ART. XV.—*A Case of Progressive Pernicious Anæmia.* By
J. M. PURSER, M.D.

PROGRESSIVE pernicious anæmia is a disease of considerable rarity in Ireland. I have myself never seen an example of it here, except that which I am about to relate; and, so far as I know, no instance of it has hitherto been recorded as occurring in this country. Besides its rarity, the following case seems to me to present sufficient interest to make its publication justifiable:—

M. F., aged sixty, was admitted into Sir Patrick Dun's Hospital early in August of this year. She was a married woman and had had several children. She had lived in the country all her life, and had always been in very comfortable circumstances. For the last twenty years she had been in service as cook. She had never had any illness before the present. She states that she was in good health until two months before her admission, when, while making an effort, she was attacked by faintness. Immediately after this her colour was observed to change. She at first became dark-brown or black, and, subsequently, very pale. She worked for six weeks, when increasing weakness obliged her to give up. She had been from the first under medical care, but, deriving no benefit, she came up to Dublin, and was admitted into hospital.

She came under my charge on the 1st September.

She is a largely-made woman; hair perfectly white. Extreme anæmia; not the least trace of jaundice. Body well covered by fat; no œdema; no fever. Tongue large, pale, and flabby; no appetite. Complains of frequent attacks of pain in the abdomen, extending from the epigastrium to the back and lumbar regions. This pain is generally increased by taking food, and occurs in paroxysms, sometimes of great severity. There are frequent sickness of stomach, and vomiting. The vomited matters consist, besides the food last taken, of a clear yellow fluid and mucus. Bowels generally constipated. No symptoms referable to heart and lungs. Urine abundant, acid, high-coloured; on standing, throws down a light cloud, containing merely a few epithelial cells and mucus corpuscles. Sleeps well, except when kept awake by pain, which often occurs at night. Is extremely weak, so that she cannot leave her bed. Is very uncommunicative and irritable; submits herself with reluctance to examination, and can be made, only with difficulty, to describe her symptoms. Percussion-sound over lungs normal. Respiratory murmur pure in every region. No evidence of enlargement of the heart. Rhythm perfect, about 70. A soft systolic murmur, loudest at the base and at the left side of the sternum, in the region of the pulmonary artery. Venous murmur in the neck. Walls of the abdomen flaccid, but very

fat. The gentlest touch throws the muscles into contraction, which makes examination difficult. Patient complains of soreness of the abdomen, chiefly of epigastrium. A tumour about the size of a walnut, and having the characters of a fatty tumour, to be felt immediately to right of umbilicus, evidently in abdominal wall. Besides this no tumour is to be felt. The liver extends slightly below the arch of the ribs, and its left lobe causes a general feeling of resistance in the epigastrium. Spleen cannot be felt. Pulsations of aorta very perceptible, maximum just above umbilicus. Urine high-coloured, free from albumen.

During September no fresh symptoms appeared. The anæmia and feebleness increased, and the attacks of pain became more frequent and severe. The sickness of stomach became almost constant, the vomited matters being small quantities of yellow fluid.

On the 3rd of October a drop of blood was taken from the finger for microscopic examination. Even to the naked eye the extremely watery character of the blood was evident. The red corpuscles were remarkably few, and showed no tendency to cohere in rouleaux. They differed among themselves remarkably in form and size. Comparatively few were of the normal size and shape; most of them presented tail-like processes or projections; several were oval, and many were bowl-shaped—one side being convex, while the other maintained the normal concavity. There was a considerable number of very small red bodies, from one-third to one-half the normal size. Some of these were spherical, others flattened. There were a few corpuscles, mostly oval, of greater than the normal size. No nucleated red corpuscles could be seen. The white corpuscles were few, but presented no abnormality. There were a few colourless granular masses floating in the plasma. On this day the patient, who was extremely weak, complained of seeing "flies and midges" before her eyes.

On the next day, for the first time, a few punctiform ecchymoses were observed on the arms and front of the chest.

On the 6th October she died. The pulse, which had been throughout full and not remarkably soft, became—for twenty-four hours before death—rapid, small, and jerky.

Post mortem examination, nineteen hours after death.

Body extremely pale. A few small punctiform ecchymoses on arms and trunk; on right forearm two faint blue marks like bruises. Cicatrices of two small ulcers on anterior and outer part of left leg. No œdema. Depending parts of body presented slight, but distinct, gravitation lividity. Unusual forward curvature of lumbar vertebræ (lordosis). On placing the hand on the surface of the abdomen, the spine seemed to lie immediately under the abdominal wall. The small tumour, noticed during life, to be felt near the umbilicus. Rigor badly marked.

Cranium not thick, but dense and heavy—in some spots so firmly adherent to dura that the latter had to be removed with the bone.

Dura in spots opaque and thickened. The points where the bone was adherent presented no evident thickening. No adhesions between *dura mater* and arachnoid, or thickening of the latter. Longitudinal sinus empty in its anterior part; posteriorly occupied by a loose pink clot. Lateral sinuses contained fluid blood. Other sinuses empty or containing fluid blood in small quantity. Cerebro-spinal fluid clear and in considerable quantity. Surface of brain remarkably pale. *Pia mater* not thickened or inflamed; separated readily from surface of hemispheres. *Vessels* at base presented spots of atheroma, and were empty. Ventricles contained a small quantity of clear fluid. Except extreme anæmia, the *brain* did not present anything abnormal; neither in its substance nor in its membranes were any ecchymoses found.

The roofs of the orbits were removed, and the posterior halves of the eyes examined. In each *retina* were several small ecchymoses. These were most numerous about the entrance of the optic nerve, where they were long and narrow, and arranged in a radiating manner; nearer the periphery they were few and of irregular shape. There were no opaque spots in the retina, except one extremely minute yellow point in the centre of one of the extravasations on the left side.

Subcutaneous fat in very large quantity—at least 1½-inch thick on anterior surface of abdomen—of a bright yellow colour. A mass of fatty omentum protruded through an opening immediately to the right side of the umbilicus. It was contained in a hernial sac, lined by peritoneum, and which lay altogether in the subcutaneous fatty tissue, thus forming no protrusion on the surface. The omentum was not adherent to the interior of the sac, but closely attached at the neck to about one-half the circumference of the latter. The omentum and mesentery were loaded with yellow fat. In the *cavity of the peritoneum* were a few ounces of clear yellow fluid. There was no appearance of recent inflammation. The surface of the peritoneum, in general, was pale; but in both iliac fossæ it was very extensively ecchymosed, the blood lying, apparently, both in and under the serosa. Ecchymoses, in smaller numbers, existed in Douglas' space, on the peritoneal surface of the bladder, and in the mesentery of the sigmoid flexure and lower parts of colon on both sides. Uterus lay considerably to the right side.

In removing the sternum, the *venæ innominatæ* were cut. A few drops only of pinkish watery blood flowed from the wounded vessels.

Lungs collapsed badly; *pleuræ* were absolutely free from adhesions, pale, not ecchymosed, and the cavities contained only a few drops of serous fluid.

Pericardium, free from adhesion or other sign of inflammation, contained about an ounce of clear yellow fluid. Parietal pericardium free from ecchymoses. On left ventricle, near the base, a few small subpericardial extravasations. *Heart* slightly enlarged, soft, flabby, uncontracted.

Subpericardial fat in considerable quantity. White spots (spots of Baillie) on anterior and diaphragmatic surfaces of right ventricle. The cavities of the heart on each side contained a small quantity of dark-coloured blood, mostly fluid, but partly coagulated. The coagula were in part decolorised, and lay loose in the cavities of the ventricles. The fluid blood, collected and allowed to stand, quickly separated into a dark red sediment and a clear reddish serum. The bulk of the former was to that of the latter as about 1 to 2. No distinct layer of white corpuscles was formed on the surface of the red. The blood, which was removed fluid, did not at any period after removal show a tendency to coagulate. The whole quantity collected from the heart and great vessels was very small.

Auriculo-ventricular orifices of normal size. The cavities of the heart were slightly dilated, and the walls, specially that of the left ventricle, were somewhat thickened. The muscular tissue of the walls very anæmic, of pale yellowish-brown colour, but of firm consistence. There were no ecchymoses in the thickness of the muscular walls or under the endocardium. On the muscoli papillares of the left ventricle were a few opaque yellow spots and streaks. Elsewhere no appearance of fatty degeneration. Valves on right side healthy. Mitral valve presented, on its anterior curtain, some opaque and thickened spots of atheroma. Aortic valves slightly thickened. All valves perfectly competent.

Aorta dilated, inelastic, atheromatous. This change was most marked in the abdominal portion, where the vessel passed (and may be supposed to have been stretched) over the convexity of the lumbar vertebræ. Here, on the posterior side of the tube was a patch about $1\frac{3}{4}$ -inch long by 1 inch broad, where there was calcification and breach of the inner coat. The large vessels coming off from the aorta were also dilated and atheromatous. There was an irregular right subclavian artery, which, coming off from the arch beyond the origin of the left subclavian, passed to the right behind the œsophagus.

Lungs.—Upper lobes remarkably dry and bloodless, of a mottled grey colour, and emphysematous, particularly along the edges. Lower lobes, specially that of right, of a pale pinkish colour. From the section a large quantity of clear frothy fluid could be expressed (œdema). Vessels contained very little blood. Bronchi pale. Lungs were of remarkably light weight.

Bronchial glands, dark coloured, of normal size and firm consistence.

Œsophagus healthy.

Spleen, externally of a dark greenish-black colour, becoming a reddish-purple after exposure to the air. The capsule was thickened irregularly. The convex surface of the spleen was turned forwards, and adherent by about half its surface to the under (posterior) surface of the left lobe of

the liver by old firm adhesions. Section of spleen, dark coloured. Malpighian bodies, few, small, and indistinct. Pulp appeared in small quantity, and looked dry and atrophic. Fibrous tissue abundant. Consistence of whole organ flabby but tough. Dimensions—length, 12·5 cm.; breadth, 7 cm.; thickness, 3·5 cm.

Kidneys surrounded by a large quantity of yellow fat. Capsule separated readily; surface of kidney smooth, of a dark greenish-black colour uniform on all parts, and altogether different from the green colour so frequently seen on anterior surface, and due to apposition with the colon. On careful examination the surface could be seen to be marked up into small polygonal spaces, each having a darker centre and a somewhat lighter-coloured periphery, the whole having an acinose appearance, in some degree resembling the surface of the liver. In some places the stellate veins were apparent as fine streaks of a pale pink colour. The appearance on section was very remarkable. The pyramids were very anæmic, of a yellowish-white colour; from their bases the pyramids of Ferrein, also of a pale colour, passed off into the cortex, while the portions of the latter between these were everywhere of the same dark colour as the surface. In fact, with the naked eye it was clear that the pigmentation was confined to the convoluted tubes—an observation which, as will appear below, was confirmed by microscopic examination. The appearances were identical in the two kidneys.

The mucous membrane of the renal pelvis was pale. In no part of the kidneys or their capsule could any ecchymoses be found.

Bladder contained about 6 oz. of dark-coloured somewhat turbid urine. Mucous membrane pale and healthy.

Supra-renal capsules presented nothing abnormal.

Duodenum contained a turbid yellow fluid, which also existed in small quantity in the *stomach*. The coats of the latter viscus were very thin, particularly the mucosa. Common *bile-duct* free. *Liver* very long, particularly the left lobe, which stretched into the left hypochondrium and was adherent to the spleen. Right lobe extended a couple of fingers' breadth below arch of ribs; surface smooth; section remarkably bloodless; acinose structure indistinct. Except anæmia, the organ presented no structural change. Gall bladder contained some ounces of dark-coloured bile.

Small intestine contracted, and, with the exception of some mucus, empty. Solitary glands not apparent. Peyer's patches very distinct; the follicles being of a dark grey colour, but not enlarged.

Large intestine contained a good deal of fæces of normal colour and consistence. Mucous membrane of intestine throughout, pale and free from ecchymoses.

Mesentery loaded with fat. Mesenteric glands not enlarged.

Pancreas presented nothing abnormal.

Uterus healthy. *Ovaries* atrophied. On left side, at orifice of Fallopian tube, were three or four small cysts, about the size of peas, containing a clear fluid.

Vagina healthy.

Muscles anæmic, but not otherwise altered; bulk of muscles not remarkably reduced.

Medulla of sternum, ribs, and lumbar vertebræ, of soft uniform consistence, and reddish-brown colour. The cancelli seemed larger and more numerous, and the bone trabeculæ slighter and fewer than normal. The medulla in the left femur resembled that in the spongy bones. There was no trace of yellow marrow.

Microscopic examinations were made of the blood, spleen, bone marrow, kidneys, and heart.

In the *blood* the same variety in shape and size of the corpuscles was found as had been observed before death. Careful examinations of a great number of preparations failed to detect a single nucleated red cell. Many cells were oval and larger than the normal corpuscles. The following are some measurements of these oval cells:—0·0113—0·0075 mm.; 0·0125—0·0062 mm.; 0·0125—0·0087 mm. Others were about the normal size, and a very large number were much smaller than these, and spherical—many of them not exceeding 0·0025 mm. in diameter.* Besides this variety in size, there was the greatest possible want of uniformity in shape. Some corpuscles were the usual flattened biconcave discs, but these were a minority; many were oval, with smooth contours; others spherical—these generally of the smaller kind; while others were of quite indescribable forms, presenting all kinds of projections from their edges, and of irregularities of surface. There was not the slightest tendency to cohesion of corpuscles with one another. The white corpuscles were few—seldom more than one or two in a field (Hartnack, §). They did not offer any abnormal appearance.

Fragments of the fresh *spleen* gave numbers of blood corpuscles like those above described, and the usual elements of the spleen tissue, lymphoid corpuscles, and the peculiar endothelial cells of the veins. No nucleated red cells, and no blood corpuscle-holding cells were found in numerous specimens examined.

The *bone medulla* presented similar characters in all the four bones examined. It was seen to consist of coloured and colourless cells. The latter varied much in size. Some were smaller than white blood corpuscles, others were 0·0250 in diameter, and transitional forms of all sizes

* Max Schultze gives the diameter of normal corpuscles as 0·008—0·010 mm. He describes small, spherical, coloured bodies as occurring in the blood of healthy men in variable numbers, and having a diameter of from 0·005—0·006 mm. In normal blood there are usually no such small bodies found as those described above. *Archiv. f. Mik. Anat.* I., 35.

occurred abundantly. These cells were generally spherical, but some were oval, and a few irregularly shaped. Their protoplasm was granular, generally coarsely so, and each cell contained one or more nuclei, visible without the use of reagents. These were less coarsely granular than the surrounding protoplasm, distinctly double contoured, and contained one or more nucleoli. The shape of the nuclei was generally round or oval, but sometimes constricted in the centre. The position of the nucleus in the cell was usually excentric. Two nuclei in one cell were not uncommon. A greater number than two was rare. Cells containing "budding nuclei" (*cellules à noyaux bourgeonnants*)* were not seen either in the fresh marrow, or after treatment with dilute alcohol and picocarmine. Myeloplaxes, also, were not met with, notwithstanding the very large number of preparations examined.

The coloured cells were of two kinds, nucleated and non-nucleated. The latter, in part, resembled those already described as occurring in the blood; but the very small particles were less numerous in the medulla. On the other hand, cells larger than any found in the blood existed here; and cells constricted in the middle were not uncommon. The nucleated cells, also, differed much among each other. The greater number were spherical or oval. They contained nuclei of two kinds, coloured and uncoloured. The coloured nuclei were of very finely granular appearance, without nucleoli. They were round or oval, and lay generally excentrically. Each cell contained, as a rule, only one nucleus, but two or even three sometimes occurred, and then the individual nuclei were smaller than when only one was present. The following are some measurements of red corpuscles and their nuclei:—0·0150, nucleus 0·0075; 0·0162, nucleus 0·0100; 0·0162—0·0100, nucleus 0·0062—0·0050. Besides these corpuscles with coloured nuclei, were others whose nuclei were uncoloured, much more distinctly granular than the coloured nuclei, and in general larger, as a rule spherical in shape, and in many cases surrounded more or less completely by a thin zone of protoplasm also uncoloured. In fact, these nuclei resembled in every respect those of the smaller colourless cells of the medulla. They always lay very excentrically in the red cell, generally touching the edge, which they often seemed to bulge outwards, and, in a great many instances, the nucleus, with its protoplasm, projected distinctly from the red cell, being only partially contained within its substance. This appearance was seen so frequently and so regularly, as to put altogether out of the question an accidental adhesion of red and white cells; and, besides, the careful use of the fine adjustment, and the different views got by making the object roll, proved beyond doubt the actual inclusion of the one body within the other.

Large colourless cells containing red corpuscles, in numbers varying

* Ranvier. *Traité technique d'Histologie*. P. 322.

from one to nine, were very numerous. Endothelial cells, singly or coherent, were not unfrequent, and almost invariably contained a number of black pigment grains grouped about the nuclei. Very few fat-holding cells were seen, even in the medulla of the femur. Long octahedral crystals were met with in the medulla of the spongy bones, but not in that of the femur.

Sections of the *kidneys* fresh, and after hardening in alcohol, showed that the pigment to which the organs owed their dark colour existed only in the convoluted tubes. It occurred in minute grains, which lay in the epithelial cells, and were most numerous in the inner portion of each cell or that turned towards the lumen of the tube. In fresh preparations it could be seen that the coloured grains lay more or less regularly in lines, holding a radial direction to the axis of the tube. The pigment was strictly confined to the convoluted tubes; the pyramids, the medullary rays, and the Malpighian dilatations were perfectly free. As a proof of the good state in which the kidneys were obtained, it may be mentioned that, in scrapings from the freshly-cut surface, long masses of epithelium, from the different portions of the tubes, were obtained, in which the character of the cells peculiar to each was distinctly visible—notably the rod epithelium of the ascending portion of Henle's loops. In every respect the kidneys appeared perfectly healthy.

Sections of the fresh kidney placed in water, and freely exposed to the air and light, lost their colour in the course of a few hours. Mounted in salt solution and covered with thin glass, but not cemented, and placed in the moist chamber, they preserved their colour upwards of forty-eight hours; those parts of the sections which projected from under the cover glass fading sooner. A pretty strong solution of potash did not affect the colour which, even after the sections had become transparent and pulpy, was still distinct. Acetic and hydrochloric acids bleached the sections at once. Ether and alcohol did not immediately affect the colour. Pieces of kidney which lay for a week in spirit were considerably paler than at first; but the difference between the two portions of the cortex was still distinct. Pieces which were placed in Müller's fluid lost their colour in a few hours. Under the microscope it was not very easy to follow the action of acids on the granules, which at once became pale when they came in contact with the reagent, and so indistinct that it could not positively be said whether they were dissolved or not. It appeared to me, however, that the solution, if it did occur, took place slowly.

Sections of the kidney hardened in alcohol, and which had nearly lost their colour when treated with a solution of ferrocyanide of potassium and hydrochloric acid, at once became a bright blue tint, the colour being due to blue granules, accurately limited to the epithelium of the convoluted tubes. Sections placed for twenty-four hours in dilute hydrochloric acid, gave no colour when subsequently treated with ferrocyanide of

potassium. The acid in which they had lain assumed a blue colour with the reagent.

The muscular tissue of the *heart* was generally healthy, excepting a slight degree of brown degeneration. The granules were few, and confined to the immediate neighbourhood of the ends of the nuclei. In the opaque yellow portions of the papillary muscles the tissue was in a complete state of fatty degeneration.

The microscopic examination of the *bile* was without result, granular masses, mucus and epithelial cells only being found.

There are several points in this case which call for comment. The account of the origin of the illness differs from that usually given. All writers agree in stating that progressive pernicious anæmia begins very insiduously, so that the patient cannot tell when the departure from health first takes place. Here, on the other hand, the disease is said to have commenced suddenly. I think, however, much weight cannot be placed on this, for when we take into account the extraordinarily unobservant character of the lower orders of Irish patients, we may readily suppose that this woman's health had been failing for some time, and that it was only when called on to make an unusual effort that her attention was directed to her feeble condition. As to the story of her becoming of a black colour, I regard it as altogether apocryphal. She may have been jaundiced; there are cases recorded where jaundice has been an early symptom.^a But it is more likely that her companions mistook her pallor for jaundice, and that some talk about "black jaundice"—a disease supposed by the Irish to be peculiarly fatal—may have put the idea into her head that as she was very ill she ought to be black. She stated that, although her fellow-servants told her she was becoming black, she never had the curiosity to look in the glass in order to confirm their statements.

When the patient came under my care I formed the opinion from the first that she was suffering from one of two diseases, either pernicious anæmia or carcinoma, most probably of the stomach. I confess I at first inclined to the latter view, and for the following reasons:—1. The great rarity of pernicious anæmia in this country. 2. The age of the patient—the disease usually attacks persons in the prime of life, from 20 to 40.^b Quinke^c records the only

^a Case of Idiopathic or Progressive Pernicious Anæmia treated Unsuccessfully by Phosphorus. By J. B. Bradbury. Brit. Med. Jour., 1876. II., 848.

^b Immermann. Ziemssen's Handbuch d. spec. Pathologie u. Therapie XIII. I., 622.

^c Volkmann's Sammlung klinischer Vorträge. No. 100.

instance I am acquainted with occurring in a child, aged 11, and two cases of persons advanced in life, one aged 56, the other 59, both women. Scheby-Buch^a gives an instance in a woman aged 60—this is, so far, the greatest age at which progressive anæmia has been observed. 3. The absence of fever; fever of an irregular continuous type has been present in most of the cases hitherto recorded (Immermann); it was, however, absent in some of Quincke's cases, and in mine, notwithstanding repeated observations, a higher temperature than 99° F. was never noticed. 4. The absence of œdema. 5. The absence of hæmorrhages. 6. The severe pain in the abdomen. Dyspeptic symptoms and vomiting have been noticed in almost all recorded cases; but, so far as I know, severe and long-continued pain has not been before observed. Unless it can be explained by the adhesion of the liver and spleen, I cannot account for it.

On the other hand, against the diagnosis, carcinoma, were—1. The absence of tumour; but from the extreme sensitiveness of the patient, her great dislike to be examined, and from the remarkable irritability of the abdominal muscles,^b a thorough examination of the abdomen presented great difficulties; and, 2. The absence of hæmorrhage from the stomach. As the case went on, my opinion inclined more and more towards pernicious anæmia, and after the examination of the blood, and still more when the petechiæ appeared, there was no longer room for uncertainty. There can be no doubt that if the eyes had been examined, and if the blood had been investigated at an earlier period, the diagnosis might have been much sooner made. It was not either from ignorance or carelessness on my part that this was not done, but purely from feelings of humanity. The patient's condition was, from the first, so deplorable and so manifestly hopeless that I refrained from pushing my examination further than was absolutely essential.

It can scarcely be said that treatment effected much in this case. All attempts to give medicine or nourishment failed in consequence of the uncontrollable irritability of stomach. All the usual methods to check this were resorted to without success. Iron was given at first, but seemed to disagree, and was stopped for some two or three weeks before her death. Latterly she got opium in pills at night, and subcutaneous injections of morphia when in much pain.

^a Virchow und Hirsch. Jahresbericht, 1876. II., 264.

^b Exaggerated muscular irritability was noticed also in Bramwell's case. *Med. Times and Gazette*, Sept. 22, 1877. P. 323.

It would have required a stronger faith in therapeutics than I possess to have made me resort either to transfusion or to phosphorus in this case. The success of the first mode of treatment has not been encouraging. All the cases in which Quinke employed it died; and in case 9 (and perhaps case 3) the transfusion was the cause of hæmorrhages in the brain, heart, stomach, retina, &c., &c.^a Indeed, the only case out of the ten recorded by Quinke which recovered was treated with bicarbonate of soda and gentian, and subsequently with iron, and can hardly be said to owe his recovery to the medicines he received. Gusserow^b has found transfusion ineffective even in prolonging life; and Glynn,^c in detailing the particulars of a case "successfully treated by immediate transfusion," records the patient's death.^d

The treatment by phosphorus can scarcely boast of greater success. Bradbury^e records an unsuccessful instance, Bramwell's^f most interesting case, which did recover, grew worse (retinal hæmorrhage, vomiting, diarrhæa, fever, increase of dropsy) while taking phosphorised cod-liver oil, and in Pve Smith's case^g the improvement was but slight and transitory. Those cases which recover, supposing them to be of the same nature as those which die, are those whose digestive functions are unimpaired. In Quinke's one successful case the appetite was "*ziemlich gut*," and in Bramwell's, although vomiting and diarrhœa had occurred at an early period, when the patient was admitted his appetite was good, and there was no thirst.

Most intimately connected with the subjects of prognosis and treatment is the question whether there is any such disease as progressive pernicious anæmia, or whether those cases which were described by Addison^h and Wilks,ⁱ and to which in later times attention has been specially directed by Biermer and Gusserow, are merely what we may call ordinary anæmia, symptomatic of various conditions with which we are already well acquainted. This latter

^a Pepper (American Medical Journal, Oct., 1875, p. 326) also has seen dangerous symptoms follow transfusion in this disease.

^b Immermann. Loc cit. 653.

^c Lancet, 1877. I., 454.

^d Strümpell's case, which recovered after venesection to 120 grams, and transfusion of 300 grams, is admittedly not one of pernicious anæmia. Centralblatt, 1877. 174.

^e Brit. Med. Jour., 1876. II. 848.

^f Medical Times and Gazette, Sept. 22, 1877. 323.

^g Virchow's Archiv., LXV. 511.

^h Works (Syd. Soc. Edit.). 212.

ⁱ Pathological Anatomy. 2nd Edit. 636.

is the view taken by Quinke, who, from the inconstancy in the condition of the blood, and in the appearances found after death, argues that—"We have not to do here with a single diseased state, but that pernicious anæmia, like anæmia in general, is the product of the most different morbid processes, and represents, as it were, the highest development, the ultimate stage of anæmia. It may, in a certain sense, be compared with uræmia, icterus, or septicæmia, which, although offering typical forms of disease, may, nevertheless, develop out of the most different fundamental conditions.—*Loc cit.*, 807.

It appears to me, however, that an unprejudiced examination of the cases which have been published shows conclusively that in a large number of them the anæmia cannot be explained by any of the usual causes of impoverishment of the blood. It is true that many of the patients have lived in very poor circumstances, but others have never known want; the digestive troubles which would impair nutrition are always secondary to the anæmia, and are manifestly the effect, not the cause, of the latter; and the accumulation of fat observed by all writers goes far to prove that the anæmia is not due to starvation from insufficient food or imperfect digestion. Again, while some patients have suffered from wasting discharges, the greater number have never done so; and if the disease is frequent in puerperal women, on whose resources there is a large drain, it is sufficiently common in men and non-pregnant women to show that the connexion with child-bearing is not essential. The *post mortem* examination fails to reveal any of the known causes for anæmia. There is no carcinoma, no phthisis, no trace of syphilitic or malarial disease; yet, nevertheless, there must be a pathological anatomy. To speak of an essential anæmia as if the whole change resided in the blood is absurd. The blood does not make itself, it does not consume itself, and it is to the organs of its formation and consumption that we must look for the explanation of its changes.

This leads me to speak of the pathological anatomy of pernicious anæmia, on which dark subject within the last few months a little light has begun to dawn. The morbid condition which was first noticed was fatty degeneration of the heart. This was observed by Addison, and has been found very commonly by all subsequent observers; yet it is variable in degree, and is not always present. Quinke found it absent in four cases; and, while Wilks says it shows itself as a mottling of

the inner surface of the walls of the heart, Orth^a finds the more extreme form in which the walls are degenerated in their entire thickness. In the two cases which I have myself seen, the fatty change was confined to the inner aspect of the heart. We have every reason to suppose that this fatty degeneration of the heart, as well as that which has occasionally been found in the capillaries and some of the viscera (liver and kidneys), is due to the anæmia, and has no share in causing it. Fatty heart is found in other conditions of impoverished blood, as in chlorosis,^b and has been produced experimentally in animals made anæmic by repeated bleedings.^c So the hæmorrhages are probably due either to embolism or to yielding of vessels whose nutrition has undergone fatty or other change in consequence of malnutrition. The spleen and lymphatic glands are universally admitted to be free from disease, but recently an allied organ—namely, the medulla of the bones—has been found in a remarkably altered state. This change altogether escaped the earlier observers. Immermann,^d writing in 1875, says:—"Spleen, lymphatic glands, and bone medulla present neither hyperplasia, nor, except pallor, anything abnormal." Quinke^e (1876) states that nothing abnormal was to be found in the medulla. Pepper,^f however, had examined the medulla of the radius in a fatal case, and found evident hyperplasia with diminution of fat, and Scheby-Buch, in his second case, found numerous groups of lymphoid cells in the medulla of the bones. Pepper fully recognised the importance of this change—so much so, indeed, as to maintain the theory that pernicious anæmia is to ordinary pseudo-leukæmia or adenia as the medullary form of leukæmia is to the splenic or lymphatic form. Fede^g also found in a somewhat doubtful case, in which the spleen was much enlarged, swellings on the heads of the ribs, with hyperplasia of the medulla, which contained many polynucleated cells and blood-corpuscle holding elements. But it is Cohnheim^h who has been the first to give a tolerably

^a Compendium d. pathologisch-anatomischen Diagnostik. 115.

^b Virchow. Ueber die Chlorose. 17.

^c Perl. Ueber den Einfluss der Anämie auf die Ernährung des Herzmuskels. Virchow's Archiv. LIX., 39.

^d Loc. cit. P. 631.

^e Loc. cit. P. 802.

^f Progressive Pernicious Anæmia, or Anæmatosis. American Journal of Medical Sciences. October, 1875. P. 313.

^g Centralblatt. 1875. 780.

^h Erkrankung des Knochenmarkes bei perniciöser Anämie. Virchow's Archiv. Oct., 1876. P. 291.

detailed account of the medullary changes, and his description agrees in the main with what has been since found by Osler and Gardner^a and myself. Cohnheim found the medulla in all the bones, long as well as spongy, of a red colour with absence of fat. The tissue consisted of—1. Colourless marrow-cells from the size of a lymph corpuscle upwards, with one or two nuclei; few giant polynucleated cells, and still fewer blood corpuscle-holding cells; 2. Coloured cells; *a.* Ordinary blood corpuscle; *b.* Spherical non-nucleated bodies varying in size from that of an ordinary red corpuscle to double the size of a white corpuscle; *c.* Nucleated spherical or oval cells of variable size, and of homogeneous structure; the nuclei, also coloured, were round or oval, the former granular, the latter homogeneous. Each cell contained one or two nuclei whose size bore no relation to that of the cell in which it lay. Similar cells were found in the liver and spleen, and (*post mortem*) in the blood. Osler and Gardner examined the fibula, as well as the spongy bones (sternum, vertebræ, ribs). It is unnecessary to describe what they found, as their description tallies almost exactly with that of Cohnheim. I have fully described above the appearances which were found in my case. So far as regards the colourless cells and the non-nucleated coloured elements, my observations agree with those of Cohnheim, except that the large non-nucleated bodies in my case were more frequently oval than spherical. My nucleated red cells were distinctly of two kinds—one had coloured nuclei, and agreed with those described by Cohnheim; the nuclei in the others were uncoloured, and the whole element agreed pretty closely with the transitional forms between red and white corpuscles which were described some years ago by Neumann^b and Bizzozero^c as normal constituents of the red marrow, and which the first-named author found greatly increased in cases of those chronic diseases which cause general marasmus. Neumann and Bizzozero supposed that colourless lymph corpuscles become coloured blood discs by the formation of hæmoglobin in the protoplasm of the cell, the change beginning at the peripheral part, while the nucleus disappears by undergoing disintegration into granules. But in many of the cells found in my preparations it was impossible to avoid the conclusion that the nucleus with its surrounding uncoloured protoplasm was either entering or leaving the coloured

^a Ueber die Beschaffenheit des Blutes und Knochenmarkes in der progressiven perniciosen Anämie. Centralblatt, 1877. 258.

^b Henle und Meissner. Jahresbericht, 1868. 13.

^c Henle und Meissner. Jahresbericht, 1869. 13.

portion of the cell. Bizzozero seems to have noticed somewhat similar forms, but does not decide whether they are due to *post mortem* change, or whether they represent a method of getting rid of the nucleus by extrusion. It occurred to me that the plasticity of the red elements observed in my case, which allowed these bodies, both in the blood and medulla, to take the peculiar forms which have been described, might also allow the small colourless cells to be pressed into and invaginated in their substance, as Steudener^a has described in the case of the cells of cancer. I cannot suppose that the white corpuscles were taken up by the red by virtue of any active movements of the latter, as in the blood examined during life no amœboid movements were seen in the variously shaped red corpuscles, although the white cells were in lively motion. It may be added that the cells in question were larger and far more numerous than in the normal medulla even of young bones.

The blood corpuscle-holding cells appear to have been more numerous in my case than in any other recorded. Cohnheim found them scantily, Osler and Gardner found them abundant only in the vertebræ, while they were absent from the fibula and clavicle. In all my preparations they were very numerous. Neumann considers these cells as pathological, since he has met with them only in cases of typhus, but Bizzozero, while admitting their great frequency in this disease, states that he has found them when death has taken place from other causes, and also in the medulla of healthy animals (dogs). It is in typhus, too, that these cells are found in great abundance in the spleen.^b There can be little doubt that the included corpuscles, which are often reduced to little grains of hæmoglobin, are undergoing destruction, and the number of blood corpuscle-holding cells may consequently be taken as a measure of the rapidity with which this disintegrating process is taking place.

The crystals noticed in the medulla are found in the marrow, spleen, and some other parts in cases of leukæmia, and in healthy marrow some time after death. Krause^c describes them as double pyramids, whose angles are 18° and 162° , having a feeble lustre, being singly refracting, soluble in water, very flexible, and readily breaking into fragments. Nothing certain is known as to their composition. Krause supposes them to be composed of a mucinous substance in a solid form.

^a Archiv. f. mikroskopische Anatomie IV. 188. Taf. XIV.

^b Orth. Compendium. 178.

^c Allgemeine Anatomie. 70.

The appearances found in the kidneys are of great interest both pathologically and physiologically. There can be no doubt that the granular pigment contained in the epithelium was undergoing elimination, and equally little that the high colour which the urine presented during life was due to this pigment, while the distinct iron reaction which was obtained showed conclusively that the pigment was derived from the blood. We can thus, as it were, see the corpuscles undergoing destruction in the medulla of the bones, and the products of their destruction being cast out of the body through the kidneys. It is a matter of the greatest regret to me that the urine was not examined for iron; and one of the main objects I have had in the publication of this case has been to direct the attention of others to this as well as to the other lacunæ in my observations, in order that these may be the sooner filled up.

The strict limitation of the pigment to the epithelium of the convoluted tubes speaks strongly in favour of Bowman's theory of the secretion of urine. We have in fact here performed by nature the very same experiment as that made by Heidenhain* with indigo carmine, and with the same result, the observations in each case showing that the constituents of the urine are, at all events as regards some of them, eliminated through the epithelium of the convoluted tubes, and not through the malpighian tufts, as maintained by Ludwig.

Quincke^b has found in some of his cases in the liver (outer parts of lobules), pancreas, and kidneys, similar black iron holding pigment to that which occurred in my patient, but the distribution in the kidney, although similar, was not so regular and universal as in the instance now recorded. Besides, in Quincke's cases there was the suspicion that the iron was in great part, at least, derived from medicine. I regret that I was not acquainted with Quincke's observations when I made my autopsy. The liver and pancreas were unstained in my case, and were consequently not tested for iron. In Quincke's cases the black staining occurred where the viscera were in contact with the intestine. In the kidneys of my patient no such localisation of colour existed. Quincke found very large quantities of iron in the liver and kidneys of some of his cases. In one liver 2·1, in another 0·6 per cent. of the dried organ was found to consist of metallic iron, and from the dried kidney 0·32

* Archiv f. mik. Anat. X., 1.

^b Loc. cit. 817 (Auch in der Niere fanden sich feinkörnige eisenhaltige Massen (Eiweisskörper) in den Epithelien gewisser Gruppen und Züge von gewundenen Harnkanälchen, während die Glomeruli frei waren).

per cent. of iron was obtained. In 50 grams of undried kidney I found 0.0176 of metallic iron.*

With regard to the blood itself, my observations add nothing new. The same fewness of red corpuscles and irregularity in their shape and size, as has been observed so often, were noticed. Like Osler and Gardner I failed to detect nucleated coloured cells. Eichhorst^b has recently stated that in all cases of pernicious anæmia the diagnosis may be made by the presence in the blood of a large number of very small red corpuscles; but such a condition of microcythæmia has been observed in other diseases, and in two fatal cases of pernicious anæmia recorded by Grainger Stewart^c this condition was absent, while Lepine has found the corpuscles remarkably large. I should myself be inclined to place more weight on the great variety in shape of the corpuscles, as observed by Osler, Bradbury, Quinke, as well as by myself, than on the presence of the small bodies of Eichhorst. I did not see the separation of the colouring matter from the rest of the corpuscles described by Mackern and Davy.^d The zooid and œcoid view of the structure of the corpuscle is a rather uncertain foundation on which to build a theory, and it must not be forgotten that, as pointed out by Ranvier,^e appearances resembling the withdrawal of the colouring matter from portions of the corpuscle are often due merely to irregularities on the surface of the latter.

Finally, this case, although more calculated to raise questions than to answer inquiries, would seem to show that in pernicious anæmia a definite, but still far from understood, lesion exists in the bone medulla; that there probably an imperfect formation, and almost certainly an increased destruction of the red corpuscles, takes place, and that the products of this destruction, at all events in great part, pass into the urine.

Cases of anæmia must be divided according as this lesion is present or absent—and while those in which it is absent may find their explanation in what we may call the ordinary causes of impoverishment of the blood, the others must be placed in the category of diseases of the blood-forming organs, of which, up to the present, leukæmia represents the best-established instance.

* I am much indebted to Prof. Reynolds, who not only allowed this analysis to be made in his laboratory, but performed the greater part of it himself.

^b Ueber die Diagnose der progressiven perniciosën Anämie. Centralblatt. 1876. 465.

^c Brit. Med. Jour. 1876. II., 40.

^d Lancet. May 5th, 1877. 642.

^e Traité technique. P. 193.