The spleen and some of its diseases : being the Bradshaw lecture of the Royal college of surgeons of England, 1920 / by Sir Berkeley Moynihan.

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THE SPLEEN

AND SOME OF ITS DISEASES

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BEING

The Bradshaw Lecture

of the Royal College of Surgeons of England,

1920.

BY

SIR BERKELEY MOYNIHAN,

LEEDS.

WITH 13 FULL-PAGE DIAGRAMS

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TO

THE PRESIDENT

AND MEMBERS OF THE COUNCIL

OF THE ROYAL COLLEGE OF SURGEONS

OF ENGLAND

PREFACE.

THIS book contains the material upon which I based the Bradshaw Lecture delivered at the Royal College of Surgeons of England in December, 1920.

The surgery of the spleen has hitherto enjoyed only a very restricted field. The removal of the enlarged or injured organ, or of the normal organ whose pedicle has twisted, or the opening of abscesses or cysts within the spleen, has been all that it was possible to do.

But in recent years the part played by the spleen in many other diseases has gradually been recognized, and an extension of surgical treatment to cases of cirrhosis of the liver, pernicious anæmia, hæmolytic jaundice, etc., has taken place.

We are beginning to realize that the spleen, too, plays its part, perhaps a considerable one, in the etiology of diseases whose most conspicuous symptoms are evoked by associated or consecutive affections of other organs. We can no longer consider diseases which affect one abdominal organ as being restricted to that organ. In the provocation and in the development of the morbid affections of any of these viscera, many of them may take a share. The spleen, which has been little regarded in this connection, may now justly claim a measure of attention.

I am much indebted to Dr. Gruner for his help in the preparation of the diagrams, and of the list of references; and, generally, for his wise counsel. He is in charge of my private laboratory, and the interstices of my surgical life are filled in by visits to him there, and by most helpful discussions at all times.

BERKELEY MOYNIHAN.

LEEDS, *St. Patrick's Day*, 1921.

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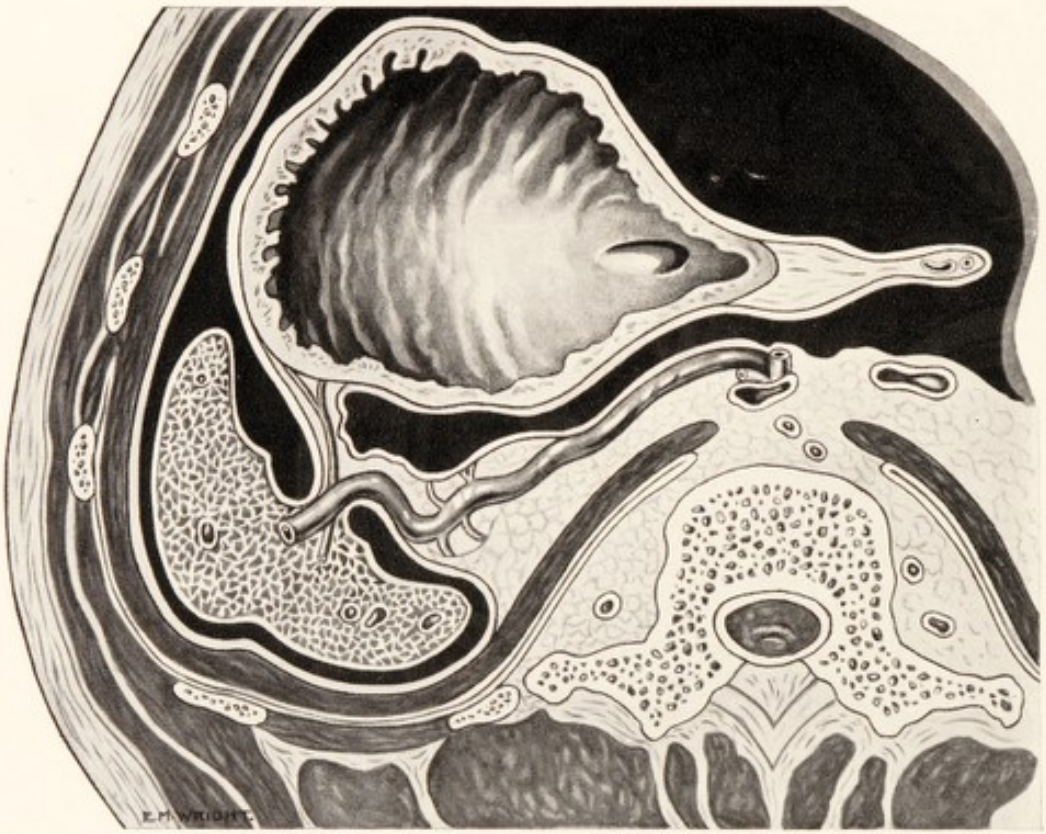

THE SPLEEN: ITS PEDICLES AND BLOOD-VESSELS

THE SPLEEN
AND SOME OF ITS DISEASES

CHAPTER I.

ANATOMY OF THE SPLEEN.

THE SPLEEN is almost entirely covered with peritoneum, and is situated behind the fundus of the stomach, being covered by the lower ribs. Its outer or phrenic surface is convex and lies against the diaphragm, which separates it from the ninth, tenth, and eleventh ribs. In its upper part it is separated from the costal wall by the left pleura and lung. The gastric surface is concave and rests upon the fundus of the stomach. Within the confines of this surface lies the hilum for the entry and departure of the splenic vessels. The renal surface is applied to the upper and outer part of the anterior surface of the left kidney, and usually overlaps the summit of the suprarenal capsule.

The basal end of the spleen bears a varying relationship to the splenic flexure of the colon and tail of the pancreas. The extent to which the tail of the pancreas comes into relationship with the spleen may vary considerably; it very frequently encroaches on the gastric surface in its lower part as far forward as the hilum.

The peritoneal attachments of the spleen are three (*Plate I*):—

1. The lienorenal ligament, a double fold of peritoneum which passes from the intermediate border of the spleen to the anterior surface of the left kidney. This peritoneal attachment only partakes of the nature of a ligament when the spleen is drawn forward; *in situ*, the two folds forming it pass off to the right and to the left on the posterior abdominal wall, the tail of the pancreas and the splenic vessels separating them widely.

2. The gastrosplenic omentum is a longer and more delicate fold which passes from the hilum of the spleen to the fundus of

the stomach: between its layers run the left arteria gastro-epiploica and the vasa brevia, branches of the splenic artery. This fold is continuous below with the gastrocolic omentum.

3. The lower end of the spleen is supported by a peritoneal shelf, the costocolic ligament, formed by a fold of peritoneum passing from the diaphragm opposite the tenth and eleventh ribs to the splenic flexure of the colon.

The spleen receives its blood-supply from the splenic artery, a branch of the cœliac axis. This vessel breaks up between the layers of the lienorenal ligament into five or six branches which enter the hilum of the spleen. The blood returning from the spleen is poured into the portal system through the splenic vein.

The spleen may be marked out upon the surface of the body by drawing two horizontal lines from the spinous processes of the ninth dorsal and first lumbar vertebræ; these are joined by a vertical line 4 centimetres (1½ inches) to the left of the mid-line of the body, and another corresponding with the left mid-axillary line. Within this quadrilateral space the spleen lies obliquely beneath the ninth, tenth, and eleventh ribs.

Such are the bald anatomical facts about the spleen. The connections of the organ with the sympathetic system are intimate; they are of an importance and a significance that as yet we are quite unable to measure. The vascular arrangements of the gland are interesting. Why is the splenic artery in its tortuous course so different from all other arteries? What is the importance to be attached to the junction of the tributary veins with the splenic vein; and is the order in which they join an index of the processes that go on in the splenic blood before it reaches the liver? The vein from the tail of the pancreas, which is the first to send its current into the splenic vein, comes from that part of the gland which is richer in the islands of Langerhans than any other. The blood from the hind-gut goes into the splenic vein before that which flows from the mid-gut. Does the current in the portal vein from these many tributaries observe any degree of separation of their constituent parts, or is there a free mingling of all the blood from all the tributaries? The relation of the spleen to the lymphatic system deserves inquiry. Though the spleen is associated primarily with this system, it differs materially from any other organized part of it. It is not a modified lymphatic

gland, nor is it an aggregation of lymphoid tissues, like the tonsil or the lymphoid element of the vermiform appendix. Though it is evolved out of the great tract of lymphoid tissue along the alimentary canal, it is, on the one hand, deliberately developed outside the physically restrictive influence of the wall of the canal; and on the other, it acquires and retains vascular and nervous connections which can only mean a careful provision for functional association with a certain part of that canal and the organs which developmentally owe their origin to it. The fact that every drop of splenic venous blood passes through the liver must surely be of the profoundest significance.

The spleen is not always present in man, though its absence is excessively rare. Its occasional absence is noticed in animals. In the vertebral kingdom its position is not constant. In *Protopterus annectens* it is embedded in the stomach wall; in *Siren* it extends along a great part of the intestinal canal, as does lymphoid tissue in man. In the majority of animals it is outside, but associated with, the gastric segment; but there are instances of its development in connection with the lower end of the canal, and others where it is scattered.

With the rarest exceptions the spleen is constant in man. It can be removed without apparent harm to the economy; life has been maintained, and good health experienced, for over thirty years after its loss; it lies completely outside the alimentary canal, though it is developed from the mesoblastic tissue of the mesogastrium; it is nourished by those same arteries and nerves which supply a certain segment of the canal; it has an exceedingly liberal vascular supply which comes to it along a vessel of unique appearance; its venous blood is a part of the portal system, the constituent portions of which are united in a manner significant and suggestive. Every drop of its venous blood passes through the liver. If Macalister was right when he said that the "question in modern anatomy has become not What, but Why", we may hope that the anatomists may some day help to elucidate these hidden mysteries: for it has often fallen to them to be the first to throw light into dark places, and to lead a crusade in search of truth.

CHAPTER II.

THE SURGERY OF THE SPLEEN.

It was known to the ancients, and their knowledge has been confirmed in all later times, that the spleen is not essential to life. Aristotle wrote: "It is the position of the liver on the right side of the body that is the main cause for the formation of the spleen; the existence of which thus becomes to a certain extent a matter of necessity in all animals, though not of very stringent necessity". Erasistratus took the view that the spleen was wholly devoid of use. Galen spoke of it as an organ "full of mystery". In an old English translation by Holland of the *Natural History* of C. Pliny (23 to 79 A.D.) the following statement is found: "This member hath a proprietie by itself sometimes, to hinder a man's running: whereupon professed runners in the race that be troubled with the splene have a devise to burne and waste it with a hot yron. And no marveile: for why? They say that the splene may be taken out of the body by way of incision, and yet the creature live nevertheless: but if it be man or woman that is thus cut for the splene, he or she looseth their laughter by the means. For sure it is that intemperate laughers have always great splenes".

Shakespeare speaks of both these functions of the spleen:—

> "Such fantastic tricks
> As make the angels weep; who, with our spleens,
> Would all themselves laugh mortal."
>
> *Measure for Measure*, II, ii, 121.

And, again, Maria, in *Twelfth Night*, as she ridicules Malvolio before Sir Toby, says:—

> "If you desire the spleen and will laugh yourself into stitches, follow me."
>
> *Twelfth Night*, III, ii, 72.

Of its effect upon the pace of a runner the Bastard speaks in *King John*:—

> "I am scalded with my violent motion
> And spleen of speed to see your Majesty."
>
> *King John*, V, vii, 49.

In ancient literature the statement is made more than once that the giraffe, noted for a turn of high speed, is spleenless—an interesting example, of which evidences are still to be discovered in the literature of to-day, that statements lacking in truth, capable of verification or refutation, but never so tested, are slavishly copied by one author from another. In the Middle Ages, as Brogsitter has told us, the belief in the inhibitory effect of the spleen upon the pace of runners is found in Murer's *Belagerung von Babylon* :—

> " Ich han mir lon dass milz Schnyden
> Dass ich mag laufen wegt und veer."

It is interesting to note that, if records are to be trusted, the removal of the spleen from a human being preceded the removal, for experimental purposes, from animals. The following account of the first recorded case of splenectomy is given in *The Treasure of Human Life*, by Leonardo Fioravanti, Chapter 8. A translation has been kindly made for me by Mr. L. A. Sheppard, of the British Museum.

" *Treatment of a woman whose spleen I removed.*—This same year (1549) in the aforementioned month of April, I was called to visit a Greek lady who lived near the garden of the Marquis of Terranuova. She was the wife of the Greek Captain Matio, who died afterwards in the year 1551, in the African War. This young woman, twenty-four years of age, had a very great enlargement of the spleen. It grew so large in her body that you could not conceive it larger. It caused both legs to be very badly ulcerated, and the poor woman could hardly live longer.

" Having been visited by various doctors, she was told that if she wished to recover it was necessary to remove the spleen ; that it was an easy matter, without danger, and so on. So the poor woman, who had been the most beautiful lady of that town, and a great favourite, pondered whether she wished to die or recover, and began to beg the captain, her husband, to find someone who would remove her spleen. She beggged so hard that the poor gentleman began to look for a doctor to perform such an operation, and while he was searching I was recommended to him. He came to see me at my house and took me to his home to see the lady. I saw her and talked to her, and cheered her as best I could. She asked me if I felt capable of removing her spleen. I

said 'Yes' readily, although I had never before removed one. But since then, in Naples, I have removed another, as I shall describe when I come to that place.

"So I promised to perform the operation, and having promised, every day she urged me to do so. But to tell the truth, although I had promised, I did not want to treat her for fear of making some blunder. But notwithstanding, I sent for a certain old man, of the kingdom of Naples, of a town called Palo. This old man, named Andriano Zaccarello, operated with the knife, removed cataracts and such things, and was much experienced in this profession. The old man soon came to my house, and I said to him, Dear Messer Andriano, a strange thing has come into the head of the wife of Captain Matio, the Greek—she wishes to have her spleen removed I should like to know from you if it is a thing that could be done without danger?' 'Yes', answered the old man, 'one can do it, because it is a thing that has been done many times in my life time'. 'Then do you feel capable of undertaking it?' I asked. He replied that he would do it with me, but not otherwise; so we agreed to do it.

"I went to see the lady, and made preparations with her and her husband, and having done so, went to the Justices, to give her up for dead, as is usually done.

"And having permission, we went one morning to the lady's house. The good old man took a razor and cut the flesh above the spleen, which, being cut, came out of the body. We went on separating it from the reticulum, and took it all out, and sewed up the flesh, leaving only a small opening. I dressed it with mixed oil of hypericum, incense powder, mastic, myrrh, and sarcocolla, and ordered her a drink of boiled water with ordinary honey, comfrey, betony, and holy-thistle, and every day I made her take a dose of theriac.

"So I continued to relieve her in such a way that the poor woman in twenty-four days was cured and went to mass at the Madonna dei Miracoli near the Dogana, and was safe and sound. The spleen that was removed weighed 32 ounces. It was taken to the Loggia of the Merchants, and there remained three days, when all the town saw it, and the honour of such an experiment was given to me. Wherefore the people came to me as to an oracle; and every day I debated with various people and learned many things in my subject, so that beyond the gain and experience

I learned yet many secrets, and, to tell the truth, there is no better way of learning than by going about the world, for every day one sees new things and learns various important secrets."

The veracity of this description has been challenged more than once, chiefly because of the discrepancy between the alleged bulk of the tumour and the insignificant weight of the mass removed. Simon, chiefly for this reason, suggests that the tumour was an ovarian cyst from which much fluid had leaked between the time of removal and the time of weighing. If the description is true, it is certain that earlier cases than this had occurred in the practice of Zaccarello. Baillon* very briefly mentions the successful removal of the spleen in the year 1578 by an operator whose name is not given. Rousset described, in 1581, the successful removal by Viard, on two occasions, of spleens which protruded through wounds on the left side. Two similar cases are recorded in the 17th century.

Observatio CXCV.—Cruger, Daniel. *De exciso liene ex homine, sine noxa. Miscellanea curiosa sive ephemeridum medico-physicarum Germanicium Academiæ naturæ curiosorum.* Decuriæ ii, Annut. Lertini anni M.D.C.LXXXIV. Norinbergræ, 1684, p. 378.

"A man named Scultetus, of Henickhagen, was knocked down by a rustic, and severely wounded in the left side by him with a knife. The wound made by the knife caused the prolapse of a large portion of the spleen. The man subsequently vomited, and wallowed in his own blood, and was left without any assistance during the night. In the morning, at the request of the magistrate, Nicolaus Matthias, a surgeon of Colberg, arrived, and found the unhappy man immersed in blood and the swollen spleen protruding from his body. All who were present, with the priest, saw the spleen, and were astonished at seeing so large a viscus protruding from the wound. By the aid of milk and herbs of a nature suitable for fermentation, the surgeon proceeded to tend the wound, and about sundown had the patient transferred to Colberg. On the following day a physician was called into consultation, and the surgeon showed him the swollen and protruding spleen, and inquired of him whether he should excise it. The physician, who

* *Opera Omnia Med.*, i, 183.

said that the authorities had taught that no one could live without the spleen, was averse to this being done; the blood flowing from the organs within the abdomen in large amounts would be without a proper passage for or method of exit. The surgeon, on the contrary, because the spleen was protruding considerably through the wound, said that he could not see that it was possible to replace the spleen in its proper position in the body, and that he considered it would be better that it should be removed. The patient consented to this; he turned in this critical moment of impending death, and said that he was prepared to suffer everything patiently. The surgeon then ligatured the protruding portion of the spleen with a silk cord and withdrew the entire viscus from the cavity of the body. Next, that portion where it was adherent to the body he constricted with a cord, and on the third day afterwards he resected the whole spleen, and checked the abundant hæmorrhage with styptic powder. By the employment of suitable medicaments he restored the patient to health within the space of three weeks, although there remained in the wound a small swelling resembling a hazel nut, because at that place the vessels were adherent to the divided tissues. To this day the man lives happily with his wife, not deprived of offspring, and carries on his ordinary occupation.

"The following is the testimony of an eye-witness:—

"I declare that I have seen with my eyes the spleen of a young man, age 23, projecting from a wound in the left side; that the spleen was of the usual size, and that it was detached from all its connections; I have also felt and touched the spleen with my hands.

"That on the third day after the receipt of the wound it was excised by a surgeon summoned from the town, named Nicolaus Matthias. I know, because the same surgeon held a conference with me, and brought the same spleen recently excised. The burgomaster, Edw. Kundenreichen, and the pastor, Herm. Thom Hoppen, were also visited by the surgeon and were shown the spleen. Before it was excised the spleen hung out from the wound; about the stomach it was torn from all its connections, also from the splenic artery and vein, and it resembled a rigid and gangrenous limb.

"The injured man soon recovered from this and other wounds; and was able to carry on his usual avocations; and is in good

health at the present time; this I have observed with astonishment in company with those people with whom he is accustomed to mix.

(signed) Joh. Auenius."

Observatio CLXV.—Clarke, D. Timotheus. *De lienis resectione in homine vivo. Ibid.* p. 209. *Miscellanea curiosa medico-physica academiæ naturæ curiosorum, sive ephemeridum medico-physicarum; Annus IV, V.* Francofurti et Lipsiæ, 1676, p. 208.

"A butcher, named William Panier, living in the village of Wayford, near Crookhome, in the County of Somerset, being greatly in debt, and fearing lest he should be arrested, was constrained to go into hiding. The constables were about to capture him, and becoming desperate, and in order to avoid them, he drove his butcher's knife into his abdomen on the left side, thus causing a great wound through which part of the omentum, and of the intestine, and also the spleen, protruded. The constables were horrified, and left the man for dead, as they believed. For three days the wound remained without a suture, but at last a surgeon was summoned. The surgeon replaced the intestines, and cut away part of the omentum, along with the spleen. The man rapidly recovered from the effects of the wound, and for the whole of the following year remained in good health and spirits. He soon afterwards emigrated to New England, where not long ago he was so far living a healthy life. Doubeny Turbervile, M.D., a man worthy of high credit, and a witness of the occurrence, renouned among our fellow-countrymen for his treatment of diseases of the eyes, has collaborated with me in communicating this observation."

The first experiments made upon the spleen were carried out in 1669, by Malpighi, who ligatured the splenic artery and vein in a dog. A subsequent operation showed that the spleen had undergone almost complete atrophy, and that the liver had enlarged. Malpighi's name is, of course, for ever associated with the lymphoid follicles of the spleen. In 1676 Clarke (*vide supra*) performed the first experimental splenectomy in a dog. The animal recovered, and the only subsequent change noticed in it was that it became much fatter. Morgagni describes a successful case of splenectomy in the dog, performed by Zambeccari, at Florence, in 1680. It is evident that he performed this operation

himself quite frequently after this date, for he observes that, after studying the matter for five years, he found that the dogs underwent no special change in consequence of such an operation; the dogs did not grow fatter, had no loss of fertility, and no change in their manners or disposition was noted.

In the nineteenth century experimental observations increased rapidly in number. In 1828 Schultz records that he had removed the spleen from 24 animals, 23 of which survived the operation. After the operation the fertility of animals was reduced, there was a greater inclination and ability to run far, and a diminished secretion of bile. Czermak also observed the lessened fertility of animals, and remarked upon the enlargement of the lymph-glands in the mesentery. In the year 1841 A. Bardeleben published the results of his experiments, which were directed towards the discovery of the functions of the spleen. They were the first well-considered and fully-recorded operations to be performed, and they have become classical. For the first time they showed with complete proof that animals could live and thrive after the removal of the spleen, and that certain changes, possibly compensatory in character, followed upon the loss of this organ. The changes noted were in the blood and the lymphatic glands. Vulpius, who followed in 1894, summarized his observations as follows:—

1. Extirpation of the spleen produces a transitory decrease in the number of red, and an increase in the number of white, blood-corpuscles.

2. The thyroid gland cannot vicariously assume the function of the spleen.

3. The lymphatic glands and the bone-marrow show an increased blood-forming activity after removal of the spleen.

4. The regeneration of the blood, after the loss of blood, is probably less rapid in individuals in whom splenectomy has been performed.

A great many observers confirmed these observations subsequently.

That the spleen is not essential to life is also shown by the fact that it is occasionally absent. Aristotle wrote: "The spleen is not invariably present; and in those animals that have it, it is only present of necessity in the same sense as the excretions of the belly and of the bladder are necessary, that is, of being an inevitable concomitant". Rokitansky and Ziegler in the middle of

the nineteenth century asserted that the spleen was not always present, but neither gave any specific instance of its absence. At the close of the century Hodenpyl* found records of nine cases of alleged absence of this organ, and related a tenth case observed by himself. Two of the cases occurred in infants six weeks and one hour old respectively; the remaining eight instances were in adults, the oldest being a woman, age 57, who had no unusual symptoms during her lifetime. The records of at least three of these are disputable. Indubitable cases of congenital absence of the spleen are related by Sternberg, Kohllass, and Riches.†

By the middle of the last century it was, therefore, clearly established by experience which was beyond cavil that the spleen was an organ not necessarily present in normal individuals, that its removal, when successful, did not seriously impair the chances of life and of good health, and that after its removal certain changes assumed to be of a compensatory character followed in due course. The way was then prepared for the question of the deliberate removal of the spleen from man in conditions in which it was enlarged by disease. The first instance of such an operation is related by Quittenbaum, of Rostock, in 1826 (the father of ovariotomy in Germany), who, after a series of experiments in which the spleen was successfully removed from cats and dogs, undertook the removal of the organ from a human being. The patient, it is interesting to note in connection with recent developments of the surgery of the organ, was a woman suffering from cirrhosis of the liver and ascites. It was "the patient's urgent entreaty rather than the surgeon's judgement" which led to the performance of the operation in a woman so ill. She survived the operation only six hours.

Controversy in surgery may often tend to be coarsening, but we cannot gainsay its occasional advantages. It serves to challenge opinions which might too readily be accepted, to oppose reason to authority, to destroy prejudices, or to support a truth which otherwise might long pass unnoticed. In the year 1855 it raged round the question as to whether the operation of splenectomy could be justified. The story is told by Simon.‡ Küchler, of Darmstadt, had removed the spleen from a patient, age 36,

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* *Med. Record*, 1898, ii, 695. † *Jour. of Ment. Sci.*, 1914, lx, 630.
‡ *Die Extirpation der Milz* (Giessen, 1857).

who fourteen years before had suffered for nine months from malarial fever. The spleen on palpation was estimated to have a length of 13 inches and a breadth of 7 inches. Death four hours after the beginning of the operation was due to hæmorrhage from a branch of the splenic artery, which had either escaped ligature at the time of operation or from which the ligature had subsequently slipped. Post-mortem examination showed cirrhosis of the liver, and about 250 c.c. of serous fluid was present in the peritoneal cavity, with 625 grms. of coagulated blood. The matter was taken up by the Surgical Association of Hesse, represented by Simon, and a long and bitter controversy resulted. Simon's greater experience and authority seemed to prevail, and he decided that the operation was only justified in cases where a wound had been inflicted which threatened otherwise to be fatal. Küchler, in his defence, published a pamphlet, entitled, *Extirpation of a Tumour of the Spleen. Light upon the Question of Extirpation of the Spleen in Man, its Practicability and its Justification.** In this publication he gives details of the operation he performed, and draws a parallel with six previously recorded cases of splenectomy in human beings. In three of these cases the operation had been performed for hypertrophy or abscess, and in three for prolapse of the organ through an abdominal wound. Küchler sent this pamphlet to the Medical Faculty of the University of Dorpat with the request that they would communicate to him their opinion of the operation of splenectomy. Adelmann was appointed by the Faculty to draw up their report. He searched the earlier literature for examples of this operation, and formed an opinion favourable to Küchler's view. His report was published in *Deutsche Klinik* for 1856. Adelmann also inspired a thesis by Johannes Braun, of Warsaw, *Lienis in homine extirpatio*, published in 1857, in which the literal text of the earliest recorded cases was given. In this year, 1857, there appeared also the paper of Gustav Simon, which has been a storehouse of information upon the history of the operation for all subsequent writers. In this publication, the author, possessed of an extensive acquaintance with the literature dealing with the physiology, pathology, and surgery of the spleen, but deeply prejudiced by his controversy with Küchler, expressed the opinion that removal of the diseased

* Darmstadt, 1855, Dietatall.

spleen under any circumstances was an unwarrantable operation. Küchler's reply was to point out that "the conclusions of Simon are in themselves unreliable and illogical, and throw doubt upon incontrovertible facts". Adelmann* gives a full account of this discussion, and decides: "From such expressions we may conclude that there was personal friction between the two Darmstadt surgeons. In September, 1858, when I made the personal acquaintance of both of these colleagues in Karlsruhe, I endeavoured, unfortunately without success, to bring about a reconciliation between them".

The first splenectomy deliberately performed in England (the fifth in the history of the operation) for an enlargement of the organ, is related by Spencer Wells.† The patient was a married woman, 34 years of age, who was "evidently dying from a large spleen", and who had no other disease. The following is the account of the operation given by Spencer Wells:—

"I made an incision along the outer border of the left rectus abdominis which extended five inches above and two below the umbilicus. Two arteries were tied before the peritoneum was opened. In opening the peritoneum a rather large artery was cut across in a piece of omentum, which was loosely adherent between the surface of the spleen and the abdominal wall. The vessel was tied. The adhering portion of omentum was separated, and by putting in my hand and turning the lower edge of the spleen first through the opening, the whole of it was easily removed. The intestines were prevented from escaping by Dr. Wright, who kept the edges of the opening carefully together behind the spleen, which was held only by the vessels and the gastrosplenic omentum. I was beginning to twist the spleen round to bring the vessels into a sort of cord preparatory to applying a ligature, when the splenic vein, which was as large as a small finger, gave way, and blood ran freely from the spleen; but none was allowed to enter the abdomen, and I at once enclosed the vessels in a large clamp, and cut away the spleen. Before tying the vessels temporarily secured by the clamp, I passed eight silk sutures to keep the edges of the incision well together. The peritoneum was thus protected and the viscera retained while I was dealing with the vessels. These were tied in two bundles above the clamp, which was then loosened,

* *Arch. f. klin. Chir.*, 1887, xxxvi, 442. † *Med. Times and Gaz.*, 1866, i, 2.

and two arteries and a vein were also separately tied before it was finally removed. On taking it off, I found that a part of one end of the pancreas, as large as the end of a thumb, had been bruised by it. All the ligatures, except those on vessels in the abdominal wall, were cut off close and returned with the included tissues. The sutures were then tied, and the abdomen was well supported by plaster, pads of lint, and a bandage."

The patient died of septicæmia 158 hours after the operation.

By this time the position of Spencer Wells in the surgical world was such that his authority was an absolute warrant for the performance of any abdominal operation. His sagacity, integrity, prudence combined with intrepidity, and technical skill were such as to command the respect of all men. And it was accordingly not very long before other operations involving the removal of the enlarged spleen were attempted. T. Bryant, of Guy's Hospital, performed the operation twice, in 1866 and in 1867, in cases of leucocythæmia. Both patients died rapidly from hæmorrhage, one fifteen minutes, the other one and a half hours, after operation. Koeberle, of Strasburg, performed a similar operation for a like condition in 1867; the patient died 'soon after', of hæmorrhage. Spencer Wells in 1873 and again in 1876 removed the spleen for this disease, and both patients died, one of peritonitis, one of hæmorrhage.

In the year 1882 H. Collier* reviewed the position of the operation of splenectomy, and gave a brief account of all the cases, 29 in number, submitted to operation up to that date. Of 13 operations performed for various conditions, 'wandering spleen', hydatid cysts, simple enlargement, 'ague cake', 8 were successful, the patients making perfect recoveries. Of 16 cases in which leucocythæmia was present, there was no instance in which the patient recovered even from the primary effects of the operation. Bryant's comment upon his two cases was as follows: "We have learnt two things from the cases related. Firstly, that enlargement of the spleen in leucocythæmia appears to be only a part of a general disease affecting the glandular system as a whole; and, secondly, that in splenotomy for such a disease there is a predisposition to hæmorrhage with which surgery is incompetent to deal. It can neither be foreseen by any amount of care, nor coped

* *Lancet*, 1882, i, 219.

with by any amount of skill. Under these circumstances there is no shirking the conclusion that the operation is physiologically unsound and surgically unsafe, and, for leucocythæmia, should not be performed ".

From this date up to the last few years the operation was reserved for cases of injury, for spleens with a rotation of the pedicle, for cysts of the spleen, or for cases of enlargement of the organ due to causes which were not always discoverable. In the year 1898 Vanverts, in a Paris thesis, collected the records of 274 cases of splenectomy with 170 recoveries.

In the last few years splenectomy has been performed in certain of the anæmias associated with splenomegaly. The technique of the operation has been greatly improved, and the mortality in all classes of cases very considerably reduced.

Dr. W. J. Mayo has most kindly given me the records of the Mayo clinic up to September 20, 1920. They show better than any other record the modern position of the operation of splenectomy.

SPLENECTOMIES FOR SPLENIC ANÆMIA.

Total number of cases to Sept. 20, 1920.. 73
Total number of hospital deaths .. .. 9 = 12·3 per cent.

Out of a total of twenty-seven cases operated on 5 years or more ago, seventeen patients lived over 5 years ; of these patients, sixteen are still living.

The results in splenic anæmia, generally speaking, have been good, but the operation is more difficult than in other conditions, and the mortality is considerable.

SPLENECTOMIES FOR PERNICIOUS ANÆMIA.

Total number of cases to Sept. 20, 1920.. 53
Total number of hospital deaths .. .. 3 = 5·6 per cent.

Five patients living 4 to 5 years after operation. Eleven patients living 3 to 4 years after operation.

The fact that 22 per cent of patients have lived two and one-half times as long as the average, shows that in early cases of pernicious anæmia the operation is at least justifiable.

SPLENECTOMIES FOR MYELOGENOUS LEUKÆMIA.

Total number of cases to Sept. 20, 1920.. 26
Total number of hospital deaths .. .. 1 = 3·8 per cent.

One patient died 5 years and 4½ months after operation. Seven patients were living 3 to 4 years after operation. Six of these are still living.

The results are poor in myelogenous leukæmia, but five patients are in good condition and two in fair condition after periods of time beyond the life-expectancy of these cases. The patients are at least relieved of the weight of the spleen, and in two instances supposed to be early cases of myelogenous leukæmia, not counted in this series, the patients have been cured, or at least they have lived a number of years following operation. The operation is not difficult after radium treatment, and in selected cases should be further considered.

Splenectomies for Hæmolytic Icterus.

Total number of cases to Sept. 20, 1920.. 32
Total number of hospital deaths .. .. 1 = 3·1 per cent.

One patient living over 9 years after operation.

The results in hæmolytic icterus have been excellent. Splenectomy is a real cure in a high percentage of cases.

Splenectomies for Septic Splenomegalias.

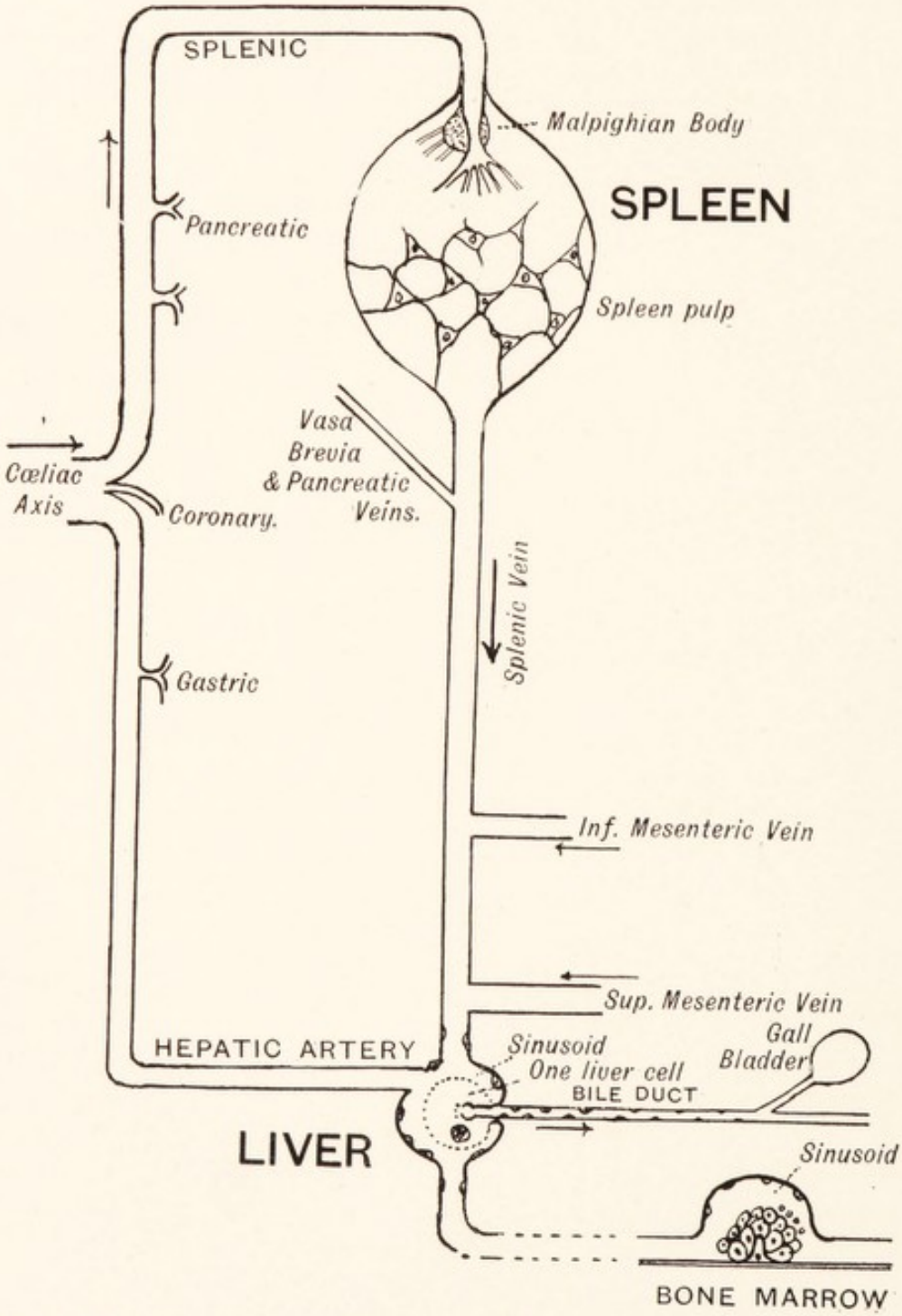
Total number of cases to Sept. 20, 1920.. 10
Total number of hospital deaths .. .. 2 = 20 per cent.

Splenectomy is undoubtedly indicated in some of these cases.

Diagnosis	No. of Cases	Hospital Deaths
Portal cirrhosis	9	4
Biliary cirrhosis	6	1
Lymphoma	3	0
Luetic splenomegalias	6	1
Lymphosarcoma	2	0
Gaucher's disease	4	1
Tuberculosis	4	0
Wandering spleen	2	0
Splenomegaly with eosinophilia ..	1	0
Splenomegaly with neutrophilia ..	1	1
Miscellaneous, questionable ..	11	2
	49	10

Thus the total number of cases is 243, with 26 hospital deaths.

PLATE II



TO SHOW THE RELATIONS BETWEEN LIVER, SPLEEN, AND BONE MARROW

CHAPTER III.

ON THE FUNCTIONS OF THE SPLEEN.

(*See Plate II.*)

The cœliac axis, the first visceral branch of the abdominal aorta, supplies those organs, the stomach, the liver, and the pancreas, which are especially concerned in disorders of the spleen. The largest of its three branches is the splenic artery. Each branch of this artery within the spleen supplies a different compartment of the organ, and its main subdivisions each end rather abruptly in a small pencil of arterioles near the periphery of the organ. Close to its termination each of the subdivisions of the artery is enveloped by a small mass of lymphoid tissue, the so-called Malpighian body, in which the manufacture of lymphocytes takes place. This small mass of tissue is supplied by a coil of minute arteries springing at right angles from the main course of the vessel. In this way the large germinal cells of the follicle are provided with arterial blood, and give rise to successive generations of lymphoid cells until a colony of ordinary lymphocytes results. These lose their attachments and drift outwards into the surrounding splenic tissue.

The pencil of arterioles finally gives place to the spongework of which the spleen essentially consists. Taken broadly, it may be said that the spleen consists of a meshwork of delicate fibres which serve to retard the flow of the blood, and to allow its constituents to come into thorough contact with the specific cellular elements which are attached to the network in large numbers. These cells are similar to the cells lining the capillaries of all parts of the body. In the capillaries they are orderly in arrangement and definite in position, and they appear as the lining of complete tubes. In the spleen-tissue or spleen-pulp they are larger, they are disorderly, and they cease to form definite channels. Since it is admitted that the endothelial cells of capillaries are capable of phagocytosis, it is not difficult to see a close resemblance between them and the so-called reticular cells of the spleen.

These latter cells, it is true, exhibit a certain sort of arrangement, since the blood runs more vigorously in some directions than in others, allowing a distinction to be made, on close examination, between blood-channels and pulp-cords. The latter are perhaps twice as broad as the more open channels which separate them, but cannot be regarded as solid tissue. The blood flows more slowly through them than through the adjoining channels. When, however, a pathological change occurs, it is not infrequent to find the channels become relatively more distinct, and the pulp-cords more indefinite in character.

Various authors describe a number of types of cell as entering into the cellular composition of the pulp; but if we exclude the purely supporting cells (which provide the reticulum proper), it is possible to group all the others in one category—that of *modified endothelial cells*. There is an abundant literature dealing with the question of the specific pulp-cells of the spleen, from which it is possible to draw the following simple picture: that these modified endothelial cells which cling to the reticular meshwork are occupied in different ways at different times. Sometimes they remain stationary and gather up passing particles suitable as food; at other times they separate from the meshwork and wander among it—likewise for the purpose of engulfing solid particles (notably effete red blood-cells); at other times still they undergo proliferation. It is very probable that they remain stationary for this purpose, and produce daughter cells and granddaughter cells which adhere to one another for a time, but ultimately separate (either in the daughter or in the granddaughter stage), and remain in the spleen as, apparently, a special type of cell, or else pass away in the blood of the splenic veins.

It is especially important to notice that the blood in this meshwork is venous, since it is asserted that the processes of multiplication of the pulp-cells, and the varieties of cell which result therefrom, are particularly modified by the carbon-dioxide atmosphere in which they reside (Loele). The purely lymphatic cells of the Malpighian bodies, which lie in a medium richer in oxygen, give rise to a very different progeny.

The blood as it leaves the spleen carries with it some of these pulp-cells, or their descendants, but leaves behind it a certain number of red corpuscles and other solid particles. As it emerges by the splenic vein it immediately meets two streams of venous

blood, one coming from the cardiac end of the stomach, and the other from the tail of the pancreas, facts no doubt of great physiological significance. Nearer the liver it meets successively a stream of blood from the descending colon, and the great mass of blood returning from the alimentary tract bearing with it the products of digestion, such as sugar and the amino-acids of protein, etc.

It is probable that a mingling of these various portions of blood occurs in the wide portal vein, but the degree to which this takes place is uncertain. There is evidence to show that, like the Rhone and the Arve, the two streams long remain separate parts of a great common stream. And the view is taken by many authorities, upon what appears reasonable evidence, that the larger part of the splenic blood goes to the left lobe of the liver. Tested experimentally by injecting in the cadaver a continuous stream of red fluid through the splenic vein and a continuous stream of blue fluid by the superior mesenteric vein, the mingling of the two streams appears to be complete when the issue from the severed portal vein is watched. The stream of blood in the portal vein finally comes in contact with the liver tissue, whose cells exert upon it their metabolic activity. If we regard the matter as concerning a single liver-cell, the following events occur. The blood flowing from the free surface of the liver-cell becomes mixed with a small stream of blood derived from the hepatic artery, the next largest branch of the cœliac axis. Oxygenated and venous blood thus come in contact with the free surface of the liver-cell, which, if represented in a diagram, would appear to be protruding into a dilated vascular channel—a 'sinusoid'. All other surfaces of the latter are lined with endothelium, the cells being of conspicuous size, endowed with phagocytic powers, and known as Kupffer's star-cells. The liver-cells are now regarded as containing a network of intracellular canaliculi emptying into a small ampulla from which a minute duct issues. This, joining with other ducts similarly arising, forms at last a tiny bile-duct visible to the naked eye. Since the liver-cell forms bile out of the blood flowing in the portal vein, the ingredients of the bile must enter the liver-cell and appear within the minute canaliculi. If these substances enter, so also may other substances conveyed by the blood, and, by penetrating the liver-cell, finally obtain access to the bile-duct beyond. It is a fact that the liver-cell takes up other substances which never pass into the bile-ducts, and stores them in the protoplasm without

any risk of their emerging by that system of vessels. It is also known that the liver-cell is capable of discharging ferments into the blood-space around it, a fact which makes it reasonable to suppose that many changes can and do take place in the blood without the substances concerned entering directly into the liver-cell at any time.

In the spleen-pulp, the endothelial cells share one of the properties of all cells—that of making ferments. The blood may undergo definite change in chemical composition as it lingers among the meshes of the spleen. Then, before it enters the liver, it has become mixed with products from the stomach, and with ferment from the tail of the pancreas, where the islands of Langerhans are three times as numerous as elsewhere. Obviously some change must take place if and when the two become admixed; and, indeed, the observations of Herzen and Bellamy* on the action of the splenic and gastric blood strongly indicate the existence of such changes. Finally, attention may again be drawn to the fact that this blood undergoes a still further change in composition by receiving the blood from the large intestine, and from the small intestine with its products of digestion, which necessarily include ferment substances absorbed with food.

The spleen has long been thought of as a blood-forming organ; and during fœtal life it appears certainly to be concerned in the formation of red cells; in consequence, dominant attention has been directed to the fact of its enlargement in many so-called diseases of the blood. It is therefore desirable to add to the picture so far drawn, details in reference to the chief of the blood-forming organs—namely, the bone-marrow. Arterial blood, entering the nutrient arteries, passes through the minute capillaries of the marrow of the long bones and enters into dilated cavities recalling those into which the liver-cells project. These also are called 'sinusoids'. The endothelial cells projecting into them are modified into large sustentacular cells, from which sprout the various cells described as concerned in the formation of red and white cells respectively. It has been said that the red cells form on such buds where they are bathed in arterial blood, while the white cells appear in those portions where the blood has become richer in carbon dioxide. As in the spleen-pulp, the daughter and

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* *Lancet*, 1900, ii, 371.

granddaughter generations remain adherent to the sustentacular cell until they are ripe, after which they become loose and float away in the blood-stream.

The ground having been cleared by these very brief anatomical and physiological considerations, it now becomes possible to review the large amount of work which has been done by many investigators in reference to the functions of the spleen, and perhaps to elucidate some of the difficulties of contradictory observations.

The lines of inquiry and research have been broadly as follows :—

1. Study of the effect of splenectomy in man and animals upon the general health, upon the blood, and ultimately upon the various tissues.

2. Study of the action of extracts of the spleen, when administered in various ways.

3. Study of the action of splenic extracts on various phases of artificial digestion in the laboratory.

4. Biochemical investigations upon the spleen, upon the metabolic activities of the body, and upon the several secretions.

5. Microscopical studies of the spleen and other organs in case of diseases of the spleen, as well as in normal and splenectomized animals subjected to the action of various drugs.

6. Consideration of clinical cases in which the spleen was known to be diseased, any special phenomena being carefully observed in order to decide to what extent the spleen was to be held responsible for them.

Of all these methods, the study of splenectomized animals has been most widely followed.

Even when allowance is made for the ultimate differences which are shown by the cases of splenectomy in man, due to the varying reasons for the performance of the operation, there remain certain *changes in the blood* which agree with those found in splenectomized animals. There is a temporary anæmia, gradually subsiding in approximately two months' time, and there is an increase in leucocytes, whose numbers return to the normal very slowly. An increase of lymphocytes persists for about a year, and gives place to a moderate eosinophilia, which increases up to about 8 per cent during the third year. Apart from these laboratory discoveries there is no particular change to be noticed in the condition or in the health of the patient. It has been asserted that a certain

degree of asthenia persists, and that the patient shows an increased liability to become infected with epidemic diseases, such as influenza. But in these respects there is no uniformity of evidence, doubtless owing to lack of knowledge of the normal resisting power of the patients, to differences of age, to the various diseases for which the operation may have been performed, and to the condition of health in other respects. When the extirpation has been for trauma, the general health of the patient may not have been previously impaired.

After the experimental removal of the organ from animals, certain additional observations have been made. The red cells have been found to become more resistant to hypotonic saline solutions, and the administration of drugs capable of causing hæmolysis has been found to cause jaundice less easily than before. Study of the animals after death has shown proliferation of the endothelial cells in the lymph-glands and in the liver, and a reddening of the bone-marrow has been disclosed.

Briefly stated, these are all the *salient* facts relative to the effects of splenectomy. They are meaningless unless the matter is carried further in order to force answers to certain definite questions which may now be asked.

1. *How much of the effect of splenectomy is due to the mere operation?* Pearce and his co-workers,* whose work is the most recent, and is distinguished throughout by great care and painstaking analysis, incline to attribute much to the operation. They point out that a certain amount of blood is lost with the spleen, and that the appearance of increased resistance of the red cells, and even of their susceptibility to hæmolytic drugs, may be related to the consecutive anæmia, or to the processes engaged in the repair of the anæmia. Banti has insisted that any such explanation is unsatisfactory, and asserts that the increased resistance persists long after the anæmia has passed away; and he further points out that in an animal rendered anæmic by appropriate drugs this change in the resistance of red cells does not occur.

2. *Does the spleen destroy red cells?* There is a general agreement that phagocytosis does go on in the spleen. The agents which carry on this work are the same kind of large mononuclear

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* *The Spleen and Anæmia*, Philadelphia, 1919.

cells which are found in the sinuses of the lymph-glands. It has been found that these cells are very much increased in numbers in the lymph-glands when drugs acting on the red cells are administered to a splenectomized animal. This suggests that these cells are carrying out vicariously the functions previously performed by the spleen—in other words, the spleen normally destroys red cells. Then, too, the occurrence in the spleen of phagocytes containing red cells in severe anæmias in man, can hardly have any other meaning than that the organ in these conditions fulfils that destructive purpose.

3. *Does the spleen make a substance which weakens the red cells prior to their being engulfed by the phagocytes?* This action has been called 'the hæmocatatonistic function' (Bottazzi), and belief in its existence was based on the observation that the resistance of the red cells begins to increase at once after splenectomy, rising to a certain maximum, at which level it is maintained. But when it was found by other workers, including Pearce, that the same result will occur in the presence of the spleen, by treating an animal with a hæmolytic immune serum, it became evident that the problem is not as simple as Bottazzi assumed. It receives its true answer when the import of the following further questions is understood.

4. *Does the spleen pass on the blood-pigment for conversion into bile-pigment?* Removal of the spleen does not lead to absence of bile-formation, nor to the accumulation of blood-pigment in the blood. The explanation of these observations may be found in the fact that red cells may be taken up by phagocytes anywhere in the body and carried round to the liver. Material for the manufacture of bile-pigment is therefore still available. Pearce, evidently believing, I think, that the blood-pigment is *free* in the splenic blood, has endeavoured to discover what quantity of hæmoglobin must accumulate before it will overflow into the kidney or appear as bile in the urine. There appears to be a definite limit beyond which the colouring matter fails to be dealt with by the liver; and there is a limit to the amount of bile which can flow out of the liver-cell. If so much hæmoglobin is converted into bile-pigment that it cannot leave the bile-channels quickly enough, the excess of bile-pigment accumulates in the blood and jaundice appears. The amount of bile-pigment formed after splenectomy is at first approximately only one-half of that which is formed prior to the operation, and, as Martinotti and Barbacci have shown, this delay accounts

for many of the phenomena arising in the course of experimental work upon hæmolytic poisons, and upon the short-circuiting of the splenic vein. All this work is based on the belief that hæmolysis in the body must be the same as hæmolysis in a test-tube, namely, a process of liberation of free hæmoglobin into the surrounding medium (that is, the blood-serum). But the splenic blood cannot be proved to contain free hæmoglobin, and the microscope shows that the red cells are not dissolved in the stream, but are consumed by phagocytic cells—facts of the greatest significance, which have been ignored or too little considered in this line of inquiry.

5. Similarly with reference to the question, *Does the spleen hæmolyse red cells by means of a ferment action?* Expressed in a more technical form, this means, Does the spleen manufacture a 'hæmolysin'? The literature on this point is very extensive, all of it showing how general is the belief that 'hæmolysis' in the body is comparable to a test-tube phenomenon. Yet all observers—Pearce included—have failed to find proof of this ferment action, which was first suggested as possible by Nolf. That the dissolution of red cells within the bodies of phagocytes takes place by an intracellular ferment action is obvious, but it is not in this sense that the question has been raised.

6. A further question often asked, as to *whether the spleen contributes an immune substance,* veils the same belief. The researches of immunology seek to establish the existence of chemical substances circulating as such in the blood-stream. Consequently, viewing these substances as secretions from cells, it is supposed that some of them are formed by the splenic cells, and would be likely to appear in more concentrated form in the splenic juice or in the blood of the splenic vein. In order to stimulate the cells of the spleen to greater activity, various substances have been used or devices adopted to bring about a greater destruction of the red corpuscles, in the hope that the spleen may be induced to secrete more of this immune substance. This accounts for the experiments devised to show the presence and purpose and mode of action of fatty acids and lipoids. These substances dissolve the red corpuscles. Is it that the spleen prepares such reagents, or that the spleen needs the co-operation of the liver, since the liver is an acknowledged source of both these substances? Eppinger found that the total fats and cholesterin of the blood are increased

after splenectomy, and King confirmed his work; but Pearce failed to substantiate it. Anitschkow, taking another side of the problem, sought to show that if the spleen makes a substance for the express purpose of dissolving the red cells, removal of the spleen should diminish the tendency to jaundice. As a matter of fact this does happen if the splenic vein is diverted into the inferior vena cava without removal of the spleen, and is, I think, to be explained by the longer route traversed by the splenic blood, which gives the liver more time to deal with the liberated blood-pigment, seeing that in the new arrangement this becomes distributed over the whole body, instead of being contained only in the portal vein.

Another argument in favour of there being such a function of the spleen is afforded by the fact that exposure of the spleen to *x* rays results in a diminished output of hæmolysin in the experiments on dogs (Hektoen). There are great difficulties in interpreting the experiments relative to this part of the subject, since the bone-marrow also must inevitably be influenced by the substances used to produce hæmolysis.

The whole subject assumes an entirely different aspect when it is discussed from the cellular side, as Sajous has fully done in his work on *Internal Secretions.* Hæmolysis in a normal animal is carried out by cells within cells; immunity-reactions are secured by the same means. These views are fully supported by the results of all the experiments to which reference has been made.

7. *Does the spleen secrete a substance capable of acting on the bone-marrow?* Danilewsky was the first to assert that this was the case, and others corroborate his view. The rapid anæmia after splenectomy, out of proportion to the loss of blood, suggests that some such substance has temporarily ceased to be formed. In one of Pearce's experiments a splenic extract, administered to a dog dying from anæmia after splenectomy, saved its life. A single dose of splenic extract given intraperitoneally will induce a rise in the red cells and hæmoglobin content in dogs who are not dangerously anæmic. The effect, it is interesting to note, is not produced when the splenic tissue is given by the mouth. Another argument in favour of this view, fortified by Pearce, is that regeneration of blood takes place much more slowly than usual when a splenectomized dog has been bled, or has been rendered anæmic in some other way.

As regards the part of the bone-marrow concerned with the

formation of white cells, it has been suggested that there is normally a restraint of its activity through some substance secreted by the spleen. Increased activity of the spleen leads to increased formation of 'leucosplenins', and therefore, consecutively, to a diminution in the number of white cells in the blood. After splenectomy, there is leucocytosis due to the removal of this restraint. Undue restraint occurs, as Schmincke points out, in typhoid, syphilis, malaria, Banti's disease, Gaucher's disease, kala-azar, and Hanot's cirrhosis. When *x* rays are applied to the spleen, they stimulate the splenic cells, cause them to form more leucosplenins, and thus indirectly interfere with the action of the bone-marrow.

Pearce has decided that the relation between the spleen and bone-marrow is rather a matter of the changes which take place in the storage and utilization of the iron of the body than a specific hormone action. Bone-marrow becomes red after splenectomy because it begins to take on the function of storing iron. It is certain that animals suffer largely from loss of iron after this operation, and it is evident that red cells cannot be produced in the absence of iron. Hence the anæmia may have a perfectly simple explanation, making it unnecessary to introduce the notion of special ferment substances into a discussion of the pathology of this subject.

8. A final question: *Is the spleen concerned with the activation of digestive ferments?* Tarulli and Pascucci compared the digestive power of the gastric juice before, and some days or weeks after, extirpation of the spleen in dogs. They also studied the effect of administering watery infusions of 'engorged' spleens (that is, spleens removed from dogs in full digestion), observing at the same time whether the animals lost weight or not. The result of their experiments is to show that the digestive power is constantly weakened after loss of the spleen during a period of two or three months. The use of a congested spleen-infusion eight hours before the meal restored the digestive power. Infusion of spleen removed in the intervals following active digestion failed to replace the loss of activity of the gastric juice of such dogs. The authors therefore conclude that the spleen provides a substance which causes the gastric glands to produce more pepsin. Hedin and Rowland, however, in 1901, found similar results with extracts of other organs.

The conspicuous feature of all this work—and the quantity of it is very considerable—is the attempt to study the organ almost entirely as a separate entity working in isolation. In future the most eager attention must be given to tracing up, and laying bare, every possible connection it may possess with other organs. The analogy with the work of the surgeon is interesting. In our earlier experience we were concerned with the clinical recognition and the operative treatment of diseases of one organ—the stomach, the duodenum, the gall-bladder, the intestine, or the appendix. We now realize that the diseases in these several organs are secondary, and that some common underlying cause for many of them may be present. Any operation upon one of the organs now involves not merely the examination of that one, but also the scrutiny, and possibly a further operation upon, any one or more of the others. Future experimental work must consider the spleen, not as an organ whose functions are confined to its own activities, but as a member of a group of organs each concerned with, and influenced by, the activities of the others. And clinical work must regard the problems of its disease in the same manner. Microscopical examination of the organ, showing as it does exactly what are the tools with which the spleen works, or the tools that go to make up the organ itself, demonstrates very clearly that we have to deal with cell-structures which other blood-forming organs also possess and use; indeed, the capillaries of many parts of the body in general show similar structures.

Intimate connections with the spleen can be found in four important systems of the body: (1) *The hæmopoietic system;* (2) *The reticulo-endothelial system;* (3) *The digestive system;* (4) *The sympathico-endocrine system.* Each of these systems has a depôt, so to speak, in the spleen; but this organ also contains within itself a histological system into which the other four merge. Although the spleen constitutes a link in each one of these systems, they are all able to dispense with its service; and although the presence of the spleen is not by any means a matter of indifference to any of them, yet they are not permanently or irreparably affected by its loss.

1. The Spleen as a Member of the Hæmopoietic System.—The part played by the spleen in the formation of red blood-cells and neutrophile leucocytes in embryonic life is everywhere

admitted. In adult life the connection is usually only demonstrable under the influence of infections and in the various forms of splenic enlargement, and rarely is there a reversion to the capacity of forming red cells. Leukæmia affords an instance of post-natal resumption of white-cell formation, though the process is, of course, enormously exaggerated. The mechanism of the change is the same in the infections as in leukæmia. The cells of the spleen-pulp become transformed into parent cells tending to give rise to neutrophile leucocytes as they originally did in the embryo. And the process is now the same as in ordinary bone-marrow, where endothelial cells, specially endowed, still give rise to these leucocytes.

A connection between the spleen and the bone-marrow has already been spoken of as dependent upon a hormone, elaborated by the spleen and expended in stimulating the bone-marrow; a hypothesis which explains certain facts. But, as has been suggested, the same facts can be explained more simply. The destruction of red cells by the spleen enables this organ to liberate effete iron in a form capable of reconstruction into a complex albuminous substance by the aid of the liver-cells. In this synthetic process the first step is checked by excision of the spleen; and sufficient iron to make the usual hourly complement of red cells is not then available for the bone-marrow. I think Krumbharr expresses this view when he asserts that the spleen furnishes a substance which is activated by the liver. But neither the substance, nor the activated products, need be new and additional; they are pre-existing substances, temporarily parted, and united again in rejuvenated form on the distal side of the liver.

In the same way, the theory of Horbaczewski that the spleen-pulp secretes a substance normally restraining white-cell formation may be looked on as too superficial, and experimental evidence to support it is not at all conclusive.

2. **The Spleen as part of the Reticulo-endothelial System.**—We owe the conception of this system of the body to Aschoff. It has evoked numerous investigations, and as time goes on it is regarded more and more as important, once again raising to supreme interest a sphere of action in the body the consideration of which has been neglected for nearly forty years.

Wherever the tissue surrounding capillaries is loose, the endo-

Kupffer cells of the Liver
Endothelial cells of the Spleen, Lymphatic glands, Bone marrow
Interstitial cells of the Testis
Reticular cells of the Thymus

thelial cells are found to be closely connected with the surrounding reticular cells. The endothelium and the perithelium form parts of a meshwork, and this again becomes connected with the reticular meshwork familiar in connective tissue. The spleen-pulp furnishes a very good picture of this arrangement, for the meshwork is made of reticular cells which can be traced continuously into the network formed of the fraying edges of the blood-vascular channels where they open out or, on the venous side, close up into the spongework of the organ.

In the liver, certain large cells, the star-cells of Kupffer, excited much speculation for many years. They are essentially phagocytic in function, and are really to be regarded as endothelial in nature. After splenectomy they undergo proliferation. In hæmolytic diseases they become filled with iron pigment. The endothelial cells of the lymphatic glands are also phagocytic, and undergo proliferation after splenectomy. They exactly resemble the corresponding cells in the spleen. Similarly, the bone-marrow provides a meshwork of cells exactly comparable to the cells of the splenic pulp, though characteristically active in their own special direction.

A complete histological system can therefore be easily traced in many important parts of the body. It is traceable, if less easily, as a generally distributing form of tissue, not specially noticed hitherto, yet performing one of the most important parts in the physiology of the body. It is rightly attracting increasing attention at the present time.

The nature of the spleen-pulp cell; the changes it may undergo in different diseases and under different forms of stimulus; its relations to the connective tissue of the organ; its chemical characters, and the powers of taking up certain 'vital' and other dyes—have all been carefully worked out during recent years, and give a satisfactory insight into the minute processes which collectively constitute the functions of the spleen. It is the phagocytic proclivities of these cells which account for the harbouring of micro-organisms in the spleen-pulp; and it is the great vitality of these organisms, even after ingestion, which accounts for the latency of many infections. The malarial parasites notoriously find here a home, from which they only emerge under provocation. The same is true of the pallid spirochæte. Whatever truth there may be in the view that cirrhosis of the liver is due to bacterial

infection finds its explanation in the two phenomena of phagocytosis together with persistent vitality of the engulfed particles.

But these phenomena are not restricted to the spleen. When poisons capable of dissolving the red blood-cells are administered, the pigment is found scattered through all the organs in which this reticulo-endothelial system occurs, especially in the liver and in the lymphatic glands, less conspicuously (because less often examined ?) in the bone-marrow. When Eppinger realized that the endothelial cells of the liver were identical in function with those in the spleen, he called them " the splenic tissue of the liver ", and seemed to suggest that they are carried bodily from the spleen to the liver, whenever the former is overburdened or maimed. Lintwarew has shown that such a procedure actually occurs ; and it is histologically evident that there is a permanent tissue as well. Aschoff's conception is, however, much more useful and suggestive.

The relation of the spleen to immunity is not merely a matter of its behaviour to the introduction of hæmolysins ; its pulp-cells are concerned in the manufacture of the immune substances with which the body is furnished in the course of infections. Herein lies a very important practical bearing in regarding the spleen as a member of the reticulo-endothelial system. The question is worthy of ample consideration.

In the early literature of splenic diseases the statement is not seldom found that the organ possesses, among its many functions, that of offering resistance to systemic infection. Its enlargement during some of the acute specific fevers, and in other conditions in which grave infections are present, was held to be an evidence that it was conspicuously active in defence. And experimental evidence, which was early sought, did at times appear to support this view ; but such evidence was often conflicting. It was necessarily so ; for no care appears to have been taken to choose healthy animals for experiment, and such results as were obtained, were in part due, in all probability, to the existence in many of the animals of such diseases as would inevitably vitiate any conclusions. Of the early work, that of Pfeiffer and Marx* was the soundest. In investigating the formation of immune bodies in cholera, these authors found that the spleen and the medulla of the long bones contained a far larger proportion of these substances than any

* *Zeits. f. Hygiene,* 1898, xxvii, 272.

other part of the body; and this reservoir, so to speak, of defensive substances continued for many months, until the bactericidal properties of the blood were slowly brought up to the standard found in the spleen and the bones. They also found that immunity could be developed in an animal whose spleen had been removed some months before; but if the production of immunity was attempted and the spleen then at once removed, the immunity failed to develop. This suggests that the early removal of the spleen had afforded time for the vicarious functions possessed by the medulla of the long bones or other parts to have developed.

In 1891, Bardach* injected 25 normal dogs, and 25 dogs from whom the spleen had been removed, with 1 c.c. of an anthrax culture (rabbits are normally resistant to infection by anthrax). Of the 25 spleenless dogs, 19 died; of the 25 normal dogs, 5 died. Similar results were obtained when normal and spleenless dogs were immunized against anthrax before injection of the culture. The deaths in the spleenless dogs were more numerous.

Tizzoni and Cattani† injected cultures of the tetanus bacillus into three groups of rabbits: normal vaccinated, normal unvaccinated, and vaccinated spleenless. Animals in the first group resisted the inoculation; those in the last two groups succumbed. They were unable to render rabbits whose spleens had been removed immune against tetanus. It therefore appeared possible that the manufacture of a substance causing immunity was manufactured by the spleen. In their later work they seemed to realize, with Righi, that the removal of the spleen merely acts as any other major operation would, in reducing the general systemic resistance to infections. These results are not confirmed by some other experimenters, but, as a rule, too few animals were used by them to avoid the chance of error.

The most careful experiments hitherto conducted are those of Morris and Bullock.‡ The following is a portion of their account:—

"Thirty-six apparently healthy young brindle rats, weighing from 50 to 100 grms. each, were splenectomized under ether anæsthesia. Great care was taken to guard against any operative complications, such as hæmorrhage or infection, and the subsequent

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* *Ann. de l'Inst. Pasteur*, 1891, iii, 571. † *Centralb. f. Bakteriol.*, 1892, xi, 325.
‡ *Ann. of Surg.*, 1919, lxx, 513.

autopsies showed that none had occurred. A similar number of control rats of like weight and breed were subjected to a laparotomy in which one testicle was removed. As the testicle is larger than the spleen, and the blood-vessels entering it are about equal in size to the splenic vessels, its transabdominal removal furnishes a very fair basis of comparison as to the effect of the operative trauma alone upon the subsequent health of the animals.

"Both sets of animals were found to be active and thriving on the day following the operation. They were then exposed to chance laboratory contagion and kept under observation for several months. Whenever an animal in either series died, an animal of the other group was killed, and both were completely autopsied. Microscopical sections were made from all important organs, and cultures were taken from the heart's blood and from the peritoneal cavity or lung.

"It was then observed that the splenectomized animals almost invariably died before the controls, and that the death-rate among them was 80·5 per cent as compared with 38·9 per cent in the normal rats. Necropsy showed the following lesions: Congestion and parenchymatous degeneration of nearly all the important organs, varying from injection of the vessels and slight cloudy swelling to focal necroses or extensive disintegration of the parenchyma. If the animal had survived long enough for a reparative process to set in, there was replacement of the degenerated areas by newly-formed granulation tissue."

They conclude from these results that the spleenless rats were more prone to contract the prevalent rat plague, and that, having contracted it, they showed less resistance to its ravages. A second experiment with 72 rats confirmed these results, and showed that under ordinary laboratory conditions spleenless rats were far less resistant to a common infection than normal rats. The conclusion is therefore drawn that the spleen must in some way help to protect the animals against infection, since removal of another organ of equal size and weight, by a similar operative procedure, caused no impairment of the defensive mechanism.

In a further experiment, two groups of 88 rats each were treated, the one by splenectomy, the other by abdominal castration, and were then injected subcutaneously with a sublethal dose of broth culture of the bacillus of rat plague. Of the castrated rats, 22·7 per cent died; of the spleenless rats, 87·5 per cent died.

The conclusions which flow from these most careful and exhaustive experiments are that the spleen affords great aid in resisting infective processes in rats, and that its removal robs the body of its resistance, or diminishes that resistance until such time at least as compensatory processes have had a chance to establish it once again in its original strength. Hektoen's experiments* appear to show that antibodies are produced in the spleen, lymphatic tissues, and bone-marrow.

So far as I am aware, no observations to support these conclusions have yet been made on man. But the evidence as to the defensive properties of the spleen which these experiments reveal is so strong that remembrance of this function of the spleen should always be borne in mind when the operation of splenectomy is under consideration.

3. **The Spleen as a Member of the Digestive System,**—Although it is well known that the spleen undergoes variations in volume during the day, becoming larger up to a period of about four hours after every meal, diminishing subsequently as a result of muscular action, there is much difference of opinion as to the purpose of these changes. Some regard the spleen as a reservoir for surplus blood, while others believe that the periodic enlargement is concerned with the digestive processes in the duodenum and small intestine. This last view is supported by two observations: (*a*) That the blood shows a leucocytosis during the period of digestion; and (*b*) That the blood of the splenic vein is richer in leucocytes than that of the artery.

We owe our early knowledge of the relationship between the leucocytes and digestion chiefly to Hoffmeister and Pohl. The great increase of lymphocytes in the intestinal mucous membrane during digestion was demonstrated by the former; and the relationship existing between this and the kind of food taken was indicated by the latter. The leucocytosis is most evident after a protein diet. Examination of the blood of the superior mesenteric artery shows a great increase of leucocytes during digestion, although the increase is due to the neutrophiles and not to lymphocytes. Subsequent observers have sought to belittle these observations. There are some who deny the existence of an increase of

* *Jour. of Infect. Dis.*, 1915, xvii, 415.

the blood-cells during digestion; others, who admit that such an increase does occur, consider it to be merely a part of a natural cyclic phenomenon having no direct relationship to any food ingested. It has been suggested that the increase may be in the nature of a protective mechanism, whose purpose is to ensure the detoxication of the products of protein digestion. The evidence on the whole seems to indicate that there is a definite relationship between the type of the dominant cell in the blood, and the quality of the food ingested. Neutrophile leucocytosis follows a meal of proteids and fats; lymphocytosis follows a meal rich in carbohydrates.

It may be that the spleen is concerned with the destruction of the surplus lymphocytes liberated during the process of digestion. If so, this would account for the undoubted enlargement of that organ which then occurs, and also for the lymphocytosis which follows splenectomy, the agent responsible for the destruction of these cells being then absent.

The relation of the spleen to the liver must be of the most intimate character, for every drop of splenic blood passes into and through this organ. The connection is well shown in regard to bile secretion, for it is everywhere admitted that the bile-pigment is derived from hæmoglobin, though the exact mechanism of the conversion is not understood. Assuming that the hæmoglobin must be carried to the liver in the free state, Banti and Furno searched for it in that form in the splenic vein. They claimed positive results, but Pearce does not confirm their observations. In the belief that the spleen contributes a substance which dissolves red cells, the blood of the splenic vein was then searched for evidence of 'fragile' red cells. Hammersten, Chalin and Charlet, and more recently Pearce, have all failed to find evidence of such a condition. This work, as well as the experiments of Pearce made to determine the 'threshold' for hæmoglobin, and the work of Anitschkow and many others, including Widal, would appear, as I have previously urged, to be quite irrelevant when once it is admitted that the hæmoglobin reaches the liver within the bodies of wandering cells, and not in the free state.

The fact that splenectomy in dogs lessens the liability to jaundice from the introduction of hæmolytic substances, has suggested that the spleen prepares a substance directly concerned in aiding the work of the liver; and the fact that the urobilin

becomes less plentiful in the urine when a case of pernicious anæmia has been treated by splenectomy, points in the same direction. The urobilin is the evidence of increased hæmolytic activity in the portal blood. But the attempt to explain certain clinical phenomena of diseases of the spleen in terms of a 'hypersplenia' (Eppinger) or 'dysfunction of the spleen' (Hirschfeld) is due to a misconception either as to the purpose of the spleen or as to the significance of hæmolysis.

It is probable that in splenic anæmia the benefits of splenectomy are due to the liver receiving less work to accomplish in a given unit of time. The cirrhosis in the later stages results from the presence of the same toxic substances which excite the fibrosis of the spleen; the liver shuts off, and entombs within a fibrous wall, those substances with which it fails adequately to deal.

In those cases of splenic anæmia in which gall-stones are developed concurrently, the irritant traverses the liver-cells and enters into the bile, causing precipitation and encapsulation within the gall-bladder. It may also be that the composition of the bile itself is altered, the raw material supplied to the liver being short of some constituent, so that the product subsequently precipitates more readily around organisms within the gall-bladder.

The relation of the spleen to the pancreas is suggested by the anatomical features. The blood from the tail of the pancreas meets the splenic blood soon after leaving the organ. The classical work on this subject is that of Herzen, who sought to establish the existence of a 'trypsinogenic function' of the spleen. All the bearings of this work were ably set forth by Bellamy in 1900. It seems quite clear that the splenic blood is definitely different in composition according to the digestive period in which it is collected. The experiments devised to show this were exceptionally clear and convincing.

More recently, Sajous* emphasizes the importance of what he calls the 'spleno-pancreatic ferment' which comes into action between the spleen and liver, apparently detoxicating the blood which bears the food products. The albuminoid substances are converted into benign products in the liver circulation, and are passed on to the body at large in order to supply the tissues with a high percentage of phosphorus. This author, as I have said,

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* *Internal Secretions*, 8th ed., 1919, 531.

strongly emphasizes the view that the functions of the spleen, in so far as they are to be revealed by a study of the blood of the splenic vein, will be found to be connected with the cellular and not with the fluid portions.

A relation of the spleen to the *small intestine* is shown by the fact that splenic extracts powerfully excite intestinal peristalsis. Such extracts are the basis of the preparation 'hormonal', which has been so much vaunted as a remedy for constipation, for lethargic appetites, and so forth.

The position of the spleen as part of the digestive system is also demonstrable in terms of the *chemical composition* of the organ, and of the phenomena of *purin metabolism*. Horbaczewski drew attention to the endothelial cells as the visible link between cellular changes and the formation of the purins shown by chemical analysis. Many eminent chemists have elucidated this part of the subject. The subject of *iron metabolism* has constituted an important chapter in the story of researches into the functions of the spleen. Asher principally, in addition to Schmey, Kruger, Bayer, and others, has shown by many experiments that variations in output of iron go with variations in the activity of the spleen. Splenectomy results in increased loss of iron from the body. The part played by the spleen in *fat metabolism* has been studied microchemically, and it seems clear that this organ provides a link in that very complicated process of body metabolism. Experiments which have been made to show such a connection have not succeeded in Pearce's hands.

4. **The Spleen as a part of the Sympathico-endocrine System.**— The endocrine organs are those which produce an internal secretion. They belong to two main groups. In the first are those which now produce, or have at some time produced, an external secretion also. The pancreas is the best instance of this type; others are furnished by the testis and the thyroid. The second group contains those organs which do not yield an external secretion, and have never done so. The former exert their action through the circulation; the latter operate through the sympathetic nervous system.

The spleen has never yielded an external secretion; it is intimately connected with the blood-stream, and at the same time it has extensive connections with the sympathetic nervous system.

The splenic sympathetic plexus forms a dense network round the splenic artery and its ramifications within the spleen. This plexus is closely connected with the solar plexus, and therefore comes into connection with the adrenal glands. Besides this, the spleen receives branches from the vagus nerve which supply the muscular tissue of the capsule and the trabeculæ. The French writers have named this system 'parasympathetic'; the American writers 'the autonomic-sympathico-endocrine complexus';* but before we can accept or make use of the term 'autonomic instability' to explain the action of certain phenomena in connection with the spleen, much more detail is required upon the whole subject.

When Cohen asserts that 'gall-duct crises' are started by changes in the splenic end of the vasomotor chain, he reminds us not to omit the action of the nervous system from our calculations, without affording us that adequate knowledge which we crave.

Extracts of the spleen, including the proprietary substance called 'hormonal', have been shown by Berlin to have a similar action to that of cholin upon vasomotor nerves. Stern and Rothlin have found that extracts of the spleen are also capable of acting specially on smooth muscle, even in very minute doses. The active agents in the extracts are called 'lienins', and it is suggested that the spleen is concerned with the preservation of the tonus of the stomach, and of the intestinal and other smooth muscles. The action is aided by the presence of adrenalin.

The relations between the spleen and thyroid have been studied by many observers, from 1883 onwards. Zander (1893) found that removal of the thyroid will not produce a fatal result if the spleen be removed first, though other experimenters found that the fatal result was only deferred. Massenti and Coronadi, quoted by Luciani, found that thyroidectomy is associated with subsequent atrophy and fibrosis of the spleen. Klinger† did not find much definite evidence of interaction between the spleen and thyroid. Asher and Streuli's observation that these two organs both influence the bone-marrow and the consumption of oxygen by the body was not confirmed by him. He thought the variations which these and others had found were not necessarily attributable to the spleen. Hauri,‡ evidently working under the

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* *Osler Memorial of* 1919 (S. S. Cohen). † *Biochem. Zeits.*, 1919, xcii, 376.
‡ *Biochem. Zeits.*, 1919, xcviii, 1.

influence of Asher, studied the respiratory metabolism in animals deprived of the spleen, or thyroid, or both, and is satisfied that there is some interaction between the two organs. Streuli* also adduces evidence to support the view that the spleen 'balances up' the thyroid.

Investigations have also been made to ascertain if there are any special relationships between the spleen and the thymus gland. According to Bayer, the activity of the thymus is re-awakened after the spleen has been removed.

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* *Biochem Zeits.*, 1918, lxxxvii, 359.

CHAPTER IV.

THE PATHOLOGY OF SPLENIC DISEASES.

THE pathological changes found in the spleen can best be grouped according to the affinities which exist between the causative agents and the various parts of the spleen-liver system which they directly affect.

1. In the first type the provocative agent excites either a mechanical effect, or a local lesion, of the exact kind produced in other organs. The results will be expressed by the formation of an abscess, by a deposit of tuberculous nodules, by a metastatic new growth, and so forth.

2. In the second type, an organism lodges firmly in the pulp of the spleen without actually producing a gross lesion there. Like any irritant of chronic character, it induces changes in the reticulum akin to, or actually constituting, fibrosis. The best example of this condition is afforded by the chronic malarial spleen, wherein, according to modern experience, the parasites lie apparently inert for long periods, to appear from time to time in the general circulation as a consequence of some excitant, suspected or unknown. The tropical splenomegaly may be regarded as a similar example, since here also the parasites are found embedded in the splenic pulp. It is probable that many other chronic enlargements of the spleen may be regarded in the same light, and it seems not unlikely that spirochætal infections, whether syphilitic or of an unknown type, may account for many forms of fibrosis and of chronic disease. The work of W. J. Mayo on cases of splenomegaly associated with incoercible manifestations of syphilis is referred to elsewhere.

3. The third type of process is that which is set in motion by toxic substances reaching the spleen from some nidus elsewhere in the body. Foci in the mucosa or submucosa of various parts of the alimentary canal, in which there is no frank suppuration, but merely a subacute inflammatory cell-infiltration of slight or moderate extent, are easily overlooked, especially in the examination of the dead body. In pernicious anæmia, of course, definite

lesions of this kind have been discovered by means of a special technique, and have been considered by Hunter, who first recognized them, as the portal of entry of the causative infection.

Given the primary infected lesion, the course of the toxic substances continually poured out into the vascular system is identical (for a part of the circuit) with that of the blood through the spleen, liver, and bone-marrow. The toxic substances may be of various kinds, which may be named according to their action. They may remain in the blood-stream and act on the floating cells, or they may pick out certain tissues of the body. The selective power of streptococci (as shown by Rosenow) and of toxins is well recognized, and mutual affinity of soil and seed may also be present. There is nothing impossible, therefore, in conceiving that some toxins will affect the cells of the spleen-pulp exclusively, either causing degeneration in them, or stimulating them to increased activity. In either case the material which leaves the spleen may consist not only of the original toxin, but also of the products of degeneration or over-activity of the existing splenic cells. The poison contained in the blood leaving the spleen comes almost at once into contact with the blood from the stomach and the tail of the pancreas. In this way it may become altered enough to cease to have any deleterious action upon the cells next encountered, namely, the Kupffer star-cells and the other endothelial cells of the hepatic sinusoid, or the liver-cell itself. On the other hand, the toxic substance or substances may arrive at the liver unaltered, and there set up changes in the respective elements which go to make up the unit of liver-tissue. These changes are usually of a degenerative nature; but in some cases, owing to the toxins passing through the endothelium, reactive changes are excited in the fibre-cells enclosing the lobule. This is the beginning of cirrhosis.

Another series of changes results when the brunt of the action of the poisonous substances is borne by the hepatic cell itself. As occurs in other parts of the body, the passage through the cell may cause no damage, but may provoke changes in the parts beyond; in this case in the smallest beginning of the bile-channel. Here the bile itself may lose its fluidity, precipitates may form, which in the minute channels cause blockage and a mechanical biliary retention (with or without jaundice). Or it may be that, without acting in any way upon the bile, the noxious substances first affect

the endothelial lining of the bile-channels, and so set up some form of cholangitis.

In other cases, however, the liver-cell is itself affected, and a series of clinical phenomena dependent on failure of the hepatic function takes place. After that, the stereotyped secondary cirrhosis may occur.

Leaving the liver, the poisoned blood may pass through the heart and lungs without losing its toxic character, and may finally come in contact with the cells in the sinusoids of the bone-marrow, and interfere with their function, if there is any affinity between them. Where repression of function occurs, a certain type of anæmia results, or a diminution in the number of the white cells which are being made there. Conversely, increase of white cells may occur, and leucocytosis form a conspicuous feature.

Sufficient evidence has now been accumulated to enable us to form some idea of the varieties of toxins which may enter or leave the spleen ; they are grouped according to their supposed actions : as causing anæmia, hæmolysis, asthenia with muscular wasting, cirrhosis of the liver, fibrosis of the spleen, or proliferation of various cells capable of active increase (for instance in the germ centres of lymphoid follicles, or in the bone-marrow in myeloid leukæmia). Banti invoked the first three types to explain the disease which goes by his name.

1. *The most active poisons causing anæmia* ('anæmizing') are such as prevent the red cells from being formed. There is little doubt, however, that many substances are comprised in this group which produce anæmia rather by destroying the red cells or by rendering them vulnerable. In this case the phagocytes of the spleen-pulp become unduly active, and a complication is introduced, inasmuch as these pigment-laden cells carry their burden to the liver, disintegrate there, and overburden this organ, besides producing another and peculiar type of change—siderosis and proliferation of endothelial cells.

2. *The hæmolysing poisons* are important. They play the chief part in hæmolytic splenomegaly, and in some forms of severe anæmia, as well as in some special types of cirrhosis. Chevallier and Tourkine have been at much pains to insist on the dual character of the hæmolysing poisons, some of these having the property of actually destroying the red cells, while the others only cause them to become 'fragile'.

3. *Poisons which excite fibrosis* are very common. The process of fibrosis has been long assumed to be merely the last stage of an inflammatory process; but there is evidence to show that fibrosis of the spleen may be a specific phenomenon, just as in the liver biliary cirrhosis is certainly the result of active and direct stimulation of the connective-tissue cells.

4. *The poisons which excite cell-proliferation* may concern the cells of the Malpighian bodies, as in lymphatic leukæmia and some kinds of Hodgkin's disease, or the cells of the spleen-pulp. In the latter case several things may happen. The pulp-cells may assume the properties usually restricted to the cells of the bone-marrow concerned with the formation of white cells; in these circumstances bone-marrow cells are produced. If this should occur in a slight degree, it is only revealed by microscopic examination. Instances of this action are afforded by various acute specific fevers. If it occurs in a greater degree, the enlargement of the so-called splenomedullary leukæmia is brought about. Sometimes the pulp-cells develop enormous numbers of cells of all kinds, and so produce a tissue of very complicated structure, as in lymphosarcoma or Hodgkin's disease.

CHAPTER V.

THE CLINICAL AND ASSOCIATED PHENOMENA IN SPLENIC DISEASE.

THE clinical and other phenomena which occur as evidences of splenic disease may now be discussed as a corollary to the various matters so far considered. The list of symptoms and signs likely to be encountered resolves itself into a short one when the mechanical results which follow upon a gross enlargement of the organ, or upon the obstruction to the portal circulation by a terminal cirrhosis of the liver, are omitted.

1. **Anæmia.**—Anæmia is caused by many diseases. In this connection it is only necessary to consider the type of anæmia which rightly directs the attention of the clinician to the spleen as its cause. The preceding discussion has briefly dealt with the subject of hæmolysis. It may now be asserted that a disease of the spleen is to be suspected when there is any evidence that hæmolysis is associated with anæmia. What exactly is the full significance of the term 'hæmolysis'? It may be taken to indicate the occurrence in orderly succession of the following events: a destruction of the red cells, the accumulation of their remains in the spleen, the ingestion of these remnants by the phagocytic endothelial and reticular cells, and finally the transmission of these engorged cells to the liver, in whose 'sinusoids' they are disintegrated preparatory to the absorption of their particles by the stellate cells of that organ. Hæmolysis will be rendered an easier, and therefore a more frequent process, if any diminution occurs in the resistance offered by the red cells to their destruction. Such a change has been described by Chauffard, who speaks of a 'dystrophy' of the red cells, a condition in which their vulnerability is increased, and there is consequently a special 'fragility'. It has been asserted that the presence of a fragility of the red cells indicates that the seat of any disease in which it occurs is in the spleen; but there is evidence to controvert this opinion. Such a

fragility might be due either to an early error in the formation of red cells by which there was an attenuation (through defective supply of the necessary material) of their lipoid component, or to the inimical effects of a substance produced by bacterial agencies in some lesion, perhaps quite inconspicuous, in the mucosa of the alimentary canal.

But every anæmia associated with disorders of the spleen is not characterized by hæmolysis. There is another important group of anæmias in which the initial disorder is either in the bone-marrow (and in the later changes in the spleen) or is dependent upon the same cause as that which affects the bone-marrow. In this class of case, the medulla being directly damaged, the process of formation of blood-cells is inhibited, or even in some cases arrested. In Hodgkin's disease, for example, the bone-marrow may become involved, and the part concerned in the formation of red cells then undergoes atrophy. In this instance there is from the onset some agent which injures the spleen and bone-marrow almost simultaneously. The train of symptoms which follows the anæmia may then become masked in those far more conspicuous features which present the clinical picture of the original disease.

When once the process of hæmolysis has developed to the stage described above, the further course of events will depend on the manner in which the liver-cells cope with their increased burden. On the one hand, the poison (which has destroyed the red cells) may pass through the liver-cells without affecting them; the extra load imposed upon them is borne without injury. On the other hand, the poison may actually injure the hepatic cells, so that the excess of blood-pigment is disposed of with a steadily increasing difficulty. Then, at last, under a continued strain, the inadequacy of the liver may become apparent, either clinically in the form of jaundice, or pathologically by reason of the appearance of urobilin in the urine. The great functional capacity of the liver-cell accounts for the gradual, insidious, and tardy onset of the symptoms connected with the involvement of the liver in such conditions.

It is interesting to find that the clinical phenomena due to a hæmolysis are absent in those diseases in which the liver-cell is equal to its work and does not suffer impairment. In the enlargement of Hodgkin's disease, of myeloid and lymphatic leukæmia,

of sarcoma of the spleen, of lymphogranuloma, all the phenomena associated with hæmolysis are characteristically absent. But none the less anæmia develops. The reason is, without doubt, the following :—

With the exception of the leukæmias, where the energies of blood-formation become overwhelmingly directed to the formation of white cells instead of red, these various diseases of the spleen are associated with progressive fibrosis ; there is consequently a gradual interference with the normal capacity of the endothelial cells to remove effete red cells. This entails a loss of iron to the body. The liver-cells do not receive sufficient iron in that form which is suitable for reconstruction in the next step of the cycle. Even if phagocytes in other parts of the body assume the function of red-cell destruction, they have not direct access to the liver, and cannot therefore supply this organ with sufficient speed or adequacy. It seems quite clear, from the experiments in connection with iron metabolism, that the spleen is situated where it is in order to enable the iron-laden endothelial cells to have a free channel for their passage into the minute capillaries of the liver, through which they are too large to pass.

2. **Jaundice.**—When we consider jaundice as the result of a toxic process in the spleen-liver system, it is necessary to define two important factors. These are the site of action of the poison, and the nature of the poison.

The site of action may be in the liver or in the spleen itself. For instance, in splenic anæmia, the site of action is not in the liver, for in this disease there is no primary interference with the activity of the liver-cells ; these do not become affected until the later stages of the disease, after cirrhosis has developed. Even then the action does not begin within the liver cells, which suffer only indirectly by compression from without ; disorganization within the cells does not appear first. Hæmolytic splenomegaly, on the other hand, provides an example of a disease in which the action of a toxic substance is on the liver-cells themselves, since from the first they are either poisoned, or burdened beyond their normal capacity for dealing with blood-pigment derived from the spleen. Associated with this action, no doubt, is a passage of toxic substances into the bile, for this is suggested by the remarkable tendency to cholecystitis and cholelithiasis which is present

in this disease. It is possible that these toxic substances act selectively upon the mucosa of the gall-bladder.

The influence of the nature of the poison is shown by its site, for the locality in which such poison lodges is dependent upon the kind of cell affected by it. The poison which acts directly on the protoplasm of hepatic cells is necessarily of a different nature from one whose energies are expended in affecting the reticular cells of the spleen. The mode of production of jaundice differs in the two cases, not so much in kind as in degree; because the errors which arise are developed at an earlier stage in the cycle of hæmoglobin metabolism when the toxin selects the spleen than in the cases in which the liver-cell is primarily damaged. In the spleen, the hæmoglobin becomes separated from the effete red cells; in the liver this pigment becomes hæmatin, which, as is well known, becomes bilirubin simply by hydrolysis.

In his able study of jaundice* Willcox shows very clearly that the bile-pigment may occur in the blood up to a certain degree of concentration without any clinical evidence of its presence becoming evident. He cites Blankenhorn's recent researches on the subject in which a certain 'threshold' can be spoken of, in regard to the amount of bilirubin in the blood. Jaundice does not appear until that threshold has been reached. In other words, a toxic process affecting the metabolism of hæmoglobin may be mild enough to pass away without jaundice appearing; it may indeed have existed for some time although the onset of jaundice would lead the observer to assume that the toxic process was only now beginning. Willcox proceeds to divide cases of toxic or toxæmic jaundice into three groups: those in which the degeneration of liver-cells predominates; those in which destruction of red cells is the chief process; and those in which a catarrh of the finest bile-ducts accounts for the phenomenon. Different toxic agents act in these three ways to differing extents. Simple anæmias are associated with little degeneration, but show well-marked destruction of the red cells; in yellow fever, and in arsenical poisoning, the liver-cells undergo degeneration, whereas in spirochætosis icterohæmorrhagica, relapsing fever, and in epidemic catarrhal jaundice, the changes in the bile-passages are the most conspicuous effect.

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* *Lettsomian Lectures*, 1919.

Thursfield & Gow* have simplified the subject by fixing attention upon one type of poison disordering the functions of the spleen in different ways, sometimes entailing the appearances of jaundice and sometimes not.

It is now clear that the site of action and nature of the poison are closely dependent upon one another. It is also clear that the changes produced in the bile depend on the site of action of the toxin. When its action is upon the commencement of the hæmoglobin cycle, that is, in the spleen, jaundice is an effect only when the concentration of bile-pigment in the blood reaches a certain point. When the interference with the metabolic cycle is at the later stage, that is, in the liver-cell, jaundice appears only as soon as there is sufficient retention in the ducts. This retention is mechanical, depending on the fact that the bile ceases to be sufficiently fluid because the liver-cell fails to make sufficient bile-salts. The jaundice is therefore produced in this case without any disturbance of the function of the cells in forming bile-pigment.

In other words, when the poison is acting in the spleen the jaundice is due to active interference with the changes in the blood-pigment; when the poison is acting in the liver the jaundice is a mechanical one, due to other parts of the liver-cell being disturbed than those which deal with the formation of bilirubin.

On the other hand, it is not safe to argue that when a patient has no jaundice his hæmoglobin is therefore normal. Apart from the fact, which Willcox emphasizes, that jaundice does not develop until a certain amount of pigment has accumulated, there is the fact that blood-pigment may fail to break up correctly and still produce no jaundice. Blood-pigment, in breaking down, gives rise to two portions—one free from iron, the other containing iron. The former, undergoing purely intramolecular change, appears in the liver-cell as bilirubin, and passes out into the bile capillaries; the iron-containing portion makes its way back to the site of manufacture of the red cells. In disease, this story becomes modified, either at the first stage or at the second. The division of the blood-pigment molecule may not take place; hæmatin is then formed, and gives rise (it is supposed) to one of two substances (maleic imide, maleic anhydride), either of which being *colourless* will escape observation in the liver-cell. Or, on the other hand, the

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* *St. Bart.'s Hosp. Reports*, 1914, i, 7.

iron-free substance formed from the blood-pigment molecule may not become converted into bilirubin, but into a hæmopyrrhol, which is also colourless. In this case, also, bile-pigment fails to appear in the liver-cells (and in the bile in the gall-bladder ?) and jaundice is not present.

These considerations provide a suggestive basis for the explanation of the anomalies which appear from time to time in reported cases of cirrhosis associated with splenomegaly.

As a rule, however, jaundice is the actual result of toxic action upon some part of the spleen-liver system, however different the mechanism may be in the particular types of toxin concerned. Even the simplest poisons may act simultaneously upon different parts of the system, so that it is difficult to describe their actions according to their chemical composition. When we find that substances whose chemical constitution is completely known, such as nitrobenzene, trinitrotoluene, toluylenediamine, do not act equally upon the red blood-cells and the hepatic cells, it is not surprising to find difficulties in approaching the actions of those complex bodies which are associated with splenic disorders. This is why it is more satisfactory to classify the poisons according to the place which they select for their action than according to their nature.

When the relation between these processes and the production of cirrhosis has to be considered, the old question as to whether cirrhosis or liver degeneration is primary need not trouble us. The view that cirrhosis begins merely as a consequence of a process initiated in the spleen is much more helpful. It is clear that the presence of iron which is not in a suitable condition for reconstruction in the liver, aided by the direct action of a poison (modified by passage both through the splenic endothelium and the endothelial cells of the liver sinusoids), may excite an overgrowth of the fibre-cells outside the liver lobules. If it should do so, not only will there be cirrhosis of the Laennec type, but there will be a special form of pigmentary deposit also. A purely hæmolytic poison, that is to say, has modified the process of disposal of blood-pigment, in spite of its own modification by the splenic products into a cirrhogenic substance. It is certainly significant that in such cases the pancreas not seldom shows a widespread change.

The interrelation between the pancreas and the spleen and liver is not capable of sufficient discussion, because, unfortunately, our information about this is slender and uncertain. A direct

connection between pancreatic disease and hepatic cirrhosis is at present clear only in one form of cirrhosis, the so-called 'pigmentary cirrhosis'. If the secretion from the tail of the pancreas (where the islands of Langerhans are most numerous) plays a necessary part in the intravascular changes which take place between the spleen and liver, attention would naturally be directed to a determination of the frequency with which interstitial pancreatitis, focal or diffuse, is associated with splenic disease; and this is just a point upon which knowledge is lacking. Suffice it to suggest that the story of the mechanism of cirrhosis is hardly complete without knowledge about the part played by the pancreas. Here, as well as in the subject of bile-duct infections, we find the two possible channels of disease—the ascending from the duodenum, and the descending from the acini: the latter being intimately connected with the formation of a toxæmic type of jaundice when the liver is involved, whereas the possible occurrence of changes descending the pancreatic ducts does not appear as yet to have been considered by any workers in this field of physiology. Hunter elaborated the view that important changes result from a descent of toxins or organisms into the duodenum,* and the French school have also urged in this suggestive direction.

3. **Petechial Hæmorrhages.**—These are occasionally seen in cases of splenic disease, in leukæmia, and in von Jaksch's disease. They always denote damage to the endothelial cells of the capillaries in various parts of the body by a particular form of poison, named 'endotheliotoxin', because its effects are known and obvious, and because there is no adequate knowledge indicating its chemical constitution. The minute petechial hæmorrhages are scattered through many organs, appear on serous surfaces, and may occur on mucous surfaces, as in the nose and on the gums or in the kidneys. In these cases they almost certainly denote the channel of excretion of the poison by which they are caused. Such clinical phenomena, as is well known, sometimes accompany the circulation of certain septic organisms or of the toxins derived from them; they here signify a special property of the leukæmia and allied poisons.

4. **Muscular Weakness.**—This may be associated with an actual wasting of the muscle, which partly accounts for the

* *Jour. Pathol.*, 1896, ii, 259.

emaciation noticeable in advanced cases of leukæmia and of splenic anæmia. When we remember the intimate association between the spleen and endocrine system, the question arises as to the extent to which the phenomena of muscular weakness and asthenia are to be attributed to a direct action upon the adrenal or thyroid glands. The inter-relation of these endocrine glands with each other and with the glands possessed of external secretions is only now being revealed to us by the work of many observers.

5. **Pyrexia.**—Pyrexia as a feature of splenic disease has only recently attracted close attention. There is a tendency to ascribe fever appearing in the course of diseases, hitherto regarded as intrinsically apyrexial, to a secondary infection with septic organisms, especially when the temperature curve, as is frequently the case, is intermittent. In Hodgkin's disease pyrexia is almost constant, is indeed regarded by some clinicians as almost essential to a correct diagnosis. In pernicious anæmia pyrexia runs in waves spread over three, four, or more weeks, to be followed by apyrexial phases ; in leukæmia there are also pyrexial periods. The question is raised at once as to whether each of these diseases may be of microbic origin. In hæmolytic jaundice fever occurs periodically ; it is generally slight, and lasts for two or three days. In other cases it is severe, but of shorter duration ; the temperature rises abruptly, remains at its maximum a very brief period, and falls quickly. There is the characteristic 'steeple' chart of cholangitis. In such cases stones are often, but not always, present in the common bile-duct.

6. **Splenomegaly.**—When the spleen is recognized, by any method of clinical examination, as being enlarged, it is certain that it is at least twice the normal bulk. Any enlargement less than this, and often even this, cannot be discovered by palpation or by percussion. Perhaps, taking an average of all cases, the very largest spleen is to be found in Gaucher's disease, the next largest in leukæmia, and the next in malaria, though occasional instances are found in this last disease in subtropical countries which surpass all others. Then comes a series in which the spleen is large, but not excessively so, and, finally, there are cases in which the spleen is not enlarged at all. Thus, the spleen may be involved in Hodgkin's disease without being clinically enlarged ; it is not always enlarged

in pernicious anæmia, and its enlargement then bears no discoverable relationship to the gravity of the case. These aspects of the subject are so well known that this symptom is only referred to for the sake of drawing attention to the fact that an absence of enlargement of the spleen does not relieve this organ from the suspicion of being the source of a patient's illness.

7. **Leucocytosis.**—The significance of this phenomenon lies in the fact that it affords an insight both into the nature of the agent at work, and into the state of those tissues which are concerned in the manufacture of the leucocytes. There are some toxic substances which expend their whole baneful power upon the circulating leucocytes; others affect their formative tissues; while a few may act upon both. The action exerted may be one of stimulation, so that leucocytosis results; or it may be one of inhibition, and result in leucopenia. In pernicious anæmia the poisonous action on the bone-marrow affects the white cells as well as the red, so that a very low white-cell count is the rule. In hæmolytic jaundice, on the other hand, the action on the bone-marrow is one of stimulation, and leads to an increased outpouring of leucocytes.

Where the poisonous substances act upon the pulp-tissue of the spleen, upon the endothelium of the liver sinusoids, and upon the whole reticulo-endothelial system, exciting the dormant cells to form myelocytes (myeloid metaplasia), stray myelocytes can be found in the blood-stream. This occurs in some forms of acute splenitis, occasionally in Hodgkin's disease, notably in infantile splenic anæmia, and sometimes in pernicious anæmia. The same process occurs in massive fashion in leukæmia, where every part of the reticulo-endothelial system competes against the rest in the effort to produce and pour out these abnormal cells. The pulp-tissue of the spleen then appears almost as a replica of ordinary bone-marrow tissue, and the immature cells pass freely into the blood-stream. In virtue of the character of these cells, which, strictly speaking, are not leucocytes, such a phenomenon should not be described as an extreme leucocytosis.

It is therefore not sufficient in any case of leucocytosis to determine merely the presence or absence of an increase in the number of white cells. It is necessary also to ascertain which varieties of cells are represented in the increase, and to recall the

significance of each specific increase. An increase of the neutrophiles indicates the presence of toxins of nucleoprotein form, or of the products of dissolution of albuminous substances. An increase of lymphocytes denotes activity of poisons of lipoid character, with whose destruction these cells are especially concerned. The large mononuclear leucocytes are increased when the particles of abnormal matter are large enough to be microscopically visible. When the eosinophils are increased, it may be concluded that the poisonous substances have an affinity for the sympathetic nervous system, although the relation of these cells to the integrity of the nervous system is not the only one they possess. Poisons may accumulate in various tissues and set up local accumulations of these cells (as in Hodgkin's disease), and at the same time excite the bone-marrow, the spleen, and the lymph-glands to join in the over-production of these cells.

The tubercle bacillus and the spirochæte of syphilis are well known to secrete lipoid substances; the association of lymphocytosis with these diseases is to be expected. That stimulation of the lymphocyte formation occurs in pernicious anæmia, splenic anæmia, and Graves' disease indicates the direction of the inquiry to be made into the ultimate causation of these diseases.

8. **The Spleen and the Hæmorrhagic Diathesis.**—During recent years the suggestion has been made that the spleen may in some degree be concerned with the life-history of blood-platelets. In a patient suffering from purpura hæmorrhagica there is a decided diminution in the number of platelets, and the spleen is enlarged. After splenectomy normal conditions are restored; in proportion as the number of platelets is increased, so the clinical symptoms disappear. Cases which illustrate this experience are recorded by Schmidt,* Benecke,† and Kaznelson.‡ The name 'splenogenic thrombolytic purpura' has been given to this condition, and a 'thrombocytolytic syndrome' is described. It is supposed that there is an increased destruction of platelets by the cells of the reticulo-endothelial system. If, however, the whole of this vast system is implicated, it is not easy to understand why extirpation of the spleen should cure the disease or relieve the patient of

* *Wien. klin. Woch.*, 1918, 487, 959. † *Therap. d. Gengenw.*, 1917, Dec.
‡ *Deut. med. Woch.*, 1918, 5.

symptoms. Katsch* has reported cases of thrombopenia where there is no purpura; and, conversely, cases of purpura where the number of platelets is not diminished.

9. **Urobilin in the Urine.**—Recent work shows that the presence of this substance in the urine is an indication of functional inadequacy of the liver-cell, which is accompanied by some degree of obstruction in the minute extracellular bile canaliculi. A certain quantity of bile escapes through the ducts, undergoes the usual transformation into stercobilin in the intestine, re-enters the liver, but cannot find a free exit through the hepatic cells. The significance of this phenomenon is that there is an increased breakdown of red cells and hæmoglobin, and that there is a state of cirrhosis in the liver; the degree of disturbance of function is in proportion to the degree of 'fragility' of the red cells. Viewed in this light, the next step to be followed, after arriving at a conclusion that the spleen is diseased, is to determine the degree of damage to the liver, and instead of regarding cirrhosis as a collective term for many distinct morbid entities, to view all cirrhoses as representative of degrees of implication in the one morbid process.

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* *Münch. med. Woch.*, 1918, 33.

CHAPTER VI.

PERNICIOUS ANÆMIA.

(ADDISON'S ANÆMIA. IDIOPATHIC ANÆMIA.)

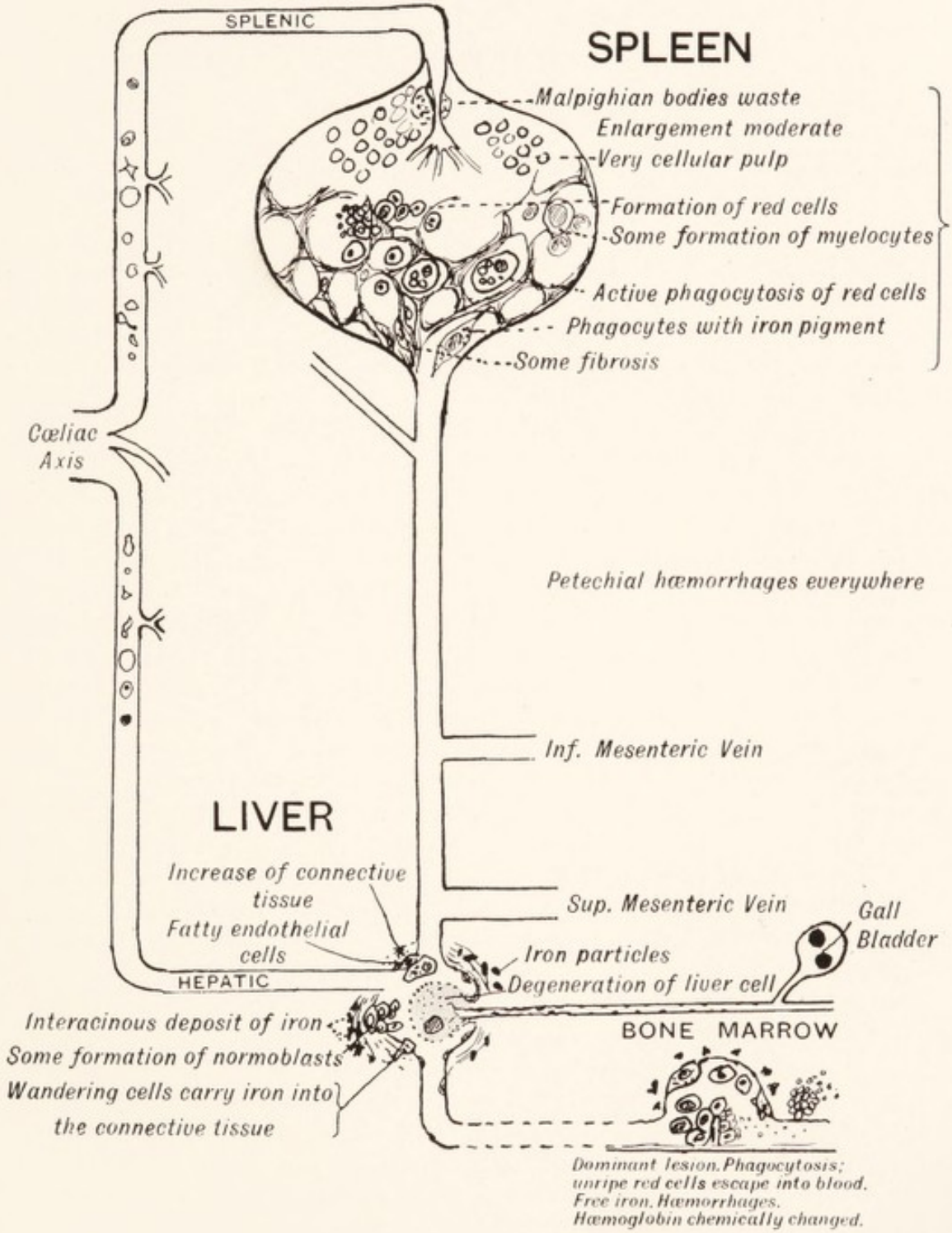
(*See Plate III.*)

THE literature of pernicious anæmia is inexhaustible. But bulk is no index of value. It is only within recent years—and especially since the work of W. Hunter, and of W. J. Mayo, Percy, and others—that some enlightenment has been thrown upon a difficult and complex problem.

The first case of idiopathic anæmia was recorded in 1822 by Combe, who applied this term to it. As Hunter says, the problem which this disease has presented throughout its whole history was never more clearly stated. Combe was recording "a well-marked instance of a very peculiar disease which has been altogether overlooked by any English author with whose writings I am acquainted. Unfortunately, however, such is the allowable diversity of opinion on most medical subjects, that it is very possible the following case (disease) may be viewed in different lights, and receive different appellations; and while some may be disposed to regard this anæmia as constituting a morbid state *sui generis*, others may consider the defect in red circulatory mass (so extreme that every organ in the body, with the exception of the spleen, was deprived of its red blood) as an accidental and occasional circumstance denoting some peculiar change in the assimilative powers, the primary stages of which we have been unable to detect. Doubtful myself which of the two opinions may be the most correct, I shall do little more than state correctly the phenomena of the case, and minutely, the appearances presented on dissection. One remark only I may at present offer—that if any train of symptoms may be allowed to constitute anæmia a generic disease, the following may be considered an example of it in its most idiopathic form".

This description of Combe's case apparently attracted no attention. In the year 1855 Addison, in his *Disease of the Suprarenal Capsules* (pp. 2, 3), gave an account of the disease which, in

PLATE III



THE CHIEF CHANGES IN PERNICIOUS ANÆMIA

fullness of detail, accuracy of statement, and clarity of language, has never been surpassed. As a preface to his description of what we now called 'Addison's disease', he considered that it might not be without interest or unprofitable to give a brief narrative of a form of anæmia the cause of which was not discoverable. It was whilst seeking to throw some additional light on this form of anæmia that he stumbled upon curious facts which led to his discovery of the disease of the suprarenal capsules which now bears his name. His account is as follows :—

"For a long period I had from time to time met with a very remarkable form of general anæmia, occurring without any discoverable cause whatever; cases in which there had been no previous loss of blood, no exhausting diarrhœa, no chlorosis, no purpura, no renal, splenic, miasmatic, glandular, strumous, or malignant disease. Accordingly, in speaking of this form of anæmia in clinical lecture, I, perhaps with little propriety, applied to it the term 'idiopathic' to distinguish it from cases in which there existed more or less evidence of some of the usual causes or concomitants of the anæmic state.

"The disease presented in every instance the same general character, pursued a similar course, and, with scarcely a single exception, was followed, after a variable period, by the same fatal result. It occurs in both sexes, generally—but not exclusively—beyond the middle period of life, and so far as I at present know, chiefly in persons of a somewhat large and bulky frame, and with a strongly-marked tendency to the formation of fat. It makes its approach in so slow and insidious a manner that the patient can hardly fix a date to his earliest feeling of that languor which is shortly to become so extreme. The countenance gets pale, the whites of the eyes become pearly, the general frame flabby rather than wasted; the pulse perhaps large, but remarkably soft and compressible, and occasionally with a slight jerk, especially under the slightest excitement; there is an increasing indisposition to exertion, with an uncomfortable feeling of faintness or breathlessness on attempting it; the heart is readily made to palpitate; the whole surface of the body presents a blanched, smooth, and waxy appearance; the lips, gums, and tongue seem bloodless; the flabbiness of the solids increases; the appetite fails; extreme languor and faintness supervene, breathlessness and palpitations being produced by the most trifling exertion or emotion; some

slight œdema is probably perceived about the ankles; the debility becomes extreme, the patient can no longer rise from his bed, the mind occasionally wanders, he falls into a prostrate and half-torpid state, and at length expires; nevertheless, to the very last, and after a sickness of perhaps several months' duration, the bulkiness of the general frame and the amount of obesity often present a most striking contrast to the failure and exhaustion observable in every other respect.

"With perhaps a single exception, the disease, in my own experience, resisted all remedial efforts, and sooner or later terminated fatally. On examining the bodies of such patients after death, I have failed to discover any organic lesion that could properly or reasonably be assigned as an adequate cause of such serious consequences."

In the year 1871 Biermer described cases of this disease, apparently believing that it had not been observed by earlier writers. His claim to be the first to recognize the disease excited the wonder of the physicians in this country, especially those on the staff of Guy's Hospital. His writing, however, undoubtedly stimulated interest in the subject, and popularized the knowledge then possessed with regard to it. He gave to it the name 'progressive pernicious anæmia'. The work of William Hunter began in the year 1888. Between 1888 and 1890 he developed his views as to the hæmolytic nature of the disease, its toxic cause and gastro-intestinal site; and between 1890 and 1900 he elaborated and expounded his thesis that the disease owned an infective etiology. In 1907 he wrote: "Addison's anæmia is in truth a very remarkable disease, of a specific infective hæmolytic nature, in which both clinical observations and necropsy reveal definite hæmolytic and infective processes as a constant feature of the disease, and in which a very definite series of points can be got out of the history throwing light on the mode of origin of the disease, and the source of the infection in the alimentary tract, and of the lesions of the tongue, stomach, and intestine connected with it". The treatment of pernicious anæmia by arsenic was introduced by Byrom Bramwell.

It has long been the custom to speak of anæmia as *primary* and *secondary*; the latter being the consequence of some disease or dyscrasia, one of whose manifestations is expressed in terms of blood-change; the former being a change occurring in the blood

apart from any other change in the body. The definition of an anæmia as 'primary' involves a belief in the existence of the blood as an organ whose cells are capable of undergoing degeneration or destruction as the consequence of a morbid process limited to itself. But as Vogel points out,* the blood is not itself an organ, but is the direct product of the activity of the various hæmopoietic organs or systems, and may in a sense be more properly regarded as a secretion than as an organ. The erythrocytes having relinquished their nucleus can no longer be regarded as true cells; and the leucocytes have the power of reproduction only in a very limited degree, if at all. The terms 'primary' and 'secondary' therefore do not hold the meaning they are intended to convey.

Within the normal blood the elements are in a state of unceasing change. This change, nevertheless, maintains the blood in a state of equilibrium. Cells are constantly dying, and undergoing destruction; and cells are constantly being formed to replace those which are lost. An anæmia may result in consequence either of the diminished production of red cells or of the increased destruction of red cells, or perhaps of both. The anæmias which arise as a result of diminished production of red cells include those seen in cachexias, wasting diseases, tumours, toxic anæmias, aplastic anæmia, etc. The anæmias which arise as a result of the increased destruction of red cells include those seen in cases of hæmorrhage, in hæmolytic icterus, in the anæmias due to hæmolytic poisons, pyrodin, phenylhydrazin, toluylenediamine, etc., and some forms of intestinal parasite, and so forth. In the latter group pernicious anæmia is included. There is in this disease, as Mott first showed, an abnormally great cell destruction, with a pathologically increased demand on the blood-forming tissues rather than an inadequacy on the part of these to meet the normal demand. But to say only this is to say no more than is true of the condition hæmolytic jaundice; yet, whatever the affinity between these two diseases may be, their clinical manifestations and their destiny are very dissimilar. In pernicious anæmia the red-cell-forming tissue in the bone-marrow is also profoundly affected by the hæmolytic poison, and is subject to a double stress; it is stimulated to over-production at a time when it is fighting to ward off the attack of a poison attempting its destruction. So great is the

* *Jour. Amer. Med. Assoc.*, 1916, lxvi, 1012.

effort of the bone-marrow to meet the demand made upon it that the parent cells of the erythrocyte are liberated before their offspring daughter and granddaughter cells are created. The greater the urgency of the demand made upon the bone-marrow, the earlier is the type of cell liberated and set adrift in the circulation. The character of the nucleated cell set free may therefore be an index of the gravity of the disease. Death occurs in pernicious anæmia because of the persistence of the increased destruction of red cells at a time when the efforts of the medulla to form blood break down under the ceaseless heavy strain imposed upon it. It will be recognized at once that the conditions existing in this disease, in so far as the changes in the blood and in the organs producing blood are concerned, resemble those seen in the embryo; a "reversion to the embryonal type of hæmatopoiesis" is spoken of as a characteristic of the disease.

If, then, the disease is primarily a hæmolytic process, a process in which red-cell destruction is the outstanding feature, what is the nature of the poison, and whence does it come? Hæmolysins of definite origin are known. In the hæmolytic anæmia of pregnancy a definite hæmolysin has been found in the placenta. In the anæmia due to bothriocephalus, cholesteryl oleate, set free by the decomposing segments of the worm, affords the poison for the red cells, although every harbourer of this parasite is not equally susceptible to the action of this substance. In some forms of cancer, especially of the stomach and ascending colon, poisons appear to be liberated which cause a blood-picture hardly distinguishable from that of pernicious anæmia. Chronic carbon-monoxide poisoning among charcoal workers, industrial lead, and perhaps also arsenic poisoning, appear to operate in the same manner. It is suggested that hæmolytic substances formed by pathological bacteria in the intestine may gain access by this route, as first suggested by Hunter.* J. H. King,† after careful study of three cases of pernicious anæmia treated by splenectomy, and after conducting a series of experiments upon dogs, concludes: "In pernicious anæmia, hæmolytic jaundice, and cirrhosis of the liver, the hyperactive spleen influences unfavourably the anæmia through its regulation of the highly hæmolytic unsaturated fatty acids of the blood. The removal, therefore, appears to be

* *Brit Med. Jour.*, 1907, ii, 1299. † *Arch. of Internal Med.*, 1914, xiv, 145.

indicated. Splenectomy of itself, besides influencing the production of hæmolytic, unsaturated fatty acids, raises the percentage of antihæmolytic substances in the blood; that is, the total fats and cholesterins".

The work of the surgeons in the last few years has afforded some evidence, if not as to causation at least as to associated conditions, in cases of pernicious anæmia. N. M. Percy, whose work on this difficult disease has been marked by a most earnest devotion and remarkable success, has pointed out that since his attention was especially directed to the testing of Hunter's view of the infective origin of pernicious anæmia, he has found evidence of infective foci in 95 per cent of cases. In a consecutive series of nine operations for pernicious anæmia, all specimens removed (spleen, gall-bladder, appendix) were sent at once for pathological examination. Bacteria were grown from 3 of the 9 spleens, from 4 of the 7 gall-bladders, and from 6 of the 7 appendices. The only case not giving a bacterial growth was one in which pyorrhœa had long been present. The chief organism found was the hæmolytic streptococcus—7 cases; in 5 the *Bacillus coli* was found; in 4 *Streptococcus viridans*. Smithies, of Chicago, has grown bacilli and cocci of the hæmolytic type from infected areas about the teeth, tonsils, and accessory sinuses. In a series of 24 cases, preceding the 9 just mentioned, Percy records the following gross lesions. In 20 there was chronic cholecystitis with or without gall-stones; in 17 of these there was evidence of old disease in the appendix; in 6 there were infective foci in connection with the teeth; and in 1 in connection with the tonsil.

A detailed description of the symptoms and the diagnosis of pernicious anæmia is not necessary. But I may be allowed to quote from a description kindly sent to me by Dr. N. M. Percy, of Chicago, whose experience of the surgical treatment of this disease is unsurpassed. Dr. Percy has been impressed with the importance and constancy of the following conditions, and believes them to be of such importance that their presence or absence may well decide the diagnosis in a difficult case:—

"1. *Achlorhydria.*—In all cases where a test was made, with one exception, no trace of free hydrochloric acid was found in the fasting contents and in the specimens of test meal. The exception was a very early case, and showed a very low hydrochloric acid content. A few cases were in such an extreme condition that it

was not deemed advisable to subject them to the strain of passing the stomach tube. In all other cases the gastric analysis was part of our routine in making the diagnosis. The absence of free hydrochloric acid occurred with such regularity that I would hesitate to make a diagnosis of pernicious anæmia in any case showing the presence of free hydrochloric acid in the stomach unless it be a very early case and the acid content very low.

" 2. *Tongue.*—The appearance of the tongue was noted in every case, which revealed a peculiar smooth, glossy surface. In some this was present only on the sides of the tongue, in others its whole surface was involved. This appearance of the tongue, which was always present but in varying degrees, is due to an atrophy of the mucous membrane and sometimes to a hyperplasia of the tongue muscle-bundles. A glossitis was present in a large per cent of our cases. Hunter lays particular emphasis upon the lesions in the mouth, and claims there is no other anæmia in which glossitis is so constant and persistent. The appearance of the tongue is so constant that it may be considered the most important external sign of pernicious anæmia.

" 3. *Pigmentation.*—Pigmentation was found to be present in the majority of cases, especially on the backs of the hands. In some this may be diffuse, in others freckle-like.

" 4. *Hypertension* (*chronic nephritis*).—It is noted that hypertension (chronic nephritis) frequently co-exists with pernicious anæmia, both probably being due to chronic infection, but they have no definite connection with each other. The cases having high blood-pressure were of middle age or beyond. Strange as it may seem, the hypertension persists through periods of severe weakness and with a blood-count as low as one million or under, only letting down when the patient becomes extremely ill in the terminal state of the disease.

" The disturbance of renal function which accompanies marked cases of pernicious anæmia—as pointed out by Christian—was noted in many of our cases. The disturbance is similar to that found in patients with advanced nephritis, but is not accompanied by hypertension or any other evidence of chronic nephritis. The disturbance seems to be due to the anæmia, and subsides as this improves. It is important from the standpoint of prognosis to determine in each case whether the disturbance of renal function is due to the anæmia or to chronic nephritis.

"5. *Diarrhœa and Vomiting* (*intermittent*).—Attacks of diarrhœa and vomiting, especially the former, were frequently noted, and were found difficult to control by medical means. These cases yielded readily to blood transfusions, followed by administration of large doses of hydrochloric acid. Vomiting invariably stopped immediately after transfusion, and the diarrhœa usually subsided within a few days. In a number of instances an attack of diarrhœa was the first symptom of the disease noted by the patient.

"6. *Nerve Manifestations.*—The nerve symptoms noted were many and varied, ranging from the most common, that of tingling in the fingers and toes, to those simulating tabes and multiple sclerosis. The tingling sensation in the fingers, the presence of which varies from time to time, was noted in practically every case. Marked psychical disturbances were noted in some cases.

"The characteristic appearance of the tongue, the pigmentation, and the achlorhydria occurred with such constancy that their presence may often be the deciding factors in the diagnosis."

Splenectomy in Pernicious Anæmia,—In the year 1913 three observers independently, and for different reasons, suggested the performance of splenectomy in cases of pernicious anæmia. Eppinger* advocated the operation because he had observed a diminished output of urobilin, and other evidences of diminished hæmolysis, after the spleen had been removed for other conditions; and he assumed that in pernicious anæmia, a disease of exaggerated hæmolysis, the removal of the spleen would control or counteract this tendency. De Castello† was guided by the observations of himself and others as to the great benefits resulting from the operation in the related conditions splenic anæmia and hæmolytic jaundice. Klemperer‡ was influenced by the clinical observation that splenectomy for such simple conditions as laceration was, in some instances at least, followed by polycythæmia. Advocacy by all of these men of great repute soon led to a wide adoption of the practice in Germany, and an adoption, not so general, in America. In England very little was done. The results, which were not long in coming, showed that the mortality of the operation was high,

* *Berl. klin. Woch.*, 1913, xxix, 2409. † *Deut. med. Woch.*, 1914, xl, 639.
‡ *Therap. d. Gegenw.*, 1913, liv, 385.

that the immediate benefit which not seldom followed was transient, that post-operative complications were frequent, and that, with few exceptions, the general course of the disease was not materially altered. That splenectomy alone might offer help seemed probable from the work of Robertson,* who found, in cases studied by himself, that the rate and degree of hæmolysis in pernicious anæmia underwent a constant and marked decrease after removal of the organ. Largely owing to the work of W. J. Mayo and his most able band of colleagues, and of N. M. Percy, a wider view of the necessities of these cases was taken, with a great improvement in results. The anæmic condition of the patients was improved by transfusion of whole blood ; and foci of infection, possibly 'primary', but certainly co-existent, in the mouth or accessory sinuses, or in organs laid bare by the abdominal operation, were removed. The purpose of the extended operations consisted, as Percy said, of three main factors : (1) An attempt to stimulate the production of new blood by massive 'step-ladder' transfusions of whole blood ; (2) An attempt to overcome the absorption of hæmolytic bacteria or their toxins by the radical removal of local foci of infection ; and (3) An attempt to protect the newly-formed and older red cells by removing the spleen. Each of these steps is important. The 'step-ladder' transfusions bring about an elevation, step by step, of the quality of the patient's blood in respect of red cells, hæmoglobin content, etc. ; they supply blood which is not only useful in itself, but acts also in a manner stimulating and nourishing to the bone-marrow, encouraging it to still further efforts. The eradication of active foci of infection relieves the patient of a chronic toxæmia which is possibly an etiological factor. The removal of the spleen reduces the abnormal amount of blood destruction. Discussion has recently ranged around the question as to whether transfusions frequently repeated are competent of themselves to produce an improvement in the patient's condition equal to that seen when both transfusion and splenectomy, or these two with the addition of the eradication of infective foci, are undertaken. Under what circumstances may these steps of treatment be taken ? They are useless in the 'aplastic type', and they are of little value, if any, in cases where cerebral or spinal symptoms are already present, unless the anæmia is profound,

* *Arch. of Internal Med.*, 1915, xvi, 429.

when transfusion alone may give some degree of transient benefit. In all other cases the repetition of a blood transfusion about every eight or ten days gives very striking results. They are briefly stated by Percy :—

" The red blood-count is increased, often doubling immediately if the count is very low. The hæmoglobin percentage rises and the number of platelets is increased. The blast-cells become more numerous, and occasionally Howell's particles will appear in the blood, indicating a stimulation of the bone-marrow. The general appearance and the appetite of the patients improve at once, the condition of the mouth (glossitis is not infrequent) clears up, and sleep returns. It is not only that new blood is given ; it appears certain that a great stimulation of the (under-nourished ?) bone-marrow occurs. In those patients who are much improved by transfusions the question of splenectomy should be considered ; it should not be countenanced unless such improvement has been unmistakable. Before it is performed, a search for foci of infection outside the abdomen will have been made, and all accessible disease removed. When an abdominal operation is undertaken its scope must be comprehensive."

Percy's work has shown how necessary a wide inspection is, and how safe the extended procedure may be made. In a private communication he tells me that in 77 laparotomies performed by him, the spleen, gall-bladder, and appendix were removed in 54 cases ; the spleen and gall-bladder in 11 ; the gall-bladder and appendix in 4 ; the spleen alone in 4. There were 8 deaths. In 74 of these patients one or more transfusions had been performed before operation ; in 40 a transfusion was undertaken immediately after operation ; in 10 cases a later transfusion was performed.

" Of the 69 cases that left the hospital, 5 had recurrence of symptoms at the end of four months, and died at intervals of eight to twelve months ; 10 had recurrence at end of six to eight months and followed about the same course. Forty-eight were in good condition at the end of twelve months. Of these, 12 are alive at the end of two years, 9 at the end of three years, 4 at the end of four years, 5 living nearly five years after operation, and 1 a little over six years. Two of the five-year cases have been retransfused, one several times, the other only twice. The one living six years since operation has had no transfusion since operation. Two of

the four-year cases have been back for transfusions, as have also 4 of the three-year cases, 5 of the two-year cases, and 8 of the one-year cases.

"The progress of the 4 cases in which gall-bladder and appendix were removed without the spleen was not so good, in any instance, as was the average of other cases. They did not experience the immediate remission of the average case of the other group, and all of them had an early recurrence of their anæmia, which had been temporarily improved by the transfusions. The spleen was not removed in these patients because it was not enlarged and there were no adhesions to indicate that there had existed a splenitis or perisplenitis. It is evident that some of our patients should not have been operated upon, as undoubtedly just as good or better results would have followed transfusion alone.

"There were 45 cases treated by transfusions without surgical procedures other than those for the eradication of local foci of infection when present. In 10 of these, most of which were of the aplastic type, no marked improvement resulted. In 12 cases, all of which presented evidence of cerebral or cord involvement, some improvement was noted in the blood-picture and general condition, but the nerve destruction progressed without interruption. In 23 cases the transfusions brought about a marked improvement, and in some a very rapid remission of the disease resulted. In no instance was the remission as complete as it was in several of the cases which were operated. The longest remission noted following a series of transfusions was eleven months; the majority, however, required transfusions at much shorter intervals. There are still 2 patients enjoying fair health after the lapse of nearly two years since their first transfusion."

The evidence as to the efficacy of the newer methods of treatment now outlined is not all on the one side, and is certainly not yet sufficient to enable final conclusions to be drawn. Two further series of cases may be here contrasted and compared. Bloomfield* analyzed a series of 57 cases treated during a period of five years at Johns Hopkins Hospital. In order to allow of an informed judgement upon the effect of treatment in cases of pernicious anæmia, regard being paid to the well-known variations and spontaneous remissions which occur, the following points were considered:

* *Johns Hop. Hosp. Bull*, 1918, xxix, 101.

(1) The effect of treatment on the total duration of the disease; (2) The readiness with which remissions are induced; (3) The length of the remissions; (4) The effect of a particular form of treatment on special symptoms; (5) The death-rate in hospital; and (6) The blood picture.

Twenty-eight cases treated by the older method of rest, diet, and arsenic in the forms of Fowler's solution, cacodylate of sodium, and salvarsan, served as controls to the other and more modern methods.

The reputation of arsenic is said to rest entirely on general impressions: analysis of the cases yielding no reliable data as to its efficacy. In twelve cases a thorough investigation of the nose, throat, sinuses, teeth, gastro-intestinal canal, and lower urinary tract was made for foci of infection, and when found these were eliminated. In none of them was there any feature in their subsequent course to distinguish them from the group in which such foci were not found, or, if found, were not treated, either as to total duration of life, or extent and degree of remissions. It was considered unlikely, therefore, that such foci were the cause of pernicious anæmia. Twenty-six patients received transfusions of blood, varying in number from one to seventeen, and from a total of 300 to 8700 c.c. of blood. In patients who were not in a stage of the disease refractory to all forms of treatment, remissions came on more often when transfusion had been performed, but the artificial plethora thus induced did not increase the duration of the remission, though the patients felt better while the red count was high. At the Johns Hopkins Hospital splenectomy for pernicious anæmia has now been given up; out of 8 cases so treated, 6 are dead, and in no instance was the clinical picture essentially altered or life unusually prolonged. In 5 of the cases transfusion of blood was performed during the period following splenectomy, but in the 4 cases in which the duration of the remission could be accurately determined there was no evidence that transfusions are 'held' better after than before splenectomy. The central nervous symptoms were as little benefited by transfusion and splenectomy as by other means of treatment.

The result of Bloomfield's report is to suggest that no sufficient evidence has been given to the value of the three procedures above mentioned—elimination of septic foci, transfusion of blood, and removal of the spleen.

A more recent review of a series of cases is published by Giffin and Szlapka.† Fifty cases are reviewed in which splenectomy had been performed more than three years previously. The effect on the total duration of the disease was found to be that life was prolonged in 20 per cent; 10 patients had survived more than three years (the furthest limit of expectation of life under ordinary circumstances), and 5 of them had lived four and a half years after the operation and are still living. As regards the readiness with which remissions are induced, it was found that the anæmia improved for at least three to six months and the hæmolytic activity diminished. The blood did not approximate to the normal, but remained at a fairly satisfactory level for a long tine. Recurrences were liable to follow an acute infection such as a severe cold. Transfusions were found to be more lasting in effect in splenectomized cases.

The special symptoms of the disease appeared to be less evident after splenectomy: 13 patients without spinal cord lesions continued without them; 14 with such lesions remained as before; 12 showed an advance in nervous symptoms; 11 who had numbness and tingling of the extremities were definitely improved after operation. Estimation of bile pigments in the duodenal contents suggested that hæmolysis was less after than before operation.

The bone-marrow showed signs of stimulation, large showers of monoblasts and megaloblasts appearing in the blood. This state continued for four years in some cases. Leucocytosis persisted much longer than ordinarily. The neutrophile leucocytes tend to preponderate. The blood-count does not infallibly indicate the progress of the patient, because several of the most successful cases show few nucleated red cells and only slight leucocytosis.

The immediate operative mortality was 3 in 50 cases (6 per cent). The deaths occurred in the first 19 cases, after which preoperative treatment was very carefully handled and more acute forms were rejected. There are no post-operative complications. Preference in respect of operation was given to persons between the ages of 35 and 45, with only one year's history and a favourable type of blood picture, and no sign of spinal-cord involvement.

Favourable indications were absence of marked leucopenia, with neutrophils dominant rather than lymphocytes, marked

† *Jour. Amer. Med. Assoc.*, 1921, lxxvi, 290.

hæmolytic activity shown by examination of the duodenal contents, a competent bone-marrow, and a moderately enlarged spleen.

The following is the summary given by Giffin and Szlapka :—

1. This review concerns fifty patients with pernicious anæmia for whom splenectomy was performed. All were operated on more than three years ago.

2. The operative mortality was 6 per cent.

3. Ten patients (21·3 per cent) of those who recovered from operation survived splenectomy three years or longer.

4. Five patients (10·6 per cent) of those who recovered from operation have survived splenectomy more than four and one-half years, and are still living. The total length of history of these five patients averages almost six years.

5. It may be stated with reasonable accuracy that, in addition to the immediate remissions which occurred constantly following splenectomy, splenectomy prolonged life in at least 20 per cent of our cases.

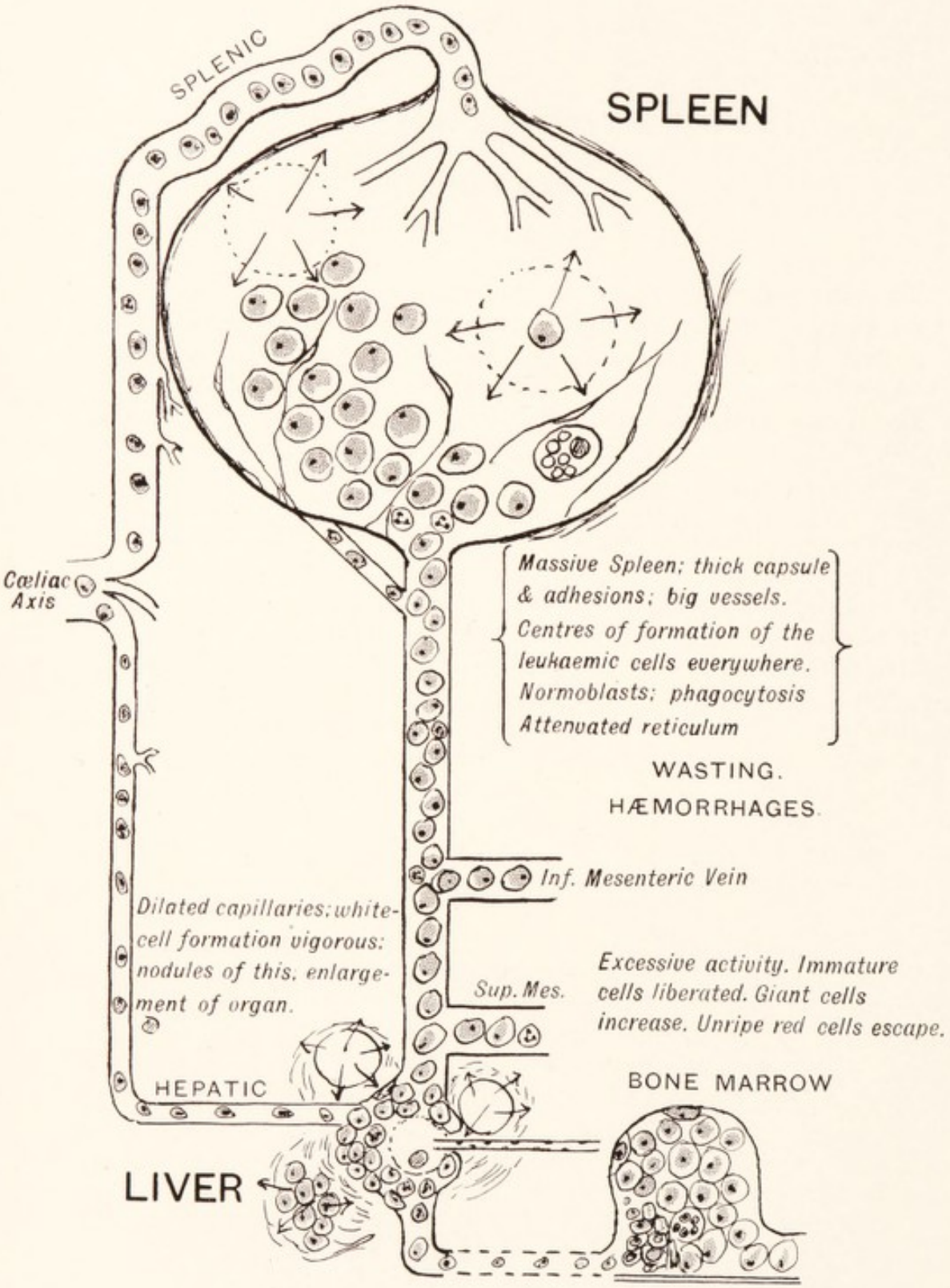
6. We cannot satisfy ourselves that any particular pre-operative characteristics of the disease are indicative of favourable results following splenectomy. However, in the type of case in which there is evidence of active hæmolysis, the patient shows a more marked immediate improvement.

7. Splenectomy may be recommended in pernicious anæmia when, in view of all the circumstances, personal as well as medical, the possibility of the prolongation of life appeals to the family and to the patients. Occasionally the operation may be performed in order to bring about an immediate remission.

What may be said, then, of the efficacy of splenectomy in this disease ? In the first place it cannot be claimed, and is not claimed, that any patient has been cured of his disease. The risks run in undergoing the operation are small, but not so insignificant that they can be ignored. A few lives are sacrificed. All the patients who survive are not benefited, but in the majority a degree of improvement results, and a prolongation of life, in greater comfort and with increased zest, can be recorded. The truth is approximately this, that as a result of repeated transfusions of blood, removal of the spleen, and eradication of all foci of infection, one-quarter of the patients are greatly improved, living happier and more useful lives, prolonged beyond the expectation by a period of

two or three years; one-half of the patients are improved in some degree, they feel better, take nourishment better, sleep better, and live perhaps a few months, or even a couple of years, longer than the average; the remaining one-quarter of the cases do not receive any help greater than that which could be derived from careful medical treatment, which may include the 'step-ladder' transfusions of blood if these are found to be helpful, and the treatment of such foci of infection as can be found in the mouth, nose, or accessory sinuses. When the position is accurately stated to patients who suffer from this disease, they are likely to decide the matter according to their temperaments. Surgeons should rarely, or never, urge operations, for they should rarely, or never, find it necessary to do so if the problem to be decided is fully and honestly stated to a patient or his relatives. In cases of pernicious anæmia an operation is indicated for those patients who are found by such tests as I have mentioned to be likely to do well, and who are eager to get the most out of the remainder of their days and to prolong them.

PLATE IV



THE CHIEF CHANGES IN LEUKÆMIA

CHAPTER VII.

LEUKÆMIA.

(*See Plate IV.*)

To turn over the pages of the history of leukæmia is to see recorded in orderly succession many of the chief features in the growth of our knowledge concerning human pathology and hæmatology. A case of this disease was first recorded in 1845 by Hughes Bennett, of Edinburgh. The spleen was greatly enlarged, and the blood, examined after death, was seen to contain a large number of cells similar to those found in the ordinary purulent discharges from wounds. Hughes Bennett described the condition as one of "suppuration of the blood". One month later Virchow described a similar case. A rather acrimonious contest for priority arose, and different views were expressed as to the nature of the white bodies found in the blood. Virchow asserted that they were not to be distinguished from the colourless corpuscles or leucocytes of the blood. Hughes Bennett had regarded them as pus-cells. But the discussion lost all its significance when it was recognized that pus-cells and leucocytes were identical. Virchow, we may well suppose, was interested, not so much in the purely clinical phenomena which his case displayed, as in the question of its intrinsic nature. He regarded "the blood as a transitory tissue with a fluid matrix, constantly changing because constantly developing", and he showed that the cells of the blood are continually perishing and continually being replaced. The occurrence of a disease such as this was for him the confirmation of his opinion as to the nature and constitution of the blood, for he had, as it were, foreseen that such a disease as this would be likely to exist. When once his prediction that there was a 'white blood' was confirmed by the examination of the blood in this disease, the problem at once arose as to the nature of the process involved in the excessive production of leucocytes, and as to the nature of the tissue changes present in this disorder.

The study of these questions led to an intensive study of the

cellular processes occurring in suppuration. Neumann, in 1878, showed the active part played therein by the bone-marrow, and Ehrlich (1898) demonstrated that it was possible by using aniline dyes as stains to differentiate between the various types of cell activity awakened by this process. From this time, the knowledge of the floating cells of the body has advanced with great rapidity; and the intimate relationships which exist between the cells circulating in the blood, the cells in the blood-forming organs, and the cells met with in inflammatory infiltrations of all kinds, have by degrees been brought to light. The changes in the blood of living patients were first described in 1846 by Dr. Fuller, of St. George's Hospital, and Dr. Walshe, of University College Hospital.

Virchow sought to place the primary seat of this disease in the spleen and in the lymphatic glands. He believed that the changes in the blood arose from the liberation into it of chemical substances which were normally retained within these organs. The cells of the blood were stirred to a greater activity by these substances, and ultimately the cells of the various organs also showed evidence of hyperplasia.

The original belief of the great pathologist received corroboration from Neumann's discovery of the state of the bone-marrow in this disease. As a result of this, leukæmia was then regarded as a disease of the spleen, lymph-glands, and bone-marrow, an interpretation not essentially different from that held to-day. But the subsequent history of this disease shows many vicissitudes. Difficulties were continually arising in the interpretation of details; and in spite of most assiduous research by many observers, no real advance was made in our knowledge of the disease until the work of Pappenheim.

As a result of the investigations of this worker and his school, the origin and fate of every type of cell found not only in leukæmia but in every 'blood' disease, and in every inflammatory process, were thoroughly investigated by special staining methods applied to all manner of tissues: to those removed by operation as well as to those obtained by post-mortem examination, in man as well as in animals.

The modern science of hæmatology received immense impetus from all this work, and a host of earnest students in all lands were eager to lend their help. The question in this disease resolved

itself into an inquiry as to whether the abnormal blood-cells were formed in one organ or in many, thence to be distributed to all parts of the body; or whether the cells were formed 'locally', that is, in the parts where they were found. It was an old problem re-stated, the problem as to whether the exudates occurring in inflammation are due to chemiotaxis and the migration of leucocytes from afar; or whether (as was the original view) these cells are developed at the seat of the disease. The general opinion of those most competent to express one, now appears to be that the origin, both of these inflammatory cells and of the leukæmic cell-infiltration, is local. This is a matter of great interest, and the historian will recall that in the year 1863, Beale, a solitary voice heard only to be opposed and derided, stoutly defended his opinion that the phenomena of tissue infiltration were the result of the irritation of the endothelial cells of the smallest local capillaries.

Leukæmia may therefore be considered as a morbid process manifesting itself diffusely, and consisting of hyperplasia of various leucocytes—sometimes of the lymphocytes, sometimes of the myeloid cells—scattered throughout the body. The severity of the degree of hyperplasia may be so great, and the type of cells produced may be such, that what is called a 'sarcoid' process results. There are cases in which, however, the newly-formed cells are found in the spleen, lymph-glands, and bone-marrow, but do not enter the blood-stream; the blood on examination is normal. 'Leukæmia' therefore may be regarded as having two relationships: on the one side to the disease known as lymphosarcoma; on the other to Hodgkin's disease.

The search for the cause of this disease would be fruitless without the clear conception that leukæmia is a disorder in the process of the formation of white blood-cells, whose birthplace is the endothelium of the reticulo-endothelial system. We have not, therefore, to search a particular organ to find the cause of the disease; we have to discover the type of agent likely to affect so diffusely distributed a system of cells. We should be able to explain why in some cases the proliferative process goes on outside the blood-vessel and produces a massive deposit of new tissue without altering the appearance of the blood (resulting in Hodgkin's disease), whereas in other cases the proliferating process extends into the lumen of the vessel and allows the myriads of

newly-formed cells to enter the circulation and produce a typical condition known as leukæmia.

It was Pappenheim who elaborated the thesis that the virus at work may travel either by the lymphatic channels (producing a 'lymphatic leukæmia') or in the blood-channels (producing a 'myeloid leukæmia'), and that the purpose of an inquiry should be to ascertain the nature of the stimuli or irritants capable of exerting such effects.

Symptoms.—The first and striking clinical feature is that the disease does not always run the same course. On the one hand, there are acute forms in which a fatal issue ensues within a few weeks; on the other, the disease may last for many months, or, usually from two to four years, or even—as in a case recorded by Grawitz—for ten years. The duration of the chronic cases depends to a certain extent upon the circumstances of the patient. The necessity for earning a livelihood, even though the work is not heavy, has a very harmful influence upon the course of the disease.

Acute Leukæmia is no doubt commoner than appears from the literature, owing to the non-recognition of cases. It begins very suddenly, and is characterized by the severity of its symptoms, which follow acute tonsillitis or stomatitis. Hæmorrhages, as in scurvy, especially from the gums or nose, form an important feature, and in a few cases general glandular enlargement is noticed. The remainder of the clinical course strongly simulates that of typhoid fever, with rapid wasting, and a degree of mental disturbance which sometimes ends in delirium. Jaundice, when present, is attributed to enlargement of the glands in the hilum of the liver, which cause pressure upon the hepatic duct. An exfoliative dermatitis has been noted. The blood-picture may be either 'lymphatic' or 'myeloid'.

Chronic Leukæmia is usually of very insidious onset. A slow progressive wasting becomes noticeable, and carries with it increasing lassitude, asthenia, and loss of mental activity. In this case also there is a tendency to hæmorrhages, usually from the nose, sometimes from the intestine, or under the skin; infrequently from the gums, from hæmorrhoids, from the stomach, uterus, or urinary passages. Ulceration of the lips and mucous membrane of the mouth is not seldom seen, and may suggest an examination of the blood to conform a tentative diagnosis. Periods

of fever are usual. Physical examination reveals a massive enlargement of the spleen; less massive enlargement of the liver; in the 'lymphatic' cases there is enlargement of the lymph-glands in various places. Every system of the body may show changes, so that patients in respect of their most troublesome symptom may come before ophthalmologists, dermatologists, gynæcologists, urologists, and surgeons, as well as physicians.

Studies in the metabolism of this disease have been extensively made. Perhaps the chief change in this respect has reference to the metabolism of the purin bodies. Uric-acid excretion is high; indeed, uric acid calculi may form. Charcot-Leyden crystals have been found in the blood and tissue-juices after death.

When a patient suffers from an added infection, the enlargement of the spleen and lymph-glands may diminish, and return almost to the normal; the blood-picture alters, the myelocytes disappear, and the polynuclear leucocytes greatly increase. The change, however, lasts only so long as the infection is present. As that fades away the conditions of the disease return. The injections of normal splenic extract, or of spermin, or of cinnamic acid, have restored the blood-count to normal for a time. As mentioned later, the administration of benzol produces a profound change in the state of the blood. Some cases have been reported in which a concurrent tuberculous lesion led to shrinkage of the spleen.

Neither age nor heredity appears to have any influence upon the disease. It does not occur in epidemics. Injuries have sometimes been considered a cause. Animals, cows, horses, dogs, cats, and fowls are said to suffer from the disease. So far no bacterial cause for it has been discovered, in spite of arduous and protracted search. Many of the clinical features could be easily explained as the result of a microbic infection; the acute form is clinically very similar to one of the acute specific fevers. It is true that many organisms have been found associated with the disease: micrococci, staphylococci, in lymph-glands; streptococci in the acute cases seen in America; and other organisms. These are instances, almost certainly, rather of chance secondary contaminations than of causative agencies. Attempts have been made to transmit the disease experimentally by the injection, intraperitoneally or intravenously, of leukæmic blood, but no success has followed. Transmission has occurred from one fowl to another.

An examination of the abnormal leucocytes has shown peculiar cell-inclusions, but no evidence exists that these are to be regarded as parasites. So many of the features of the disease are 'toxic' that a further research for a biological cause is worth while. It has been suggested that the 'toxic' features are due to secondary infections occurring in patients whose normal protective neutrophile leucocytes are gravely diminished in numbers and in efficiency, being overwhelmed by the abnormal cells. It is possible that the absence of the normal leucocytes may account for the wasting seen in this disease, for many of the processes enacted in the tissues are deprived of the help which it is the part of these cells to give.

TREATMENT.—Until recent years no treatment seemed to have any considerable effect in cases of leukæmia. In the year 1909, Selling, of Johns Hopkins Hospital*, reported three cases of poisoning by benzol, two being fatal. The patients suffered from purpura hæmorrhagica with aplastic anæmia, and the bone-marrow was found aplastic. The red cells showed no changes other than slight pallor and anisocytosis. No regeneration forms of the red cells and no normoblasts were found. Platelets were few. There was a diminution in the granular type of leucocytes, and a relative increase in mononuclear types. Leucopenia was present.

In 1912, Koranyi† observed the effects of benzol poisoning in girls working in a factory where benzol was used as a solvent for rubber. The symptoms produced by this drug suggested to him the possibility of its use in the treatment of leukæmia. In reporting his experience, he states that there were no failures with benzol in cases of chronic leukæmia; that the spleen and lymph-nodes were little affected; that benzol given alone was of benefit, and, although more gradual in its effect than *x* rays, it succeeded where these failed; but that patients responded better to benzol treatment after the spleen had been exposed to *x* rays. No serious ill-effects were observed to follow the treatment, but certain disagreeable symptoms were noticed: a sense of burning in the stomach, and the eructation of offensive gas, with transient catarrh of the trachea and bronchi, and giddiness. In one case the white cells were reduced from 220,000 to 8000 within three months; and the general health improved considerably. Dr. Frank

* *Johns Hop. Hosp. Bull.*, 1910, xxi, 33. † *Berl. klin. Woch.*, 1912, xlix, 1857.

Billings,* who reports a series of five cases treated by this drug, was impressed with it as a very powerful agent, and as one apparently of great promise in the treatment of leukæmia; but it was 'a two-edged sword' which, used carelessly, might defeat the purpose of its use and produce an equally serious condition, namely aplastic grave anæmia, with a hypoplastic bone-marrow, and result in a fatal issue. He noted a diminution in the size of the spleen, a rapid fall in the number of the leucocytes, and, in all the cases of a myelogenous type, an improvement of the red-cell count and hæmoglobin. Later experiences have confirmed many of these opinions; but it was soon found that there were cases resistant to treatment by benzol, and that in others a short period of improvement was followed by a rapidly fatal termination. Such dramatic endings to the disease occur both without treatment and with other forms of treatment, but benzol seemed often to be a factor in causing an earlier death than had been anticipated. The pure drug is administered in capsules containing about 1 grm., and olive oil is given simultaneously to diminish the irritating local effect. A dose of 5 grm. daily is gradually reached. When the leucocyte count is reduced to 20,000 the administration is stopped. Boardman† states that 16 out of 100 cases failed to show improvement, and that another 8 cases, although reacting favourably at first, died during or soon after the discontinuance of treatment.

The application of radium produces the most astonishing effects in reducing the size of the spleen. Within eight or ten weeks a spleen which appears to occupy almost the whole of an enlarged abdominal cavity shrinks until it is only just palpable beneath the costal margin. If the abdomen is marked week by week to indicate the size and shape of the tumour, the evidences of rapid shrinkage are very remarkable. As the spleen diminishes, the general condition of the patient steadily improves, and the blood-count approximates to the normal. In a very interesting paper Ordway‡ discusses the whole question of radium therapy very fully, and illustrates the improvement seen in cases under his care by photographs. He draws the following conclusions:—

1. Surface applications of radium in leukæmia produce striking, indeed remarkable, improvement in: (*a*) The blood-picture, which

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* *Jour. Amer. Med. Assoc.*, 1913, lx, 595.

† Quoted by Ordway, *Boston Med. and Surg. Jour.*, 1917, clxxvi, 490. ‡ *Ibid.*

becomes almost normal; (*b*) The size of the spleen and glands, which are reduced almost to normal; (*c*) The general condition of the patient, who, from being emaciated and weak, may become plump and strong.

2. The duration of the remission is variable; it may last from months to years.

3. The results of radium treatment are not regarded as curative. It is believed to be, however, the safest as well as the most prompt palliative measure in cases of chronic leukæmia, whether refractory or not to benzol or *x*-ray treatment.

From the results of radium therapy in leukæmia it is believed to be the best form of treatment now at our disposal.

The facts which were clearly established by this work and by similar experiences at the Radium Institute in London in cases under the care of Hayward Pinch, led to the inference that the spleen might possibly be a factor of greater significance in the etiology of the disease than had been supposed. This view was strengthened by the further experience that the exposure of the long bones, or other parts, as well as the spleen, to the action of radium, did not produce results in any degree better than those in which the spleen alone was treated. As a result of the work at the Mayo clinic, by W. J. Mayo, Balfour, Giffin, and others, it seemed not improbable that if the spleen were a factor of causal significance, its removal, when it had been greatly reduced in size by the application of radium, and when the patient's condition was at its best, might be of benefit to the patient. In the old days removal of the spleen has been undertaken because the organ was grossly enlarged; the new view was that the smaller the spleen the safer its removal would be.

The first case in which the spleen was excised in myelogenous leukæmia is recorded by T. Bryant, in 1866,* and the second by the same author in 1867. Both patients died as a direct consequence of the operation; in both the spleen was very large. After this, splenectomy was performed on many occasions in this disease, and by no means all of the cases found their way into surgical literature. The condition in most of these was profoundly unfavourable; the patient was in grave ill-health, and the spleen was of very large size; indeed, only those patients appear to have

* *Guy's Hosp. Rep.*, 1866, xii, 444.

been selected for surgical treatment in whom the mammoth spleen was a serious and burdensome discomfort. The mortality up to the year 1900 is said to have been just under 90 per cent. Bessel Hagen* gave the records of 42 cases, with 38 deaths, and 'temporary improvement' in 4. I know of a few cases, all fatal, occurring before this date, which never found their way into the literature. In 1908, J. B. Johnston† recorded a further 7 cases, of whom 2 lived to show slight improvement after the operation.

H. Z. Giffin‡ reports that the total number of cases appearing in the literature up to Jan. 1, 1918, is 51. Of these, 43 died at once: 8 showed a temporary improvement; but of these, 4 died within so short a period of the operation that their death should count as a fatality from it. If this is done, the mortality is to be reckoned as 93 per cent. It is not surprising to find that all voices speaking with authority, such as Bland-Sutton's, were raised against a continuance of such surgical work. The record was a martyrology.

The experience of the Mayo clinic is epitomized in the following summary by Dr. Giffin :—

"1. Twenty patients with myelocytic leukæmia have been splenectomized—18 of them after preliminary treatment by means of radium exposures over the spleen. The spleen and the leucocyte count were very much reduced by means of radium, and the general condition of the patients was greatly improved.

"2. One patient died—an operative mortality of 5 per cent. The operative mortality of cases reported in the literature in which little or no preliminary medical treatment had been given was 86 per cent.

"3. Ten of the 20 patients are living in good general condition from nine months to one year and seven months following splenectomy. However, these patients have not yet outlived the life expectancy for the disease.

"4. Of 7 patients operated on within six months of the onset of the disease, 6 are alive.

"5. It is probable that, at least in certain chronic types of myelocytic leukæmia with fibrous spleens and relatively low leucocyte counts, splenectomy may be justifiable for the comfort of the patient.

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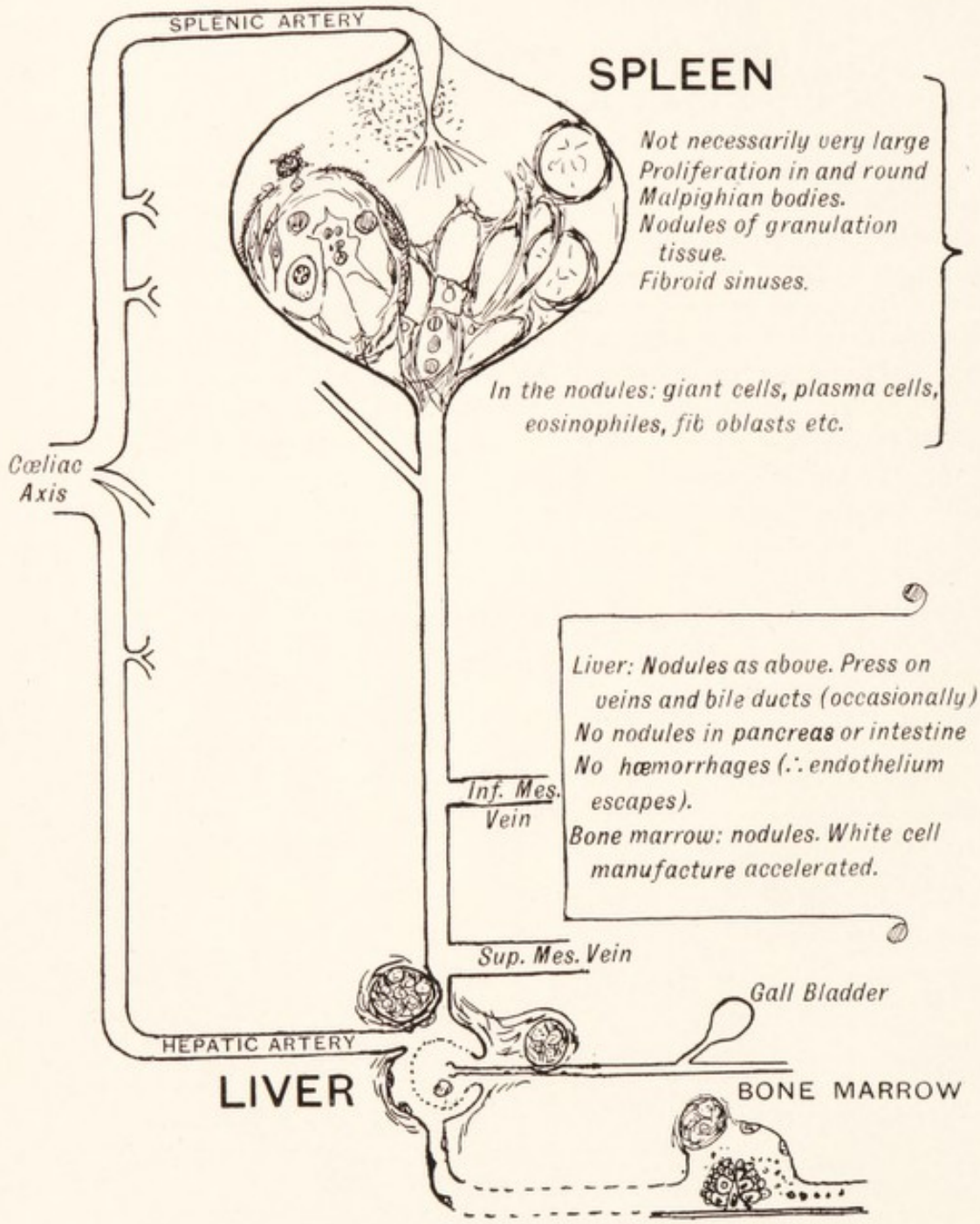
* *Arch. f. klin. Chir.*, 1900, lxii, 188. † *Ann. of Surg.*, 1908, xlviii, 50.
‡ *Med. Record*, 1918, xciv, 1020.

" 6. A review of the cases at this time reveals no evidence that the duration of the disease is altered in any definite way by splenectomy."

The statistics of the Mayo clinic up to Sept. 20, 1920, which Dr. W. J. Mayo has kindly given to me, show a total of 26 cases with 1 death, a mortality of 3·8 per cent. The immediate mortality is therefore strikingly different from that which occurred when the cumbersome size of the spleen was the chief indication for the removal of the organ. The last report shows, too, that 5 patients are in good condition and 2 in fair condition after periods of time beyond the life expectancy of the disease. It is interesting to learn that two cases, supposed to be early examples of myelogenous leukæmia (not included in this list) have been cured, or at least have lived many years after the operation. Dr. Mayo writes: " The operation is not difficult after radium treatment, and in selected cases should be further considered ".

PLATE V



THE CHIEF CHANGES IN HODGKIN'S DISEASE

CHAPTER VIII.

HODGKIN'S DISEASE.

(*See Plate V.*)

In the year 1831, Hodgkin, Lecturer on Pathology at Guy's Hospital, observed a series of cases in which the spleen and the lymphatic glands were enlarged.* Among these were four examples of the condition now known as 'Hodgkin's disease'. All remembrance of this paper seems to have been lost, for in the year 1862 Wilks, then Lecturer on Pathology at the same Hospital, described the same disease under the title 'anæmia lymphatica'. By the year 1865 Wilks had, however, discovered the previous description by Hodgkin, and though his own observations were entirely original, he suggested, as a title for the disease, the name it has ever since borne, 'Hodgkin's disease'.

The morbid anatomy of the condition has been investigated since by a great number of observers, among whom Reed, Longcope, and Andrewes deserve special mention. A number of diverse views have been held as to the nature and causation of the condition.

One of the most recent writers, Mellon,† considers that the disease has not any relationship with tuberculosis—as Sternberg asserted—, with lymphosarcoma, or with pseudoleukæmia. The prevailing view of most of those who have recently investigated the condition appears to be that all these diseases should be regarded as disorders of the reticulo-endothelial system, probably infective in origin, and therefore to be classified as infective granulomata or "lymphomatosis with granulation-tissue formation". In his review of recorded cases Mellon found only two in which it seemed possible that the spleen was the primary focus of the disease; in neither was an autopsy obtained, yet the necessity for this could not be better shown than in a case recorded by Mellon as coming under his own care. In this there was no evidence of glandular enlargement, and a primary splenic origin of the disease

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* *Trans. Roy. Med. Chir. Soc.*, 1832. † *Amer. Jour. Med. Sci.*, 1916, cli, 704.

seemed most probable. After death the inguinal, bronchial, and retroperitoneal glands all showed hyperplasia of the lymphoid cells, and endothelium with multinucleated giant cells. The spleen showed advanced changes; the lymphoid tissue of the splenic pulp was practically obliterated by the intense proliferation of the hyaline connective tissue. There were many areas of anæmic necrosis which indicated that the disease in the spleen was of long standing. A similar case was recorded by Wilks in 1856: the patient was a man who died in Guy's Hospital in an extremely debilitated and anæmic state, with an enlarged spleen. The autopsy showed that the mediastinal and lumbar glands were very much enlarged, although the superficial glands were quite healthy.

The true nature of the disease has baffled inquiry. It may be regarded as a separate and distinct disorder having no ostensible attachment to any other. Or, alternatively, it may be regarded as a special form of a certain type of morbid process which exists also in other conditions—tuberculosis, pseudoleukæmia, and lymphosarcoma. The latter opinion has the advantage of correlating various morbid states as to the nature of which there has long been confusion, and attributing them all to one common underlying cause.

Hodgkin's disease has, as its essential anatomical feature, the presence of tumours made up of granulation tissue. The lesions differ from those of tuberculosis partly in the heterogeneous character of the inflammatory cells concerned in the formation of the nodules, and partly in the fact that the original cells of the affected tissues undergo active multiplication. The ordinary structure of the glands or spleen becomes lost in the abundance of lymphocytes, which appear intermingled with those epithelial cells, giant cells, fibre cells, and eosinophil leucocytes, all of which together help to build up the masses found in Hodgkin's disease.

In the reticulo-endothelial system there are the following two types of disease. There is that in which the cells undergo an intense proliferation and are liberated into the blood, as in the leukæmias. And there is that in which the proliferation goes on outside the vessels without the entry of any of the new cells into the blood. The microscopist, studying the spleen and allied organs, might well believe that he had an ordinary leukæmia tissue under examination, although the clinical phenomena might make such a diagnosis impossible. For him, the nature both of Hodgkin's

disease and of leukæmia is essentially the same, and the state of the blood (upon which the clinician lays so much stress) is a mere incident.

The histological study of these diseases of the reticulo-endothelial system suggests a similarity, if not an identity, of causation, both for the widely disseminated lesions, and for those in which a definite 'tumour', as, for example, lymphosarcoma, occurs.

The following classification, for help in the preparation of which I am indebted to Dr. Gruner, embraces all the disorders of the reticulo-endothelial system, and shows, as well as our present knowledge allows, their relationship to each other :—

DISORDERS OF THE RETICULO-ENDOTHELIAL SYSTEM.

I. *Those in which there is an excessive formation of specific tissue elements.*

A. With the appearance of cells which are normal to blood-forming tissues :

1. The cells grow away from the vascular channel :
   i. The disorder is disseminated throughout all parts of the system : (Disseminated) PSEUDOLEUKÆMIA.
   ii. The disorder is *focal* :
      a. In the lymph-glands : LYMPHOMATOSIS ; also in TYPHOID lesions.
      b. In the bone-marrow : 'MEDULLARY PSEUDOLEUKÆMIA'.
      c. In the spleen (and liver) : 'LIENAL PSEUDOLEUKÆMIA'.
2. The cells grow partly into the vascular channel, so that myelocytes appear in the blood : ACUTE SPECIFIC FEVERS ; VON JAKSCH'S ANÆMIA.
3. The cells grow mainly in the vascular channel. Therefore large numbers of myelocytes (or lymphocytes) appear in the blood :
   a. Disorder in the lymph-glands or lymphatic tissues : Clinically acute or chronic LYMPHATIC LEUKÆMIA.
   b. Disorder in the bone-marrow, spleen-pulp, or any 'myeloid' tissue : Clinically acute or chronic MYELOID LEUKÆMIA.

B. With the appearance of entirely new cells :

1. Definite tumour-formation :
   a. Widely disseminated through the body : LYMPHOSARCOMA.
   b. Only local masses : in the spleen : LYMPHOSARCOMA.
   in the bone-marrow : MYELOMA.
   in the lymph-glands : CHLOROMA.
2. Definite tumour formation not present, but tumour cells are intermingled with myelocytes or lymphocytes of large size : 'SARCOID' LEUKÆMIA.

(Each of these may also show 'leukæmic' blood.)

II. *Those in which there is excessive formation of the stroma cells*:
   A. One kind of cell is noticeably predominant in the tissues:
      1. Fibre cells: PASSIVE CONGESTION OF THE SPLEEN; SYPHILITIC SPLENOMEGALY; MALARIA; KALA-AZAR; CIRRHOSIS with SPLENOMEGALY.
      2. Epithelioid cells: GAUCHER'S SPLENOMEGALY.
   B. Many cell-types involved, so that a granulation-tissue tumour is formed:
      1. Disseminated through the whole system: HODGKIN'S DISEASE; LYMPHOGRANULOMA.
      2. Local, e.g., in the spleen only (very rare): primary HODGKIN'S DISEASE; TUBERCULOSIS OF SPLEEN; GUMMATA OF SPLEEN.

III. *Those in which there is an excessive formation of stroma cells, with disturbance of the formation of the specific tissue cells*: PERNICIOUS ANÆMIA; SPLENIC ANÆMIA; HÆMOLYTIC JAUNDICE; SPLENOMEGALY IN RICKETS.

The clinical symptoms of Hodgkin's disease are very familiar. They are largely mechanical in origin, and are due to the presence of widespread glandular enlargements which may press upon important structures. The periodic pyrexia of this disease may be regarded as a specific and typical feature. It is uncertain as to whether it is sometimes, or often, the result of secondary infections.

The symptoms certainly suggest the existence of a definite infection. There is a latent period, with occasionally slight swellings of the glands. A stage of declared disease may then begin quite abruptly. There may be a sudden general enlargement of the lymphatic glands, which themselves cause pressure symptoms, recurring attacks of fever, with increased heart action, and progressive wasting. It is said that the blood often shows no change, but it is very probable that an increase of the large mononuclear leucocytes and transitional cells is generally to be expected.

TREATMENT.—It is only very rarely that an operation upon the spleen is necessary in a case of Hodgkin's disease. I have performed one such operation. The case occurred in a man, 44 years of age, who had a colossal enlargement of the spleen with no discoverable change in any of the lymph-glands. Under radium the spleen diminished rapidly in size, but after two months again began to increase and became as large as ever. A second and third application of radium caused an equal reduction, and when the spleen was small I removed it. It showed the typical evidences of Hodgkin's disease, and this diagnosis was confirmed by the later

enlargements of the cervical glands on both sides, which receded after the application of radium. The original operation was performed twenty-two months ago, and the patient is still in good health and at work. It is very doubtful if the removal of the spleen has had any effect, good or ill, upon the progress of the disease.

The general treatment of the disease needs no mention here.

CHAPTER IX.

SPLENIC ANÆMIA. BANTI'S DISEASE.

(*See Plate VI.*)

HISTORICAL.—'Banti's disease' is the name given to the condition described in 1883,* and again in 1894,† by Guido Banti, of Florence. In 1866 Gretzel‡ described a clinical condition of anæmia associated with splenomegaly to which Griessinger applied the name 'splenic anæmia'. The case occurred in a child ten months old who suffered from dysentery and severe anæmia, with considerable enlargement of the spleen, and enlargement, less considerable, of the liver and lymphatic glands. Examination of the blood showed that the proportion of white to red cells was not increased; the condition was therefore not leukæmic. In 1871 Wood§ described a 'splenic form' of pseudoleukæmia, and reported a case in which the spleen was greatly enlarged, and there was severe anæmia without leucocytosis. Banti, in his later description mentioned above, considered the disease as possessing clinically three stages, merging gradually into each other. These stages were: (1) One in which there was enlargement of the spleen and a secondary anæmia—the duration being three to twelve years; (2) One in which the liver gradually enlarged, and the amount of urine underwent progressive diminution—the duration was brief; (3) One in which the liver gradually shrank in size and ascites appeared, the symptoms being those of an ordinary atrophic cirrhosis—the duration of this stage was between one and two years. The disease was invariably fatal, and death occurred either from hæmorrhage, or from auto-intoxication from cirrhosis.

In a third publication, Banti‖ asserts that the disease is also characterized by the following definite pathological changes: (1) The chief change noted in the spleen is a fibrosis of the

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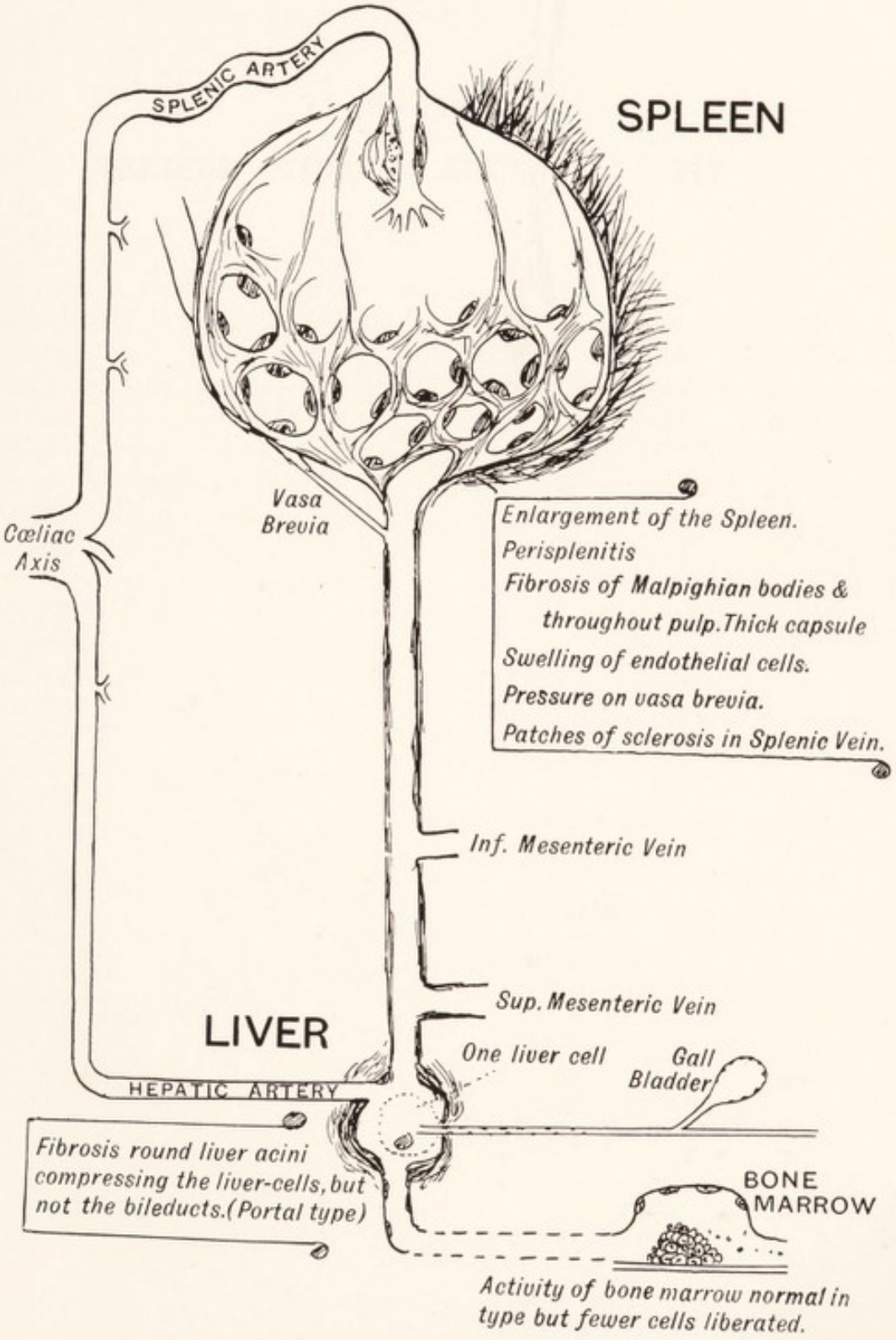
* "Dell' anæmia splenica," *Arch. L. Schula Anat. pathol.*, Firenze, 1883, ii, 53.
† *Sperimentale*, xlviii, 407. ‡ *Berl. klin. Woch.*, 1866, ci, 212.
§ *Amer. Jour. Med. Sci.*, 1871, lxii, 373. ‖ *Folia hæmatol.*, 1910, x, 1.

PLATE VI



THE CHIEF CHANGES IN SPLENIC ANÆMIA

Malpighian follicles, spreading outwards from the central artery, which often shows a hyaline degeneration; (2) There is fibrosis of the splenic reticulum, with narrowing of the splenic veins, a thickening of the splenic capsule, and of the trabeculæ, larger and smaller, running through the organ; (3) Endophlebitis, with calcification of the splenic veins, extending up to, and even into, the portal vein; (4) Cirrhosis of the liver, of the 'Laennec type'; (5) The characteristic red marrow of a secondary anæmia; (6) There is no general glandular involvement.

Banti's hypothesis is that there is a primary splenomegaly due to an infective agent. The splenic enlargement itself produces another toxin which, acting on the liver and on the splenic veins, produces the changes just described. The anæmia is the result partly of the toxæmia and partly of the hæmorrhages. The hypothesis is unnecessarily complex, for there is no reason why a single infective agent should not produce effects alike in the liver and in the spleen. The production by a sclerosing organ of a toxin destined to cause sclerosis in another organ is unknown elsewhere.

The difficulty in the strict recognition of Banti's disease, as he describes it, is great; for there are many conditions with symptoms very closely resembling those described by him, and the chances of obtaining a pathological examination of the spleen and its vessels, and of inspection of the liver, are so remote, in view of the restriction of operative treatment, that an accurate diagnosis is only then obtainable after death. The etiology in Banti's disease is held to be unknown. If, therefore, a case clinically and pathologically resembling Banti's disease has a known causation, it cannot be accepted as an example of this disease.

Again, both clinically and pathologically the conditions in certain cases may so closely resemble those of Laennec's cirrhosis that many authors have considered that there are not two diseases, but one disease with different names.* If the ordinary clinical course is followed, there is no doubt that in Banti's disease the splenic enlargement precedes the affection of the liver, whereas in Laennec's cirrhosis the liver is first attacked; though in some cases the splenic enlargement may be so considerable as to distract attention from the less obvious change in the liver.

The truth appears to be that a large clinical group of cases,

* Krull, *Mitteil. a. d. Grenzgeb. d. Med. u. Chir.*, 1915, xxviii, 718.

distinguished by enlargement of the spleen and anæmia, is being gradually encroached upon by keener distinctions, pathological and etiological, than formerly existed. Griessinger's original description of splenic anæmia included, for example, the condition we know now as Gaucher's disease, the disease now called 'hæmolytic jaundice', and that form of infantile pseudoleukæmia called von Jaksch's disease. In connection with the latter, the view is taken by some observers that it is an infantile form of Banti's disease in which "a moderate leucocytosis, due to the higher values of leucocytes in the normal blood of infants, is to be found" (Mayo).

Splenomegaly associated with anæmia may have its etiology determined, and so be withdrawn from the group of 'splenic anæmia'. This has happened, for example, in connection with chronic syphilitic enlargements, with the enlargements due to kala-azar, to malaria, and so on. The group is raided from every side. What remains? Only the forms of 'splenic anæmia' the cause of which is unknown. Or, as Mayo wisely and wittily says, "Put in the form of an Hibernianism, incomplete knowledge is essential to the diagnosis. If we know the cause of splenic anæmia it is not splenic anæmia". 'Banti's disease' and 'splenic anæmia' are therefore synonyms for the same condition, the former title indicating especially the later, the latter the earlier, stages.

Clinical History.—Splenic anæmia was defined by Osler as "an intoxication of unknown nature characterized by great chronicity, primary progressive enlargement of the spleen which cannot be correlated with any known cause, anæmia of a secondary type, with leukopenia, a marked tendency to hæmorrhage—particularly from the stomach,—and in many cases a terminal stage with cirrhosis of the liver and jaundice". The clinical features of the disease, then, are the following:—

1. *A very chronic course*—in which the symptoms progressively and steadily increase in severity, without amendment, and without any hope of spontaneous recovery.

2. *A slowly progressive enlargement of the spleen.*—This is the first of all evidences of disease; the bulk of the organ undergoes an increase, at first apparently slight, but later more rapid. The ratio of increase probably remains unaltered throughout. The enlargement may finally be very considerable, though it is rare

for the spleen to become as large as in myeloid leukæmia, or in some cases of Hodgkin's disease, or in malaria, or in Gaucher's disease. The spleen is not altered except in bulk, so far as physical examination shows: the surface is smooth, the notches are apparent; there is no tenderness, nor is a friction rub felt or heard. It is said that a 'bruit de diable' has been heard (Sippy, Rolleston) " due to eddies produced by slight torsion of the dilated veins in the gastro-splenic omentum or of the splenic vein ". Seeing that clinical recognition of splenic enlargement is not possible until the spleen is at least double the normal size, it is more than probable that the inaugural and early symptoms of splenic anæmia are quite unrecognized.

3. *Changes in the blood* are of the type found in 'secondary' anæmia. The red cells may drop to less than 2,000,000 per c.mm.; the average number is one-half of the normal. The colour-index is low. In a series of fifteen cases Osler found the number of red cells to be 3,425,000 per c.mm. and the hæmoglobin 47 per cent. A recent hæmorrhage will of course affect the count very considerably; though it has often been observed that recovery after a hæmorrhage is rapid, and that within two or three weeks the blood-count may so improve as almost to reach the normal. The white cells are never above the normal unless there has been a recent hæmorrhage, or an inflammatory complication is developing. Leukopenia is the rule. In Osler's case the average count was 4520.

4. *The tendency to hæmorrhages* is remarkable. Hæmatemesis especially is seen, occasionally with copious melæna. Other forms of bleeding are also mentioned in recorded cases; epistaxis, purpura, and hæmaturia are the most commonly seen. The amount of blood lost, especially from the stomach, may be enormous. I have seen two cases in which the apparently pure blood vomited within a couple of hours measured over three pints. Osler records a case in which three quarts of blood were lost within thirty-six hours. Recurrence of the hæmorrhage is frequent. A remarkable case is related by Hutchison and Ledingham* of a woman who was admitted to the London Hospital for severe hæmatemesis no fewer than thirteen times within a period of fifteen years. The blood comes in such cases, it is believed, from œsophageal

* Allbutt's *System of Medicine*, v, 759.

varices and dilated vasa brevia, both of which are found in a large proportion of the cases.

5. *Affection of the liver.*—In the later stages of the disease the liver enlarges, and presents the clinical picture of Laennec's cirrhosis. Ascites is present with the hepatic enlargement, or in some cases without it. This terminal condition, in which the liver is enlarged and dropsy is present together with the earlier conditions described, is often spoken of as 'Banti's disease'; but if this latter term is retained, it is perhaps wiser to use it only as a synonym of 'splenic anæmia'.

6. *An unknown causation.*—The discovery of a cause for the splenic condition removes the case from the category of splenic anæmia. As I have said, the term 'splenic anæmia' as originally used included a group of diseases characterized by certain clinical features common to them all. Upon this group encroachments have steadily been made, and may well continue to be made, as our knowledge of the etiology of special diseases becomes by degrees more accurate.

7. *Other phenomena of less importance* may briefly be enumerated. A general enlargement of lymph-glands is not present. Until the latest stage there is no alteration of the urinary function. Occasional attacks of heaviness in the epigastrium, flatulence, and indigestion are observed, which lead, when hæmorrhage occurs, to a diagnosis of 'gastric ulcer'. Such dyspepsias are less frequently seen than might be supposed. Rarely there may be slight pigmentation of the skin. If jaundice is present the case is not one of splenic anæmia.

The Differential Diagnosis.—This as a rule is not difficult. The mistake I have most commonly seen is the making of a diagnosis of *gastric* or *duodenal ulcer.* I have now seen five cases in which a patient suffering from splenic anæmia was referred to me as an example of these diseases. The absence of a clear history of dyspepsia, the presence of an easily palpable spleen, and the blood changes, soon revealed the true condition. The contrary mistake may be made. Rolleston relates the following case* :—

"Some years ago a middle-aged man was under my care in St. George's Hospital. He was very anæmic, and with a history

* *Practitioner*, 1914, April, 480.

of recurrent hæmatemesis. There was a tumour which appeared to be an enlarged spleen, and the condition was regarded as splenic anæmia. The necropsy showed that the tumour was a large hydatid cyst in the left kidney, and that a chronic gastric ulcer was responsible for the repeated hæmatemesis."

In any doubtful case an *x*-ray examination would almost certainly clear away the uncertainty and demonstrate the presence of a chronic gastric ulcer.

Cirrhosis of the liver has occasionally presented difficulties in diagnosis. The number of cases in which the splenic enlargement is considerable, and the hepatic enlargement slight, must be excessively small. That the spleen may be much enlarged in cases of Laennec's cirrhosis is certain; and in such a condition a copious hæmatemesis might well raise a doubt as to the true diagnosis. Naunyn and others consider that splenic anæmia is merely a type of hepatic cirrhosis in which the liver changes are relatively slight, at least until the final stages are approaching. If a patient is first seen when the spleen is grossly enlarged, the liver cirrhotic, ascites abundant, hæmorrhages recurrent, and ill health and emaciation advanced, it is not certainly possible to say whether the case is one of advanced Laennec's cirrhosis, or is in the terminal stages of Banti's disease. The accurate diagnosis is, however, made without difficulty if the earlier stages of the disease are carefully sought.

Syphilitic enlargement of the spleen and liver may be associated with a moderate degree of anæmia. In such cases the symptoms of splenic anæmia are reproduced with remarkable accuracy. The differential diagnosis is achieved by a close study of the history, by a discovery of a positive Wassermann reaction, and by a recognition of the effects of antisyphilitic treatment. The latter, however, is not always successful. W. J. Mayo records five cases* in which he removed enlarged spleens in conditions of chronic intractable syphilis with severe anæmia, when the patients had been resistant to careful treatment for syphilis, carried out during a period of several months. After removal of the spleen the anæmia rapidly disappeared and the syphilis was cured with comparatively mild antiluetic treatment such as had previously failed to affect either the syphilitic condition or the spleen. Coupland records a

* *Trans. Amer. Surg. Assoc.* 1919, xxxvii, 483.

case in which the spleen was removed for 'splenic anæmia' with much benefit; the patient died two years later, and syphilitic disease of the liver was found.*

Chronic obstruction of the splenic vein.—Many years ago Dock and Warthin† called attention to the occurrence of phlebitis and calcification in the splenic vein, in cases in which the group of symptoms and signs associated with splenic anæmia was present. Other changes in the splenic vein in similar cases have been recorded by various observers. These are summarized by Rolleston‡ as follows:—

> The splenic vein may be:
>
> 1. Reduced to a fibrous cord.
> 2. Represented only by a plexus of veins, as in a case in which hæmatemesis occurred at intervals of ten months for twenty years.§
> 3. Thrombosed as the result of extensive endophlebitis.‖
> 4. Occluded by an organized thrombus at its proximal end.**

These various morbid changes may be different stages of the same process, but the sequence of events may vary: thus endophlebitis may undoubtedly cause thrombosis, and it is quite possible that organization of a primary thrombosis may be followed by endophlebitis and calcification.††

In cases such as these the differential diagnosis is impossible. The view that all cases of splenic anæmia are the result of changes such as these in the splenic or portal vein cannot be sustained. In some cases of splenectomy for splenic anæmia, it is true, these changes may be found, in greater or less degree, and at times they have been known to embarrass the operator by causing a difficulty with the ligation of the pedicle, and troublesome hæmorrhage. But in the great majority of instances no such changes are discoverable, though recently search has been carefully made for them.

The influence of trauma in exciting phlebitis and thrombosis

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* *Brit. Med. Jour.*, 1896, i, 1445.
† *Amer. Jour. Med. Sci.*, 1904, cxxvii, 24. ‡ *Practitioner*, 1914, xcii, 479.
§ Langdon Brown, *St. Bart's. Hosp. Rep.*, 1901, xxxvii, 155.
‖ Oettinger et Fiessinger, *Rev. de Méd.*, 1907, xxvii, 1109, etc.
** Bland-Sutton, *Proc. Roy. Soc. Med.*, 1913, vi, 239.
†† Thompson and Turnbull, *Quart. Jour. Med.*, 1911, v, 291.

in the splenic or portal vein must be remembered. Ledingham * writes that "many cases which showed symptoms of splenic anæmia or Banti's disease have presented a history of previous severe abdominal injury, and that thrombosis of the portal vein, with consequent splenomegaly, anæmia, and moderate cirrhosis of the liver, has been proved on several occasions to follow injury". A recent case in my own experience confirms this association of early and severe trauma with the symptom-complex of splenic anæmia.

Moschowitz, in an admirable summary and discussion of the subject of Banti's disease,† calls attention to the simulation of this disease by cases in which there is persistence of the umbilical vein. In recent years four such cases have been described in which the clinical symptoms were closely similar to, or identical with, those of Banti's syndrome. There was also a hypoplasia of the liver attributed to persistence of the vein, which on post-mortem examination was found enormously dilated in all cases, and communicated in some with the deep hypogastric or deep epigastric veins. The unusual and excessive amount of blood carried in this vein caused a damming back of blood in the splenic vein, which in turn was responsible for the gigantic overgrowth of the spleen.

The Pathogenesis of Banti's Disease.—The fact of utmost significance in connection with the causation of this disease is that it is cured or arrested by removal of the spleen. This fact may be accounted for either by assuming that the disease is primarily and essentially located in the spleen, or by assigning to the organ the rôle of modifying the action of some agent situated elsewhere in the body.

If the disease is primarily splenic, a search for a specific microbic infecting agent should ultimately be successful. Hitherto no convincing evidence of this has been found, although Hollins has argued strongly in favour of incriminating the colon bacillus. There is scope for further research in this direction; and the organ removed during life, if straightway examined, should provide profitable material for routine bacteriological investigation.

The enlargement of the spleen has been attributed to excessive

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* Allbutt's *System of Medicine*, v, 759.
† *Jour. Amer. Med. Assoc.*, 1917, lxix, 1045.

hæmolytic activity by those who consider the disease to begin in some other part of the body. But such a view does not sufficiently explain the fibrosis which is the outstanding histological feature of the disease. A chronic infective process would account for the enlargement as well as the fibrosis, and accord better with the absence of undue hæmolysis of the red blood-cells. In splenic anæmia the red cells never show 'fragility'. If there is a change, the corpuscles may exhibit increased rather than diminished resistance.

The anæmia, in like manner, may be regarded as an incident, or as an essential part of the disease. Rolleston, a very distinguished authority, does not regard the anæmia as primary; he believes it to be secondary to attacks of very severe hæmorrhage, chiefly because he finds that regeneration of blood takes place after these events. This view, however, is, I think, subject to the criticism that such severe hæmorrhage is not invariable, and that the substance elaborated in the spleen need not be capable of affecting the bone-marrow until after it has left the liver, where it has undergone modification. Further, whatever the poisonous substance may be, it need not completely arrest blood-cell development. A parallel case is, I think, sometimes furnished by subjects of leukæmia in which an intercurrent infection supervenes, with a temporary restoration of the normal blood-picture.

Hollins regards the disease as being due to an active 'intoxication' produced by the colon bacillus, whose 'colilysin' brings about the anæmia, whilst its actual presence in both spleen and liver accounts for the fibrosis of each organ. This view would put every kind of cirrhosis of the liver on the same level, because 'colilysins' could not be expected to vary radically in their action. The facts would be better met were it suggested that the spleen harbours various organisms, some of which only excite a local fibrosis, others induce a simple cirrhosis of the liver, and still others produce that form of cirrhosis associated with Banti's disease, with a toxic anæmia and other specific symptoms.

In respect of the hæmorrhage which is so conspicuous and alarming a feature of some cases, Rolleston considers that the enormously distended vasa brevia rupture into the stomach as a result of the torsion of the splenic vein caused by the great bulk of the organ. This opinion is certainly correct in many cases. The hæmorrhage is so profuse and so swiftly escapes from the

stomach that large vessels must be implicated. Such vessels as Rolleston describes are often seen in operations upon cases of splenic anæmia when abundant hæmatemesis has occurred. But this cannot, I think, be the whole explanation. The relationship between enlargement of the spleen and gastric hæmorrhage is cryptic, but certain; for, as Balfour was the first to show, removal of the spleen may cure a patient whose life has been jeopardized by severe and recurrent hæmorrhages from the stomach. Gastric hæmorrhage is known to be toxic in origin in certain cases as, for example, those in which there is a lesion in the appendix, intestine, or gall-bladder; and those also in which the lesion lies in the spleen or liver, or both.

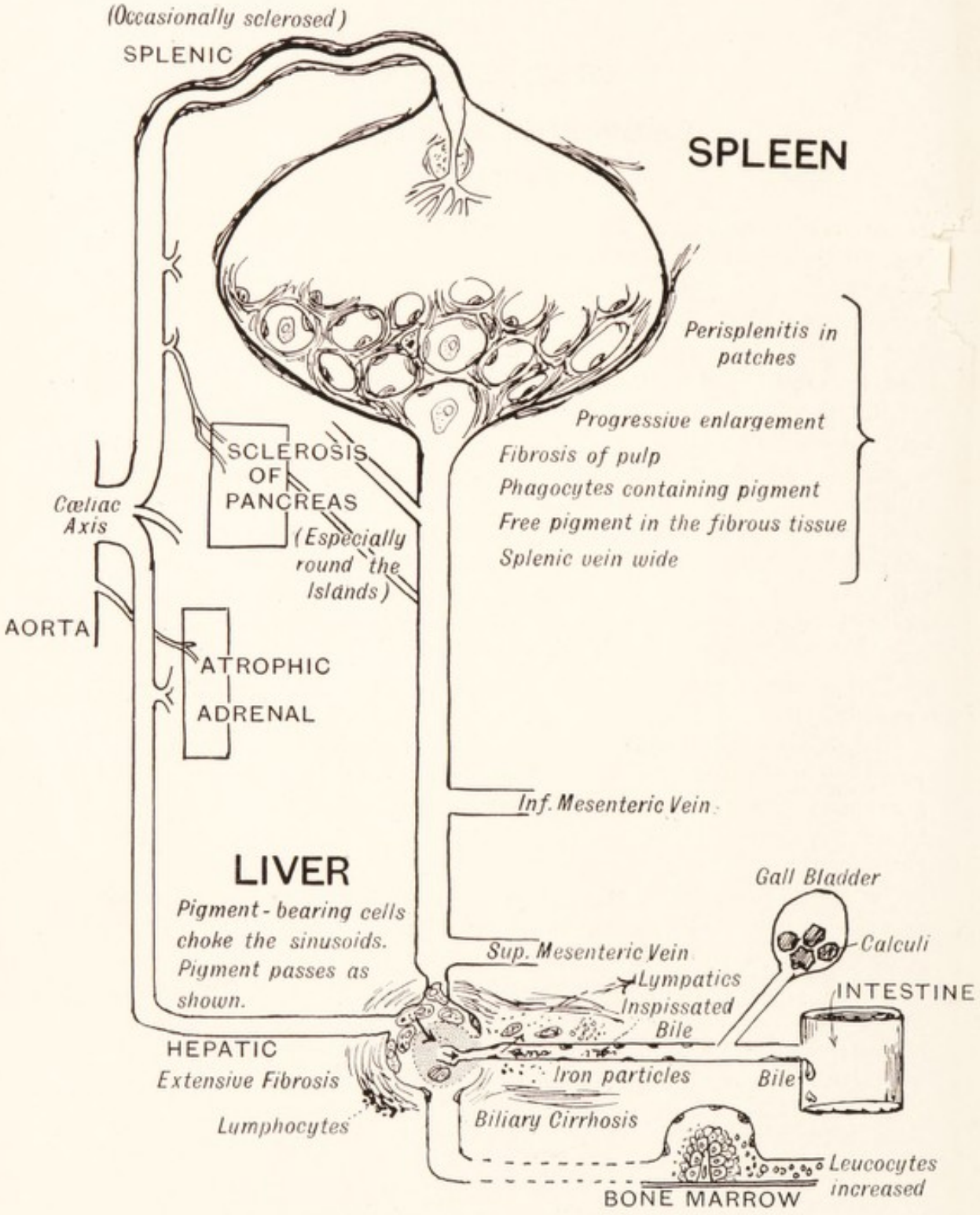
Treatment.—The only treatment for splenic anæmia is splenectomy. The appropriate moment for the removal of the organ is chosen. It is inadvisable to operate soon after a grave hæmorrhage, or when the spleen is extremely large. In the latter case the effect of radium on the tumour should be tried; almost certainly it will cause a rapid and considerable shrinkage in the organ. If this should happily be the case, splenectomy is done when the spleen is at its smallest, and before it has begun to enlarge afresh, as it will certainly do after a few weeks. It is imperative to operate upon cases of this disease as early as possible. No other form of treatment needs consideration; the dangers and difficulties of the operation increase with the lapse of time; early operation means a more certain chance of recovery and a quicker convalescence. In the later stages the mortality of operation is higher, amounting to 25 per cent as compared with an average of about 10 per cent. In the terminal stages operation becomes so dangerous that only the inevitably fatal outcome of the unhealed disease justifies its performance.

The degree of improvement that may take place is astonishing, even in the late stages of the disease with advanced involvement of the liver. It is, as W. J. Mayo says, an evidence that the great power of the liver to regenerate its specific cells is utilized to the full.

The difficulties of the operation are greater in splenic anæmia than in any other disease. In almost all cases adhesions binding the organ especially to the under surface of the diaphragm are present. They may be numerous and exceedingly dense, and

their separation may cause a copious and grave hæmorrhage. But they are never so dense nor so strong as to prevent the completion of the operation. The details of the operation in other respects are the same here as elsewhere. At the Mayo clinic up to Sept. 20, 1920, 73 operations had been performed, with 9 deaths, equal to 12·3 per cent. The after-results are excellent; the rather operative mortality is due to the technical difficulties of th cases, which, apart from operation, would all be fatal.

PLATE VII



THE CHIEF CHANGES IN HÆMOLYTIC JAUNDICE

CHAPTER X.

HÆMOLYTIC JAUNDICE.

(*See Plate VII.*)

In his work, *Diseases of the Liver*, Murchison, a well of wisdom, describes cases of chronic slight jaundice occurring in several members of the same family: an association with splenic enlargement is not mentioned. Cases of congenital jaundice and splenomegaly occurring together were first recorded by Claude Wilson in 1890 and in 1893.* Hayem, in 1898, described five cases of icterus† similar in character to these, though acquired and not congenital, and presenting certain features in common. There were in all a slight chronic jaundice, and normal stools and urine. The absence of such conditions as pale stools, mahogany-coloured urine, and tormenting itching of the skin was especially noted. The spleen in all was large and hard, and the liver a little increased in size. In all anæmia was present, the erythrocytes numbering between one and three millions; and in all there was a history of acute exacerbations. In none was there any family history of similar conditions; in three the first appearance of jaundice occurred in adult life.

In 1900 Minkowski described the occurrence of chronic jaundice in eight members of one family, extending over three generations; in these the symptoms and signs were similar to those described by Hayem, but in addition urobilin was noticed in the urine; there were pigment deposits in the kidney; there was enlargement of the spleen as the result of hypertrophy and vascular engorgement; there was no cirrhosis of the liver.

Two types of disease were thus recognized: the acquired form of Hayem, and the congenital or familial form of Wilson and Minkowski. The former type was more fully described, and its clinical history and blood condition more critically examined, by Widal. The latter type in respect of its hæmatology was especially

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* *Trans. Clin. Soc.*, 1890, 162, and 1893, 165.
† *Bull. et Mém. Soc. Méd. de Paris*, xxv, 122.

studied by Chauffard, who first pointed out that the resistance of the red blood-cells to hypotonic salt solutions was greatly diminished. This increased 'fragility' constitutes the factor of chief importance in the disease. Of the two, the acquired form (the 'Hayem-Widal type') is the more serious, and apart from surgical treatment appears to be inevitably fatal.

The Symptoms in the two types are very similar. There are acholuric jaundice—that is, jaundice with unaltered stools and urine—enlargement of the spleen, and anæmia. There is no itching of the skin, and there is not that degree of rapid wasting so often seen in cases of obstruction to the common duct. The blood changes show a reduction in the number of red cells, an increased number of reticulated cells, and a lessened resistance to hypotonic salt solution. In two of the cases of the acquired type which I have seen, the symptoms have very closely resembled those of obstruction of the common duct by calculus. In both there were exacerbations of jaundice preceded and accompanied by fever, and by pain and tenderness in the epigastrium. In one of these my diagnosis would certainly have been confidently given as 'cholangitis due to calculus', but that a surgeon of great experience had explored the duct and discovered no stone. The diagnosis may be very difficult in cases in which gall-stones also are present. In about 60 per cent of recorded cases stones have been found in the gall-bladder or in the ducts at the time that operation for removal of the spleen was undertaken.

These acute exacerbations during the otherwise tranquil course of the disease were first described by Widal as 'crises of deglobulization'. They are acholuric crises, and are due, it is supposed, to massive hæmolytic activity, an activity which Eppinger estimates as being competent to destroy the whole of the red blood-cells in the body within a period of twenty-four hours, with the result of throwing an immense strain upon all the organs of the body concerned in blood production. In these crises there are great malaise; an elevation of temperature to 101° or 102°; increase in the size of the spleen, which may become very tender; a deepening in the tinge of jaundice; acute anæmia, intense hæmolysis with, in the graver cases, a temporary hæmoglobinæmia; and urobilin is found in the urine. More rarely the liver also is enlarged, and the epigastrium is often tender. There is no itching of the skin,

and there are no petechial hæmorrhages. It will be seen how close is the mimicry of the symptoms caused by a comparatively small gall-stone floating in a comparatively wide common duct; and remembrance must always be given to the fact that in so large a proportion of cases gall-stones, whether in the gall-bladder or in the common duct, are found at operation. Probably the very worst forms of crises are often, if not always, due to impaction of calculi in the common duct, and the evidences of biliary obstruction in the urine and fæces may then be found. Elliott and Kanavel,* in an admirable paper, say that in the crises "one can always find evidence of excessive regeneration, i.e., polychromatophilia, nucleated red cells, and certain reticulated bodies in the red cells stained by vital stains as first recorded by Vaughan".

The distinction between the congenital and acquired forms is real. The congenital form is exceedingly chronic in its duration and quiescent in its manifestations. Chauffard said of patients suffering from this form, that they were "more jaundiced than ill". I have more than once been consulted by patients on account of other diseases (loose cartilage in the knee, and carcinoma of the breast) who were suffering from the congenital form of this disease; the jaundice was regarded with as little interest as the colour of the hair. In the familial type of the disease several observers have noted that the condition is of a graver type in the parent; the jaundice is deeper, the crises are severer and more frequent, and complications are more prone to develop. Not a few of the patients, affected though not afflicted by the disease, live their days out in comfort, and die, at advanced ages perhaps, of maladies unconnected with this condition. A few patients have lived to the age of 80, and one at least to the age of 90.

The acquired form may begin abruptly, and run an eager rapid course from the first. Anæmia quickly becomes profound, the red cells falling to one million within a few weeks. The crises of pain, temperature, and deepened jaundice are more frequent than in the congenital type. In one direction the disease, whether congenital or acquired (generally the latter), may wander away into the neighbourhood of pernicious anæmia. Chauffard describes an "icteric form of pernicious anæmia which, when accompanied by

* *Surg. Gynecol. and Obst.*, 1915, xxi, 21.

diminished resistance and reticulated red cells, represents the least compensated form of hæmolytic icterus". Weissenbach records a case of this type also.

PATHOGENESIS.—The older views that this disease is primarily hepatic in origin are for ever set aside by our surgical experiences; for it is known beyond dispute that removal of the spleen 'cures' the patient, who, if the operation has been done in stages earlier than the terminal, remains entirely free from symptoms at all subsequent periods. The spleen, if not the exclusive cause or seat of the disease, exerts the profoundest influence upon its pathogeny.

Several views as to the ultimate causation have been held. Chauffard at first, and Widal later, believed the essential factor to be a dystrophy, an increased fragility of the red cells. This view is held by the great majority of those who have studied the question in recent years. Other authorities, led by Minkowski, hold the opinion that the primary change is an increased hæmolytic activity, probably restricted to the spleen. Widal, the most earnest supporter of the former view, considers that the red cells which are congenitally infirm are destroyed in the general circulation; their remnants are taken up by the spleen—which undergoes enlargement, forming a tumour for which Ponfick introduced the term 'spodogenous'—and also by the bone-marrow, kidney, and liver, all of which are found on post-mortem examination to be deeply pigmented. This opinion has lost ground since the many good results following splenectomy have been witnessed, though, as I shall mention, it does not appear from the very late examination of Sir Spencer Wells's case that the dystrophy of the red cells is always altered, even after many years of perfect health following splenectomy. Consequently the altered character of the red cells may be sometimes evidence of faulty manufacture, their lipoid component being deficient, as I have already suggested. This does not nullify the opinion that the spleen has much to say in the subsequent treatment of such defective cells. In my own cases fragility of the red cells disappeared soon after splenectomy, and has not returned. The experience in Spencer Wells's case is, I think, exceptional.

Minkowski's view is held by a few later writers, including Banti, who consider that the spleen is not only enlarged as a consequence

of the retention within it of cell remnants, but that within the spleen cells are prepared for destruction and are there actively destroyed. An examination of the spleens removed during life or obtained at autopsy shows no specific change. The deep congestion of the splenic pulp and of the sinusoids, constantly found, is common to many other forms of splenic disease. Occasionally biliary cirrhosis is found at autopsy.

TREATMENT.—Treatment of this condition is by no means always necessary. The symptoms may be very slight, or may even be absent. If crises occur they may be so infrequent and so speedily pass away that the patient, having suffered from them for years, may pay no serious heed to them. In cases rather more severe, general medical treatment and the use of radium therapy have proved to be valueless. Where the symptoms are troublesome to the patient, and especially so in the acquired form, recourse to operation should be had in as early a stage as possible. It is better not to operate in, or near, a time of crisis, and if the spleen is unduly large its size may be reduced temporarily by the application of radium. Splenectomy has proved to be a specific in this disease. Its dangers are slight: in Kanavel's collection of 48 cases there were 2 deaths; in Mayo's series of 32 cases there was 1 death. And the results are excellent. Within a few days the patient loses the tinge of jaundice entirely, all symptoms disappear, and there is never any recurrence. No operation in surgery gives such swift and striking results. It is very remarkable to witness the change in a patient who has been jaundiced for years or from birth; the skin becomes clear and white, sometimes within forty-eight hours. The first case submitted to operation was recorded by Sir Spencer Wells.* The patient was a young unmarried lady, age 22, who had an abdominal tumour "the size of a young child's head". The tumour was below the umbilicus, central, elastic, but without fluctuation. Its movements were closely associated with those of the uterus, and its lower border was felt behind and to the left of the uterus. Sir Spencer Wells was doubtful as to the precise seat and character of the tumour, but thought that it must be either uterine or ovarian. The patient's very florid complexion inclined him to the former view. Since the age of nine the patient

* *Med. Chir. Trans.*, 1888, lxxi, 255.

had been subject to frequent attacks of jaundice, and the mother said the urine had "always been dark in colour". The operation was performed on Dec. 5, 1887, was followed by a good recovery, and six weeks later the patient's medical man wrote: "I question whether she has for many years past been six weeks without an icteric tinge". It is interesting to note that the patient was alive and well in the year 1914, and Lord Dawson then reported* "that the red cells still showed increased fragility". Two similar cases, in which the symptoms have been completely relieved by splenectomy but the increased fragility remains unchanged, are recorded by Kahr† and Roth, but, as I have remarked, this experience is probably unusual. The matter needs further inquiry.

The second case of hæmolytic jaundice to be treated surgically was operated upon, in 1895, by Bland-Sutton; the result was excellent, and the patient was reported alive and well five years later. Sir John Bland-Sutton tells me that he has not seen the patient for five years, but that she was then quite well, and the fragility of the red cells was normal. In my own cases the fragility, tested two months and over after the operations, was normal. There can therefore be no hesitation in advising operation in all appropriate cases.

Giffin‡ reports that the result of the examination of patients in the Mayo clinic, by the method of Schneider, shows that the quantity of the bile pigments found in the duodenum, always in excess of the normal in this disease, steadily declines after removal of the spleen.

In all operations the condition of other abdominal organs will of course be examined as a part of the usual routine. The association in so many cases of cholelithiasis, and of a greatly-thickened bile, in stages earlier than those of calculous deposit, will involve the removal or the drainage of the gall-bladder, and possibly an exploration of the common bile-duct. No operation for hæmolytic jaundice is complete until the bile-passages have been thoroughly explored. The removal of the appendix will be performed in all cases in which the condition of the patient does not prohibit the very slight additional manipulation.

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* *Proc. Roy. Soc. Med.* (Clin. Sect.), 1914, vii, 86.
† *Verh. d. deut. Kong. f. inn. Med.*, 1913, xxx, 326.
‡ *Surg. Gynecol. and Obst.*, 1917, xxv, 152.

The results at the Mayo clinic up to Sept. 20, 1920, showed 32 cases with 1 death, a mortality of 3·2 per cent. Like all other statistics of this clinic they represent the results obtained by a group of men of the highest technical skill, working under conditions unsurpassed elsewhere. They show the level which highly organized surgical endeavours can attain, and are an example and an encouragement to all.

CHAPTER XI.

GAUCHER'S DISEASE. VON JAKSCH'S DISEASE. POLYCYTHÆMIA.

GAUCHER'S DISEASE.

Our knowledge of Gaucher's disease has become much more definite as a result of the work of F. S. Mandelbaum,* who has shown its essential difference from Banti's disease. The following are the salient clinical features :—

The appearance of a greatly enlarged ('colossal') spleen in childhood ; a chronic course without disturbance of the health until late in the history of the case ; a family tendency ; and a frequency seven times as great in girls as in boys. There is a uniform discoloration of the skin of the face, neck, and hands, and a wedge-shaped thickening of the conjunctiva on either side of the cornea. There may be a tendency to bleeding from the nose, the gums, or under the skin after slight injuries. Glands are not enlarged. There is no jaundice, and no ascites. The liver is much enlarged. The blood shows a diminution of the number of white cells, but no anæmia until late in the disease ; the urine contains urobilin but no bile. The disease generally begins during childhood, before the twelfth year, and may last over a quarter of a century.

Interest in the pathology of the disease centres round the so-called 'Gaucher cell', which occurs in masses in the Malpighian bodies and in the venous sinuses of the spleen, as well as in the bone-marrow and in the sinusoids of the liver. The cells are very large (at least five times the diameter of a red cell), and contain usually from one to four nuclei. The protoplasm is streaked or wrinkled, and can be traced into the reticulum, according to Downey (1916). This observer concludes, after a very careful study, that the cell is a modified reticular cell—a view which

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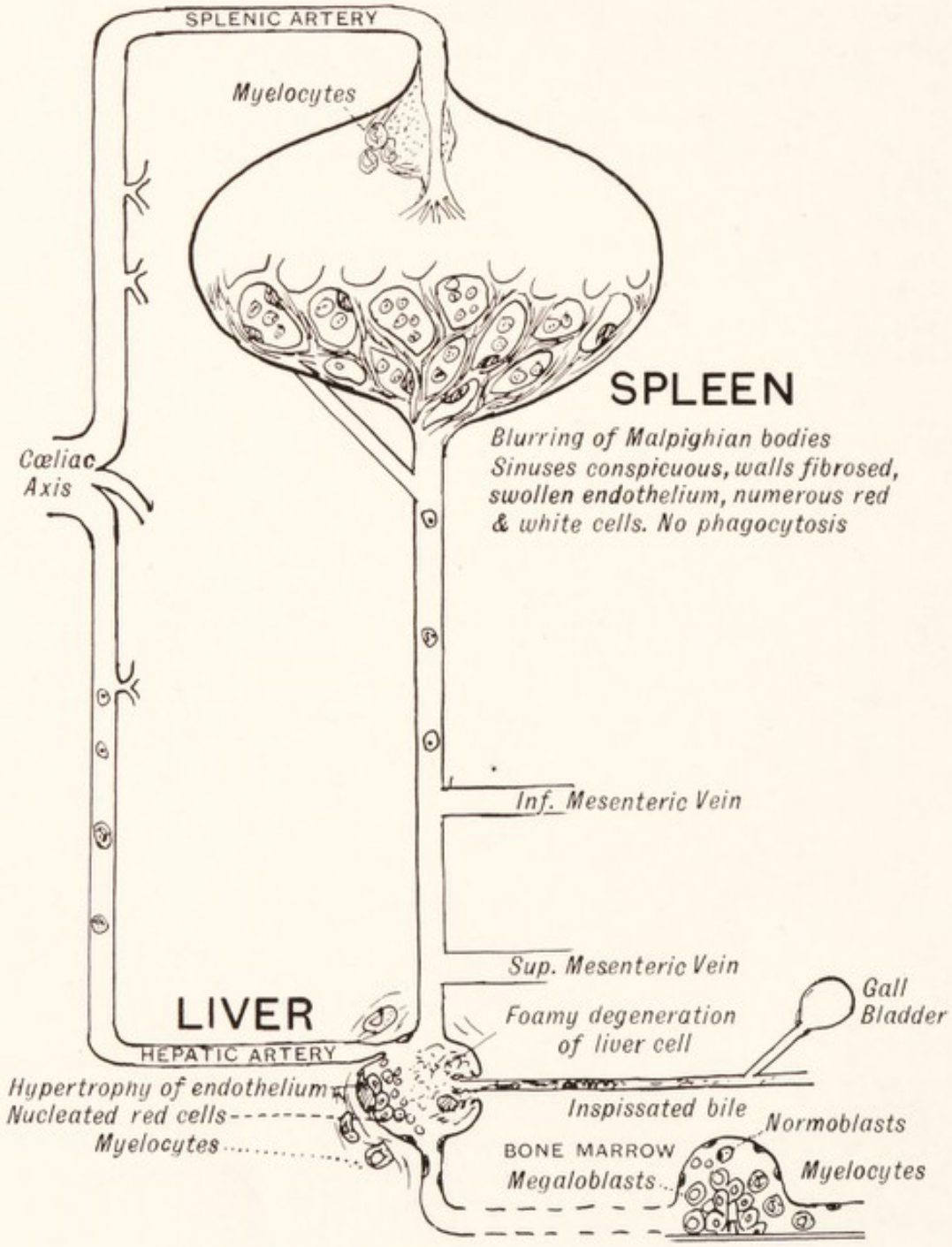
* *Jour. Exper. Med.* 1912, p. 697.

PLATE VIII



THE CHIEF CHANGES IN VON JAKSCH'S DISEASE

is not essentially at variance with that which looks on it as a modified endothelial cell.

As the disease progresses, cirrhosis of the liver develops, but this produces clinical features which are different from those of biliary cirrhosis and the cirrhosis of acholuric jaundice. The difference lies chiefly in the absence of much disturbance of health.

In biliary cirrhosis there are jaundice, fever, and leucocytosis. In this form, where there is also leucocytosis, there are marked changes in the state of the red blood-cells. It seems as if the presence of the large endothelioid cells in the interstitial tissue of the liver produces merely a passive deposition of fibrous material, without the liberation of poisonous substances. But when the fibrosis has advanced, the liver-cells undergo pressure atrophy, and emaciation becomes a symptom.

VON JAKSCH'S DISEASE.

(Anæmia Pseudoleukæmia Infantum.)

(*See Plate VIII.*)

The disease to which von Jaksch first drew attention was considered by him to be a form of leukæmia occurring in infants. The cases which he gathered together resembled each other chiefly in the fact that the blood showed a very high degree of leucocytosis. This feature came to be regarded as the chief criterion of the diagnosis, and consequently confusion arose; many various conditions being classified as instances of this one disease. When Hayem, and subsequently Luzet, directed attention to this disease and came to analyze the material at their disposal, they found that the important features were the presence of numerous nucleated red cells in the blood, and the appearance of centres of formation of red cells in the spleen and liver.

The discussion of the relation between this form of anæmia and pernicious anæmia and leukæmia is almost a thing of the past. No one, I think, regards von Jaksch's anæmia to-day as a form of pernicious anæmia, and it is quite clear that it is not a variant of leukæmia.

The salient features of the disease are: that the infant is strikingly anæmic, and develops œdema, hæmic murmurs, dilatation of the heart, shortness of breath, and bleeding from the nose,

gums, and bowel. Examination shows the presence of a much enlarged spleen, a moderately enlarged and flexible liver, and possibly some enlarged glands. The pathologist finds a diminution of the red cells even to 2 million per c.mm., with a colour index of 0·5 to 0·7. The white cells number from 20,000 to 100,000 per c.mm., and the differential count shows a decided increase of the lymphocytes, with not a few myelocytes. Normoblasts are found in all cases; megaloblasts are sometimes noted. There is considerable variation in the size and shape of the red cells.

It is especially noteworthy that this blood picture remains constant over long periods of time. The outlook is not often serious. After a chronic lingering course, recovery slowly takes place. Arsenic sometimes brings about a rapid recovery. If death occurs it is usually the result of pneumonia or some acute infection.

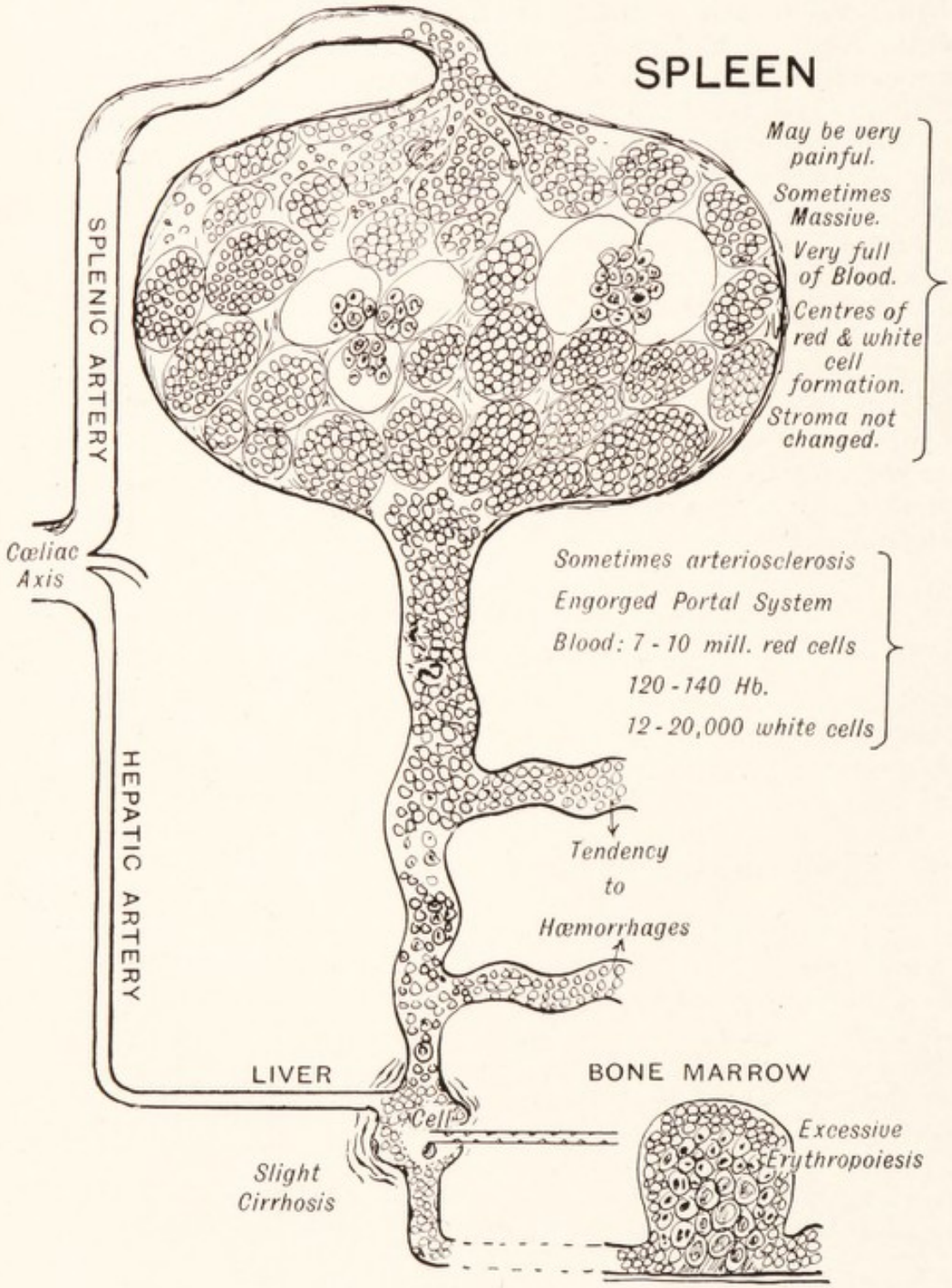
W. K. Hunter* records ten cases which he describes as instances of infantile splenic anæmia. He states that the two criteria of diagnosis are: the presence of anæmia, and decided enlargement of the spleen. The cases fall into three types:—(1) That in which there is a fall in the number of leucocytes, the lymphocytes preponderating; (2) That in which there is a moderate leucocytosis (up to 20,000 per cm.) and a few myelocytes appear in the blood; and (3) That in which there is a great increase of the leucocytes. The last-named class conforms to the condition generally known as von Jaksch's disease.

His diagnosis leads him to regard all forms as secondary to other conditions—lack of fresh air, lack of suitable food, presence of syphilis, rickets, and previous infectious disease, notably measles.

Both Naegeli† and Grawitz‡ have expressed this view very clearly, showing that the disease is merely an unusual type of secondary anæmia. It is because the blood-forming organs are still unstable that the abnormal stimuli (rickets, gastro-enteritis, syphilis) bring about the appearance of megaloblasts and myelocytes in the blood, whereas in an older child the 'reversion to the embryonic type' would not be possible. The increased activity of the blood-forming organs accounts for the enlargement of the

* *Lancet*, 1909, i, 230. † *Text-book*, 1908. ‡ *Text-book*, 4th ed., 1911.

PLATE IX



THE CHIEF CHANGES IN POLYCYTHÆMIA VERA (VAQUEZ' DISEASE)

spleen (a merely transient hypertrophy), of the liver (which resumes its previous blood-forming activity) and the bone-marrow (which is now very red and plentiful). If the lymphatic glands enlarge, it is the result of the formation of myelocytes in them—that is, of the resumption of functions of blood formation.

Hunter has questioned whether the rachitic cases may not owe their existence to the fact that the bone changes of the epiphyses extend into the marrow. The whole bone is engorged. In this case the increased activity of red-cell formation would be the inevitable outcome of the congestion of all parts of the bones. He found that the cases with leucocytosis were rachitic, those without leucocytosis were not. The associated changes in other parts of the body would be explained by the fact that rickets is a general disease.

It is evident that the most satisfactory view of this disease is that which regards it as a symptom of some other disorder. It is accordingly desirable to remove it from the list of separate disorders of the spleen, and its introduction here is merely for the purpose of emphasizing this view.

POLYCYTHÆMIA. VAQUEZ' DISEASE.

(*See Plate IX.*)

A person is said to be suffering from polycythæmia when his red-cell count has risen to 6 million per c.mm. and upwards. Such a condition has been found to occur for *short periods* of time in association with the profuse sweating, diarrhœa, or diuresis which various diseases produce. It is characteristic of the new-born child, and it appears in adults visiting tropical countries or ascending high mountains. An increase in the number of red cells which persists during a much *longer time* is also a feature of congenital cyanosis due to malformations of the heart, and of some cases of acquired heart disease in which there is marked cyanosis. It is met with in cases of fibrosis of the lung, emphysema, and similar conditions in which there is respiratory difficulty. Such poisonous substances as arsenic, phosphorus, and hæmolysins associated with hæmoglobinuria are capable of producing this change in the blood.

Polycythæmia may occur also in the course of recognized diseases of the spleen. Widal and Lefas noticed it to be present

in cases of primary tuberculosis of the spleen, and believed it formed part of the syndrome. Rist, Kindberge and Parvu found it in a case of hydatid cyst of the spleen, the blood-count returning to the normal after excision. Schupfer noticed that a case of Banti's disease developed polycythæmia after splenectomy, and Renon and Richet observed a similar change in a case of hæmolytic jaundice.

In addition to all these forms of polycythæmia there is the true polycythæmia, the so-called polycythæmia vera, Vaquez' disease, the 'malady of Vaquez-Osler', which possesses certain features that raise it into a clinical entity. It begins in adult life, in males, and runs a progressive and fatal course lasting a few years.

The skin becomes a deep purple colour, with dilated venules. The spleen becomes greatly enlarged, though it never reaches the size of some leukæmic spleens. The ordinary causes of cyanosis are absent. There is a tendency to hæmorrhage, but this is due to the engorgement of all vessels, not to changes in coagulability.

The red-cell count is usually at least 7 million per c.mm.; it has reached 13 million (Aubertin); and it is always progressive. The individual corpuscles are not altered in size. There is generally a considerable increase of the leucocytes also, up to 15,000 or 20,000—a point which serves to distinguish these cases from splenic anæmia. The hæmoglobin rises concurrently with the number of red cells, and estimations of the volume of blood have shown that there is a definite increase of this (true plethora of Parkes Weber).

The nature of the disease is not clear. Vaquez himself believed it represented a functional over-activity of the hæmopoietic organs. Menetrier and Aubertin, writing in 1906, placed the disease in the group of myelomatoses, according to which there is a tumour-like over-formation of red cells, as in leukæmia there is a similar formation of white cells. French writers seem disposed to accept this view, and therefore speak of 'myelogenic polyglobulism'. An important objection would seem to lie in the fact that in this case the red cells which are turned into the circulation are quite normal, whereas in leukæmia the excess of cells are all immature, and entirely abnormal. On the other hand, cases are described (as 'subleukæmic erythræmia') in which transitions to true leukæmia appear to develop.

It is possible that the disease may not be due to direct stimulation of the red-cell-forming tissues, but may be a collateral effect of some deeper and more general disturbance of metabolism.

In consequence of the uncertainty as to the etiology, it is only as a tentative measure that the spleen has been removed. This was done in 1905 by Blad, with a fatal result. In 1907 it was performed by Schneider without fatal result, but without altering the state of the patient either way. Other forms of treatment have been equally ineffective. The enlargement of the spleen is in the nature of a work hypertrophy. It is the spleen which keeps the disease in check; removal of the organ is therefore theoretically unsound and practically most dangerous, and should never be performed. The warning is necessary, for I have had one case of this disease submitted to me for splenectomy, the examination of a specimen of blood sent by post to a distinguished laboratory worker having shown the characteristic count of splenic anæmia.

CHAPTER XII.

DIFFERENTIAL DIAGNOSIS.

THE differential diagnosis of the several diseases I have now described is often a matter of grave difficulty. The table which follows, adapted from Krumbhaar, presents the points of similarity and of difference in a form that can be quickly seen :—

	GAUCHER'S DISEASE	SPLENIC ANÆMIA	ACQUIRED HÆMOLYTIC JAUNDICE	FAMILIAL HÆMOLYTIC JAUNDICE	PERNICIOUS ANÆMIA
Etiology .	Toxin ? Tumour ? Tumour ?	Toxin ?	1. Primary ? 2. Secondary to infection	Hereditary	Enterogenous
Pathology of Spleen	Peculiar cell hyperplasia	Hyperplasia. Fibrosis	Congestion and pigmentation	Congestion and pigmentation	Fibrosis. Toxin ?
Family History	Occasionally positive	Negative	Negative	Positive	Negative
Time of Onset	Childhood	Adult life	Any age	Congenital or childhood	Adult life
Duration .	Many years	Few years	Many years	Many years	Few years, with remissions
Icterus .	Rare	Rare	Present	Present	Very rare
Splenomegaly	+ + +	+	+ +	+ +	Slight or diminished
Hæmorrhages	Occasionally	Occasionally	Rare	None	Rare
Anæmia .	Slight	Slight to severe	Severe	Slight	Severe
Resistance of Red Blood-cells	?	Normal	Diminished	Diminished	Increased
Reticulated Red Blood-cells	?	Normal	Increased	Increased	Increased
Urobilinuria	?	? +	+	+	+
Leucocytes in Blood	—	—	—	—	— or +
Liver . .	+	First + Later —	+ or normal	+	Normal
Treatment .	Splenectomy ?	Splenectomy	Splenectomy	Splenectomy	Iron, arsenic, etc. (splenectomy and transfusion)

CHAPTER XIII.

ON THE LIVER IN SOME OF ITS RELATIONS TO THE SPLEEN.

THE diseases of the liver of special interest to the surgeon in this connection are those in which 'cirrhosis' develops.

Clinical medicine recognizes two main forms of cirrhosis—the portal type first clearly described by Laennec, and the biliary type to which the name of Hanot is often attached. Pathology recognizes many forms of cirrhosis, which are named either according to the distribution of the fibrous tissue in the liver, or according to the supposed channel of infection. A study of the literature shows clearly enough that these different modes of classification have always been a source of great confusion, escape from which is possible only by conceiving of a single disease which may affect now this, now that, anatomical portion of the liver-tissue. The real question at issue, therefore, comes to be: Is there any essential difference between the two clinical types of cirrhosis? If this question can be answered negatively, it will be found that the multiple classifications of pathology are needlessly complex and may be disregarded.

In the preceding descriptions of the hepatic aspect of diseases of the spleen, the anatomical basis (as represented in the diagrams) consisted of a vascular channel and a single liver-cell with the bile-duct issuing from it. The position of the various post-mortem types of cirrhosis can be diagrammatically represented on this scheme, it is true; but it is necessary to modify the picture a little, for the purpose of moving the central theme from the spleen to the liver. Instead of regarding the changes which occur in a single cell, a whole column of cells must now be depicted and considered, and the outflowing bile-channels may be regarded as issuing from a few only of the components of the cell-columns. It will be necessary also to introduce a part of the lymphatic system as intervening (in the case of the ultimate radicles) between some part of the vascular walls and the corresponding hepatic cells.

In this way we are able to survey a scheme which is midway between the purely diagrammatic form hitherto used, and the histological appearances actually found in sections of the liver, wherein the columns of cells occur in large numbers and radiate from the centre to the periphery of innumerable hexagons, or lobules. The advantage of concentrating attention upon a single hepatic cell (the only satisfactory way of discussing the diseases which affect the liver as a whole, and one adopted in the celebrated hand-book of Castaigne and Chiray*) is now supplemented and extended in order that the various strictly anatomical problems of cirrhosis, which affects cell masses, may be discussed. It will be realized that the clinical types necessarily overlap the histological varieties.

The blood in the portal vein is usually described as passing from the periphery of a lobule of the liver inwards to the centre of the lobule, and thence into the radicles of the hepatic vein. In its course, the blood bathes the columns of liver-cells, which are commonly regarded as uniform in function. No discrimination in the activity of the cells in respect of their relationship to one or other of these veins is recognized. This method of description is the result of the study of ordinary histological preparations in which the vascular channels are quite conspicuous when the healthy organ is examined, and the interlobular fibrous tissue is conspicuous when the cirrhotic liver is investigated.

The bile-ducts, with the exception of the larger channels in the 'portal canals', are not made visible without arduous preparation. The part played by them in disease is therefore learnt by deduction rather than by observation; indeed, but for the existence of the bile-ducts and the gall-bladder, this aspect of the whole problem might possibly escape scrutiny altogether.

A new scheme is here suggested for consideration in which a single column of liver-cells may be regarded as forming a *glandular acinus*, with a fundus and an outlet (*Plate X*). At the fundus the cells are massed together; they are sometimes several layers deep. At a little distance from the fundus the origin of the bile canaliculus is seen; it runs downwards as a channel lined only by a single layer of cells which gradually give place to the endothelial lining of the efferent bile-duct. The bile-duct from the one acinus joins that of

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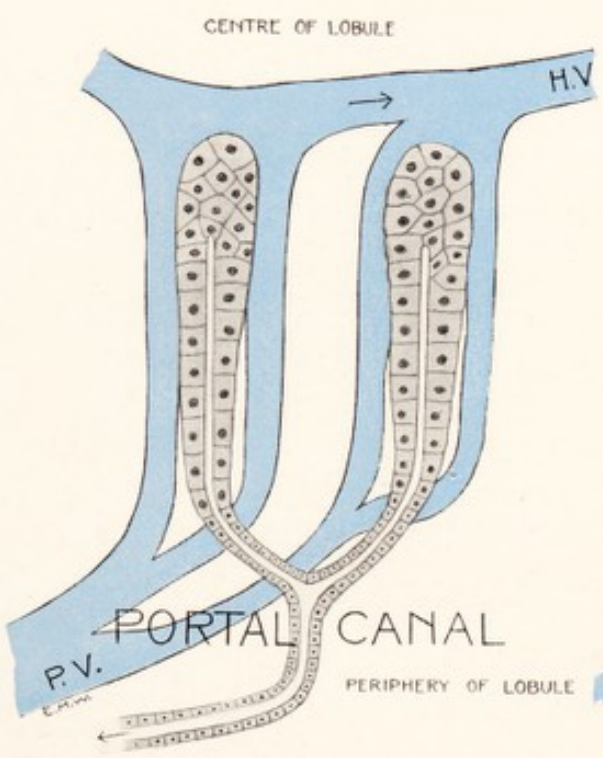
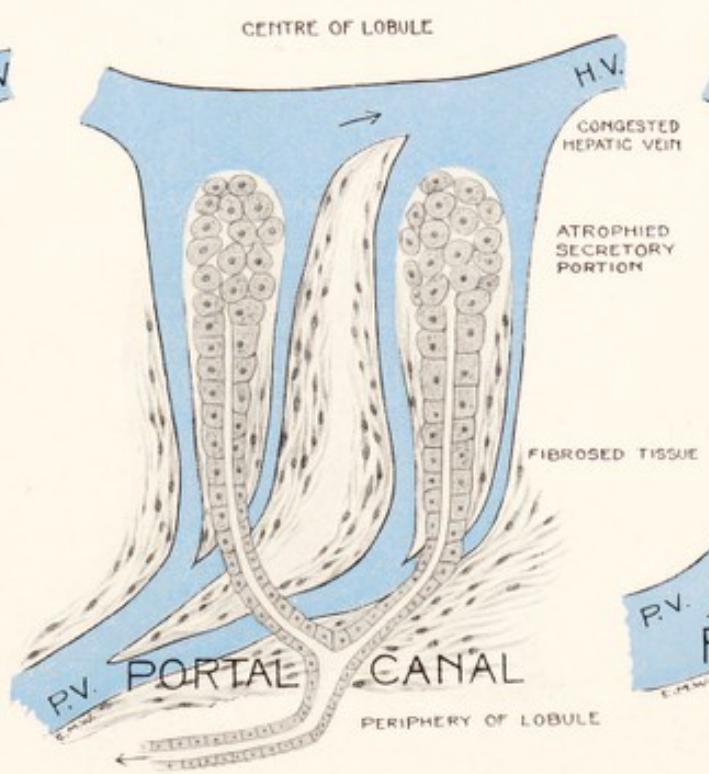
* *Maladies du Foie*, Paris, 1910.

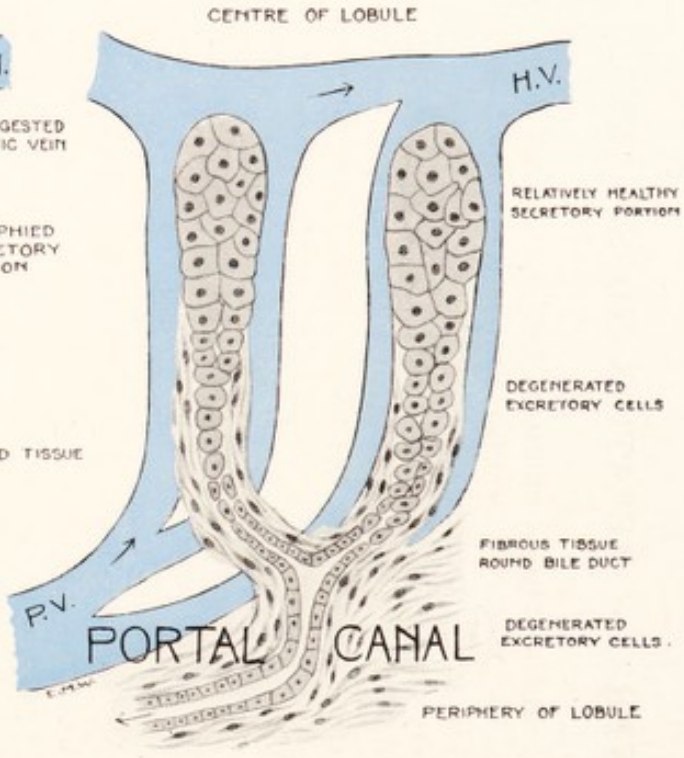
PLATE X



SCHEME SHOWING THE RELATIONS OF THE STRUCTURES CONCERNED IN THE PRODUCTION OF CIRRHOSIS.



THE ESSENTIAL EFFECTS OF PORTAL CIRRHOSIS.



THE ESSENTIAL EFFECTS OF BILIARY CIRRHOSIS.

its neighbours, and the fused channels become progressively larger, still situate in the so-called 'portal connective tissue', until they are easily visible to the naked eye.

The portal blood first bathes that portion of the glandular acinus in which the duct is formed, and then courses towards the fundal end of the gland, where the blood-vessel containing it undergoes a change of name, and becomes the 'hepatic vein'. Whatever the physiological action may be that is accomplished in the 'portal' blood, it has therefore to be achieved within a short length of vascular channel. The capillary suddenly becomes larger at the fundal end of the gland, as several similar capillaries all meet at this point; the volume of blood to be carried away from that moment becomes suddenly greatly augmented. An obstruction of the flow from this larger channel is apt to make the capillaries distend, especially around the fundal portion of the gland. In order to produce a distention of the capillaries round the portion of the gland acinus nearest to the portal vein, there must be an excessive inflow of blood in that vein, not an obstruction to the outflow from the hepatic vein.

If now we consider the gland loop itself more closely, we shall find that the character of the cells is not the same throughout. The fundal portion, as I have stated, is a solid cord or mass; the tubular portion consists of cells arranged round a lumen. The tubular portion connected with the duct is *excretory*; the fundal portion is *secretory*. The flow of material from the cells is *into the bile-channel* in the tubular portion of the loop, and is *into the blood* in the fundal portion. In other words, the portion of the loop which is first in contact with the portal blood separates out from it the biliary constituents; so, in consequence, a great accession of pressure in the portal vein may influence the biliary portion of the hepatic physiology and lead to the development of jaundice. The portion of the loop last touched by portal blood (no doubt already purified to a not inconsiderable extent) is concerned with the foodstuffs brought in to the liver, and pours out into the blood the 'internal' secretion of the liver. Stagnation of blood in this part of the system means disturbance of this aspect of the liver function in the first instance, and consequently does not entail any icteric manifestations until the disease has so far progressed that the biliary end of the gland-loop is implicated also. It is clear, then, that the story of the function of the liver can be read

accurately and more easily if we discard the traditional conception of liver 'lobules'. Instead of making the hepatic venule the pivot of the anatomy, with cell-columns radiating from it, and directing the attention to a blood-current converging as it were along the spokes of a wheel, the present scheme makes the point of origin and the direction of the secretions the centre of attention, the liver-cells being grouped into acini exactly comparable to the acini of any other racemose gland.

The reason for this will presently be obvious, in that the unification of all the forms of cirrhosis into mere variants of one single process thereby becomes possible.

So far the gland acinus has been regarded as a finished structure. In life, however, it is not stationary. It grows or it withers. The growing point is in the solid portion of the acinus, the fundal portion. When there is more food-supply the hepatic cells multiply. They cannot do so where they abut upon the lumen of the excretory duct, but easily grow in a direction away from the excretory duct; that is, in the fundal portion. Should there be interference with the activity of some of the fundal cells, portions of the column of cells around the duct tend to multiply, to form a new fundus, and a new or 'regenerated bile-duct' then arises. What was originally that part of the gland connected with the duct now becomes the new solid column, the original column having withered. Irregular slender double lines of cells which have been 'newly formed' come to lie amongst the connective tissue of the portal canal, and form the new tubular portion of the gland acinus.

The blood-vessel and the secretory cell in most parts of the body are separated by a lymphatic space. In the case of the liver acinus the same arrangement is to be expected. As already suggested, however, there is not a continuous lymphatic sheath to the acinus, but the liver-cells are in direct contact with the blood in some situations. To complete the diagrammatic scheme, therefore, it is necessary to picture a lymphatic sheath only between the cells of that portion of the acinus in proximity to the duct, no sheath being present over the fundal portion. Lymphatics thus emerge in common with the bile-channels and the tributaries of the portal vein.

The hepatic artery must also be considered, and a place for this is found at the part of the liver acinus lying nearest to the bile-duct. The arterial blood meets the venous blood in close

relation to the bile-secreting portion, not in relation to those fundal cells which deal primarily with digestive products. The hepatic artery supplies, not the liver-cells, but the network of biliary channels in the liver. When the hepatic artery of a cirrhosed liver is injected it is seen to supply the newly-formed fibrous tissue. The branches into which the portal vein breaks up are with difficulty distinguished, and may appear to be almost obliterated.

The fundamental components of the liver have now been introduced and arranged into their appropriate positions. Hence it becomes possible to discuss what cirrhosis is and how it is produced, our attention for the time being fixed upon these few microscopic elements rather than upon the liver as a whole.

It has been found very easy to induce a cirrhosis experimentally; the mere ligature of the bile-channel always produces this effect. The histological picture is that of a 'biliary' cirrhosis, which has long been supposed to be the result of stagnation of bile in the small ducts. The extensive recent experiments of Rous and Larimore upon this subject appear to contribute all that can bear upon this conception of biliary cirrhosis. These authors found* that ligature of the main ducts in rabbits caused rapid distention of the minute bile-channels, then pericholangitis, and finally a stellate cirrhosis within three weeks. Death occurred in five weeks.

When the ducts were ligated at a higher level, so as to involve only one lobe of the liver, leaving a passage free for the bile from the other lobe, it was found that the liver parenchyma of the unligated side was capable of compensating completely for the biliary inactivity of the mutilated lobe. In consequence, the pathological changes in the liver were not nearly so marked, and the cirrhosis which developed on the ligated side appeared much more slowly than when the main duct was tied.

The other experiments by Rous and Larimore are best understood after the preliminary explanation that the rabbit's liver consists of two distinct portions, each provided not only with its own duct, but also with its own distinct branch of the portal vein. If the bile-duct of one lobe and the portal vein supplying the *other* lobe were tied, it was found that very little change occurred in the side with the ligated bile-duct. This shows that the liver-cells can

* *Jour. of Exper. Med.* 1920, July, 249.

continue to excrete even though they do not receive a direct blood-supply. It also shows that the state of the portal circulation has something to do with the vulnerability of the liver-cells to interference with their excretory channels.

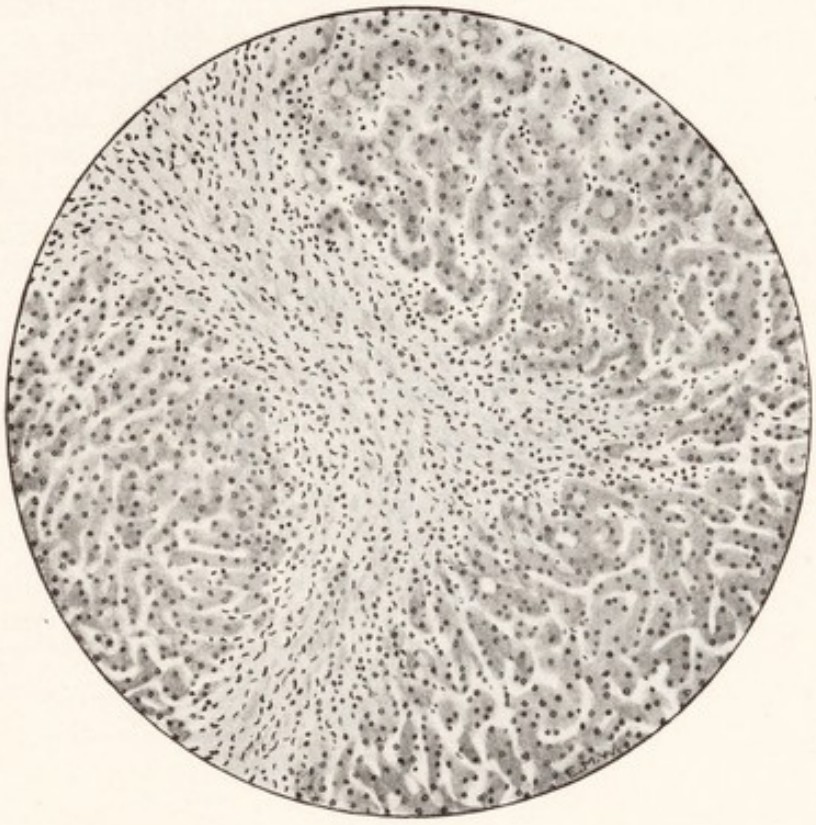
The most drastic interference with the liver is exemplified by their fifth experiment. In this case the one bile-duct was tied, and after the animal had recovered the other bile-duct was also tied, and the gall-bladder (which belongs to the larger portion of liver) removed. The portal vein to the second (the main) lobe was also tied, later. The result was that there was no outlet for bile at all, and only one lobe—the smaller—was furnished with blood. The changes produced were: swelling of the bile-channels of the smaller lobe, with accumulation of bile between the liver-cells; the whole lobe became infiltrated with bile, and the liver-cells finally died. But the main lobe of the liver did not become jaundiced, and kept alive. The nutrition of the animal suffered greatly, however.

The explanation of the various phenomena is supposed by these authors to lie in the presence or absence of interference with the portal circulation. Swelling of the bile-ducts interferes with the flow of blood in the portal veins, and brings about a passive congestion followed by 'an orderly atrophy' of the excretory cells. This atrophy carries with it a steadily diminishing output of bile until, when the last cell has disappeared, the last drop of bile has been formed. Cirrhosis appears round the lobules, but does not penetrate between the cell-cords.

It is believed that mere inspissation of the bile, as it occurred in these experiments, exerts no ill effect on the liver. Nevertheless, rabbit's bile is a powerful irritant to tissues. Therefore, when the common duct is blocked, and the bile is dammed back so much that it ruptures the finest channels—for the liver-cells appear to continue to secrete bile despite the ever-increasing pressure—it sets up parenchymal necroses, the so-called 'biliary infarcts and necroses'. Cirrhosis begins, progresses, and finally occludes the blood-vessels and interferes with the nutrition of the tissue to a still greater degree. Consequently the injury to the liver is due not so much to the bile, even in the rabbit, as it is to the mechanical interference with the vascular supply.

The type of cirrhosis is different according to the position of the obstruction in the ducts (*Plates XI, XII*). When the finest

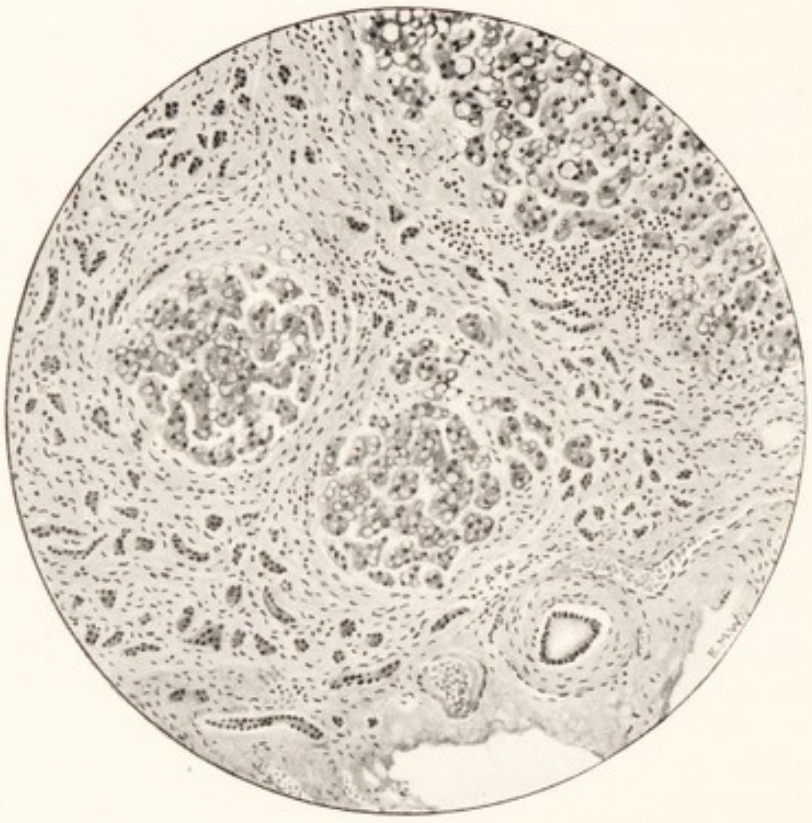
PLATE XI



PORTAL CIRRHOSIS.

A low-power view showing the essential changes in portal cirrhosis of the liver with splenomegaly. The amount of fibrous tissue between the lobules is considerably increased, and there is some round-celled infiltration especially in the immediate neighbourhood of the liver-cells.

PLATE XII



BILIARY CIRRHOSIS.

A low-power view of the liver in which the cirrhosis has extended widely, causing the atrophy of the two lobules shown in the middle of the drawing. The cells show fatty degeneration. The connective tissue between them is coarsely fibrous. A collection of small round cells is seen close to the larger lobule. The vessels in the portal tract at the foot of the drawing are sclerosed.

The numerous small fragments of tubules are regenerated bile-ducts. This is a biliary cirrhosis of the type occurring in hæmolytic jaundice.

canaliculi are obstructed, a diffuse intralobular cirrhosis develops; when larger ones are involved, the cirrhosis is of a pure monolobular form; when the largest channels are involved, stellate lesions result. In all cases an obstruction to the hepatic veins ultimately occurs, and the changes of chronic passive congestion supervene, with the usual clinical phenomena aroused by such a condition.

The work of these two investigators indicates that the problem of cirrhosis is rather one of vascular supply than of biliary outflow. They conclude that the character of the bile does not play a notable part in the production of cirrhosis; that stagnation of bile is secondary to changes in the liver-cells; and that infection of the stagnated bile—an event very prone to occur—is the *last* step in the history of biliary cirrhosis. In other words, biliary cirrhosis develops in increasing amount during the progress of the following four steps: first an interference with vascular supply; then derangement of function of liver cells; then modification of the character of the bile; and finally infection of the bile.

These conclusions bring the portal and biliary types of cirrhosis together, and do not exclude the type associated with passive congestion due to cardiac disease. In this respect they accord with the views expressed by W. J. Mayo*, whose studies have led him to believe that there is no essential difference between the Laennec type and the biliary type of cirrhosis. In the case of the former, however, he places much weight on the importance of the circulatory disturbances; in the Hanot type, on infectious agents. The associated enlargement of the spleen may be mechanical in the one, by introducing circulatory distress to an organ already hampered by stagnant blood; and causative in the other, by harbouring micro-organisms which are passed on to the liver. In either case the response by the liver is in the form of cirrhosis. Its anatomical form is simply the outcome of a combination of the two factors in varying proportions. The more extensive the infection, the more mixed the type of cirrhosis.

The view that the source of biliary cirrhosis is an infection ascending the bile-ducts is supported by Rosenow's observation† that streptococci occur, not in the bile, but in the walls of the gall-

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* *Jour. Amer. Med. Assoc.* 1918, May, lxx, 1361.

† *Jour. of Infect. Dis.* 1916, 19, 527.

bladder and larger ducts. It is also supported by the fact that the glands near the pelvis of the gall-bladder and the cystic duct are enlarged, because they drain the lymphatic spaces in the substance of the wall of the gall-bladder. Further support is afforded by the observation that the pancreatic ducts may become excessively sclerosed in these cases, for the infective agent would be liable to travel up the pancreatic ducts as much as the biliary passages. McCarty and Corkery* report a series of histological changes in the gall-bladder wall, found in 4998 gall-bladder specimens, which might be held to show equally either that the process is a descending one, infected bile passing into the bladder from the liver, or that infection is due to the ascent of organisms from the intestine. Lyon,† experimenting with an Einhorn tube in order to study the duodenal contents and the character of the bile from the common duct as distinct from that in the gall-bladder, concluded that the latter is germ-free, whereas the former is liable to contain streptococci.

The hypothesis that the source of infection of the bile-passages is in the spleen, whereby both portal and biliary cirrhosis are regarded as different forms of the same process, has been especially mentioned by Mayo.‡ The mechanism by which cholangitis and cholecystitis are produced necessarily implies a descending infection in such cases; the organisms carried by the blood-stream pass through the excretory epithelium of the liver acinus.

It would almost seem, then, as if the question of biliary cirrhosis centres in the process of bile-secretion. That this is not really so is shown by a consideration of hæmolytic jaundice, where the liver is as greatly enlarged as it is in biliary or 'hypertrophic cirrhosis'. In each case there is a development of 'new bile-ducts', which is another way of expressing the statement that the secretory tissue of the liver is hypertrophying. As Mayo points out (loc. cit.), the enormous amount of blood destruction compels the liver to dispose of a much greater quantity of bile constituents than the organ can deal with in the ordinary manner. There is therefore a 'work hypertrophy', without any increase of fibrous tissue necessarily appearing. On the other hand, the spleen being a strainer for typhoid bacilli, for protozoa, and other organisms, which

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* *Amer. Jour. Med. Sci.* 1920, i, 646. † *Ibid.* 1920, i, 509.
‡ *Jour. Amer. Med. Assoc.* 1918, May, xi, 70, 1361.

ultimately pass on to the liver, disease of the spleen of this kind obliges the liver to dispose of the poisons brought to it by the portal blood. Whatever the liver-cells cannot absorb and eliminate accumulates in the pericellular spaces, and evokes the deposition of fibrous tissue in this situation.

As has been shown, in hæmolytic jaundice the poisonous substances may pass through the liver-cell satisfactorily and yet irritate the bile-channels and apparently be absorbed by the lining epithelium, and thence pass into the connective tissue of the portal canals and excite fibrosis of the biliary type.

It is in this supposition that the basis of splenectomy as an appropriate treatment for cirrhosis lies. Evidently the experimental work already detailed does not furnish a clue to the cause of the circulatory changes which are regarded there as initiating the whole process of cirrhosis.

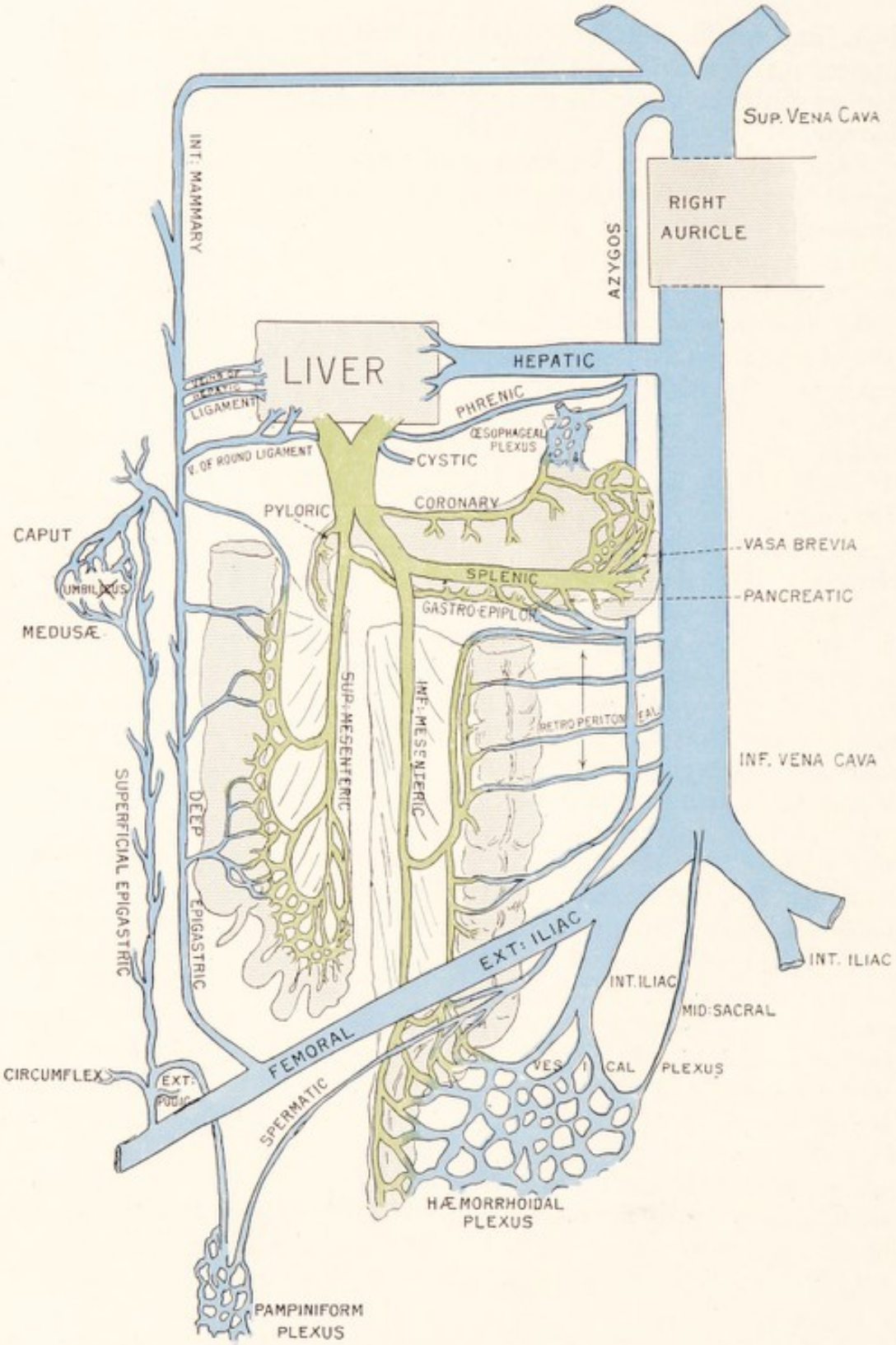
An important feature brought out by the schema remains to be considered. It will be noticed that the fundal portion of the hepatic loop is a solid column of cells, and it has been stated that the cells of this portion are concerned with the secretion of food material into the blood. The portal blood, bringing carbohydrates, proteins, fats, and toxic substances from the intestine (and probably colon bacilli), is caused to linger round the fundal portions of the glandular loops owing to the narrowing of the channels towards the centres of the lobules, and also, no doubt, on account of the junction of several currents in the sublobular vein. The splenic blood is therefore of greater interest to the tubular portions of the acini, while the intestinal component of the portal blood is sought after by the solid fundal portions. This conception enables the nutritional factor in cirrhosis of the liver to receive its due and proper place in the consideration of this subject. Interference with the vascular supply within the liver will cause more serious disturbance of health when the fundal cells begin to atrophy; and such a change is evidently not likely to occur till a late stage. These cells are spared in virtue of their position, because the distention of the portal vessels begins, as far as the liver acinus is concerned, at the tubular portion, and the fundal cells are left undisturbed both in the discharge of their nutritive functions and in their powers of reproduction. As cirrhosis extends, the tubular portions atrophy, and the fundal portions are stimulated to regenerate and consequently bring about the appearance of

increasing numbers of tortuous slender 'bile-ducts' amongst the fibrous tissue.

This sharp demarcation between solid and tubular portions of a liver acinus is of course largely descriptive, being introduced in order to clarify the conceptions concerning a subject which is admittedly intricate. It does not follow that some cells secrete no bile, and that others pour out no glycogen or urea into the blood-stream, although it is not necessarily true that every cell does all this work. On the other hand, this kind of demarcation is met with in salivary glands, in the pancreas, and in other glandular structures, and accounts for the multiplicity of functions which evidently belongs to such organs. The advantage of such a conception is not confined to its provision of an easy explanation of the phenomena of cirrhosis, but helps to bring out a fact of very great importance—namely, that the amount of active tissue of the liver is constantly varying, even during a single day. Where there is a great afflux of portal blood, as after a meal, the increased volume is naturally due to the amount of blood in the viscus. But the presence of an increased amount of food also causes a hypertrophy of the secreting tissue. In the schema which has been used as the basis of this account of the liver, the fundal portion of the acinus may be regarded as variable in size and in the number of its constituent cells. Increase of the size of the cells is frequently noticed in post-mortem material, and many changes which are regarded as pathological are now being recognized as indicating only transient variations of a purely physiological activity. In the early stages of hypertrophic cirrhosis, where the liver-cells are excessively active, there is room for difference of opinion as to whether the microscopic characters are to be regarded as intrinsically morbid or not.

If we translate the term 'fundal cells' into 'the portion of the liver cells concerned with the absorption of food material and with the output of glucose and urea', the description of the nature of the liver tissue would be more accurate without being so easy to grasp. It may confidently be hoped that some of the difficulties in the subject of cirrhosis will be removed by a careful study of the disposition of the parts furnished by this simple schema. When read in conjunction with the abridged representation which occurs in the diagrams of the spleen, the part played by diseases of that organ in inducing cirrhosis of the liver will become increasingly

PLATE XIII



To show the Anastomotic Connections between the Portal (Green) and the Systemic (Blue) Veins appearing in cases of Portal Obstruction

clear, and make the contention increasingly reasonable that surgical interference might do something to give effective relief to diseases hitherto regarded as only within the scope of expectant therapy.

The two types of cirrhosis, which are now seen to be pathological variants of a single type, are clinically distinguished as *portal* and *biliary*. They depend upon the development within certain parts of the liver of connective tissue laid down in defensive response to irritation.

Portal cirrhosis results from the admission *to the portal vein* through one of its tributaries of substances capable of causing irritation. Clinically the condition is recognized by a change in the size of the liver, by a tendency to hæmorrhages, and by other changes due to obstruction in a vascular system devoid of valves (*Plate XIII*), by ascites in the later stages, and rarely by jaundice. The disease is not seldom latent, for examples of it are occasionally found on the operation table when no disturbance of health has resulted. If death occurs from the disease it is due to circulatory changes.

Biliary cirrhosis results from infection, which may be ascending or descending, gaining access, that is, either by the splenic vein or by the common bile-duct. Clinically it is recognized by an enlargement of the liver, by jaundice, which is the predominant feature, and very rarely, and only finally, by ascites. If death occurs it is due to toxæmia caused by jaundice.

Portal cirrhosis is often associated with the name of Laennec. The disease was well known before his time, but the application by him of the distinctive name 'cirrhosis' to the disease gave it prominence, and led to its closer investigation. Laennec chose the name because of the yellow (κιρρός) colour of the granular tissue of the liver. He believed that the coloured masses were neoplastic; they are, of course, portions of the liver substance enclosed by new-formed connective tissue. Biliary cirrhosis has been confused with other diseases, notably with hæmolytic jaundice. In Hanot's description we cannot recognize a specific type of disease separable from other types. The title of the thesis, published in 1875, in which he first described the disease, is " A Form of Hypertrophic Cirrhosis with Chronic Jaundice ", and he asserted his intention to be to describe " a variety of hypertrophic cirrhosis, meaning by this an hepatic affection which had only distant

relationships with Laennec's cirrhosis". As Castaigne defines it, "this disease is one in which the patients are markedly jaundiced, but have no acholic stools, whose liver and spleen are hypertrophied, but without ascites or development of a vicarious venous circulation, or even any urinary evidence of hepatic insufficiency". Such a group of symptoms do not constitute the indications of a separate and distinct disease. They are merely symptoms common to several disorders, hæmolytic jaundice, biliary cirrhosis, or some cases of cholelithiasis.

This is also the opinion of W. J. Mayo, who says, "This type of cirrhosis has no pathologic basis, and little clinical evidence to support its existence. The large majority of cases that have taken the term Hanot's cirrhosis are either hæmolytic icterus, or the ordinary type of biliary cirrhosis". The mistake can be condoned when we remember the frequent association of gallstones with hæmolytic jaundice. If the term Hanot's disease is to be retained, it would be best to range it as a synonym for biliary cirrhosis.

In both forms of cirrhosis the spleen may be enlarged. The frequency of the association has been very variously estimated. Frerichs and Lange assert that it is found in one-half of the cases; Bamberger in nine-tenths of them. No estimate is reliable unless it is based upon post-mortem evidence, for, as I have said, the spleen cannot be palpated until it is more than double its normal size. If the enlargement of the spleen were due merely to portal obstruction it would be similar in all its details to that form which follows upon cardiac disease; yet it is well known that there is a great difference. In portal cirrhosis of the liver, according to Quincke and Hoppe-Seyler*, swelling of the spleen appears very early, before other symptoms of stasis, and a hyperplastic condition of the pulp followed by a connective-tissue increase is noted. It would appear, therefore, that active processes occur also in the spleen, and vary with the primary cause of the disease.

If the original source of disease in a case of 'biliary cirrhosis' has ascended along the bile-passages, the nature of the infecting organism may have an important word to say in regard to the exact clinical and anatomical form of the cirrhosis produced. Should streptococci or other hæmolysin-secreting organisms be

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* *Nothnagel's Encyclopædia*, 702.

the active agents, it is likely that the blood will become changed as it passes the foci in which the substances are made. The spleen will then be set into increased activity, and the cycle of phenomena associated with a primary disorder of the spleen would be superadded to the existing clinical picture. Transition or mixed forms which are not typical examples of hæmolytic jaundice would then occur.

It would appear to be exceedingly probable that forms of biliary cirrhosis due both to ascending and to descending infections come under the care of the surgeon dealing with cases of gall-stones. It is a common experience in cases of cholelithiasis with a typical early history ending in an obstruction of the common duct by stone, to find the duct grossly dilated, and the gall-bladder thick and shrunken by cicatricial tissue. When such a duct is opened, many large stones, and much thick and perhaps offensive mud, are emptied away. A stone or stones may be found also in the common hepatic duct, whose walls also are thickened. But beyond this stones are not often found; when the hepatic duct is cleared by gauze strips the bile flows freely, and is generally almost or quite clear. The duct being drained, the patient recovers easily and normally. There are also cases of a different type in which jaundice has been a precocious and almost constant symptom from the earliest recognizable onset of the disease. Operations upon them disclose the presence of stones in the common duct, in the common hepatic duct, in the right and left hepatic ducts, and in their branches within the liver. The higher one goes the smaller are the stones, and the stones are always polished, smooth, and well made. There is little or none of the mud seen in the other type. No matter how careful one may be in extracting stones, the end of them seems never to be reached. Small shiny pebbles and beads still keep coming down into the operative field, and are discharged through the tube which is left in the duct at the completion of the operation. It appears to me very possible that the former type is associated with a biliary cirrhosis due to an ascending infection, and that the latter is due to a descending infection. In the former, stones form first in the gall-bladder, escape into the common duct, and thence migrate upwards into the hepatic ducts. Stagnation and infection there may lead to a further deposit of calculi. In the latter type tiny calculi are formed in the finest ducts, and migrate downwards to the larger

and still larger ducts. The affected lobe of the liver is filled with tiny stones in the minute ducts and with larger stones in the larger ducts. The condition is incurable by operation, and 'recurrence' will always take place, no matter how carefully the ducts are cleared. Biliary abscess is often the terminal stage in each condition.

The surgical treatment of cirrhosis of the liver is concerned with two problems: (1) The diminution of the vascular burden carried by the liver; (2) The destruction, or the diversion from the direct path to the liver, of the poisons carried to this organ from the spleen.

1. The diminution of the vascular burden of the liver may be effected :—

a. By the creation of new channels of anastomosis between the portal and systemic circulation. Many such channels exist normally, communicating on the one hand with the portal system and on the other with the inferior vena cava (*see Plate XIII*). But new vessels can be created by causing adhesions to form between the liver and diaphragm, or between the omentum and the anterior abdominal wall. The first operation intended to secure this result was performed in 1889 by von der Meule; the patient died shortly after it. Talma also suggested this operation and practised it. The first successful case was performed by Rutherford Morison at the suggestion of Drummond, who had also conceived it independently, in 1895. The method is one that has been widely adopted: at times with much success, at times with disappointment. I have performed the operation on seven occasions: one result has been perfect, the patient living seven years and having no further trouble referable to the cirrhotic liver or from ascites; one patient was decidedly improved, and required only two tappings of the abdomen in the first twelve months; the remaining cases were not appreciably benefited by the operation. In one case nervous phenomena, the result probably of auto-intoxication, were observed; they have been recorded by Morison as occurring in the third patient upon whom he operated.

The direct anastomosis of the portal vein to the inferior vena cava, by the establishment of 'Eck's fistula', has very rarely been practised upon the human being, and will never enjoy the approval of surgeons.

b. By the obliteration of tributaries of the portal vein, which

will compel the formation of new anastomoses, or the dilatation of normal ones, between the portal and systemic circulation. For example, the inferior mesenteric vein may be ligatured, or the spleen may be removed.

2. The purpose of splenectomy in cases of cirrhosis of the liver may therefore be either the relief of the vascular turgescence of the liver, or the removal of the poisons sent direct to the liver. The proportion of the portal blood derived from the spleen is usually assessed at about one-seventh of the total volume; but if the spleen is grossly enlarged it is likely that the quantity of blood passed through the splenic vein will equal that of all the other portal tributaries. When this vast quantity of blood is turned aside from the liver, the relief to the hepatic cells must be very considerable: these will be given full opportunity for that capacity for repair which they possess to so remarkable a degree.

Ligature of the splenic artery has been adopted rather than splenectomy in a few cases. Consequent upon it there is an atrophy—not necrosis—of the spleen. The operation was first suggested by J. Gerster, and cases are related by Hartmann and others. The mortality has been large.

CHAPTER XIV.

CONCLUSION.

It is evident that a consideration of the whole subject of diseases of the spleen must take a very wide view. A number of symptoms may direct attention to the spleen, even when clinical examination does not reveal the presence of splenomegaly. It is through the correct insight into the significance of the clinical symptoms and other morbid phenomena that the real understanding of any supposed case of splenic disease becomes possible. Instead of searching only for the existence of this or that splenic disease, *an inquiry should be directed to the determination of the functional capacity of all the various organs* likely to be deranged. The symptoms already referred to may be looked upon as evidence of some disorder in the particular *systems* here considered. This derangement must be regarded not merely as a restriction of the morbid changes to the spleen, but as a disturbance of wide ramification throughout the whole body, affecting one or other, or perhaps even all, of the four systems in which the spleen plays a part. The focus, at the moment, may in truth be in the pulp of the spleen; but even so, the general picture presented by the patient is the outcome of the participation of the other systems in the process which started in the spleen. It may be that splenectomy in any of these diseases will remove the obvious culmination of the morbid process, and thus bring about a 'cure' of the disease or an arrest of its development; but it does not by any means follow that all the other related parts are thereby caused to return to their normal states. Absence of symptoms does not imply the restitution of normal functions. The case of Sir Spencer Wells and Lord Dawson (*see* p. 99) discloses this truth unequivocally. In this case fragility of the red cells was found twenty-seven years after the removal of the spleen for hæmolytic jaundice.

A further step in the investigation of the clinical condition of the patient should aim at the exact discovery of the *site* of the lesion in certain particular cell-types: (*a*) In the spleen-pulp;

(*b*) In the bone-marrow and in any part where reticulo-endothelial cells may exist in specially congregated or active masses; (*c*) In the liver; (*d*) In the endocrine organs, including the pancreas. This lesion being predicted, or recognized, the question will arise as to whether it consists in, or entails, the elaboration of poisons capable of causing hæmolysis, cirrhosis, or asthenia.

The tissue affected, and the changes therein resulting, being recognized, further research must be directed to the discovery of *the type of infective agent* at work, whether bacillary, spirochætal, or other. In other words, the patient is no longer to be regarded merely as the victim of some type of 'disease', but as the victim of disorders of a certain character in certain parts of certain anatomical or functional systems of the body. It is the form of the disorder, the form of distribution (determined by an assessment of the functional capacity of the several organs concerned or likely to be concerned), which, when correctly studied, will inevitably lead to the source and cause of the morbid state, and ultimately to the prospect of the 'cure' of the patient.

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