An Investigation
INTO THE
PATHOLOGY OF PERNICIOUS ANÆMIA.

BY WILLIAM HUNTER, M.D., F.R.S. EDIN.,
JOHN LUCAS WALKER STUDENT OF THE UNIVERSITY OF CAMBRIDGE.

(*Continued from p. 559.*)

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 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.

Subsequent observations, however, especially of Quincke[5] and his scholar, Peters,[6] 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. 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,[7] Cahn,[8] and Glavecke[9] 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 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.

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[10] 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 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.

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

[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.*
[5] Deutsch. Archiv f. klin. Med., Bd. xxv., p. 567; Bd. xxvii., p. 202; Bd. xxxiii., p. 23. [6] Ibid., Bd. xxxii., p, 182.
[7] Archiv f. exper. Pathol. u. Pharmak., Bd. xvi., 1883, p. 390.
[8] Ibid., Bd. xviii., 1884, p. 146. [9] Ibid., Bd. xvi., 1883, p. 469.
[10] Op. cit.

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.

Results of Micro-chemical Observations.—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 periportal 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 (*a*)
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 (*b*)
12	Syphilis neonati.	—	0·103	—	,,
13	Leukæmia.	—	0·055	—	v. Bemmelen (*c*)
14	(?)	Anæmia.	0·396	—	Graanboom (*d*)
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 (*e*)
21	—	,,	**0·539**	—	,,
22	—	,,	**0·364**	—	,,
23	—	,,	**2·1**	—	,,
24	—	,,	**0·6**	—	,,
25	Cachexia.	—	0·294	—	,,
26	Typhus; hydroceph.	—	0·581	—	,,
27	Diabetes mellitus.	—	(3·607)	—	,,
28	Human fœtus (8 months).	—	0·147	—	Zaleski (*f*)
29	Diabetes mellitus.	—	0·068	—	,, (*g*)
30	Purpura hæmorrhagica.	—	0·036	—	,,
31	—	Pernicious anæmia.	**0·623**	—	,,
32	Purpura hæmorrhagica.	—	(1·24)	—	Hindenlang (*h*)
33	—	Pernicious anæmia.	**0·518**	**0·227**	Rosenstein (*i*)

(*a*) Virch. Archiv, Bd. lxxxv., 1881, p. 26.
(*b*) Oidtmann u. Zaleski: Zeitschrift fur physiol. Chemie, Bd. x., 1886, p. 477. (*c*) Ibid, Bd. vii., 1883, p. 497.
(*d*) Archiv fur exper. Pathol. u. Pharmak., Bd. xv., 1882.
(*e*) Deutsch. Archiv fur klin. Med., Bd. xx., 1877, p. 1; Bd. xxv., p. 567; Bd. xxvii., 1880, p. 193; Bd. xxxiii., 1883, p. 22.
(*f*) Zeitschrift fur physiol. Chemie, Bd. x., 1886, p. 474.
(*g*) Virch. Archiv, Bd. civ., 1886, p. 91.
(*h*) Ibid., Bd. lxxix., 1880, p. 492.
(*i*) Berl. klin. Wochensch., 1877, p. 113.

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

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, remarkable enough, almost the same—viz., 0·083, 0·083, and 0·081.

In eight analyses of the liver 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 microchemical 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 microchemical 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 organ; 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.

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 micro-chemical 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 matters 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 in 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.

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.

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.

(To be concluded.)

ON PERFORATION OF THE VERMIFORM APPENDIX IN ITS RELATION WITH ATTACKS OF PERI-TYPHLITIS.

BY JOHN A. MACDOUGALL, M.D., F.R.C.S. EDIN.,
CONSULTING SURGEON TO THE CUMBERLAND INFIRMARY, ETC.

(Concluded from page 566.)

To typhlitis stercoralis I make no especial reference; its causation and its characteristics are so readily recognised that it cannot, as a rule, well hold a place in the solution of a differential diagnosis. It is otherwise, however, with the conditions of which I have furnished illustration, each one of which possesses a family likeness which is readily appreciated, but the underlying cause of which it is at times most difficult to determine. If we could accept the belief of some "that every case of so-called peri-typhlitic abscess must be regarded as primarily one of a perforating appendicitis unless proven to the contrary," then our quest would