hurry and exertion for about a fortnight, when he appeared to get quite well. In the beginning of November, the morning after a game of football in which he was several times charged violently, he became again short of breath. The breathing continued short for about a month, but at the end of that time he found himself quite well again, and continued well until the present attack three weeks later. The two previous attacks were, he stated, all similar to the present one.

In the absence of direct evidence, there is a very strong probability that the previous attacks were, like the present, due to pneumothorax. The last attack was without doubt pneumothorax, but he came under observation rather by accident than of necessity, for it was not until he had had the dyspnoea for ten days that he presented himself at the hospital, and even then the dyspnoea was so slight that he grumbled at being kept in bed.

There are two facts about pneumothorax which, though well established, are not generally known: the one, that it is of not uncommon occurrence in the apparently healthy; and the other, that it may develop in the latent insidious way it did in this case, and without the violent symptoms which frequently accompany it. The interest of this case and of that published by Mr. Gabb does not lie in their illustrating these points, but in the fact, which they establish, that a patient may have more than one attack of pneumothorax and recover completely. I do not see any reason why this should not be so, but I do not recollect any recorded case of the kind, so that Mr. Gabb's case is a very important contribution to the literature of the subject.

THE PATHOLOGY OF PERNICIOUS ANÆMIA.¹

By WILLIAM RUSSELL, M.D., F.R.C.P.E.,

Lecturer on Pathology in the School of Medicine; Pathologist to the Royal Infirmary; Physician to the New Town Dispensary, Edinburgh, etc.

I SHALL not occupy the time of this Section by recounting the clinical features of what is known as pernicious, essential, or idiopathic anæmia. This is hardly the place to dwell much on these; but there is a more pertinent reason for my not doing so, and it is that they are well known to the profession, and are to be found in all books on practical medicine. The same may be said of the changes to be noted in the blood during life, so they need not detain us either. I may at once say that I do not flatter myself that I can wholly decipher the writing left to us in the *post-mortem* room by this disease, but I am not without hope that I may be able to bring some facts under your notice which are of interest and may be suggestive.

The question which presents itself at the threshold of any inquiry into the pathology of pernicious anæmia is: Is it the result of diminished formation or of increased destruction of red corpuscles? For it is to be borne in mind that there is a true oligocythæmia in pernicious anæmia, the corpuscles, in my own experience, falling before death to 12 per cent. of their normal number. There is one other well-known fact about the red corpuscles which is to be remembered, namely, that they are individually as rich, or even richer, in hæmoglobin than in normal blood. This distinguishes the disease from chlorosis, in which the blood-condition is more a spanæmia, the individual corpuscles being far below the normal in hæmoglobin richness.

Let us look first at the question of diminished production. This involves the physiological question as to the seat of origin of the red blood corpuscles. The various views to be found on this rudimentary and fundamental question are that they originate (1) from colourless corpuscles, (2) from nucleated red corpuscles, (3) from the hæmatoblasts of Hayem, known also as the elementary particles of Zimmermann, granule masses of Schultze, and blood-plates of Bizzozero, (4) that they are formed in the spleen, and (5) that they have their genesis in the red marrow. The last view is supported by Bizzozero, Neumann, Schäfer, Rindfleisch, and other eminent authorities; in fact, we may accept it as a physiological doctrine that the red marrow is at least one, if not the most important, seat of the formation of the red corpuscles.

If we turn now to the physiological question as to the seat of destruction of the red corpuscles, we find that it is held to take place in the liver, the spleen, the bone-marrow, and the lymph glands. In the last three the number of cells containing pigment is said to be enormous in some morbid conditions, as fevers and cachectic states. It is also greatly increased after transfusion and after subcutaneous and intraperitoneal injection. While there is a diversity of opinion as to whether all of these organs are seats of destruction, there is practical unanimity in regarding the liver as a necessary site. Although the importance of these physiological questions cannot be overrated in their bearing on pathological problems, and are still open to discussion and require further investigation for their solution and completion, we may with seeming safety base our argument on what is accepted, although I admit my feeling is not one of absolute security.

Looking at pernicious anæmia from the standpoint of diminished production (anæmatosis), you are aware that Pepper and Tyson in 1875 found the ordinary yellow marrow of the long bones replaced by red marrow. This observation has been confirmed by many observers since that time. Now, if this change must be present before any individual case can rank as one of pernicious anæmia, we are in a position where it seems only one opinion is possible, and it is this, that if we know anything of the formation of red blood corpuscles it is that they are formed from red marrow and that when there is this great increase in the red marrow there cannot be a deficiency in the formation of red corpuscles. Not only are we impelled to this, but it may further be assumed that there is here an extraordinary effort on the part of this important tissue to meet the demand for red corpuscles, and that it accordingly undergoes hyperplasia. The plausibility of this induction is further strengthened by the fact that this replacement of yellow marrow by red has been observed in other wasting, cachectic, and anæmic conditions, and Neumann has recorded a case of profuse metrorrhagia in which the change had taken place.

It is unnecessary to detain you by detailing the microscopical characters of the red marrow of the long bones in a case I had in the end of 1886, as the changes I noted closely corresponded with those recorded by others, and considered as the stages of the development of red corpuscles. I may, however, say that I was not satisfied at that time that physiologists had arrived at the whole truth, although I was not in a position to advance our knowledge on the point.

We have next to consider pernicious anæmia from the side of increased blood destruction (hæmophthisis). The pigment of the red corpuscles is hæmoglobin, a substance with an elaborate chemical formula, and which contains iron. When the corpuscles disintegrate, the hæmoglobin decomposes, with the result that a yellowish pigment remains, which is hæmatin, or some body of nearly allied chemical composition. Whatever the precise chemical composition may be, it contains iron in a state in which the iron reaction is obtained by ordinary chemical examination. The iron present in the normal red blood corpuscles cannot be demonstrated in this simple way. The method used when an organ is to be tested for decomposed hæmoglobin is as follows: a bit of it is put into a solution of ferrocyanide of potassium for some minutes and then transferred to dilute hydrochloric acid, when, if decomposed hæmoglobin be present, a blue coloration is produced. The depth of colour depends upon the amount of hæmoglobin present. The tissue after the reaction is obtained may be cut and mounted in balsam in the usual way, or sections of the tissue may be first cut and then tested and mounted. The distribution of the pigment can be determined by microscopical examination, but this is facilitated by staining the sections with eosine in order to make the elements of the organ examined more visible. The pigment is not as a rule obscured by this proceeding.

In the case of pernicious anæmia, to which I have already referred, there was marked evidence of blood destruction in the liver, a yellowish pigment being abundant in its cells. That this pigment contained iron was shown by the deep blue coloration which the sections assumed when tested as above. On microscopic examination the blue staining was seen to be in the form of discrete particles or granules, and in globular masses lying in the liver cells of the outer and middle zone of the lobules. In the central zone there was a yellowish pigment in the cells which did not give the iron reaction, while in the capillary spaces of this zone there were granular masses of a deep blue colour. The spleen and kidney also gave a deep blue colour. The iron pigment in the spleen is mainly in the walls of the pulp sinuses

¹ Read in the Section of Pathology at the Annual Meeting of the British Medical Association held at Glasgow, August, 1888.

while in the kidney it is confined to the epithelium of the convoluted tubules.

When I was studying the distribution of the iron pigment in this case the question naturally suggested itself whether the disease might not be due to hepatic conditions, as diabetes mellitus can with considerable reason be contended to be. Was it really a liver disease? Was the destruction of blood in it the essential element in the disease, and if so, was the destruction the result of a heightening of the blood-destroying function on the part of the liver (a blood-hunger I called it at the time, but some of my physiological friends object to the subjectivity of the term) or was it the result of the red blood corpuscles being brought to the liver in such a condition that the liver cells in the performance of their normal function necessarily destroyed them? I discussed this subject in a paper I read to the Pathological Club of Edinburgh in the session 1886-7, and contended that the latter view was the correct one. I arrived at that conclusion partly from the fact that the nuclei of the liver cells did not stain with Mitchell's logwood, a nuclear stain on which I place great reliance when properly prepared, or with picrocarmine. This indicated that the vitality of the liver cells had been materially affected by the increased work of destroying the blood corpuscles. An increase in function dependent on the exaltation of the capacity of the liver cells would not produce this result, while the continued stimulation by the presence of abnormal blood would inevitably lead to the exhaustion of the cells. This view is supported by the fact that the renal epithelium was similarly affected, and that it shows the same absence of reaction in cases where excessive work is thrown upon it. The evidence of excessive destruction of blood in the liver in this disease as tested by the method I have described has been observed by Osler, Müller and others, while Quicke has found the percentage of iron, estimated quantitatively, considerably above the normal in cases he had examined.

Having found such marked evidence of blood-destruction in three organs, it seemed to me desirable to make a series of observations as to the iron reaction to be obtained in other cases. I accordingly tested forty-four livers, taken without selection from my hospital cases, with the following result:—

No.	Organ.	Marked Reaction.	Slight.	No Reaction.
44	Liver	7	17	20

Those which gave a marked reaction were as deeply coloured as the liver from pernicious anæmia; in fact, in some of them there was even more pigment present. A number of cases gave a slight blue reaction, the colour being so diffuse that it was not visible on microscopic examination, and there were no granules, as is the case when pigment is present in any amount. Those which gave a slight reaction, or no reaction, included a great variety of diseases. The seven which gave a very deep blue coloration were:—1. Cirrhotic kidneys with hypertrophied heart, in which death occurred from acute pleurisy on the right side; 2. catarrhal jaundice, cirrhotic kidneys, and fatty heart; 3. carcinoma of lung, liver, and suprarenals, with a degree of diffuse cirrhosis of the kidneys; 4. malignant obstruction at the cardiac orifice of the stomach, where death occurred after gastrotomy; there was slight peritonitis, and the kidneys were somewhat cirrhotic; 5. diffuse malignant thickening of stomach and large intestine—acute peritonitis; 6. jaundice due to cancer of the head of the pancreas, also cancer of liver; 7. chronic parenchymatous nephritis.

Although the lesions in these cases were of a very decided nature, there is not one of them which had not its apparent counterpart in the other groups, so that it appears to me no inference can be drawn from them as to the class of diseases in which this marked evidence of blood-destruction is to be expected.

I next tested the spleen in six of the seven cases which gave the marked reaction in the liver (the spleen from the other case had not been preserved), and found that they all gave a very deep blue reaction, which was even more pronounced than in the same organ from pernicious anæmia. To check this further I tested ten cases taken at hazard from the twenty in which the liver gave no reaction, and I found six gave no reaction, and four gave a marked reaction (to show the difference between reaction and no reaction pieces of three different spleens were shown). The kidneys of the seven in which the livers gave the marked reaction were then tested, and of these three gave the reaction, four gave no reaction. These check observations may be tabulated as follows:

Of Forty-Four Livers there was:—

Marked Reaction in 7.		Slight reaction in 17.	No Reaction in 20.
<i>Spleens.</i> 6 marked.	<i>Kidneys.</i> 3 reaction	—	In 10 of these <i>Spleens.</i> 4 gave reaction
1 not examined	4 none	—	6 no reaction

There are some points of detail which need not at present be entered into. In connection with the spleens, however, I may repeat that the granules and masses of blue were almost exclusively in the walls of the pulp sinuses, not to any extent in the interior of the sinuses, and not in the Malpighian bodies. In addition, there were masses of black pigment which did not give the iron reaction.

From these observations it appears that there is a considerable proportion of cases in which there were the evidences of blood destruction in the liver and spleen, and even in the kidney, on which is based the contention that pernicious anæmia is a disease with increased blood-destruction. In these cases there was presumably no evidence during life of a profound anæmia, such as characterises the pernicious form.

From the fact that only seven out of forty-four cases showed the evidence of blood-destruction in the liver, it must be regarded as an abnormal condition when present in this marked degree. The observations, therefore, support the contention that in pernicious anæmia there is increased blood-destruction. The same may be said of the blood-destruction in the spleen. In this organ, of sixteen examined ten gave a reaction, while six gave none, showing that evidence of destruction is not constant even in it, but is present in certain conditions, of which pernicious anæmia is one.

The further contention, that the blood-destruction is due to the condition in which the blood reaches the liver, is also supported by these observations. Not only in the case of pernicious anæmia, but in six of the cases in which the liver gave a marked reaction, the spleen gave the same. This seems to me to imply that the disease is not primarily a liver one, but that there is an antecedent blood-condition leading to exaggerated destruction in both these organs, which presumably would not be the case were changes in the liver the primary cause of the destruction. It is a point the significance of which is not apparent, that in a number of cases there was evidence of great destruction in the spleen, and no evidence of it in the liver.

If my contentions so far be correct, the ultimate question is, What is the blood-condition which leads to this exaggerated destruction? To this I can offer no direct answer. Certain poisons, as lead, mercury, arsenic, etc., induce anæmia by increasing destruction, and malarial poison has a similar effect. In one of the above cases, a case of Professor Greenfield's, the diagnosis was chronic malaria with splenic abscess; the diagnosis was verified *post mortem*, and the liver showed no evidence of increased destruction. As bearing on the possible nature of the blood-condition, we have to bear in mind the fully-established reputation which arsenic has now held for years in temporarily arresting many cases, and in curing others which were believed to be cases of this disease. There is one further consideration which ought not to be lost sight of, and that is that, until the whole history of the blood-elaborating and blood-purifying processes in the body are more fully known, we are hardly in a position to dogmatise. It may be that some step in the elaboration of the corpuscles may be defective, or that some blood-purifying organ is at fault. Which it is cannot yet be decided; but, in view of the history of the discovery of the important function of the thyroid, it is possible that some such explanation may yet be forthcoming.

I may be allowed to suggest to pathologists the desirability of making observations on the presence of decomposed hæmoglobin in the liver and spleen, as the method is a simple one and can be followed in the *post-mortem* room. It is specially desirable to know if the liver and spleen always give a marked iron reaction in undoubted cases of the disease. From the presence of iron in the epithelium of the convoluted tubules of the kidney one would anticipate its presence in the urine. In my own case the urine was of a very dark brown colour before death, but an elaborate examination was, unfortunately, not made of it. When the urine assumes this appearance it is, I think, quite possible that the iron reaction may be obtained.]