primarily in the bile ducts. In my opinion it is a very open question indeed. The latter I am disposed to regard as in all probability the common mode of origin of catarrh of the bile ducts. I designate it "excretory catarrh."

But such a view is at variance with that commonly accepted, which regards catarrhal jaundice as arising secondarily to catarrh of the duodenum; and under these circumstances I do not consider that to apply the term "catarrhal" in a sense entirely different would be fitting.

Moreover, the term catarrhal, however appropriate, would not indicate the special feature of this variety of jaundice, namely, its relation to previous disorder of the blood.

That disorder, in the great majority of cases, is marked

anatomically by increased destruction of blood (hæmolysis); and the term therefore which, in my opinion, would very fitly describe its character, would be that of "*hæmolytic jaundice.*"

And yet even this term is not altogether free from objection.

It is true that in most cases increased hæmolysis accompanies and precedes the form of jaundice now under consideration, whether induced experimentally by destructive agents, such as water, ether, pyrogallic acid, toluylendiamin, etc., or occurring clinically in paroxysmal hæmoglobinuria, pernicious anæmia, malaria, yellow fever, icterus gravis, etc.

But, as I have shewn, it is not the increased hæmolysis *per se*—with its hæmoglobinæmia or the associated polychromia—that can be held accountable for the jaundice; but rather is it, that both the hæmolysis and the jaundice have a common cause underlying them.

The factor that occasions the catarrh on which the jaundice depends is, in my opinion, the poison; hence, on this view, the term which would in all respects most aptly describe this form of jaundice would, in my opinion, be the term "*toxæmic.*"

It is free from the objection to which, as I have shewn, the term hæmo-hepatogenous is open. It has the advantage over the term hæmolytic—which, in most respects, would be a very suitable one—in being, I consider, more generally accurate, and more closely indicative of the toxic nature of the relationship between the jaundice and the blood disorder. Lastly, it has the advantage of being not only appropriate as regards the pathogeny of the jaundice, but also as regards its features clinically, and the general clinical course it pursues. It is in toxic conditions generally—in pyæmia, yellow fever, epidemic jaundice, icterus gravis, etc.—that this variety of jaundice is generally met with.

Of this character also is, I consider, the sub-icteric condition so often observed in the disease—pernicious anæmia.

In this relation, the hyperæmia and swelling of the mucous membrane observed in one case by Homolle (see p. 46) is specially interesting.

In a case I recently saw, the duodenal congestion was of a very marked character.

I regard it as similar to the condition of duodenitis produced in my experiments by toluylendiamin; and due to a like cause—the excretion, namely, of irritant products through the bile.

THE END

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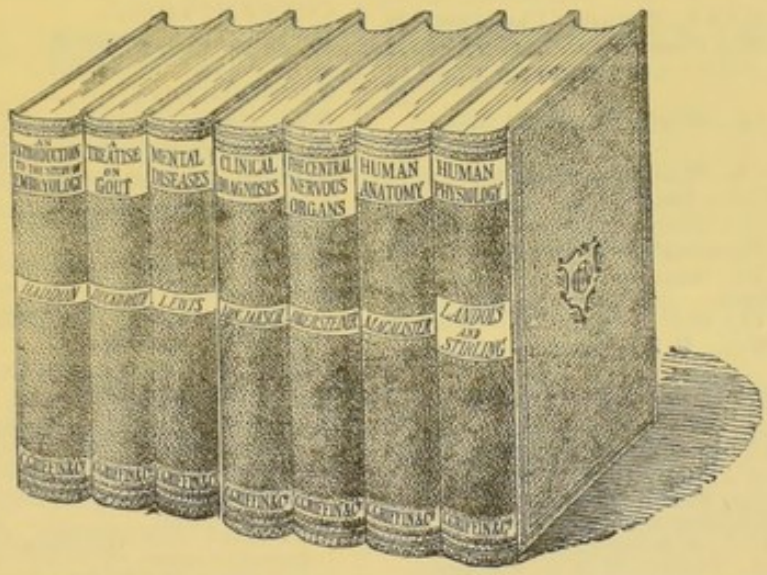
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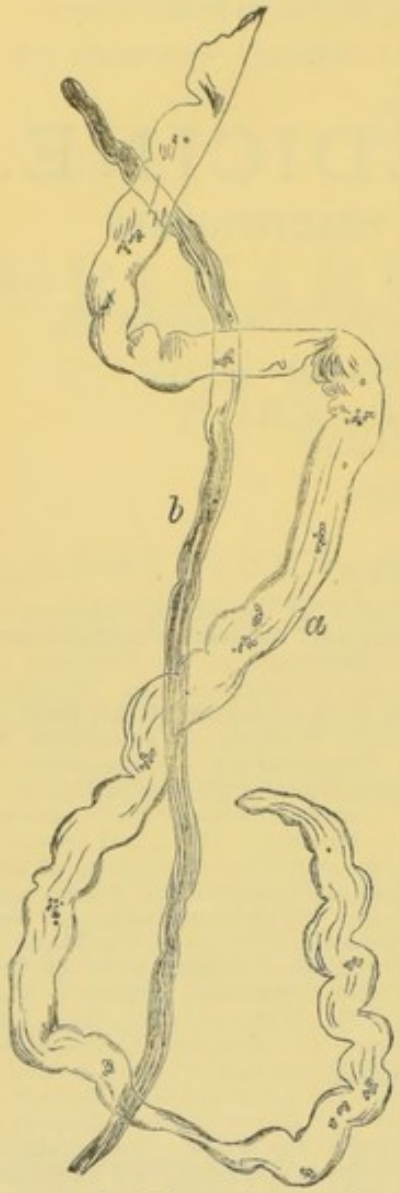
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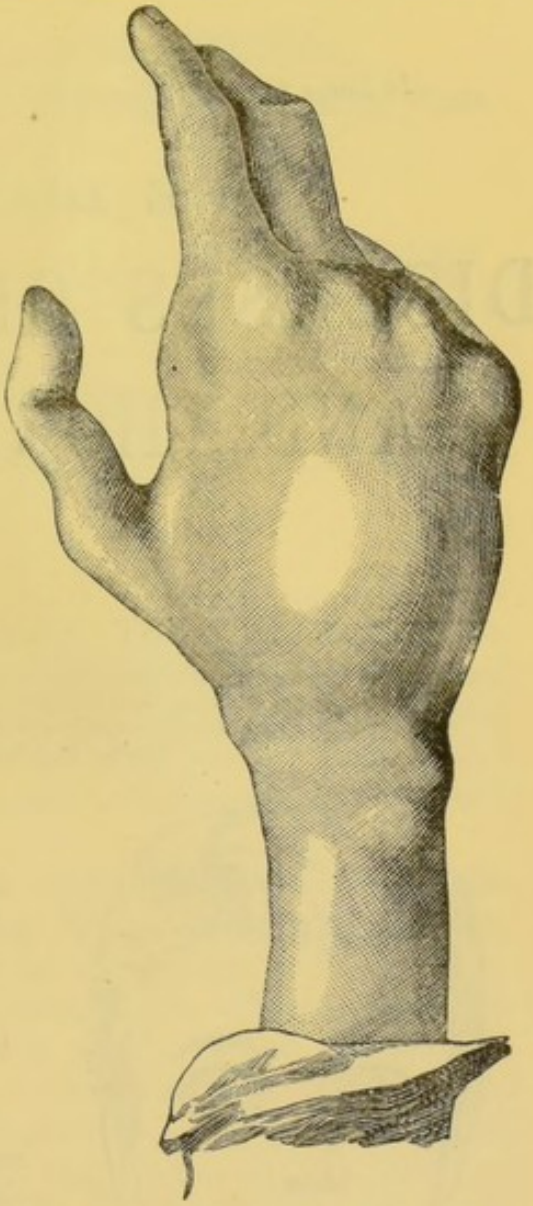


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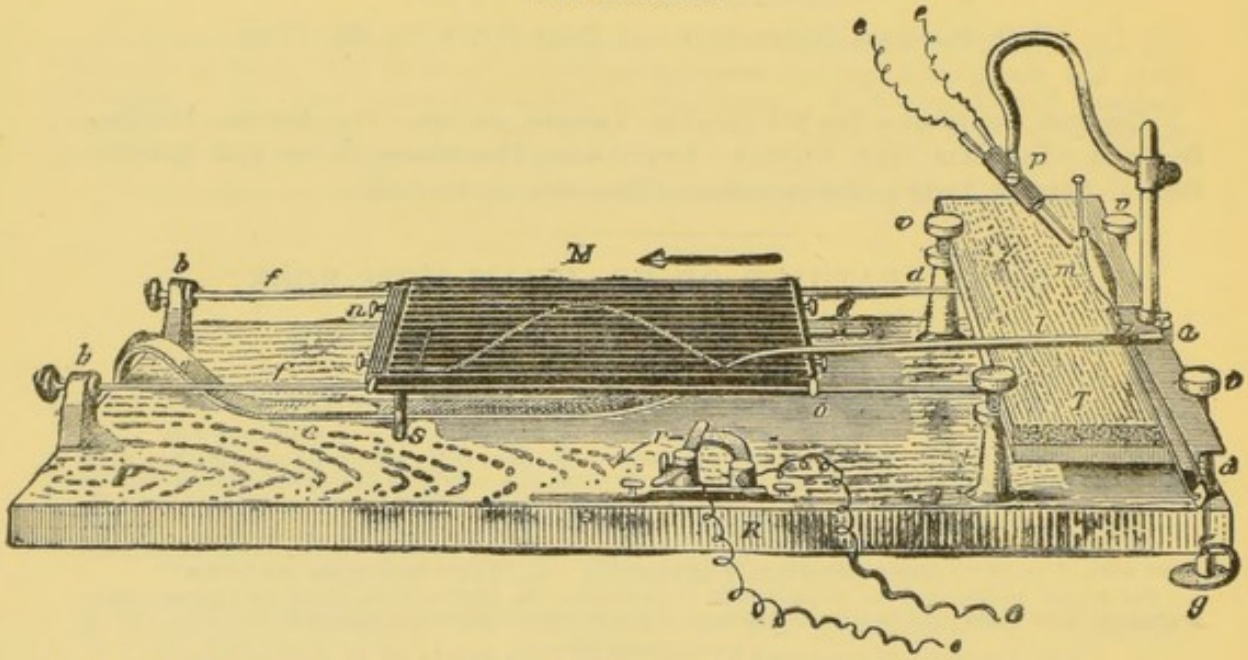


Fig. 118.—Horizontal Myograph of Frédéricq. *M*, Glass plate, moving on the guides *f*, *f*; *l*, Lever; *m*, Muscle; *p*, *e*, *e*, Electrodes; *T*, Cork plate; *a*, Counterpoise to lever; *R*, Key in primary circuit.

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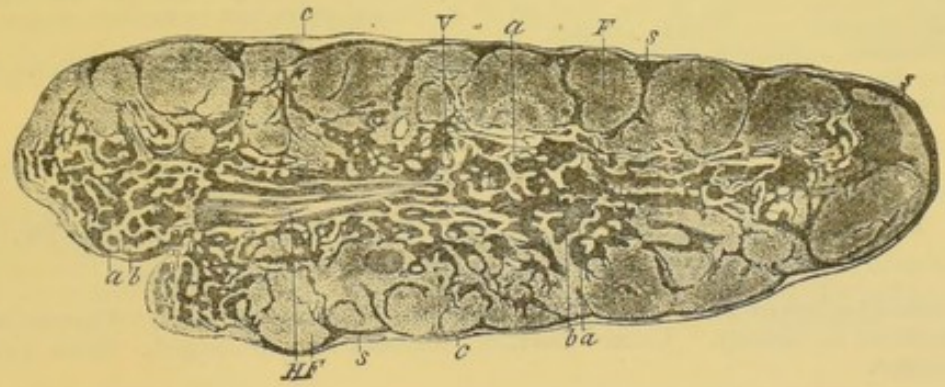


Fig. 200.—L.S., Cervical Ganglion of Dog. *c*, Capsule; *s*, Lymph sinus; *F*, Follicle; *a*, Medullary cord; *b*, Lymph paths of the medulla; *V*, Section of a blood-vessel; *HF*, Fibrous part of the hilum, × 10.

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