An investigation into the pathology of pernicious anaemia / by William Hunter.

With the Author's Compliments

2

AN INVESTIGATION

6.

INTO THE PATHOLOGY OF

PERNICIOUS ANÆMIA.

BY

WILLIAM HUNTER, M.D., F.R.S. EDIN.

JOHN LUCAS WALKER STUDENT OF THE UNIVERSITY OF CAMBRIDGE.

(*From the Cambridge Pathological Laboratory.*)

Reprinted from "THE LANCET" of September 22, 29, and October 6, 1888.

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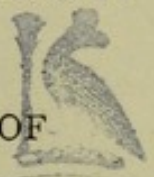

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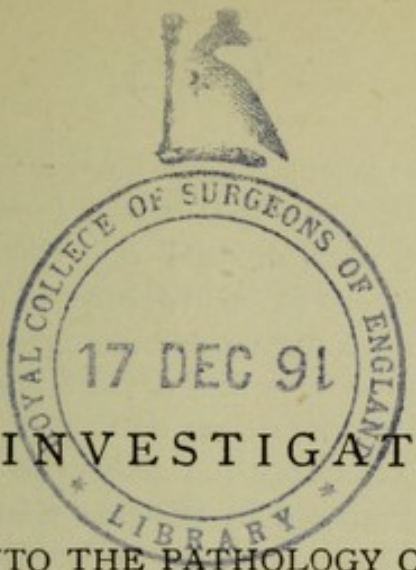

AN INVESTIGATION

INTO THE PATHOLOGY OF

PERNICIOUS ANÆMIA.

INTRODUCTORY.

I PROPOSE in this paper to record the results of a series of investigations which I have recently made with the object of throwing light on the pathology of the disease variously termed *progressive pernicious* or *pernicious* anæmia. My investigations have been of a twofold nature—partly clinical, partly pathological. It is with the latter that I propose here specially to deal. My observations have had reference to the question how far we must believe in the existence of this form of anæmia as a special disease.

What is *pernicious* anæmia? Is it a special disease with features clinical and pathological peculiar to itself, or does it differ from other forms of anæmia merely in its intensity? Are we to hold with the view at first expressed by Quincke, and since held by many, that the disease may originate in many ways and be the product of very various morbid processes—loss of blood, continuous discharges, insufficient nourishment all being possible factors in its development provided they are of sufficient intensity and duration? Or are we to hold with the later view of the same observer, that

while pernicious anæmia may have a *clinical*, it has no *pathological*, existence; that while forms of the disease found associated with definite organic disease, such as malignant disease, are to be regarded as *secondary*, others in which no such definite morbid changes can be found may be regarded as *primary*, while a third series are to be considered as *intermediate* in their nature?

The difficulty attending the answer to be given to these questions may be gauged by the fact that within the past few weeks so able an authority as Dr. Bristowe[1] has confessed it to be "impossible at the present time to make 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," even while, at the same time, he expresses his belief in the existence of some fundamental difference between the two conditions.

It has been the object of my investigations to learn, with special reference to pernicious anæmia, whether any, and if so what, fundamental difference exists between this and other recognised forms of anæmia.

Much of the confusion which still prevails regarding the title of this form of anæmia to be considered even *clinically* a special disease is undoubtedly to be ascribed to the vague use of the terms *progressive* and *pernicious* unfortunately applied to the disease in the first instance by Biermer. These terms have been constantly used by observers to designate conditions of anæmia having little or nothing in common. The assumption has been that the term *pernicious* is applicable to every condition of anæmia sufficiently profound, irrespective of its true nature, especially if it terminates fatally. *Pathologically*, much of the obscurity regarding the true nature of pernicious anæmia as distinguished from other forms of anæmia is similarly to be ascribed to the vague use of the term *anæmia* itself. The term is constantly used as almost synonymous with *pallor*,

[1] Brit. Med. Jour., vol. i. 1888, p. 1149.

and is hence used to designate the most diverse conditions of the blood, the assumption being that the changes in the blood on which pallor may depend are the same in kind in all cases, however much they may vary in their degree in individual cases.

Both these assumptions I find to be groundless. I have adduced evidence elsewhere[1] to show that clinically there is good reason for believing in the existence of a form of anæmia essentially *pernicious* in its nature distinguishable even during life from the other forms of anæmia. In the present paper I propose to complete the consideration of the subject by showing what the pathological features are which determine this difference, and in what respect the disease is to be regarded as also a pathological entity.

PATHOLOGICAL.

My pathological observations have been of a twofold nature—partly *anatomical*, partly *experimental*. I have sought to learn, in the first instance, what anatomical changes are to be constantly found associated with this form of anæmia; and then I have endeavoured in various ways to produce similar changes in animals experimentally. The results of these observations may therefore be conveniently discussed under two headings—anatomical and experimental. I shall first describe the various anatomical changes found in this disease, and discuss their relative importance; and then I shall show what light I have been able to throw on the true nature of this disease by means of experiments.

Part I.—ANATOMICAL.

The anatomical changes found in this disease are as various as they are numerous. A consideration of them at first sight seems little fitted to throw much light on the true pathology of the disease. I find that they may with con-

[1] "Is Pernicious Anæmia a Special Disease?" Practitioner, Aug. 1888.

venience be divided into three groups:—1. Those *occasionally* found associated with the clinical features of pernicious anæmia, including especially malignant disease and various gastro-intestinal lesions. 2. Those which may with justice be regarded as the result of the anæmia, including especially pallor and fatty degeneration in various organs of the body. 3. Those found in the blood itself or in those organs concerned either in blood formation or blood destruction.

Section I.—Various Anatomical Changes occasionally found associated with Pernicious Anæmia.

The possibility of all the features which we have come to regard as more or less characteristic of pernicious anæmia being in certain cases apparently the result of well-marked organic disease, such as cancer, is a fact which has to be borne in mind and explained at the very outset of any inquiry into the pathology of this disease. It is this association, of the existence of which there cannot be a doubt, which is relied upon by those who hold that pernicious anæmia is not a special disease, but is merely a profound form of ordinary anæmia differing from others in its intensity. It is largely from this association that pernicious anæmia is often regarded merely as a symptomatic condition.

Malignant disease.—Of the existence of the clinical features of pernicious anæmia in association with malignant disease, especially cancer, there cannot be a doubt. At the same time, the frequency of this association has been probably over-estimated, mainly owing to the indiscriminate use of the term *pernicious* to designate any anæmia sufficiently profound, irrespective of its true nature. Apart from these more doubtful cases, however, a sufficient number of cases have been recorded by competent observers to prove conclusively that all the characteristic features of pernicious anæmia may be presented by patients the subjects of malignant disease. The question to determine is: What is the nature of this connexion? Is it accidental or essential?

That malignant disease is not usually characterised by the clinical features of this variety of anæmia is certain. Hence, when the two are found in association, the question arises: Have the features, or association of features, which constitute clinically the disease we term 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 anatomical changes special to, and characteristic of, pernicious anæmia been added to those already and independently existing? It is interesting to note that most of the cases of the nature recorded have been cases of malignant disease of the stomach. Nevertheless, there is no doubt that cases of malignant disease of this organ are constantly met with, running their course to the fatal termination without presenting any changes in the blood or any clinical features other than those which usually mark ordinary wasting diseases. 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 the conclusion seems justifiable that when the two conditions—malignant disease and pernicious anæmia—are found associated, the connexion is to be regarded, if not precisely as accidental, at least as not essential; that the malignant disease does not constitute the essential anatomical change underlying the pernicious anæmia associated with it, however much in certain situations it may favour the development of those changes.

It is only on such a view of the nature of the connexion between malignant disease and pernicious anæmia that we can explain why malignant disease, especially in the stomach, is not more usually found associated with the features of pernicious anæmia, and it is only on this view that such a case as that recorded by Eisenlohr[1] can be explained, in which the ordinary symptoms of malignant

[1] Deutsch. Archiv f. klin. Med., Bd. xx., 1877, p. 499.

disease of the stomach had existed for over two years and then *suddenly* took on those of pernicious anæmia. The natural view to take of such a case is that to the malignant disease already existing there had more or less suddenly been superadded those anatomical changes characteristic of pernicious anæmia. Such is the conclusion we must arrive at, unless, with Dr. Coupland,[1] we are prepared to recognise two forms of pernicious anæmia: one *symptomatic*, exemplified by cases such as the above, in which definite organic disease is found; the other *idiopathic*, exemplified by cases in which all such changes are absent. Even if we accept such a classification, the difficulty still remains to discover what the anatomical changes are which underlie the idiopathic variety of the disease; for, however obscure they may be, such changes must exist to account for a condition of the blood such as that met within pernicious anæmia. It is more reasonable to suppose that the same anatomical changes underlie the features of pernicious anæmia in all cases alike, than to suppose that in one case the anæmia is the result of the malignant disease, while in another the same features, perhaps intensified, are to be found altogether apart from recognisable anatomical changes of any sort.

Gastro-intestinal lesions.—In the case of another group of anatomical changes it is not so easy to decide what the precise connexion between them and the anæmia is. I refer to the very various gastro-intestinal lesions so frequently met with in patients dying of this disease.

The frequency with which gastro-intestinal changes have been found appears at first sight to lend colour to the view held by many—that pernicious anæmia cannot be regarded as a special disease, but is merely the outcome of a disturbance of nutrition such as is met with in no other disease. In addition to *cancer of the stomach*, to which reference has already been made, these gastro-intestinal changes include *atrophy of the mucous membrane of the*

[1] Gulstonian Lectures, THE LANCET, vol. i. 1881, p. 571.

stomach, and especially of the gastric glands; cirrhotic contraction of the stomach, with disappearance of the gastric glands; *interstitial inflammation of the gastric mucosa*, with partial or total atrophy of the gastric glands; *ulcers of the stomach and duodenum; duodenitis; degenerative changes in the sympathetic ganglia* of the abdomen; and similar *changes in the nerves of Meissner's and Auerbach's plexuses* in the intestinal wall; and lastly, in this connexion, *the presence of intestinal worms*. Here, as in the case of malignant disease, the question to determine is how far these lesions are to be regarded as the essential morbid anatomical changes underlying the anæmia sometimes associated with them.

In the first place, it is to be remembered that it is only in a comparatively few cases that even these changes have been found. As the essential morbid change, therefore, in this disease, they cannot possibly be regarded. 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.) It will be noted how frequently *changes in the gastric mucosa*—thickening, interstitial inflammation, and atrophy of the gastric glands—have been described. To this point particular attention has been drawn by Dr. Fenwick.[1] What significance is to be attached especially to this condition 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." Thus, of fifteen cases of cancer of the breast, in only four were no anatomical changes to be found in the gastric mucosa. Some degree of atrophy was found in every case of cancer of the stomach. If atrophy of the gastric glands is to be regarded as the essential anatomical change in pernicious anæmia, it would seem reasonable to expect that pernicious

[1] THE LANCET, vol. ii. 1877, pp. 1, 39, 77.

anæmia should be found frequently associated with cancer of the breast, and almost invariably with cancer of the stomach. Curiously enough, however, I have not found a single case recorded in which cancer of the breast has presented the features of pernicious anæmia; and as regards cancer of the stomach, it is the exception and not the rule for it to be marked by the 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 we shall afterwards have occasion to refer to,—they cannot be regarded as the essential anatomical lesions underlying this form of anæmia, even in those cases in which they are found present.

(2.) The same holds true of the *degenerative changes in the nervous apparatus* of the intestinal wall and of the abdomen described, amongst others, by Sasaki[1] and Banti,[2] and regarded by these observers as independent lesions and as the cause of the anæmia. The view which naturally suggests itself, that these changes may possibly be as much the result as the cause of the anæmia, is fully supported by the observations of Scheimpflug[3] made with special reference to these observations of Sasaki. In opposition to Sasaki, Scheimpflug finds that in a large number of cases the 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 appearances presented by the plexuses of Auerbach and Meissner in various conditions. The result was to show that in many various conditions these plexuses were to be found more or less fattily degenerated. As regards the general frequency of pathological changes in the

[1] Virch. Archiv, Bd. xcvi., p. 287.

[2] Jahresber. u. d. ges. Med., Bd. ii., 1881, p. 239.

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

nervous structures of the intestinal wall, he finds that such changes are 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, &c.—are by no means unfrequent in their occurrence.

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

(3.) The only other gastro-intestinal condition I shall notice at present is the *presence of intestinal worms*, the connexion between which 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 found to be due to the presence of the Anchylostoma duodenale, sometimes in large numbers, in the intestinal tract; it usually disappeared rapidly on their removal, More recently a number of cases have been recorded by Reyher and Runeberg, in which the connexion between anæmia of this kind and the presence of Bothriocephalus latus has been apparently equally close and equally marked. In neither case has the nature of the relation between the condition of anæmia and the presence of the worms been altogether satisfactorily explained. In the anæmia associated with the Anchylostoma duodenale the condition has been ascribed, probably in great part with some truth, to the loss of blood occasioned by the presence of the parasite. This explanation cannot, however, apply to all cases. On such a view, we are unable to explain why in certain cases recorded[1] the anæmia was by no means proportionate to the number of worms present, and why in others it is almost absent altogether, when large numbers of the eggs of Anchylostoma

[1] Sahli: Deutsch. Archiv f. klin. Med., Bd. xxxii., 1883, p. 422.

are to be found in the stools.[1] Hence, the *rôle* played by the worms in producing the anæmia is by no means so simple a one as the above view would indicate. As Sahli clearly shows, 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 in the first instance digestive disturbances may be entirely absent.

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. Runeberg's observations[2] clearly show that not only may worms be present sometimes in considerable number, unassociated with 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. This observation agrees with our experience of the disease in this country, where of its constant occurrence, independent altogether of the presence of worms, there cannot be a doubt.

The conclusion is therefore forced upon us that none of the conditions just considered, whether malignant disease or other gastro-intestinal lesions, can be regarded as the essential anatomical change even in the few cases in which they are present, or as fitted in any way to account for the peculiar features of this as distinguished from other forms of anæmia. With regard to them all, the same statement may be made—viz., that in all of them it is necessary to assume that there have been superadded certain anatomical changes essential to pernicious anæmia, and on which the features of pernicious anæmia 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

[1] Deutsch. Archiv. f. klin. Med., Bd. xxxii., 1883, p. 428. [2] Ibid. 1838.

features of pernicious anæmia; and (2) that cases of pernicious anæmia are constantly met with in which no such gross anatomical changes are to be found.

Section II.—Anatomical Changes, the Result of the Anæmia.

These include, in addition to the *pallor* so generally observed in the various organs of the body, notably the heart and kidneys, the *fatty degeneration* so frequently met with in varying degree in certain tissues of the body, more especially the heart muscle, the liver, kidneys, and smaller arteries and capillaries. They include also the *extravasations* met with, especially in the retina and elsewhere. Fatty degeneration of the heart 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 made up of an 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 muscle is found in the great majority of cases of pernicious anæmia. Thus Dr. Coupland found that, out of seventy-six cases recorded, in no fewer than sixty-four this condition of the heart was expressly stated to have been present; in six no mention was made of it, and in six the heart was described as healthy. Apart altogether from the likelihood—so strong as, in my opinion, to amount to certainty—that this change in the heart is the result of the anæmia, it is clear that its absence in certain cases of apparently undoubted pernicious anæmia must suffice to exclude any essential importance being attached to it. And this conclusion is further strengthened by the fact that fatty degeneration of the heart is met with in many other conditions of disease, and has been described as occurring to a very marked degree in a case of anæmia the result of metrorrhagia.[1]

[12] Neumann: Zeitschrift f. klin. Med., Bd. iii., 1881, p. 414.

The result of our considerations so far, therefore, points to the conclusion that pernicious anæmia cannot, like the anæmia of phthisis or other organic disease, be regarded as *symptomatic* in the ordinary sense of that term; and that even in cases in which it is found along with definite organic disease, such as malignant disease, or definite morbid anatomical changes, such as atrophy of the gastric glands, all the features of the disease cannot be explained solely by reference to these changes. The essential morbid changes must therefore be sought for in the blood itself, or in those organs concerned either in blood formation or blood destruction.

Section III.—Changes in the Blood.

These I shall only briefly refer to, as I have already discussed them more in detail elsewhere. They affect both the number and variety of the coloured corpuscles of the blood, as also their richness in hæmoglobin.

As regards the *corpuscles*, the changes are of a threefold nature:

1. An extraordinary diminution in their number—an *oligocythæmia* far more marked than that ever met with in ordinary forms of anæmia, sometimes more marked even than that resulting from loss of blood. This marked oligocythæmia is not unfrequently found apart altogether from loss of blood.

2. An extraordinary variation in form and size of the red elements of the blood, aptly described by Quincke under the comprehensive term *poikilocytosis*. These changes are common to all forms of anæmia, provided they are of sufficient intensity. They express merely the degree of anæmia existing, not in any way its nature. I find especially that they are common to pernicious anæmia and the anæmia the result of loss of blood, and hence they cannot be regarded as in any way peculiar to the blood in pernicious anæmia.

3. The presence of small coloured elements not usually found in the blood — the so-called "microcytes" or "Eichhorst's corpuscles," which have from time to time been

regarded as pathognomonic of the disease. These small bodies are remarkable in three respects: (*a*) their small size, their diameter in many cases not exceeding the fourth part of that of a normal red corpuscle; (*b*) their perfectly spherical form, resembling in this respect minute red corpuscles; and (*c*) their uniform deep yellow colour, resembling sometimes in this respect droplets of oil rather than elements of the blood. By their uniform spherical shape and depth of colour they are distinguishable, in my opinion, from the various other coloured microcytes so constantly seen in the blood in various conditions of profound anæmia, especially that due to the loss of blood. These present usually the most various shapes—drawn out, pointed, oval, &c.; 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. These "yellow spherical microcytes" are to be found in the blood in the great majority of cases of pernicious anæmia, but not constantly. They vary much in number in different cases, and even in the same case at different times. They may disappear from the blood for a time altogether, to appear later on in greater number perhaps than before. They have been variously regarded as stages in the development of young red corpuscles, or as products of blood destruction. They have been considered as pathognomonic of pernicious anæmia;[1] and, on the other hand, they have been described by at least two observers[2] as occurring in other forms of anæmia and in some other conditions.[3] Whatever view may be held as to their nature or pathognomonic value, there can be no doubt that the presence of these bodies constitutes a marked feature of the blood in many cases of pernicious anæmia.

Some of the other changes occasionally met with in the

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

[2] Litten: Berl. klin. Woch., 1877, No. 1; and Lepine, Union Méd., 1877, No. 114.

[3] Afanassiew: D. Archiv f. klin. Med., Bd. xxxv., 1884, p. 233.

blood may here be briefly referred to. The presence of *nucleated red corpuscles* in the blood cannot be regarded as peculiar to pernicious anæmia. It is only in a few cases[1] that they have been described. In no case were they ever found by Quincke[2] in his many observations. On the other hand, Ehrlich[3] has 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 the result of long-standing and profuse metrorrhagia.

As regards the *colourless elements of the blood*, the great majority of observations agree in showing that there is no absolute increase in the number of white corpuscles in this disease; and there is usually no 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.

As regards the *richness of the blood in hæmoglobin*, one extremely interesting fact is to be noted—viz., that the percentage diminution in hæmoglobin is by no means proportionate to the percentage diminution in the number of corpuscles. Thus, Quincke states, as the result of his numerous observations, that, while the corpuscles were reduced on an average to 10 or 12 per cent. of their original number, the hæmoglobin percentage was only reduced to from 20 to 40 per cent. Some of Dr. Coupland's observations[5] entirely agree with these; and this condition of the blood I have noted in most of the cases which have come under my notice. The condition is precisely the reverse of that found in chlorosis, where the poverty in hæmoglobin is far greater than can be accounted for by any fall in the

[1] Litten: Berl. klin. Woch., 1880, p. 693.
[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] THE LANCET, vol. i. 1881, p. 571.

number of corpuscles. To this condition of the blood I am inclined to attach no little value, both clinically and pathologically. Its full significance will be afterwards seen.

In connexion with the relative richness of the blood in hæmoglobin there may be noted, further,

(1) The readiness with which, in this condition, the colouring matter of the corpuscles separates itself from the stroma, and diffuses out or becomes collected toward one part of the corpuscle.[1]

(2) The readiness with which crystals of hæmoglobin may be obtained from the blood ;[2] and

(3) The extraordinary richness of the individual corpuscles in hæmoglobin, even in cases (as in one recently under my notice) in which the diminution in their number is excessive —an observation which I have repeatedly had occasion to make.

These, then, are the anatomical changes found in the blood in this disease. It will be noted that, unless perhaps in degree, scarcely one of them, with the single exception of the relative richness in hæmoglobin, can be regarded as peculiar to pernicious anæmia. As regards the other changes—the oligocythæmia, poikilocytosis, presence of yellow microcytes, the occasional presence of nucleated red corpuscles, the absence of increase in the number of white corpuscles, or of the colourless granular elements of the blood—they are neither absolutely constant nor peculiar. It is only when they all exist in a certain degree and in a certain association that they can be regarded as sufficiently distinctive to constitute the form of anæmia we term *par excellence* pernicious. This point, however, I have discussed at some length elsewhere. (*Op. cit.*)

[1] Mackern and Davy : THE LANCET, vol. i. 1877, p. 642.
[2] Copeman : St. Thomas's Hospital Reports, 1887.

Section III.—Changes in the Blood-forming and Blood-destroying Organs.

The changes in the blood are nevertheless the most marked and the most constant anatomical changes to be found in cases of pernicious anæmia. One naturally turns, therefore, to the organs concerned either in blood formation or blood destruction, since 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 that we must look for the characteristic anatomical changes underlying the disease. These changes I shall first consider *seriatim* in connexion with the various organs in which they are found—viz., the liver, spleen, bone marrow, and lymphatic glands.

Subsection 1.—Changes in the Bone Marrow.—In the red bone marrow the changes found are both macroscopic and microscopic. The increase in the quantity of the red marrow at the expense of the yellow marrow of the shafts of the long bones, as well as the striking change in its appearance—its peculiar rosy-red or violet-red colour in the great majority of cases,—has long directed attention to this as the possible seat of important changes in this disease. The microscopic changes associated with this change in the appearance of the bone marrow are of a two-fold nature—the presence of large numbers of nucleated red corpuscles apparently pointing to some profound disorder of hæmogenesis (blood formation); the presence of large numbers of corpuscle-carrying cells, cells enclosing old red corpuscles or their pigment remains, apparently pointing to some disorder of hæmolysis (blood destruction). When first described, both of these changes were thought to be peculiar to pernicious anæmia. Both have since been shown to be common to pernicious anæmia and other forms of severe anæmia.

As regards the former, *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 peculiar. On the one hand, they have been described as absent altogether in certain cases; or, in others, as only few in number. In a well-marked case of this disease, which I have 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 the result of severe and long-lasting hæmorrhages, as in the case of metrorrhagia described by Neumann.[1] Similar changes in the bone marrow have been produced experimentally in dogs by Litten and Orth,[2] and by Bizzozero and Salvioli,[3] by repeatedly withdrawing blood from these animals, and thus bringing about a condition of severe anæmia. The presence of nucleated red corpuscles cannot therefore be regarded as a change essentially peculiar to this disease; still less does it serve to explain the characteristic clinical features usually presented by this form of anæmia.

The same remark applies to the *corpuscle-carrying cells.* First regarded as pointing to some excessive destruction of red corpuscles peculiar to the disease, 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 connect their presence specially with any one disease. They were especially numerous in phthisis, pneumonia, typhoid, and ulcerative endocarditis. My own observations entirely confirm those of Osler. On the one hand, I have found that their presence in any excess is not a constant feature of pernicious anæmia. Thus, in one case in an elderly man I found them 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

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

them very numerous in many other conditions, especially those of wasting disease occurring in elderly people.

In connexion with these changes in the bone marrow, it may be noted, as my observations have shown, that in most cases the nucleated red corpuscles present a high degree of colouration—this appearance therefore indicating a great richness of the corpuscles in hæmoglobin, similar to that already described as occurring in the red corpuscles of the blood.

Further, in most cases, as determined by micro-chemical reagents, such as sulphide of ammonium, the bone-marrow tissue contains a considerable excess of iron, partly in 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 number of effete red corpuscles it sometimes contains.

SUBSECTION 2.—CHANGES IN THE LYMPH GLANDS.—Few or no changes have been described in connexion with the lymphatic glands. The absence of any enlargement or other marked change enabled Biermer in the first instance to distinguish at once this form of anæmia from leucocythæmia, and this observation has been confirmed by all subsequent observers. One case is described by Eichhorst[1] in which the mesenteric glands presented some appearance of redness and swelling. Another is described by Weigert[2] 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 any great value cannot therefore be attached to it. In Eichhorst's case the microscopical changes were not noted; and as regards the importance to be attached to the appearance of redness and swelling, it

[1] Die progressive perniciöse Anæmie. Leipsig, 1878, p. 288.
[2] Virch. Archiv, Bd. lxxix., 1880, p. 387.

is only necessary to state that precisely similar changes were found by Neumann in the case of anæmia the result of severe metrorrhagia already referred to. In this case, with the exception of a very few nucleated red corpuscles, no changes were found microscopically.

SUBSECTION 3. — CHANGES IN THE SPLEEN.— As regards the spleen, the changes hitherto described have, as in the case of the bone marrow, been partly macroscopic, partly microscopic. The changes, however, have by no means been so constant or so marked as in the case of the bone marrow. In a certain number of cases the spleen has been found enlarged, the enlargement being even recognisable during life.[1] Thus, in a case recorded by Dickinson, it weighed "at a guess" 10 oz. In two cases described by Dr. Finlay it weighed 19½ oz and 16 oz. In three cases, for the opportunity of examining which I am indebted to the great kindness of my friend, Dr. Byrom Bramwell, the spleen is noted as weighing 19 oz., 11 oz., and 10 oz. respectively; and in another case, on which I made a necropsy recently for Mr. Wherry of Cambridge, the spleen weighed 13 oz. In all these cases, therefore, the enlargement has been very marked.

But these 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. Thus in a case of Dr. Stephen Mackenzie's,[2] it is described as "of natural size"; "not enlarged," as in a case of Dr. Carrington's;[3] weighing only 4 oz., as in another case;[4] or only 3½ oz., as in a case of Dr. Smith's.[5] Its other naked-eye characters have equally varied. It has been found soft and diffluent;[6] pale and

1 Bristowe : Brit. Med. Jour., vol. i. 1888, p. 1149.
2 THE LANCET, vol. i. 1878, p. 13.
3 Ibid., vol. i. 1883, p. 193.
4 Dr. Finlay : Brit. Med. Jour., vol. ii. 1885, p. 864.
5 THE LANCET, vol. ii. 1881, p. 133.
6 Dickinson : Brit. Med Jour., vol. i. 1878, p. 531.

soft;[1] and soft;[2] and, on the other hand, firm and red, or firm in consistence and of deep purple colour.

In a case which recently came under my notice the spleen weighed 13 oz., was soft and pulpy in consistence, and 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.

Microscopically, no changes at all have been described in the great majority of cases. In a few cases a few nucleated red corpuscles have been found. Micro-chemically, the spleen has been found in certain cases to contain a considerable amount of pigment rich in iron; not, however, in any great excess.[3]

In seven cases of pernicious anæmia which I have now 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. In none, for example, has it been more marked than in several cases of cirrhotic Bright's disease; and in three cases the spleen gave no micro-chemical reaction of iron at all—less even than that usually met with in normal conditions.

The changes in the bone marrow, lymphatic glands, or spleen—the chief seats of *blood formation* in the body—are thus neither sufficiently constant nor sufficiently distinctive to be regarded as the essential morbid anatomical changes in this disease. These must, therefore, be sought for in the organs concerned in the other great process of the blood—namely, *blood destruction*.

SUBSECTION 4.—CHANGES IN THE LIVER.—We have seen that the changes in the spleen, red bone marrow, and lymphatic glands are not sufficiently constant to be regarded as the essential anatomical changes in this disease. The

[1] Coupland: THE LANCET, 1881, p. 569.

[2] Carrington, op. cit.; Bradbury, Brit. Med. Jour., 1876.

[3] Quincke, Deutsch. Archiv f. klin. Med., Bd. xxvii., p. 199; Peters, ibid., Bd. xxxii., p. 182.

case is very different when we come to consider the changes in the liver.

More or less marked fatty degeneration, found especially in the centre of the lobules, as noted in one case by Coupland, is the only change in this organ to which attention has been hitherto directed by observers in this country.

In the earlier cases published by Quincke[1] in 1876, the interesting observation was made that in three cases the liver contained a great excess of iron, as determined both on microscopic examination and chemical analysis. The value of the observation was detracted from in his eyes by the circumstance that in two of the cases the kidney and pancreas also contained an excess of iron; and, further, that the possibility of the condition being due to the administration of that drug during life could not be entirely excluded. In the following year this observation of Quincke was confirmed by Rosenstein,[2] who also, in a case in which no changes were to be found in any other organ of the body, found a great excess of iron in the liver. The same doubt, however, attached in this observer's mind to the significance of this observation, his patient also having been under treatment with iron for some time before death.

At first, therefore, little or no importance was attached to these observations, especially at the hands of English observers, both Stephen Mackenzie[3] and Coupland[4] in their able lectures expressing themselves with caution regarding them. They both considered that the condition of the liver 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.

[1] Med. Times, vol. ii., 1876, pp. 374, 428.
[2] Berl. klin. Woch., 1877, p. 113.
[3] THE LANCET, vol. ii. 1878, p. 836.
[4] Ibid., vol. i. 1881, p. 531 *et seq.*

Subsequent observations, however, of Quincke[1] and his scholar, Peters,[2] have shown that this excess of iron in the liver is a more or less constant condition, and apparently by no means an accidental one.

Results of Micro-Chemical Observations.—My own observations in nine cases of pernicious anæmia enable me fully to confirm these observations of Quincke. 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. The presence of this pigment is the only constant morbid change to be met with in this disease. As such it 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.

The possibility of it being due to the administration of iron before death may be at once set aside. The observations of Kobert,[3] Cahn,[4] and Glavecke[5] all agree in showing that the richness of the liver in iron is in no way affected by the administration of that drug by the mouth, and is but slightly affected even when the drug is injected subcutaneously (Glavecke). The source of the pigment in the liver in cases of pernicious anæmia can only, therefore, be the hæmoglobin of the blood.

The question then arose, how far 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

[1] Deutsch. Archiv f. klin. Med., Bd. xxv., p. 567; Bd. xxvii., p. 202; Bd. xxxiii., p. 22. [2] Ibid., Bd. xxxii., p, 182.

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

[4] Ibid., Bd. xviii., 1884, p. 146. [5] Ibid., Bd. xvi., 1883, p. 469.

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.

Micro-chemical Methods for detecting Iron.—The richness of the liver in iron is 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 contained more or less loosely bound up—most usually in the form of an albuminate. Iron as it is found 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.

An equally good micro-chemical reagent is ferrocyanide of potassium, which in the presence of dilute hydrochloric acid gives with such pigment a beautiful reaction of Prussian blue. In using this reagent, however, two precautions are necessary to be borne in mind : (1) that the solution of ferrocyanide of potassium be freshly prepared ; and (2) that a very dilute acid be employed, since under prolonged contact with strong hydrochloric acid a blue reaction may be developed even with iron in hæmoglobin. With either of these reagents there is no difficulty in at once recognising the extraordinary excess of pigment in the liver in cases of pernicious anæmia.

The various conditions in which these observations were made as to the richness of the liver in pigment included many examples of each of the following diseases : phthisis, empyema, chronic suppuration, malignant disease, &c.,—conditions all marked by profound anæmia ; also typhoid fever, chronic Bright's disease, leucocythæmia, Addison's disease, diabetes, cardiac disease, tubercular and syphilitic diseases, and various morbid conditions of the liver itself—

viz., acute yellow atrophy, toxic poisoning, portal cirrhosis, chronic venous congestion, and fatty degeneration.

A similar investigation made by Peters[1] at the instigation of Quincke had yielded some interesting results. Out of seventy-seven cases examined, he found that, according to the reaction of iron given on micro-chemical examination, the cases could be divided into three groups.

1. In seventeen cases, including cases both of acute and chronic disease—e.g., croupous pneumonia, scarlet fever, tubercular disease, carcinoma—no iron reaction was obtained either in the liver, spleen, or bone marrow.

2. In twenty-seven cases, *including more especially all forms of wasting disease*, a slight reaction was obtained only in the spleen and bone marrow, *none in the liver*.

3. In thirty-three cases, including four of granular atrophy of the kidneys, four in which the liver showed changes the result of congestion, five of chronic lung disease, twelve of intestinal catarrh in children, and the remainder of diseases partly subacute, partly diseases of the blood, such as pernicious anæmia, purpura hæmorrhagica, &c., some reaction of iron was given by all three organs—liver, spleen, and bone marrow. In most of the cases the reaction obtained in the liver was, however, extremely slight, merely appreciable; whereas in pernicious anæmia the reaction was very marked.

These observations of Peters appear to show that some excess of iron in the liver, recognisable even on micro-chemical examination, is a condition by no means peculiar to pernicious anæmia, but is one met with in a very considerable proportion of cases (44 per cent.). The method of grouping the cases adopted by Peters is, however, faulty in this respect—that it has no regard to the *amount* of pigment or to its *situation* within the liver, but merely to its presence or absence. 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, the amount of pigment

[1] Op. cit.

in the first of these diseases being so small as scarcely to give any appreciable reaction, while in the latter the liver often contains a very large quantity of pigment.

Even the two latter conditions are easily distinguishable from each other on microscopic examination. In purpura hæmorrhagica the pigment is found in large irregular heaps, scattered irregularly throughout the liver. In pernicious anæmia the pigment is in form of fine granules, lying for the most part within the liver cells and distributed 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 some excess of iron. At the same time his observations are of importance, in so far as they clearly show that the anæmia of wasting disease is not accompanied by any weakness of the red corpuscles and consequent accumulation of pigment in the liver, such as is implied in the view generally held that the condition of the liver in pernicious anæmia is due to this cause.

The results of my own observations go to show that this excess of pigment in the liver in pernicious anæmia is neither the result of extravasation, nor yet can be regarded simply as the result of the profound 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 *presenting clinically any resemblance to pernicious anæmia* does the richness of the liver in iron approach in its degree that characteristic of pernicious anæmia. This is specially true of those forms of anæmia associated with wasting disease regarded by Coupland as the *symptomatic* variety of pernicious anæmia. My observations show—in entire agreement with those of Peters—that in this form of anæmia the liver usually contains no excess of iron at all. This difference is, I find, sufficient to enable me at once to distinguish post mortem between a true case

of pernicious anæmia and one which has only resembled it during life.

The amount of pigment naturally varies in different cases, but in all cases it is distinguished by two peculiarities: (1) its distribution—always most abundant in the outer two-thirds of the lobule; (2) its situation—always most abundant within the liver cells.

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 are usually markedly fattily degenerated and atrophied, and the yellow pigment granules often found within them fail to give any reaction of iron.

The peculiar *distribution* of the pigment above noted 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.

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

Results of Chemical Analysis.—Having satisfied myself as the result of my micro-chemical observations,

that the excess of pigment in the liver, taken in conjunction with the peculiar distribution and situation of the pigment, might be regarded as a characteristic feature of pernicious anæmia, it became a matter of interest and importance to determine how far the conclusions arrived at were borne out by the results obtained by actual chemical analysis. It was conceivable that the apparent richness of the liver in iron in pernicious anæmia, as compared with other diseases, might be solely due to some difference in the form in which the iron was present in the various conditions. In other diseases the liver might contain an equally large proportion of iron—so intimately bound up, however, as not to give the reaction of iron with ordinary micro-chemical reagents.

I have therefore collected all the analyses which have been made of the liver in various diseases, including pernicious anæmia. These are thirty-three in number, made by various observers.

In Table I. the analyses have been arranged in two columns: the one showing the percentage of iron in the liver per 100 parts of dried substance in various diseases other than pernicious anæmia; the other showing the percentage of iron in cases of pernicious anæmia. In Tables II. and III. these results are summarised.

TABLE I.—*Analyses showing Percentage of Iron in the Liver and Spleen in Health and various Diseases.*

No.	Various diseases.	Anæmia.	Percentage composition 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	(?)	Anæmia.	0·396	—	Graanboom (4)
15	Pneumonia.	—	0·099	—	,,
16	Burn.	—	0·039	—	,,
17	Phthisis.	—	0·114	—	,,
18	Nephritis.	—	0·129	—	,,
19	Carcinoma uteri.	—	0·023	—	,,
20	—	Pernicious anæmia.	**1·890**	—	Quincke (5)
21	—	,,	**0·539**	—	,,
22	—	,,	**0·364**	—	,,
23	—	,,	**2·1**	—	,,
24	—	,,	**0·6**	—	,,

(1) Virch. Archiv, Bd. lxxxv., 1881, p. 26.
(2) Oidtmann q. Zaleski: Zeitschrift fur physiol. Chemie, Bd. x., 1886, p. 477. (3) Ibid., Bd. vii., 1883, p. 497.
(4) Archiv fur exper. Pathol. u. Pharmak., Bd. xv., 1882.
(5) Deutsch. Archiv fur klin. Med., Bd. xx., 1877, p. 1; Bd. xxv., p. 567; Bd. xxvii, 1880, p. 193; Bd. xxxiii., 1883, p. 22.

TABLE I.—*continued.*

No.	Various diseases.	Anæmia.	Percentage composition per 100 parts dry substance.		Observer.
			Liver.	Spleen.	
25	Cachexia.	—	0·294	—	,,
26	Typhus; hydroceph.	—	0·581	—	,,
27	Diabetes mellitus.	—	(3·607)	—	,,
28	Human fœtus (8 months).	—	0·147	—	Zaleski[1]
29	Diabetes mellitus.	—	0·068	—	,, [2]
30	Purpura hæmorrhagica.	—	0·036	—	,,
31	—	Pernicious anæmia.	0·623	—	,,
32	Purpura hæmorrhagica.	—	(1·24)	—	Hindenlang[3]
33	—	Pernicious anæmia.	0·518	0·227	Rosenstein[4]

TABLE II.—*Summary of above Analyses, showing Percentage of Iron in Liver in various Diseases other than Pernicious Anæmia.*

Observer.	No. of analyses.	Average percentage composition in iron per 100 parts dry substance.	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 0·147
Total	20	0·078	0·023 to 0·201

[1] Zeitschrift fur physiol. Chemie, Bd. x., 1886, p. 474.
[2] Virch. Archiv, Bd. civ., 1886, p. 91.
[3] Ibid., Bd. lxxix., 1880, p. 492.
[4] Berl. klin. Wochensch., 1877, p. 113.

TABLE III.—*Summary of Analyses showing Percentage of Iron in Liver in Pernicious Anæmia.*

Observer.	Pernicious Anæmia.			Other Dis. exam. by same observers.	
	No. of cases.	Average percentage composition in iron per 100 parts dry substance.	Highest and lowest percentages.	No. of cases.	Average per cent. comp.
Stahel ..	1	0.614	—	9	0·083
Rosenstein	1	0·518	—	—	—
Zaleski ..	1	0·623	—	3	0·083
Quincke ..	5	1·098	0·364 to 2·01	2	0·437
Total ..	8	0·713	0·364 to 2·01	14	0·203

Excluding five analyses, which for various reasons are not suitable for purposes of comparison, the analyses in the first group are twenty in number. *The average percentage of iron in twenty diseases other than pernicious anæmia was* 0·078 *per cent.*, varying from 0·023 to 0·201. In no fewer than seventeen of these cases, in which the analyses were made by three observers (Stahel, Graanboom, and Zaleski), the average percentage obtained is, remarkably enough, almost the same—viz., 0·083, 0·083, and 0·081.

In eight analyses of the lioer in pernicious anæmia the average percentage was 0·713, varying from 0·364 to 2·1. In no fewer than five of these cases the percentage varied from 0·518 to 0·623. The highest and lowest percentages recorded are both by Quincke.

If we compare the average percentage of twenty cases other than pernicious anæmia (viz., 0·078) with the average of eight cases of pernicious anæmia (viz., 0·713), it is at once evident that the difference in the two cases represents a more than ninefold increase in the percentage of iron in the liver in pernicious anæmia.

Comparisons of this nature are only of value, however,

when the analyses in both cases have been made by the same observer. As is well known, 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 be expected to 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, however, is a matter of the greatest 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 thorough and complete removal of the blood has not been equally present to the minds of all observers, and, if one may judge from the results of his analyses, it has been less present to the mind of Quincke than to that of any other observer. In nearly every case his analyses give a higher percentage than that obtained by other observers. For purposes of comparison, therefore, I prefer to exclude Quincke's analyses altogether, and have regard merely to those of other observers; and although this reduces the number of analyses available for purposes of comparison by more than one-half, two or three analyses of a trustworthy nature are of more value than a number of possibly very unequal weight.

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 must, I think, be regarded as establishing conclusively—

(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 ; and

(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 the disease—

(1) That a destruction of blood occurs in this disease far greater than is met with in any other form of anæmia, and notably much in excess of that occurring in the anæmia of wasting disease ; and

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

Relation of this Pigment Accumulation in Liver to that in Spleen.

Further evidence of the importance of the *rôle* taken by the liver in the disposal of the products of this blood destruction in pernicious anæmia is afforded when the percentage richness of the liver in iron is contrasted with that of the spleen, the other organ of the body most concerned in the disposal of pigment remains.

I find from Stahel's analyses (Table I.) that in most diseases, as in health, the relation between the liver and spleen as regards their percentage richness in iron is maintained unaltered—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 compared with 0·083 per cent. for the liver.

In only one case 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 that in the liver.

This relation between the liver and spleen appears to be disturbed, and that, too, in a very striking way, in pernicious anæmia.

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 result of these analyses is so strikingly in harmony with the results obtained on micro-chemical examination that they may be regarded as sufficient to establish the fact that a marked disturbance in the relation of liver and spleen to each other is to be found in this disease. Thus in Rosenstein's case, in which the percentage of iron in the liver was 0·518, that of the spleen was only 0·227 per cent.—less therefore than one-half ; and in Stahel's case, in which the liver contained 0·614 per cent. of iron, the spleen contained only 0·091 per cent.—less, therefore, than one-sixth.

It is necessary to bear in mind that these analyses express merely the percentage of iron per 100 parts of dried substance of the organs; and that, if the spleen be enlarged, it is quite conceivable that a considerable excess of iron might be contained in that organ as compared with the normal, without that excess in any way appearing in the percentage of iron obtained by analysis.

Without attaching too much value, therefore, to the results of these analyses, they must, I think, be regarded as pointing to the conclusion that the iron present in the liver in pernicious anæmia is not only absolutely, but still more relatively, greatly increased.

The result must appear 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 merely indicate some general weakness on the part of the red corpuscles and their premature decay, the accumulation of their pigment remains taking place in those organs—such as the liver—usually concerned in the disposal of such products. On such a view we should 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.

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 show that the spleen is even more concerned than the liver in getting rid of the excess of red corpuscles circulating in the blood under such circumstances. So far from the increase in cases of pernicious anæmia being proportionate, the sevenfold increase in the amount of iron contained in 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; and it must undoubtedly serve, in conjunction with the great increase in the amount of iron in the liver, to accentuate considerably the importance to be attached to this peculiar condition of the liver as one of the most essential, if not the most essential, pathological changes to be found in the body in this disease.

Section IV.—Changes in the Kidney.

To the anatomical changes already described it remains to be added that in certain other organs some excess of pigment is occasionally to be found in cases of pernicious anæmia. This is specially true of the kidney. It is only, however, in a certain number of cases that any pigment is to be found in the organ. Its presence is by no means constant. 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. Nor is it found in all the convoluted tubules. The pigment, both in its appearance and in its situation, differs entirely from that the result of extravasation. It only gives a somewhat imperfect, though easily recognisable, reaction of iron with microchemical reagents. The quantity present varies much in different cases, and in some, in which a very large excess is contained in the liver, it is absent altogether from the kidney. In no case have I found it lying within the glomeruli; and within the renal cells of the convoluted tubules it presents the appearance of colouring matter of the blood in process of excretion.

Summary of foregoing Anatomical Observations.

These, then, are the anatomical changes to be found more or less constantly in patients dying of pernicious anæmia. 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, bone marrow, and 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 characteristic pathological feature of this form of anæmia.* In their order of frequency, these changes are to be found constantly in the liver, more or less constantly in the spleen, very frequently though not constantly in the bone marrow, not unfrequently in the kidneys, and occasionally in other organs, such as the pancreas and thyroid gland. In the case of the liver, bone marrow, and kidneys, the changes consist in 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 recognisable on examination of the fresh tissue, and consist for the most part of changes in the corpuscles themselves.

Nature of Pernicious Anæmia.

We are now in a position to consider what is the true pathology of this form of anæmia.

Are the changes in the blood, which are certainly one of the most marked features of the disease, the result of 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*, we have seen that there is nothing to show why pernicious anæmia should differ so markedly from other forms of anæmia.

In the case of the spleen and lymphatic glands, there is no evidence at all of any disturbance in blood-forming function.

In the red bone marrow the evidences of some such disturbance are much 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 blood-forming function on the part of this tissue—some interference with the proper development of the red corpuscles. It is obvious, however, that the appearances may 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 such large numbers of nucleated red corpuscles rich in hæmoglobin seems rather to indicate that the conditions are by no means so unfavourable to blood formation as is implied in the view that this form of anæmia is essentially hæmogenic in its nature. While their presence in such number points to some marked necessity for increased blood formation, their large size in many cases and their richness n hæmoglobin, along with the richness of the individual corpuscles of the blood in hæmoglobin, seem equally to

indicate that the demand is being always met by the bone marrow, even up to the time of death. Unless the conditions were very favourable, we should expect to find less evidence of blood-forming activity in the bone marrow. And if we look for any conditions which might be supposed specially to favour blood formation in this form of anæmia, we shall find them in the presence within the body in this disease of a large supply of material suitable for purposes of blood formation. So far from there being any want of iron in this disease, as is the case in chlorosis, the evidence I have already adduced shows that there is a great excess; and although this is found for the most part in the liver, an organ not concerned in blood formation, it is also found in excess in the bone marrow. It is this tissue which, as all my observations show, must be regarded as the chief seat of blood formation both in health and disease. In this fact we find 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, little or no part in pernicious anæmia.*

The foregoing observations must, I think, be regarded as clearly establishing that the *essential nature of the disease is excessive blood destruction.* When the fact is clearly established, we find an explanation of many of the most characteristic clinical features of the disease.

Explanation of Chief Clinical Features.

Changes in the Blood.—I have already shown how the relative richness of the blood in hæmoglobin can be at once explained on this view. I have now to add, as regards the other changes in the blood, that my experiments with destructive agents—such as pyrogallic acid and toluylendiamin—clearly show:

1. That a profound degree of oligocythæmia is more readily

producible in animals by means of blood-destroying agents than by repeated losses of blood.

2. That the destruction is accompanied by changes in the form and size of the red corpuscles, similar to those constantly met with in pernicious anæmia.

3. That in certain cases the destruction is accompanied by the appearance of small yellow spherical microcytes 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.

Jaundice.—Further, the establishment of the fact that the liver 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 account for the disturbances in liver function so constantly found in this form of anæmia, and evidenced chiefly by recurrent attacks of jaundice or the persistence of a certain degree of jaundice throughout.

The observations of Stadelmann and Afanassiew have shown 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), which always in the first instance results, is soon followed by increased consistency of the bile, greater viscidity, and consequent stagnation in the bile ducts. A similar explanation doubtless applies in many instances to the case of man; and it is in this fact, as I shall show elsewhere, that we find an explanation of this peculiar feature so often associated with pernicious anæmia.

PART II.—EXPERIMENTAL.

The foregoing observations may be regarded as conclusively establishing that pernicious anæmia is essentially *hæmolytic*, not *hæmogenic*, in its nature.[1] Its true nature, however, is by no means thereby elucidated. Increased destruction of blood is characteristic of other diseases, notably of paroxysmal hæmoglobinuria, and to a less extent of malaria. How does 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. Is this difference one of kind, or merely one of degree?

Such were the questions which presented themselves very early in the course of my 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 of the conditions which regulate it, our knowledge hitherto has been as vague as it is limited.

Nature of the Experiments.

My experiments were therefore undertaken with a twofold object: (1) To ascertain the nature and seats of blood destruction in health; and (2) to endeavour to produce a condition of the liver and other organs of the body similar 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

1 These conclusions as to the hæmolytic nature of the disease were arrived at early in the course of my investigations, and were communicated by me before the Medico-Chirurgical Society, Edinburgh, early n 1887, in a paper on "The Pathology of Blood Destruction within the Liver" (Trans. Med. Chir. Soc. Edin., April, 1887). A paper on "The Pathology of Pernicious Anæmia," embodying the results of my investigations, anatomical and experimental, was read before the Pathological Club, Edinburgh, in May of the present year.

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 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.

My observations and experiments were made on animals representative of the different classes : on dogs and cats, as representing the omnivora; 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 have numbered over a hundred. The largest series were made with pyrogallic acid and toluylendiamin. They were varied in a number of ways. The effects of large toxic doses, as well as the cumulative effects of smaller doses administered over longer or shorter periods of time, were studied. 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 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, bearing on the nature of blood destruction in health and disease, with special reference to the true pathology of pernicious anæmia, have engaged my time and attention during the last three years. The results obtained will be published in detail elsewhere. In the present paper it is impossible for me to do more than refer to such of them as seem fitted to throw light on the true nature of the blood destruction characteristic of pernicious anæmia. My object

will, perhaps, be best attained if I refer to two conditions—malaria and paroxysmal hæmoglobinuria, of which excessive blood destruction is also an important pathological feature,—and contrast the blood destruction found in them with that found in pernicious anæmia.

Section I.—The Difference between the Blood Destruction of Pernicious Anæmia and that found in Malaria.

1. *The excessive blood destruction of pernicious anæmia differs essentially in its nature from that which occurs in malaria. In the latter it is a death of the individual corpuscles; in the former it is a disintegration of the corpuscles with liberation of their hæmoglobin.*

That an increased destruction of corpuscles occurs in *malaria* is evidenced by the number of pigment remains 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] What the nature of this morbid change is need not at present concern us. The result of it is that even while circulating the blood the red corpuscles present evidence of diminished vitality and gradually become effete. The fate of their pigment remains is that of all other foreign pigment particles circulating in the blood. They are taken up by the leucocytes of the blood, 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. It lies for the most part within the capillaries enclosed in leucocytes. It is always more abundant in the capillaries than in the liver cells. In all cases it is also found abundantly in the spleen.

A similar distribution of the blood pigment is sometimes found after transfusion of blood in dogs.[2] The red cor-

[1] Marchiafava and Celli, Fortschr. d. Med., i.

[2] Quincke: D. Archiv f. klin. Med., Bd. xxv., p. 567; Bd. xxvii., p. 193.

puscles under such circumstances, as my observations have shown,[1] do not break down at once. They remain for a longer or shorter time[2] in the circulation, only gradually losing their vitality and becoming effete. The blood pigment into which they ultimately become converted is always found most abundant in the spleen, the liver sometimes containing none at all.

In *pernicious anæmia*, on the other hand, the liver is the chief, sometimes the only, 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 always found most abundant, not within the capillaries as in malaria, but within the liver cells themselves. In some cases the pigment is found within the liver cells, and there alone, none being present in the surrounding capillaries.

Source of the Pigment within the Liver Cells.—The peculiar distribution of the pigment granules in pernicious anæmia has been held by Quincke, Kunkel, and Peters to indicate that the pigment has been originally conveyed to the liver in granular form, probably by leucocytes, and afterwards stored up within 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. Under such circumstances the particles are never to be found within the liver cells, however abundant they may be in the surrounding capillaries. The original observations of Ponfick[3] on this subject I have repeated and confirmed.

Further, my observations show that the pigment is sometimes to be found *within the liver cells and there alone*, none

[1] Hunter: Journal of Anatomy and Physiology, vol. xxi., p. 139 *et seq.* 1887.

[2] Hunter: Brit. Med. Jour., vol. i., p. 192. 1886.

[3] Studien über die Schicksale körniger Farbstoffe im Organisms. Virch. Archiv, Bd. xlviii., 1869, p. 1.

being found in any other organ, an appearance irreconcilable with the view that the pigment has been carried to the liver within leucocytes. We must conclude, therefore, that the pigment found within the liver cells has been formed *in situ;* and that the colouring matter of the blood from which the pigment is derived has passed into the liver cells in soluble form—in the form of hæmoglobin. I was at first inclined to believe that the red corpuscles themselves might pass into the liver cells. I have found no evidence, although it has been carefully looked for, that such is the case. Their disintegration, so far as it occurs within the liver, takes place within the capillaries. It is only their colouring matter which passes into the liver cells themselves.

Important differences thus exist between the excessive blood destruction characteristic of pernicious anæmia and that found in malaria.

In the latter, the nature of the destruction is mainly a death of the red corpuscles, their pigment remains, as in all such cases, being afterwards found abundantly in the liver and spleen; sometimes also in other organs. Within the liver the pigment lies enclosed within leucocytes, and is found therefore, for the most part, in the capillaries.

In the former, the nature of the destruction is a liberation of the colouring matter of the corpuscles occurring in some part of the circulation, and not a death of the individual corpuscles as such. This is evidenced by the constant presence of a large excess of pigment material within the liver cells, as also by the occasional entire absence of similar pigment from the spleen. The two diseases resemble each other, and differ from the disease about to be considered—paroxysmal hæmoglobinuria—in this one respect, that in both the increased blood destruction which occurs is a chronic process extending over a varying period of time.

Section II.—The Difference between the Blood Destruction of Pernicious Anæmia, and that which occurs in Paroxsymal Hæmoglobinuria.

2. *The excessive blood destruction in pernicious anæmia differs both in its nature and its seat from that which occurs in paroxsymal hæmoglobinuria.*

In *paroxysmal hæmoglobinuria* and other forms of 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, therefore, it differs markedly from that occurring in pernicious anæmia.

This is, however, by no means the only or the chief difference between these two diseases. In pernicious anæmia hæmoglobinuria never occurs, although the actual amount of blood destruction during the progress of the disease is greater than that met with in any other disease. The absence of hæmoglobinuria cannot be solely ascribed to the fact that, while in paroxysmal hæmoglobinuria the destruction is rapid, in pernicious anæmia it is more gradual, and perhaps at no time equals that which occurs in the former disease. It is indeed true that pernicious anæmia is a chronic disease. It is none the less true, however, that its progress is often marked by exacerbations more or less acute, in which, as evidenced by the diminution in the number of corpuscles, a destruction of blood occurs, probably as great as that occurring in certain cases of paroxysmal hæmoglobinuria. Nevertheless, pernicious anæmia is never at any time attended by hæmoglobinuria. Hæmoglobin is never found in urine in a form recognisable by the ordinary tests, chemical or spectroscopic.

How are we then to explain the presence of the pigment found in the kidney in many cases of pernicious anæmia?

Hæmoglobin in some form or other has been excreted through the kidneys. Why is it not recognisable in the urine by the ordinary tests?

Section III.—Why Hæmoglobinuria is absent in Pernicious Anæmia?

The presence or absence of hæmoglobin in the urine has been hitherto regarded by all observers as simply dependent on the quantity of hæmoglobin present in the circulation. When hæmoglobin appears in the urine, it has been regarded 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. Thus, according to Ponfick,[1] hæmoglobinuria occurs when the quantity of free hæmoglobin exceeds the sixtieth part of the whole of the hæmoglobin contained in the body. How are we, on this view, to explain the differences in the behaviour of the colouring matter of the blood in the two diseases, pernicious anæmia and paroxysmal hæmoglobinuria? In both hæmoglobin in great excess is set free in the blood; but while in paroxysmal hæmoglobinuria the hæmoglobin is at once excreted through the kidneys, and appears as such in the urine, in pernicious anæmia hæmoglobinuria is absent.

These differences can, I find, be simulated experimentally. 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. The injection of even large doses of toluylendiamin, on the contrary, in the same animals, is never attended by hæmoglobinuria, although the appearances presented by the liver, spleen, or other organs may clearly show that a great destruction of blood has occurred.

How are these differences in the results to be explained? The answer is supplied by my observations, which show *that the occurrence of hæmoglobinuria is dependent not so much on the quantity of hæmoglobin free in the blood as on* (1) *the seat of its liberation and* (2) *the form assumed by the hæmoglobin after being liberated.*

[1] Ueber Hæmoglobinurie: Berl. klin. Woch., 1883, No. xxv.

It is necessary to premise that in the process of *blood destruction* two stages must be distinguished—(1) disintegration or death of the corpuscles; (2) the disposal of the products of this disintegration, free hæmoglobin or blood pigment. The seats of these two processes are not necessarily the same. The former may occur in the circulation itself or in certain organs; the latter is effected chiefly by the liver, the spleen, and the bone marrow, and sometimes also by the kidneys.

Subsection 1.—Seats of Boood Destruction.

(*a*) *In Health.*—Contrary to the view usually held that disintegration and death of the corpuscles occur in all parts of the circulation alike, I find that *in health the chief seat of disintegration of the red corpuscles is the portal, as distinguished from the general, circulation.*

The chief seats of this disintegration within the area of the portal circulation are, in their order of importance, the spleen, the liver, and, lastly, but to a very much less extent, the portal blood itself outside the liver and spleen. The conditions within the portal system, and especially within the spleen, are peculiarly favourable to this destruction. Elsewhere they are much less favourable; so much so that the amount of blood destruction which occurs in health outside the confines of the portal circulation may be disregarded as of little or no moment.

Within the bone marrow a certain amount of blood destruction does occur, favoured doubtless by the conditions of the circulation in that tissue, as also by the nature of the tissue itself. The bone marrow, however, is more concerned in the disposal of old and effete red corpuscles and their pigment remains than in the actual destruction of red corpuscles.

In health, therefore, no evidence of the constant daily destruction of corpuscles, which undoubtedly occurs, is obtainable outside the limits of the portal circulation. The chief evidence of this destruction is, in fact, that

afforded by the liver—viz., the formation of the bile and urinary pigments. The amount of destruction which takes place is constantly varying in health, and still more in disease. Nevertheless, what may be termed *physiological hæmoglobinuria* never occurs. However great the destruction may be, hæmoglobin never appears in the urine. And this is the case so long as the disintegration of the red corpuscles and the liberation of their hæmoglobin is limited to the portal circulation. The products of this destruction are successfully disposed of by the liver before reaching the general circulation.

(*b*) *In Paroxysmal Hæmoglobinuria.*—On the other hand, the liberation of hæmoglobin in the general circulation, even in small quantity, is at once evidenced by the appearance of hæmoglobin in the urine. This is the condition typically exemplified in paroxysmal hæmoglobinuria, as also after the injection of distilled water, glycerine, or pyrogallic acid in animals. The occurrence of hæmoglobinuria in such cases depends not so much on the *quantity of hæmoglobin* set free as on the *seat of its liberation.*

We have seen that in animals 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 locally on the red corpuscles, withdrawing their hæmoglobin.

So also in man, the mere dipping of the fingers for a short time in ice-cold water will suffice in some cases to bring on an attack in those subject to paroxysmal hæmoglobinuria, the actual disintegration of the corpuscles, according to Boas,[1] being confined to the small portion of the general circulation exposed to the influence of the cold.

(*c*) *In Pernicious Anæmia.*—In pernicious anæmia, as in health, this destruction is confined to the portal circulation. No hæmoglobinuria ever occurs. In paroxysmal and other forms of hæmoglobinuria the liberation of hæmoglobin occurs

[1] Beitrag zur Lehre von der paroxysmalen Hæmoglobinurie. D. Archiv f. klin. Med., Bd. xxxii., 1883, p. 371.

in the general circulation; hæmoglobinuria then results. So important is this difference, that after the administration of poisons, such as pyrogallic acid, having an intensely destructive action on the red corpuscles, *the destructive action is limited in the first instance to the spleen, even in cases in which the drug has been injected directly into the general circulation.* When small doses are given, the destructive action of the drug is then limited entirely to the portal circulation, and chiefly to the spleen. The products of this destruction are disposed of by the liver, no hæmoglobinuria occurring. When larger doses are given, the destructive action of the poison is no longer confined to the blood within the portal circulation and its *annexa;* an excessive liberation of hæmoglobin occurs both in the portal and general circulation, and marked hæmoglobinuria ensues.

The excessive destruction of blood characteristic of pernicious anæmia is mainly confined to the blood within the portal system, chiefly to that within the spleen and the liver. It is this fact which explains why, in all cases alike, whatever be their severity, the one constant anatomical change—viz., excess of blood pigment—is to be found within the liver, the pigment being always most abundant in the outer two-thirds of the liver lobule. Evidence of any excessive blood destruction may be wanting in every other organ of the body. But in no case, however slight the destruction may be, can the liver escape. The products of this destruction must in all cases pass through it.

Provided that the destruction is within limits, the whole of the products are disposed of, no pigment being found either in the kidneys or elsewhere. If these limits are passed, hæmoglobin then passes into the general circulation, and is excreted through the kidneys. The evidence of this is the presence in certain cases of pigment within the renal cells of the convolute tubules, apparently thrown down in granular form in the process of being excreted.

SUBSECTION 2.—CHANGE IN THE CHARACTER OF HÆMOGLOBIN UNDER THE ACTION OF CERTAIN AGENTS.—The

absence of hæmoglobinuria under such circumstances is explained by my observations, which show that *the occurrence of hæmoglobinuria also depends on the form assumed by the hæmoglobin after being liberated from the corpuscles.*

Hæmoglobin set free in the circulation by the action of such reagents as distilled water or glycerine is excreted as such by the kidneys, and chiefly through the glomeruli of the kidney, only in part through the epithelium of the convoluted tubules.

Under certain circumstances, it would appear as if the hæmoglobin, on being set free, effects a combination with the albuminous constituents of the plasma, and is then no longer excreted as ordinary hæmoglobin. Instead of passing through the glomeruli, it is mainly excreted by the cells of the convoluted tubules, and is no longer recognisable in the urine by the ordinary tests applied for the detection of hæmoglobin.

This change in the character of the hæmoglobin, I find, is characteristic of the action of certain destructive agents, notably of toluylendiamin.

I have already stated that the injection of even large doses of this drug into the blood of rabbits is not attended by hæmoglobinuria, although the appearances presented by the liver and spleen show that there has been a great destruction of blood. Although hæmoglobin is not discoverable in the urine by the ordinary tests, spectroscopic and otherwise, on microscopic examination small globules of yellow colouring matter of varying size are to be found abundantly in the urine, and are easily recognisable as products of blood destruction by their bright yellow colour. These globules are always spherical in form, and they so closely resemble at first sight ordinary spherical red corpuscles that they may, on cursory examination, be mistaken for such. They have more usually been regarded as fragments of red corpuscles. The interesting point regarding these globules of colouring matter—for such they are—is that in size, form, and colour they exactly resemble

the granules of pigment found in the cells of the convoluted tubules of the kidney in certain cases of pernicious anæmia.

Source of the Pigment in the Kidney.—What, then, is the nature and source of this colouring matter or pigment? The answer to this question is, I think, supplied by some observations of great interest which I made while studying the action of toluylendiamin on the blood outside the body, which show that *under certain circumstances hæmoglobin in solution can assume a corpuscular form.*

If a small quantity of blood (5 c.mm.) be added to a perfectly neutral 5 per cent. solution of toluylendiamin, the following changes may be observed. At the end of twelve or twenty-four hours the corpuscles will be found to have all disappeared. On microscopic examination not a single corpuscular element of any sort is to be found in the perfectly transparent, slightly hæmoglobin-tinted solution. After this time a deposit begins to form at the bottom of the vessel, found on examination 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. The bodies are of viscous nature, the smaller fusing readily with one another to form larger. The uniformly spherical form and deep yellow colour are, however, always retained.

A solution of pure crystalline hæmoglobin does not throw down bodies of this nature when similarly treated. *I therefore conclude that the hæmoglobin has formed some combination with the albuminous constituents of the plasma.*

It is extremely probable that a change of this nature occurs in the hæmoglobin in cases of pernicious anæmia. Its removal from the blood is then effected chiefly through the cells of the convoluted tubules. While in process of being excreted, it may be thrown down in the form of globules within these cells, the colouring matter gradually becoming reduced, and giving afterwards more or less

perfectly the characteristic reaction of iron in albuminate form.

As we have seen, it is only in certain cases that the kidney contains this pigment. This is explained by the above observations. So long as the destruction is slight, the products of it will be disposed of almost entirely by the liver and before reaching the general circulation. If it is excessive at any one time, then hæmoglobin in its modified form passes into the general circulation, and is excreted as such through the kidneys. 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 exacerbations of the destructive process more or less acute, and 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. 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.

Section IV.—Explanation of the varying Size of the Spleen.

I regard these observations as establishing that pernicious anæmia is due to an excessive destruction of blood occurring in the portal system, especially that portion of it contained within the liver and the spleen. How is this conclusion reconcilable with the fact that in certain cases of pernicious anæmia the spleen apparently shows no changes either to the naked eye or on microscopic examination? In some cases it is described as of small size, firm, and red, or small and pale; while in others it is found enlarged, swollen, soft in consistence, and of deep violet colour, as in a case which recently came under my notice.

The explanation of these variations in the size of the spleen I find to be that *the size of the spleen cannot be taken as an*

indication of 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 contains remains of red blood-corpuscles and other evidences of blood destruction are numerous, the spleen may be found small, shrunken, and contracted, containing little blood and showing little evidence of having been at all concerned in the process.

Now we have seen that the course of pernicious anæmia towards the fatal termination is usually marked by relapses alternating with periods of convalescence; also, that these exacerbations are always followed by further deterioration of the quality of the blood and by more marked oligocythæmia. This must be taken as an indication that the excessive blood destruction occurring in pernicious anæmia is not constant. The process is marked by periods of activity alternately with periods of quiescence. The condition of the spleen found after death will vary according as an exacerbation of the destructive process has recently occurred or not. It is this fact which explains, in part, the extraordinary variations in the size of that organ in different cases. If destruction is in active progress at the time of death, the spleen will be found enlarged.

Section V.—Explanation of the varying Quantity of Pigment in the Spleen.

As regards its other characters, we have seen that in the hardened tissue microscopic examination usually fails to reveal any changes at all, and that in most cases the amount of iron contained in it is 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, and for the following reason :—

My observations showed that after transfusion of blood the spleen always contains much more pigment than the liver, and this organ is the chief seat of the disintegration of the red corpuscles in such cases. The conditions of the circulation in the spleen are specially favourable to the accumulation of effete red corpuscles and their conversion into pigment.

I found, however, that the presence or absence of pigment in the spleen is dependent to a great extent on the *nature* of the blood destruction which has 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 corpuscles may have been great. After poisoning with pyrogallic acid little or no pigment may be found in the spleen, although marked hæmoglobinuria has occurred ; and the appearances presented by the red corpuscles within the spleen itself show 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 ultimately arrived at on the ground of these observations was that, as regards the spleen, much more importance was 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 was found apparently normal on being examined after hardening, while examination of the fresh organ had shown that blood destruction had been in full progress at the time of death.

This conclusion was confirmed in a very striking way in a case of pernicious anæmia which came under my observation recently. The appearances presented by the spleen in particular were extremely well fitted to explain why in so many cases that organ after hardening shows so little change.

The spleen was much enlarged (weight 13 oz.), soft and flabby in consistence, and, on section, presented an ex-

tremely 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.

On microscopic examination of scrapings from the fresh organ the red corpuscles were found few in number. 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 colour reaction with sulphide of ammonium. It contained no excess of blood pigment.

The explanation of these appearances is at once evident. 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 being, in the present case, 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 thick, intensely deeply stained bile found 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, as it is contained in the form of hæmoglobin, gives no reaction with micro-chemical reagents.

Section VI.—Conclusions as to the Nature of the Blood Destruction.

What, then, is the nature of the blood destruction in this disease? I have satisfied myself that it cannot be regarded simply as a dissolution of the red corpuscles in the general circulation, such as occurs periodically in paroxysmal hæmoglobinuria, and such as may be experimentally induced by the injection of such reagents as distilled water, glycerine, or pyrogallic acid into the circulation.

Hæmoglobinuria then occurs, and hæmoglobinuria is always absent in pernicious anæmia.

In this relation the condition of the liver is of the greatest importance.

As the result of my observations with distilled water and glycerine after injection into the blood, I have been led to conclude that *mere excess of hæmoglobin free in the blood is not capable of giving rise to a condition of the liver such as is found in pernicious anæmia.*

Nor can it be produced by the action of a destructive agent such as pyrogallic acid, which, in addition to its action on the blood, has a distinctly poisonous action on the liver cells, evidenced by the occurrence of intense fatty degeneration of the liver cells, especially in the centre of the lobules.

My observations, however, show that, by the action of a drug such as toluylendiamin, a condition of the liver as regards (1) *richness in iron*, (2) *situation of the pigment within the liver cells*, and (3) *occurrence of fatty degeneration in the cells in the central third of the lobule*, can be produced closely resembling, although never so marked as that found in, pernicious anæmia. A similar condition of the liver has been found by Stadelmann after chronic poisoning with toluylendiamin in dogs.

Now, the peculiarity of the action of toluylendiamin, as distinguished from that of a poison such as pyrogallic acid, I find to be this—that it combines with its destructive action on the blood a *specific* action, not necessarily a poisonous action, on the liver cells. I find that a similar specific action is to some degree 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 induces the excessive destruction of blood in pernicious anæmia is one whose action on the blood and on the liver cells is the same as 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.

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 do not as yet supply 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. It is therefore probable that the poison is of a cadaveric nature, produced within the gastro-intestinal tract—in excessively small quantity, however, and not necessarily constantly. On such a view, we can at once explain (1) why changes in the gastro-intestinal tract—malignant disease, atrophy of gastric glands, presence of intestinal worms—may all be important etiological factors in the production of this form of anæmia; and (2) why, on the other hand, they may all exist without giving rise to the disease. They merely, under certain circumstances, favour the production of the essential pathological changes underlying the disease—viz., an excessive destruction of blood, limited for the most part to the portal circulation and its important *annexa*—the spleen and liver.

SUMMARY OF RESULTS.

Let me, in conclusion, briefly summarise the results of my observations.

1. Pernicious anæmia is to be regarded as a special disease both clinically and pathologically. It constitutes a distinct variety of *idiopathic* anæmia.

2. Its essential pathological feature is an excessive destruction of blood.

3. The most constant anatomical change to be found is the presence of a large excess of iron in the liver.

4. This condition of the liver serves at once to distinguish pernicious anæmia post mortem from all varieties of *symptomatic* anæmia, as also from the anæmia resulting from loss of blood.

5. The blood destruction characteristic of this form of anæmia differs both in its nature and its seats from that found in malaria, in paroxysmal hæmoglobinuria, and other forms of hæmoglobinuria.

6. The view can no longer be held that the occurrence of *hæmoglobinuria* simply depends on the quantity of hæmoglobin set free.

7. On the contrary, the *seat* of the destruction and *the form assumed by the hæmoglobin* on being set free are important conditions regulating the presence or absence of hæmoglobinuria in any case in which an excessive disintegration of corpuscles has occurred.

8. In paroxysmal hæmoglobinuria the disintegration of corpuscles occurs in the general circulation, and is due to a rapid dissolution of the red corpuscles.

9. In pernicious anæmia the seat of disintegration is chiefly the portal circulation, more especially that portion of it contained within the spleen and the liver, and the destruction is effected by the action of certain poisonous agents, probably of a cadaveric nature, absorbed from the intestinal tract.

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