SPLENOMEGALY COMPLICATED BY PREGNANCY AND FOLLOWED BY SPLENECTOMY.

Thesis for the Degree of M.D.

by

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M.B., Ch.B. (2nd Class Honours 1904)

1915

The spleen, because of its size, position and anatomical relations and more especially because of its apparent uselessness, has been the genesis of more speculations, theories and doubt than any other large organ of the body. Even to-day the full function of the spleen and the part it plays in the human economy give rise to great dubiety.

The ancients believed the spleen to be the dwelling place of an evil spirit or at least the organ from which evil influences emanated. At the "humour" stage of medical learning it became the seat of an evil humour. This attitude towards the spleen by the older physicians has hampered our knowledge in reference to its functions and uses, in no small measure, as no good thing could possibly come out of "Nazareth". As for example a great deal of useful knowledge had accumulated about the blood long before the time of the discovery of its circulation by William Harvey in 1619. Aristotle describes it as a "nutrient fluid streaming through the arteries". Michael Servetus (1150) discovered the pulmonary circulation. But to Harvey the pupil of Fabricius it was left to complete the whole.

With the empiric form of treatment, based upon a/

a fairly accurate knowledge of anatomy but a total lack of that of histology, many theories had been formulated and ideas propagated to account for the spleen having a place at all in our anatomy. If the red blood corpuscle or the white blood corpuscle was destroyed or required destruction or was diseased, the spleen was the malevolent agent. If anything bad or doubtful occurred in the economy the spleen was blamed. In the past the spleen has suffered greatly and undeservedly from this mode of reasoning and it is only within recent times, with the close study of the blood by keen observers coupled with the work of the pathologist - indeed it is with the rise of the science of Haematology and Bacteriology with the studies of Duncan, Erlich, Gulland, Martin, Cherry, Wassermann and a host of others, that the place, use, and function of the spleen has been placed on anything like a scientific basis.

As the various writers in the past and even of to-day maintain various and different uses for the spleen, it is to be expected and naturally accepted that in the diseases of that organ the wildest confusion in their classification will be found. In all text books the spleen will be found amongst the ductless glands, given half a page and dismissed as unworthy of further notice. There appears to be little/

little doubt that the older physicians grouped together diseases of the spleen under the general term 'Scorbutus' for want of a better. It was not until about the middle of the nineteenth century that the pathology of the blood began to be understood. In 1845 Hughes Bennett described Leukaemia with enlarged spleen. And later, in the same year, Virchow described a case attributing the appearance of the blood to leucocytes. In 1852 Vierordt enumerated the red blood corpuscles. In 1867 Duncan of Edinburgh definitely proved that chlorosis was due to deficient haemoglobin. In 1872 Mosler gave an accurate description of the white cells in the blood. But as previously said it is to the modern Haematologist and Bacteriologist that the study of the blood has been put on a sound and sure foundation and incidentally thereby cleared away much of the confusion in regard to the spleen.

Spleen Structure.

In spite of Osler's idea that the spleen in origin is epiblastic it is practically certain that along with the lymphatic glands - thymus and bone marrow - its genesis is mesoblastic, the cells of the vessels being hypoblastic. But from whatever layer of embryonic tissue the spleen is derived there is no doubting its lymphoid nature and that along with/

with the bone marrow - lymphatic glands, solitary glands, and tonsils, etc., it is part, and an important part, of the lymphatic system which pervades the whole human body. Under the serous peritoneal covering lies the thick tough, elastic fibrous capsule. This capsule closely invests the spleen and gives a covering to the vessels entering or leaving the hilum. The capsule is composed of bundles of connective tissue mixed with numerous elastic fibres and non stripped muscle fibres. From the deep surface of the capsule numerous trabeculae pass into the organ where they branch and anastomose thus forming a sustentacular network of connective tissue and which is continued into the reticulum.

W. Muller states that these cells are uni-nucleated or large multi-nucleated and that they do not take up the carmine stain very well. Klein describes them as proliferating and supposes them to be a source of white blood corpuscles.

Within the meshes of the trabecular framework is a delicate framework of adenoid tissue which along with the coloured elements fill up the meshes and form the splenic pulp. The splenic pulp is dark red, alkaline in reaction, semi fluid and consists of lymphocytes, red blood corpuscles and granules. The splenic artery enters and the splenic veins leave

at/

at the hilum. The artery splits up into many branches which are invested by a fibrous sheath from the trabeculae and continuous with it. The smaller branches lose this sheath and break up into a pencil of arterioles. Along the course of the arterioles generally near their division are small oval masses of adenoid tissue - the Malpighian corpuscles $\frac{1}{20}$ to $\frac{1}{80}$ inch in diameter. The meshes of these corpuscles or adenoid sheaths are filled with lymphoid corpuscles and are structurally the same as the tonsil or solitary glands. They are in fact lymphatic accumulations around the artery. Cadiat states that the lymphatic tissue is separated from the splenic pulp by a lymph space and which has efferent vessels passing to the pulp.

The termination of the arterioles and the genesis of the veins have given rise to several theories, by Stieda, Kollicker, Frey and others. Probably the whole facts may be stated as that the rootlet of the vein originates in the same manner as the capillaries end, forming a continuous endothelial path which in turn becomes the radicle of a vein. Stieda supposes an intermediate intercellular space, Kollicker that the space is a dilated space of erectile tissue, Frey that the blood flows into the adenoid tissues of the pulp and from these intermediary passages cribriform venous/

venous radicles arise. At all events the blood passes through the splenic spaces either by itself or protected by an endothelial covering.

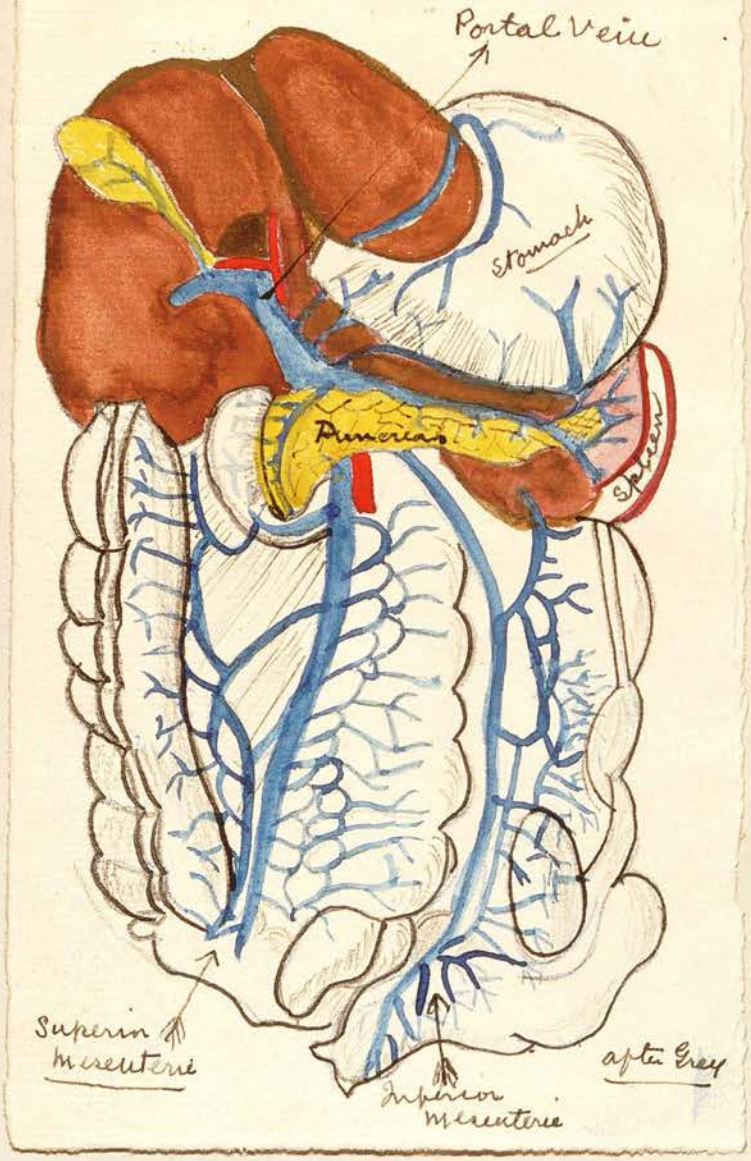
The lymphatics are supposed to begin in the spaces of the Malpighian corpuscle, run along the artery and join the superficial lymphatics at the hilum. The nerves are non medulated and go to the muscular tissue of the capsule and trabeculae and the blood vessels. As pointed out by Remack and W. Stirling in the course of the nerves are small ganglia placed wide apart since after section of the splenic nerve the rhythmic contraction still goes on.

The undersurface of the diaphragm separates the spleen from the 9th, 10th and 11th ribs and is in relation to the left lung and pleura.

The splenic artery is the largest branch of the coeliac axis and is remarkable for the tortuosity of its course. The splenic vein lies below the artery and runs along the upper border of the pancreas and joins the superior mesenteric vein in front of the vena cava and behind the upper border of the great end of the pancreas. These together form the portal vein which enters the liver at the transverse fissure. It is worth while to recapitulate some points. The capsule is to some degree extensile and contractile as it contains elastic fibres and muscle fibres and

is/

is under nerve influence. Further, attached to the capsule like ribs to an umbrella, are elastic trabeculae also with muscle fibres. This mechanism is evidently devised to have a uniform squeezing action upon the contents of spleen spaces, that is upon the blood contents. The splenic artery is remarkable for its tortuosity which is to say that it has length in little space; but also each twist of the artery is equivalent to an obstruction or valve being placed in its course. Just such a valve which nature places when a vein becomes varicosed. The blood coming direct from the Aorta with the full force of the left ventricle has its pressure so vastly diminished by the resistance of the arterial wall and by friction that it will enter the smaller arterioles as a continuous trickle after passing through the arteries. There can be little or no arterial pressure inside the spleen. So it follows that the blood circulation must be extremely slow and greatly dependent upon the contraction of the capsule and trabeculae and also upon the squeezing influence of the diaphragm upon which it lies along with the lesser strains of the lungs and pleura. It will thus be seen that nature intends the arterial blood to enter the fragile spleen gently and has provided it and surrounded it by a mechanism to expel its contents. And not only so but regurgitation/


Portal Vein
Stomach
Pancreas
Spleen
Superior Mesenteric
Inferior Mesenteric
after Gray

regurgitation of the splenic contents is prevented by these same valve-like tortuosities.

It would be well to point out here the portal system has no valves in the larger veins. And also that the portal vein enters the liver at a distinctly higher level than the splenic vein leaves the hilum of the spleen. There is thus created a not inconsiderable fall due to the difference of their levels.

Further, the spleen consists chiefly of lymphoid tissue. Its capillary vessels form wide spaces which is in agreement with a slow circulation with the constant presence of a large quantity of blood. The blood passing through the endothelial vessels is surrounded by lymphoid tissue and brought into close and slow relationship with the pulp.

Functions.

One of the chief difficulties in studying the spleen with which one has to contend is that although it is a large organ it yet plays no apparently definitely important part in the human economy. Consequently its physiological function is still indefinite. To add to the difficulties the spleen may be congenitally absent without the individual being markedly inconvenienced and secondly it may be removed and cause no marked change.

The spleen is supposed to be engaged in the following/

following pursuits.- (1) A part of the lymphatic system. (2) A blood forming gland. According to Gerlach and Funke the blood of the splenic artery contains fewer colourless corpuscles than the splenic vein. These leucocytes are supposed to be derived from the lymphoid tissue. This argument is supported by the fact, as was pointed out by Hughes Bennett in Leukaemia, you have a hypertrophy of the lymphoid tissue with a great increase of the colourless blood corpuscles.

Bizzozero and Salvioli pointed out that after severe haemorrhage the spleen becomes enlarged and haematoblasts are found in the parenchyma. (3) A destructor for red blood corpuscles (Kollicker). The worn out devitalized red blood corpuscle is attacked and disintegrated by the lymphocytes. You thus have haematin granules in the lymphocytes and an iron reaction by ferrocyanide of potash and hydrochloric acid (Tezzoni's fluid). In support of this it is stated that the spleen contains more iron in it than the blood present warrants and that it contains a large number of extractives derived from proteid Katabolic change.- Haemoglobin, Uric acid and Xanthin bodies. And further, in pernicious anaemia where you have a great destruction of red blood corpuscles you have a great accumulation of iron in the spleen.

(4)/

(4) The formation of Haemotoblasts similar to those found in the bone marrow.

(5) Variation in volume. About five hours after food when the digestive organs have become less vascular and when the individual is therefore fasting, the bulk of the spleen is at its greatest. During the process of active digestion when the blood is drawn to the intestine the spleen becomes smaller, contracted, and in appearance granular. The spleen is thus a vascular reservoir. If it is a systemic reservoir to regulate the blood supply to the stomach and intestine, it can serve no useful purpose as the blood must be practically venous blood and the reservoir is far removed from the scene of its proper activities and that through a tortuous artery. While the blood from its exit has to pass into the portal vein and through the liver into the vena cava and so through the pulmonary system before it reaches the Aorta again. The explanation of this accumulation of blood is more likely to be derived from the close association of the spleen with the portal vein. When the food absorption is at its height the spleen is full of blood but when active digestion is going on and the blood accumulated in the mesenteric arteries the spleen is empty because there is no absorption and the portal vein is practically depleted of its blood contents, all having been drained away to supply the systemic system./

system. Dr Osdon has noted that by stimulation of the nerves of the spleen as the spleen contracts the liver enlarges as if it were injected by more blood than usual. It is evident that the spleen is in close sympathetic relationship with the liver. It would serve no useful purpose to provide a spleen with its elaborate mechanism of expulsion for the mere purpose of pumping venous systemic blood into the portal vein. The human economy is more conservative of its mechanism and energies than that. The increased volume is due to the products of digestion being carried into the spleen and there undergo their first metabolic change.

Roy, by his oncometer, has shown that the spleen undergoes rhythmic variation, systolic and diastolic and may continue for hours. The two events together occupy about one minute.

Enlargement of the Spleen.

Apart from physiological reasons such as digestion, age, individual, there is a great group of cases where you have a pathologically enlarged spleen.

Enlarged spleens are classified into two great groups - primary and secondary. As the secondary group is by far the larger, let us discuss it first:

Secondarily enlarged spleen may be said to arise from any toxic condition. This can be readily understood/

understood when one remembers that the poison which causes changes in any organ is likely to cause a like change in a similar tissue in the spleen. It may be a hyperplasia of connective tissue or a waxy degeneration. Or it may enlarge from some blood cause such as obstruction in the portal or systemic systems thereby causing the spleen to be congested just as the liver or lungs might be.

Secondary enlargement occurs in the so-called

(1) Blood diseases
- Myelocythaemia
- Leucocythaemia
- Pseudo-leukaemia
- Pernicious Anaemia

(2) Toxic diseases
- Malaria
- Syphilis
- Tubercle
- Cancer
- Cirrhosis of Liver
- Typhus, Typhoid, Diphtheria, etc.

(3) Circulatory obstruction in systemic, pulmonary or portal systems and particularly the latter.

In the systemic circulation it may be from aneurism, endocarditis, emphysema, pressure tumours of the pancreas, liver, uterus, kidney, ovary, etc. In the portal system from the liver, pancreas or bowel. In/

In the pulmonary from tumours of the lungs, e.g. glands or pleura.

(4) Hydatid tumour of the spleen.

(5) Wandering or floating spleen.

The characteristic of these conditions is that you generally have a local and a general disturbance: the attention to the spleen being drawn through the primary cause. In the blood diseases an examination of the blood reveals the condition. In the toxaemias other organs or parts are affected such as the kidney, liver, lymphatics. A floating spleen is replacable. In circulatory obstruction you have a passive hyperaemia disturbing the portal or systemic systems. In the congested indurated spleen the capsule and trabeculae are greatly thickened. The veins are distended and filled with blood. There is often extensive pigmentation from destruction of the red blood corpuscles. The organ becomes hard and tough from connective tissue hyperplasia and atrophy of the splenic pulp.

Primary enlargement of the spleen. In 1861 Wilks described a case and further reference is made in textbook of Pathology by Wilks and Moxton. Again in 1871 H. C. Wood called attention to this condition. Well and Squire also described cases. In 1882 Banti described three cases with the summary of others and again/

again it was discussed by Bruhl in 1891. The subject was gone into in 1896 at the London Medical and Chirurgical Societies Meeting and in the same year at that of the British Medical Association.

Although not classified there are evidently three distinct primary anaemias or primitive splenomegalies:-

(a) An ideopathic enlargement with little or no symptoms and no special pathology. (Bovaird & Brill).

(b) Banti's disease where you have anaemia, repeated haemorrhages, recurrent fever, cirrhosis of the liver and jaundice. The spleen is irregular in uniformity and outline and has infarcts. Marked fibrous thickening in and around the arteries and the Malpighian corpuscles are almost entirely absorbed. The splenic pulp spaces are filled with blood and proliferation from the endothelium of the spaces. There is an entire absence of accumulation of leucocytes in the spaces. There is a marked diminution in the haemoglobin - 15 to 28 per cent - and a diminution in the red blood corpuscles - 1 to 3 million. But the striking feature is the diminution to about 1000 per cent of leucocytes.

(c) Splenic Anaemia. Where you have enlarged spleen with marked anaemia. The red corpuscles are diminished in number, haemoglobin and colour index. There is often a slight leucocytosis, at all events the/

the loss is not marked. There are periods of health with reduction in the size of the spleen and an agreement of the corpuscles with normal conditions. This state alternates with a period of severe anaemia and enlargement of the spleen.

The following is the history of a female patient, A. W., age 34 (1918) with one female child age 4 years, who had an enlarged spleen removed by Mr Stiles and whose case differs somewhat from those already recorded.

History.

Mrs A. W. came under my care when she was 26 years of age and had been married two years but had no children. Six weeks previously she had had a miscarriage. Her complaint was a swelling on the left side.

The patient was born in the Levant, of Scottish parents and resided there for six years when she came back to Scotland with her mother, where she has resided ever since. As a child she had measles and diphtheria and at the age of 15 years pneumonia. At 16 years she had her tonsils removed as they were enlarged and frequently suppurated. Since her childhood she has had no serious illness. She has always been of a happy and bright disposition.

About 1½ years ago she noticed a swelling in her left/

left side, that is six months after marriage. As there was no pain and little or no inconvenience excepting a sense of weight on that side, little attention was paid to the tumour. The swelling did not vary in size, but during the past six months she has noticed that it has become decidedly larger: this fact was borne in upon her by reason of her inability to bear anything tight about her waist. At 13 years of age menstruation began and since its inception it has always been irregular - every 22 to 28 days. At the unwell times a pain in the back and lower part of the abdomen was always experienced for the first day, which pain probably was uterine in origin. The blood loss was always considerable as she used from between 18 to 22 diapers during the unwell period. Since her marriage menstruation has practically been every 21 days. Within the past year she has noticed that during the night she has had to rise at least 3 times to pass urine and during the day practically every two hours. The urine is passed without pain or difficulty. The bowels are regular each day and in this respect experiences no pain or difficulty, neither is there diarrhoea or haemorrhage. She has always suffered in a degree from indigestion and anaemia which gave way to Bismuth and Iron, but since her marriage these digestive symptoms have become much exaggerated. The patient never had malaria or any tropical fever.

The family history is excellent. The father and mother are alive (1918) and in good and vigorous health. The patient has 3 brothers and 3 sisters all in good health. There are no deaths. The grandparents lived to an old age. There is no history of syphilis, rickets or alcohol in the family.

Examination. The patient is 5 feet 3½ inches in height, well developed and of a stout build and healthy looking. The face has a slightly worried look. The complexion is pale but not markedly so. The conjunctivae are pale. The pulse 80 is soft and elastic and in time-force and rhythm is regular. There is no evident glandular enlargement, neither is there any sign of varicosity. The lungs are healthy. The heart is not enlarged, the sounds are closed and clear in all the areas. The urine is pale straw in colour and contains no albumin and no sugar or other abnormal constituent. The blood count is red blood corpuscles 4,100,000 and while blood corpuscles 8,000.

In the abdomen there is a marked fulness in the left hypochondriac and lumbar regions and extending into the umbilical region in the direction of the 10th rib. The skin is very slightly pigmented. No enlarged veins are to be seen. The swelling does not move with respiration. There is no visible pulsation.

One/

One can feel on palpation a firm, regular, hard, flattened mass in the left hypochondrium and lumber regions and extending into that of the umbilical towards the iliac fossa of the same side. The anterior border of the mass is distinctly notched and is smooth and rounded. There is no pain on pressure, neither fluid, thrill nor friction. The percussion note is hard and dull.

As the patient, at this time was suffering little or no inconvenience, she was given an iron and arsenic tonic with instructions regarding her diet.

The patient in April 1911 found herself again pregnant. As the previous abortion was attributed to the enlarged spleen resting upon the pregnant uterus, and as she was extremely anxious to carry to full term, she again came under my care. There was no doubt or hesitation regarding what was to be done if a full time child was desired, and that was removal of the enlarged spleen. This decision was agreed to by Professor Gulland and Dr Cartright Wood and Mr Stiles; who also pointed out that by removal of the spleen the primary splenomegaly would be arrested and thus ultimately the patient's life would be preserved. To this removal the patient consented. At the beginning of May 1911 the following points were noted. The heart is slightly dilated and with a pulmonary systolic/

3/4 Size

systolic murmur. The liver dulness does not reach to the costal margin and is probably pushed up. The lungs are clear and the urine is normal although still troubled with frequency of micturition. There are no enlarged glands. The patient is easily tired and feels weak. The tumour is giving rise to discomfort and pain by reason of its weight. The blood count is as follows - red blood corpuscles 4,500,000 and white blood corpuscles 3,500 with, if anything, the lymphocytes more numerous; haemoglobin = 75% and colour index = .74.

Operation was performed by Mr Stiles upon 16th May 1911. An incision was made external to the left rectus muscle. The wound extended from the costal margin downwards for about 8 inches. While the patient was under chloroform the abdomen was very prominent below and around the umbilicus. Below the left costal margin there was no projection. At first Mr Stiles could feel no spleen and expressed the opinion that every one was wrong. All that could be felt was a large rounded smooth semi-fluctuating movable tumour reaching up to the umbilicus and tapering somewhat towards the pubis. On percussion it was dull and its upper limit was quite distinct. Mr Stiles pushed his fingers down between it and the left costal margin where he expected to find the spleen. With these physical/

physical signs and the possibility of the tumour being pelvic in origin, Mr Stiles thought it better to open the abdomen lower down than otnerwise he would have done.

After opening the peritoneum the first organ that came into view was the pregnant uterus, the soft mucoid muscular wall of which was of a dark maroon colour covered with a multitude of dilated veins. It extended nearly to the umbilicus upwards and looked exactly like an ovarian cyst the walls of which had become very congested. There were no fibroids. The ovaries were normal. The tumour led down to a normal cervix. No spleen was visible. The hand was now passed into the left hypochondrium which enabled the operator to draw the enlarged spleen right out of the wound. Before this could be done Mr Stiles divided and ligatured some omentum which had become adherent in the neighbourhood of the wound. The spleen which was about 8 inches long having been delivered, it was seen to have retained the classical shape and notched margin. The anterior surface was deeply indented by the costal margin. The capsule looked healthy. Beyond its size in general appearance the spleen looked healthy. Its measurements were $8\frac{1}{2}$ inches by $4\frac{1}{2}$ inches by $2\frac{3}{4}$ inches and weighed 1 lb 10 ozs.

The colon was now partly pushed back and handkerchiefs spread all round. Mr Stiles proceeded to deal with/

with the pedicle. For this purpose the spleen was turned over a little to the left so as to expose the gastric surface of the pedicle more distinctly. The large vessels of the pedicle could be seen glistening through the anterior gastro splenic omentum which was thin. The comparatively small vessels being deeply ligatured the peritoneum was divided between the ligatures. On this being completed the undivided vessels going to the hilum of the spleen were fully exposed. They formed a pedicle the breadth of one's hand, the vessels being very numerous and some, especially the veins, as large as the little finger. By means of a Kocher dissector these were gradually and carefully isolated by the cellular tissue between them being separated. By blunt dissection an opening was made round the vessels and an aneurism needle passed through the opening and round the vessels. The opening was large enough to admit a pair of crushing forceps. The forceps were applied to the portion of pedicle to be ligatured on its distal side, that is close to the spleen. A thick cat gut ligature was then passed round the vessels but a little to the proximal side. As the first loop of the knot was being tied the vessels were divided between the ligature and the crushing forceps. This process was repeated four times before the whole pedicle was secured, the only/

only difference being that instead of the large crushing forceps Ochsner's large artery forceps were used. Some smaller vessels were ligatured in dividing the posterior layer of the lieno-renal ligament. The peritoneal ligament passing from the upper part of the spleen towards the diaphram was next ligatured along with some smaller vessels in its substance, forceps being applied on its dorsal side. The pedicle was now completely severed. It should be noted that the lowest part of the pedicle was ligatured on the distal side of the left gastro-epiploic vessels so that these were not injured. In ligaturing the vessels forming the deepest portion of the pedicle just a little bit of the very tip of the tail of the pancreas was included.

In closing the wound Mr Stiles took great care so that a subsequent hernia might be avoided. It was done as follows.- (a) A continuous cat gut suture of medium thickness including the peritoneum-fascia posterior layer of the sheath of the rectus muscle along with a few of the muscular fibres.
(b) Interrupted sutures of thick silk worm gut passing through rectus muscle - anterior layer of sheath, subcutaneous tissue and skin. (c) Before these were tied another continuous cat gut suture of medium thickness brought together the anterior layer of

the sheath. (d) Finally interrupted silkworm gut and horse hair for the skin; the silk worm gut sutures being threaded with rubber tubing.

The patient stood the operation exceedingly well. There was practically no blood lost.

Progress. Although the patient stood the operation well there was a good deal of post operative exhaustion. On the 7th day after operation she complained of pain over McBurney's point on the right side which was accompanied by rise of temperature. Mr Stiles made an opening on that side and let out some fluid from which staphylococcus pyogenes aureus was grown. The temperature did not fall to normal until the 12th day. As the temperature continued to fluctuate it was decided to inject a vaccine prepared from the staphylococcus aureus. This was injected on the 12th and 16th day; but with little or no result. The temperature still continued to fluctuate between 97.6° and 99.8°. Upon the evening of the 22nd day after the operation and when the time of the menses was due the patient unfortunately aborted. Following this event the temperature run up to 101.8° and continued to swing between 97° and 100° for the next twelve days. Upon the 29th to 31st and 33rd day after operation the patient was again injected with a similar vaccine and again the result

was/

DISEASE.

Notes of Case.

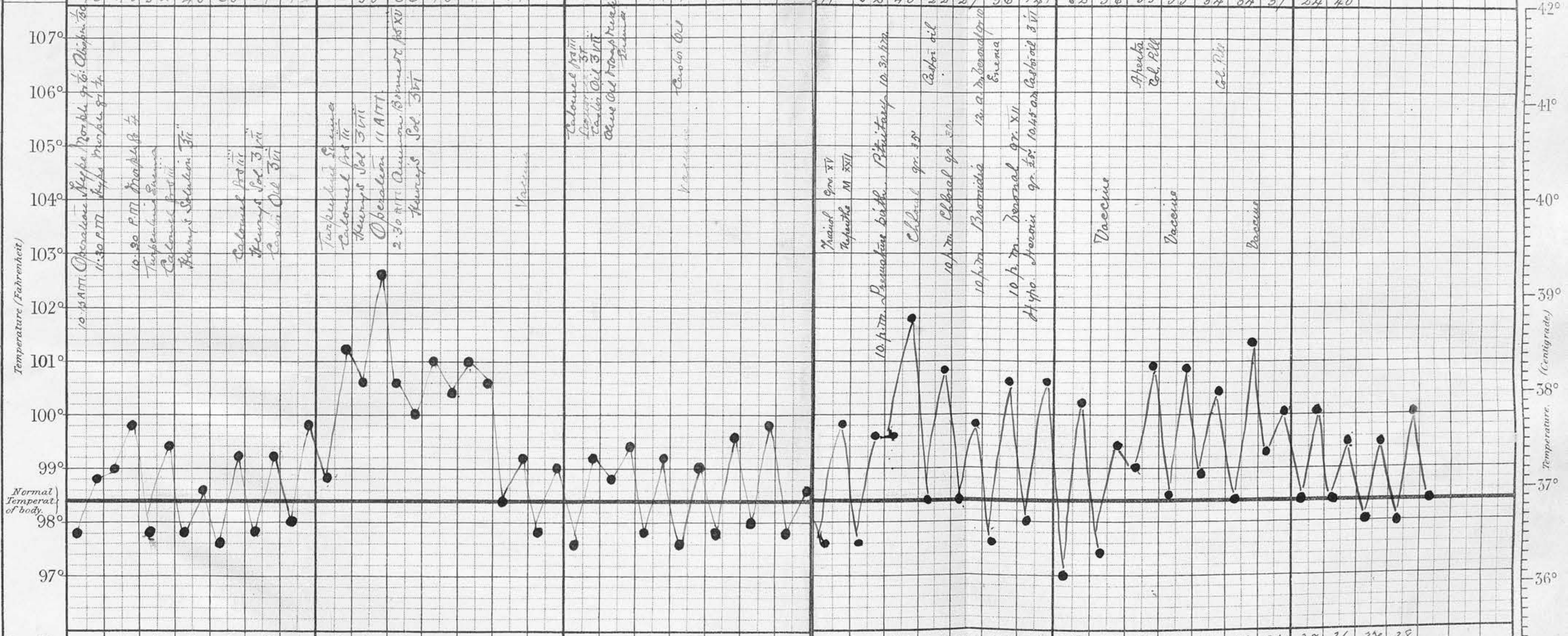
Name
Age
Diet
Case Book No.

Brandy ℥ii 4 hrly. 10.2.6.

Mixture 8.4.6

Fluid Mag ℥i in water occasionally

Pot: Cit. grs XXV 10.2.6.



Date	Day of Dis.	Bowels (M E)	Urine	Pulse
16		1 0	40	76 / 72
17	1	0 0	48	96
18	2	0 0	52	96 / 99
19	3	1 1	46	93 / 94
20	4	0 0	38	86 / 86
21	5	0 1	29	88 / 92
22	6	3 2	42	88 / 94
23	7	0 1	40	88 / 104
24	8	2 0	38	108 / 120
25	9	1 0	36	114 / 120
26	10	1 0	43	118 / 122
27	11	0 1	45	120 / 118
28	12	1 1	64	112 / 108
29	13	0 0	58	104 / 110
30	14	0 0	33	104 / 108
31	15	1 1	27	104 / 100
June 1	16	0 2	44	104 / 104
2	17	1 0	42	100 / 101
3	18	0 2	54	98 / 104
4	19	1 1	31	98 / 104
5	20	1 1	46	98 / 104
6	21	2 3	44	96 / 106
7	22	0 0	52	100 / 106
8	23	0 0	40	100 / 110
9	24	1 1	22	92 / 108
10	25	1 0	27	104 / 98
11	26	1 0	36	98 / 104
12	27	1 1	14+	104 / 100
13	28	1 2	62	92 / 96
14	29	1 0	56	92 / 98
15	30	1 1	53	101 / 99
16	31	1 2	55	92 / 99
17	32	1 0	54	92 / 100
18	33	2 3	34	88 / 102
19	34	1 0	37	98 / 96
20	35	1 1	24	76 / 102
21	36	1 0	40	84 / 96
22	37	1 1		92 / 92
23	38	2 5		86 / 96
24				

Resp.

Date of admission.

Result May 16th 1911

Entered at Stationers Hall. Printed and Published by Wodderspoon & Co. 6, Gate Street, Lincoln's Inn. Gould's Clinical Chart.
Stationers Hall. Printed and Published by Wodderspoon & Co. 6, Gate Street, Lincoln's Inn. Gould's Clinical Chart.

was negative. On the 39th day after operation the patient was removed home.

During the whole period of 39 days the patient suffered greatly from flatulence and abdominal pain, chiefly in the region of the caecum. This distension and pain undoubtedly prevented sleep. Insomnia was a marked feature of the convalescence. In spite of morphia, chloral, bromide, trional, the patient did not secure more than 1 to 2 hours continuous sleep.

The abdominal distension and pain combined with the sleeplessness and the shock of a severe operation caused the patient to develop a decidedly neuraesthenic condition. It is curious to note that immediately preceding the abortion the temperature was swinging between 97.6° and 99.8°. At the time of abortion the temperature was 99.6° and after the event it rose to 101.8°. For the next eleven days the temperature ranged between 97° and 101.4° whereas previous to the mishap it ranged between 97.6 and 99.6. The sudden great swing in the temperature is a noticeable one and so closely connected with the maternal events that one is inclined to associate the sudden increase in the rise with that event rather than with a direct toxic origin. In her weakened condition it must have been a further great nervous shock to the patient to undergo this other trial. It is also to be noted that/

that the six doses of vaccine had no material effect on the temperature. It was also curious to note the change in the patient's disposition. Mrs A. W. was always regarded at her own home as kind, gentle, placid, considerate to a degree and extremely obliging but now she was irritable, very indifferent to the interests of others and to the trouble which her wishes might cause - peevish, selfish and discontented. The reflexes were exaggerated and the pupils unequal, and she had fine muscular tremors. These latter symptoms were more marked when the patient was removed home. It seems probable that a great part of the fluctuation of the temperature was due to a nervous origin which may have had its origin in a toxic absorption from the bowel. It has to be remembered that with the removal of the spleen from the economy there had been taken away an organ closely connected with the portal system and thus in very close association with the whole process of absorption. On her removal home the patient suffered almost daily or nightly from a twisting screwing pain in the region of the caecum and with drenching night sweats. These night sweats were so profuse as to suggest a tuberculous origin, but no such focus, although sought for carefully, was ever found. It is interesting to note that a nightly dose of Tincture of Belladonna M $\bar{X}$ secured a good night's/

night's rest and comparatively free from sweating.

For the eleven days succeeding her removal home the temperature and pulse of the patient fluctuated much the same as it did in the home. After the 52nd day after operation the temperature and pulse began to steady itself so that on the 60th day the temperature only rose from 97.8° to 98.4°.

Again a minute examination of the relation of pulse and temperature is interesting. On the 2nd day of operation the pulse in the morning was 99 and in the evening 96, but in the evening of the same day with the fall of the pulse rate we have a rise of the temperature to 99.4°. On the 7th day in the morning the pulse was 104 and in the evening 88, but the temperature rose in the evening from 98.4° to 101.2° and on the 8th from 100.6° to 102.6° but the pulse rate in the morning is 120 and evening 108. A glance at the chart shows that the morning pulse is higher than the evening, whilst the morning temperature is lower than the evening temperature. On an average the figures are.-

Pulse.		Temperature.	
Morning	102.1	Morning	98.4°
Evening	98.8	Evening	100.0°

It might be that the explanation of the relation of temperature and pulse lies in a toxic absorption

taking/

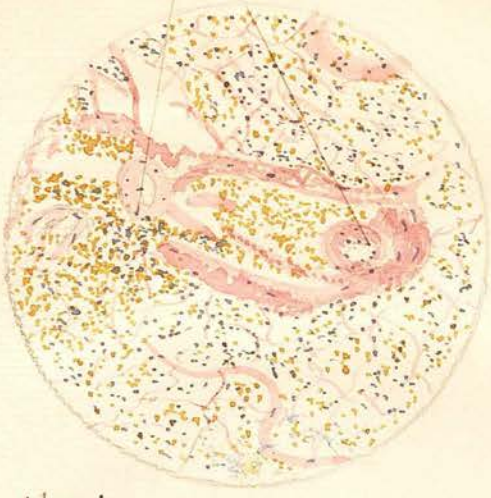
taking place from the bowel. This view is supported by the profuse night sweating and the screwing, twisting pain in the region of the caecum. The chart reminds one of a case of pneumonia with a large patch of phthisis which ran a similar course and showed the same nervous symptoms. A similar train of events one has often seen in a hysterectomy with complete removal of the ovaries. Indeed one could not but be struck with the great similarity of events which become so often manifest at the menopause which is undoubtedly due to the suppression of the activities of the ovaries which no longer are able to neutralize some toxaemia of the blood and which poisoning finds expression in flushing, sweating and a general nervous neuraesthanic condition. The close association of the extirpation of the spleen and the rise of those toxic nervous manifestations would lead one to suppose that the splenic influence now being removed these toxins were at first circulating free in the blood stream until other organs, probably the lymphatics and solitary glands, were stimulated into greater functional activity to neutralize these poisons possibly by fixation and destruction. It probably does not mean that the spleen has an internal secretion but rather that it is a detoxicating organ and perhaps the first which the absorbed fluids meet upon leaving the bowel and upon entering/

entering the portal channel. The beneficial influence of Belladonna would seem to bear this view out since by dilating the superficial vessels and stimulating the vaso motor mechanism it would allow of other lymphoid tissue adjusting itself to meet the altered economic state. There is evidence also that the spleen besides rendering poisons negative by fixation by the tissue and by digestion by the leucocytes is able to institute a metabolic change as lecithin and glycero phosphoric acid which is a decomposition product of lecithin is normally found in its analysis. The presence of lecithin denotes that the base cholin with fatty acids and glycerophosphic acids must be present to form the lecithin. And cholin is an inert body but in a weak watery solution cholin is transformed into neurin which is highly toxic and is the cause of great irritation to the mucous membrane. It is therefore likely that the spleen is also a synthetic or metabolic organ and it is unlikely that the elements for this synthesis is derived from the systemic blood but rather from that of the Portal vessels.

From about the 70th day after operation normality of pulse and temperature was established. From this time onwards the progress towards recovery was slow but steady. Towards the end of August the patient was able/

SLIDE No I

Small Arteriole
or
Capillary - Vein

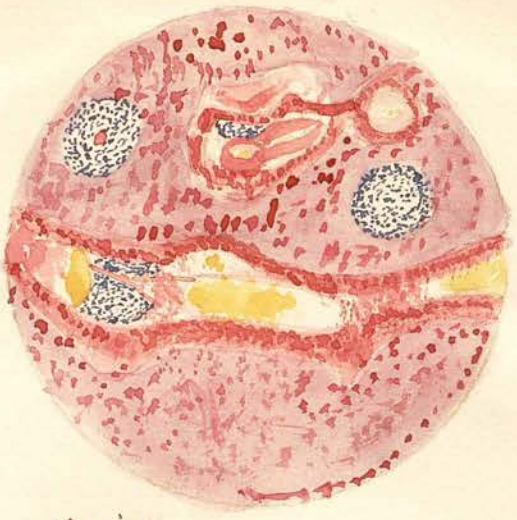


+ 1/5" in

Venous Sinus with very thickened walls which have ruptured.

This slide also shows the connective tissue hyperplasia exceedingly well.

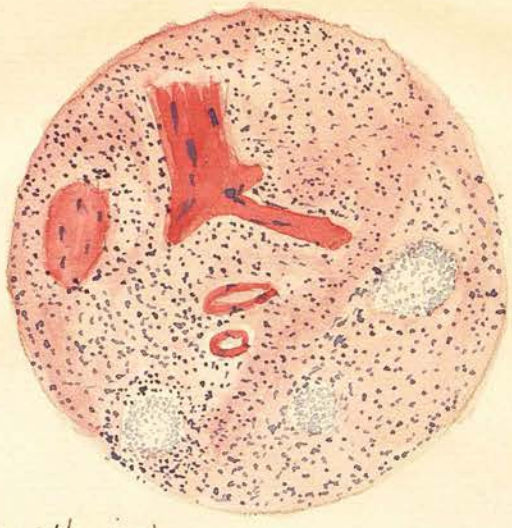
SLIDE No 11



+ 1½ inch.

Showing the connective Tissue hyperplasia along the walls of a venous sinus.

SLIDE No III



+ 1½ inch.

a. Shows the enormous increase of the fibrous trabeculae.

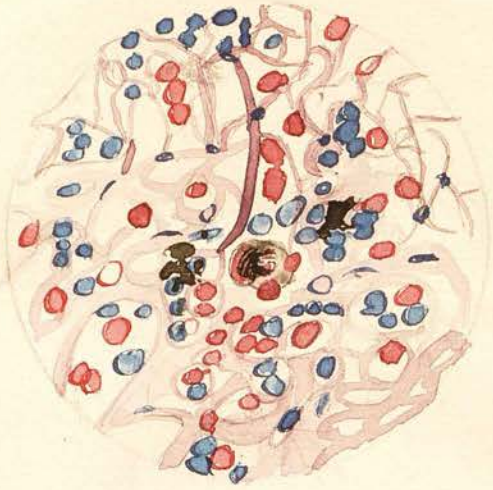
b. The effect of the fibrous hyperplasia on the Malpighian corpuscles which are small - pushed wide apart and more open in the network.

able to walk and at the beginning of September she was removed to the country for convalescence.

In the month of August menstruation was re-established and continued regularly every 21 days until April 1913 when she found herself again pregnant and 9 months later was delivered at full term and without difficulty of a healthy female child, the wound standing the strain magnificently.

Microscopical Examination of the Spleen shows a marked thickening of the capsule and fibrous trabeculae in which are seen dilated veins filled with blood. There is only a slight fibrous thickening of the wall of the arteries. Some of the trabeculae show along their course extensive and recent haemorrhage. The most marked feature is the general increase in reticular stroma of the spleen spaces. This fibrous hyperplasia is seen to spread in a very uniform way along the walls of the venous sinuses throughout the section. The sinuses are dilated and filled with red blood corpuscles and numerous lymphocytes. There are very few phagocytic cells to be seen in the venous channels. The fibrous condition of the pulp has caused atrophic changes in the Malpighian corpuscles. This has caused these corpuscles to be of small size and widely separated. A few of the Malpighian corpuscles show minute areas of altered blood corpuscles and fibrin both/

SLIDE No III



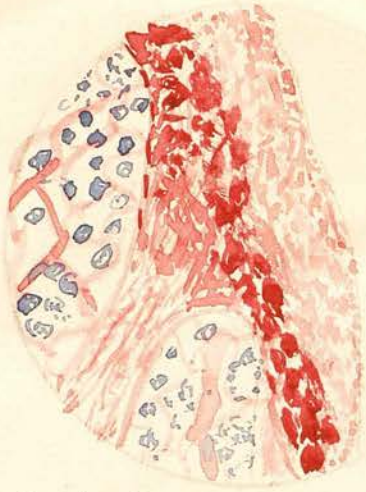
+ 1/10 inch. Immersion

a. Phagocytosis.

b. Pigment granules.

c. Hyperplasia of the sustentacular network.

SLIDE NO II



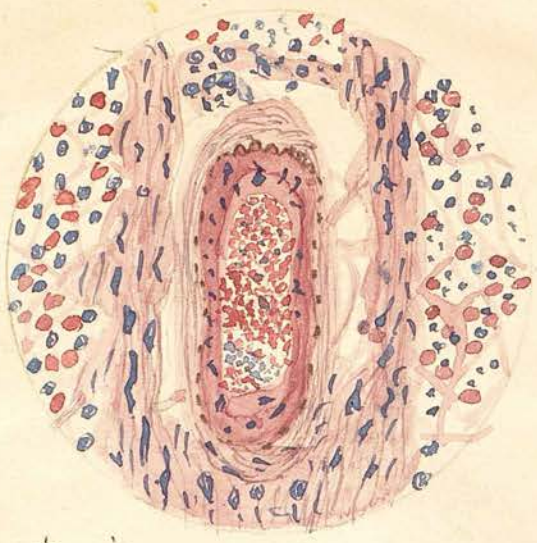
+ 1/10 in. Immersion

Capsule.

a. Great thickening of the capsule by fibrous hyperplasia and which continue into the trabeculae.

b. Increase in the non stripped muscle fibres.

SLIDE No 4



+ 1/3 inch.

Throughout all the slides the arteries show a fibrous thickening along their course. But many of the smaller arteries besides show a great thickening internal to the elastic lamina - Arteritis Deformans.

Some of those arteries are almost completely obliterated.

One or two arterial vessels are ruptured.

both in the germinal and lymphatic areas.

The great size of the spleen there is no doubt is caused by a fibrous hyperplasia of the reticular stroma coupled with an increase in thickness of the fibrous trabeculae and haemorrhage into the pulp. Because of this fibrous hyperplasia the Malpighian corpuscles are squeezed and atrophied and pushed apart.

Up to July 1913 when the patient passed out of my hands she enjoyed on the whole very good health. There were periods of acute pain in the right iliac fossa, with rumbling and flatulence in the bowel. The tongue being irritable, flabby and furred - little appetite and poor digestion. During these periods there was no rise of temperature, only a slight quickening of the pulse rate.

In May 1913 the blood condition was as follows.-

A few of the red blood corpuscles showed a granular degeneration probably due to an intestinal toxaemia. The corpuscles as a whole were well formed and coloured.

Red blood corpuscles	4,800,000
White blood corpuscles	800,000
Polymorphs	48%
Large Lymphocytes	14%
Small Lymphocytes	34%
Oesinophiles	4%

Among/

Among the large lymphocytes there were many large transitional and large mononuclears which are supposed to be derived from the spleen 'spleenocytes'.
The blood plates appeared to be over the average.

Upon arriving at the conclusion, before excision of the spleen, that the case was one of primary splenomegaly which was best treated by excision - all the blood and toxic conditions were excluded. A malarial origin of enlargement was improbable as the patient was removed from the Levant in her infancy and both parents were emphatic that she never had any tropical fever; on the other hand one is struck by the fact that the presence of the tumour dated from her marriage although a degree of anaemia existed all her early adolescent life. The possibility of syphilis as a cause is there, although not probable as the Wassermann reaction was negative and the patient at no time showed any sign of such infection. The miscarriages were solely and entirely due to the enlarged spleen resting upon the fundus of the pregnant uterus and acting as a mechanical irritant to the uterine muscle. When this irritant was removed the patient bore a full time child.

The patient in childhood had both pneumonia and diphtheria. It is unlikely that those toxaemias were the cause of the hyperplasia of fibrous tissue, otherwise/

otherwise the spleen would have manifested its presence much earlier.

There were two factors which the patient carried into her married life and these were (1) flatulent bowel dyspepsia - enteritis. (2) A slight degree of anaemia. A third factor presented itself shortly after the nupital bonds were tied, namely, worry and anxiety over previously unknown causes which were disrupting her domestic happiness. The ceaseless anxiety by undermining the tone of the whole body caused a rapid and uncontrollable increase in bowel flatulence that is in the proteid putrefaction which after all is the outcome and manifest sign of a great multiplication of the bacteria composing the flora of the bowel. Constipation was a marked feature during this period so that there must have been a considerable absorption of both intra and extra cellular toxins from the bowel into the portal system.

After excision of the spleen the blood condition greatly improved. Before operation the red-blood corpuscles numbered 3 million and shortly after operation 4 million. The white corpuscles rose from 3 thousand to 8 thousand. Therefore with the removal of the spleen you removed the destructive element. It incidentally shows that the forming of red or white corpuscles is not dependent upon the spleen but upon some/

some other organ, e.g. the bone marrow. And also that the new formation takes place at a very rapid rate. It is not probable that with the enlargement of the spleen that its functional activity was increased but rather that it was diminished in proportion to the hyperplasia of connective tissue and the decrease of the lymphoid tissue. Is the hyperplasia of fibrous tissue in the spleen, along with corpuscular diminution and venous haemorrhages, due to some Katabolic change in the spleen itself or is it due to some added quality derived from elsewhere? In other words is there such a disease as true primary splenomegaly or are all splenomegalies really secondary? Some light may be thrown upon this by grouping all the symptoms of primary splenomegaly together and discussing them separately. This method appeals to me more so as the case of Mrs A. W. cannot very well be put into any one class of primary splenomegaly. It is neither idiopathic splenomegaly nor Banti's disease nor splenic anaemia, but partakes largely of all three, but most closely resembles that of Banti's disease. In the case of Mrs A. W. slight diminution in the red blood corpuscles - marked diminution in the white blood corpuscles, slight diminution in the haemoglobin - a fibrous hyperplasia but little around the arteries and markedly and uniformly along the ~~nervous~~ Ven sinuses. Numerous/

Numerous lymphocytes in the venous sinuses with few phagocytes. Haemorrhages from the trabeculae into the pulp. The symptoms were aesthenia, tiredness, lack of energy, lack of appetite, flatulent dyspepsia enteritis, constipation and frequency of micturition. In Banti's disease you have also a diminution in the corpuscles but it is very marked in both white and reds.
Red corpuscles = 2 million. White = 1 thousand.
Haemoglobin markedly diminished - 15% - 28%. Repeated haemorrhages from mucous membrane, e.g. bowel, nose, etc., or under the skin. Jaundice, pigmentation of the skin, recurrent and irregular fever, cirrhotic liver. The spleen is enlarged from a fibrous hyperplasia and is irregular in uniformity and outline and usually has infarcts. The fibrous thickening is marked in and around the arteries. The splenic spaces are usually filled with blood and proliferation from the endothelium of the spaces - phagocytes. There is an entire absence of accumulation of leucocytes in the spaces. An important point to remember also in this connection is that in Banti's disease you have recurrent pyrexia and haemorrhages which certainly would tend to reduce the red count and raise that of the white.

Splenic anaemia has as characteristics marked anaemia with diminution of the red blood corpuscles and haemoglobin. The leucocytes are not markedly diminished/

diminished and you may even have a slight leucocytosis. Periods of severe anaemia with periods of health with normal blood proportions and diminution of the enlarged spleen.

In primary splenomegaly the following are the marked symptoms.-

(1) Pyraexia - irregular

(2) Gastro-enteritis (Vomiting
(Constipation
(Diarrhoea

(3) Haemorrhages (Bowel
(Uterine
(Skin
(Epistaxis

(4) Haemolysis (White blood corpuscles
(Red Blood corpuscles.

(5) Jaundice

(6) Ascites.

Pyrexia is difficult of explanation. It may be taken that the cause of fever is an increased heat production along with an interference with the nervous mechanism which allows of the heat escape, e.g. the sweat glands. A rise of temperature is seldom found apart from some forms of toxaemia. It is therefore probable, as a general rule, an irregular pyrexia is an indication of an irregular poisoning whether that toxaemia may be due to an irregular invasion of bacteria or the absorption of its toxins or other poisons.

Gastro-enteritis is favoured by all conditions which exhaust the nervous system such as anxiety, worry, mental strain. (a) Vomiting in the great majority of cases is due to an irritant change in the stomach contents. But the centre of vomiting is in the medulla and may be stimulated by the vagus, glossopharyngeal, sympathetic. That is, vomiting may be brought about not only by digestive tract but also by the liver, kidneys, gall bladder and urinary apparatus. The spleen does not cause vomiting. The chief causes of afferent discharge is irritation of the nerve endings, especially in the stomach and bowel, by gastritis hyperacidity - changed food particles, etc.

(b) Gastritis is nearly in all cases due to a microorganism. Whether it be for the good of the economy or not, the fact remains that microorganisms are regularly present in great number in the stomach and bowel and are introduced by the food, e.g. lactic acid bacillus, yeast, sarcinae, colon bacillus. These organisms although not essential to well being have their uses such as fat splitting, the cleavage of the fat mollicule into glycerine and fatty acids and the destruction of foreign pathogenic organisms. These normal organisms set up four different kinds of fermentation in the stomach. (a) Acetic, (b) Lactic, (c) Butyric, (d) Alcoholic. Any one of these ferment-

ations/

fermentations may be excessive. That is that yeast and excessive carbohydrate intake will yield a very considerable quantity of alcohol. And so in gastric atony we find an undue quantity of lactic acid. Butyric acid is the end process of lactic acid fermentation. The lactic acid fungus uses oxygen very largely and is the natural precursor of butyric acid and therefore is a powerful reducing agent. Butyric acid fermentation is the last change of many carbohydrates, especially starch. Acetic acid is not common and is probably not derived from the alcohol but from the proteid during its putrefaction with exclusion of oxygen. (Neucki). These fermentations give rise to gas eructation - distention which may take place in the bowel with passage of flatus per anum. This distention gives rise to motor inefficiency and the passage of alcohol, lactic, acetic, butyric acids into the bowel and may give rise to enteritis as well as setting up a gastritis by diminishing the hydrochloric acid secretion.

What clinical effect has these fermentative processes on the bowel? (a) Distention due to carbon dioxide. (b) Diarrhoea. (c) Colic especially at the flexures. Besides there is a loss of strength, weight and energy owing to a loss of food potential. Lactic, acetic, butyric and alcohol are all capable of/

of setting up diarrhoea, but acetic and butyric are the chief causes of active peristalsis.

The entrance of an excessively acid gastric content into the bowel sets up a catarrhal inflammatory condition of the cells lining the gut; moreover the bowel acts best in an alkaline medium so that its activity must be greatly diminished by the introduction of excessive acidity and thus takes place a great interference with proteid digestion, hence you have headaches, drowsiness and depression and lack of energy. An excessive decomposition of carbohydrates gives rise to proteid putrefaction so that the individual is thrown upon his body tissue for nutriment. This factor along with diarrhoea leads to wasting and loss of body weight. The fats are in a measure saved as the bacteria are capable of splitting them into fatty acids and as such they may be absorbed.

The urine is hyperacid and contains acetic, formic, oxalic acids and being irritative the water is passed more frequently than usual.

(c) Enteritis. In the urine sulphuric acid exists as ethereal sulphates, as neutral or acid salts of the alkalies. Sulphuric acid is capable of uniting with the aromatic substances found in the intestine and thus we get an index of the putrefactive processes going on there. The sulphuric acid in aromatic

combination/

combination occurs chiefly in union with (a) Phenol, (b) Indol, (c) Methylindol = skatol, (c) Kresol. It was Baumann who first proved that the putrefactive processes in the intestine is the cause of the ethereal sulphates and that in cases of intestinal indigestion the ethereal sulphates are increased. Normally they may be increased by drugs of an aromatic nature such as salol or creosol. The aromatic bodies are toxic but the ethereal sulphates are non toxic so that the original aromatic bodies have been thus deprived of their toxic properties. In short a synthetic detoxicating process has taken place. Now the potential supply of aromatic substances is very great while the sulphur supply of the body is limited and may give out so that the preformed sulphate may also give out which it actually does in carbolic acid poisoning with the absorption of phenol from the bowel and the appearance of pyrocatechin and hydroquinon in the urine.

Phenol in the urine appears as phenol sulphate of potassium, skatol as skatoxyl sulphate of potassium and indol as indoxyl sulphate of potash or indican.

Among the products of pancreatic digestion are amido acid, leucin and tyrosin. Tyrosin by putrefactive processes alone is broken up into indol. Phenol seems to be increased by the same circumstances that/

that increase indol. Skatol has been prepared artificially by Neucke and Secretion from egg albumin. According to Salkoroski, skatol and Indol are derived from the same substance depending upon whether the indol or skatol fungus is the most abundant.

Senator's experiments by sulphuretted hydrogen have not been confirmed, but it is difficult to understand how a gas so toxic can be absorbed from the bowel without bringing on a derangement of the economy. The bacteria of the intestine produce nascent hydrogen which prefers to unite with oxygen to form water and may even draw this oxygen from the haemoglobin and so cause perhaps the anaemia so often met with in constipation. If no oxygen is met with it unites with the sulphur. Thus the sulphites, the hyposulphites and even the sulphates suffer a reduction. It may be that the sulphur radicle in the proteid molecule is split.

To summarize in gastric fermentation you have alcohol, acetic, lactic and butyric acids formed, which, passing into the intestine set up an increased peristalsis and inflammatory catarrh of the lining endothelium, besides rendering the intestinal ferments inactive and which in turn produces intestinal putrefaction with production of indol, skatol and phenol and sulphureted hydrogen. The carbohydrate fermentation/

fermentation gives rise to vomiting, diarrhoea and frequency of micturition, distension, flatulence and colic due to carbonic acid gas and butyric acid. The proteid putrefaction produces Indol, Skatol and Phenol (especially the former) and the formation of sulphureted Hydrogen, a cause of further distension of the lower bowel besides being a very toxic gas. The sulphureted hydrogen is expelled as such. The ethereal sulphates enter the portal stream, pass into the liver and there are detoxicated and appear in the urine as the potassium salt. Sometimes proteids set up a diarrhoea, especially indol, but generally you have constipation with naturally an excessive amount of aromatic substances. If in physiological excess these substances are absorbed into the blood stream and there have an opportunity to modify cell structure and function.

Jaundice. It has long been known that instances of jaundice are by no means rare in which the common bile ducts and the larger bile ducts are entirely free. Reill in 1782 described such a case: so did Saunders in 1809 who suggested a relation to the blood. In 1858 Frerichs expressed the view that sodium glycocolate and taurocholate are normally in the blood charged with pigments so that a defective oxidation of the blood leads to a deposit of pigment in/

in the skin. Kuhne found that the injection of haemoglobin into the blood was followed by bile pigments in the urine. Thus he was able to state that the bile salts act as stated by Frerichs but that it was owing to the destruction of red blood corpuscles. He also made the very important statement that all agents which liberate haemoglobin in excess are capable of causing bile pigment and jaundice may follow. The liver is the chief seat of the formation of bile colouring matter. The poisons or agents which destroy the red blood corpuscles release a great quantity of haemoglobin and thus an alteration in viscosity of the bile follows which obstructs the small bile ducts. Minkowski - Naunyn showed by experiment that the liver is the seat of the formation of bile pigment - that the liver transforms haemoglobin into bilirubin and biliverdin. Shadleman verified these experiments. The sequence of events may be summarized as follows.- Destruction of the red blood corpuscles - formation of haemoglobin. Haemoglobin carried by the blood stream to the liver and changed into bile pigment. If this is in excess, the viscosity of the bile is increased and thus obstructs the smaller bile ducts and an accumulation of pigment in the blood stream = jaundice. On the other hand if for any reason the destruction of red blood corpuscles ceases the haemoglobin/

haemoglobin diminishes, the bile becomes less viscid, the smaller ducts are no longer blocked and the jaundice diminishes - haemohepatogenous jaundice. The great destroyer of red blood corpuscles are poisons which of itself may set up a catarrh of the bile ducts and thus lead to obstructive jaundice. Haemohepatogenous jaundice is usually accompanied by other evidence of toxaemia such as haemorrhage from the nose, bowel or stomach, or may be haemoglobinuria. As the larger ducts are not closed you generally do have bile pigment in the faeces and there may even be a marked excess = polycholia. If the obstruction of the small ducts are not so great as to prevent some bile escaping into the intestine, no bilirubin will appear in the urine.

Red blood corpuscles

Haemoglobin

Haematin

Bilirubin - O - N
1
Biliverdin Urobilin = Stercobilin.

Therefore from the jaundice you will have clinical symptoms arising from (a) the bile elements in the blood: (b) the exclusion of the bile secretion from the intestine: (1) yellow pigmentation due to bilirubin: (2) bilirubin may or may not appear in the urine and urobilin or stercobilin in the faeces depending/

depending upon the degree of obstruction. (3) Cholemia. Glycochol = Amido acetic acid. Taurin = amido ethyl sulphuric acid - are both amido acids and are derived from the proteids. Glycochol and taurin unite with cholic acid and form glycocholic and taurocholic acids, the former existing mostly as sodium salt. In jaundice the bile acids are supposed to be diminished else they would appear in the urine if accumulated in the blood. The bile salts besides has a haemolytic action on the red blood corpuscles and lengthens the coagulation time of the blood which gives rise to a distinct inclination towards haemorrhage after operation in jaundice cases, due to paralysing effect on the vessel wall probably by its action on the vagus.

Bile obstruction also leads to increased proteid putrefaction with defective absorption of fat: as the presence of fat and absence of bile gives the bacteria of the intestine a rare opportunity to break up the proteid. The chief function of the liver cell is the conversion of (1) ammonia, a by-product of digestion and which enters the portal vein, into Urea = amide of carbonic acid. Glycocol = amido acetic acid and leucin = amido isobutryl acetic acid are converted into urea by the liver. Therefore in disease of the liver cells you have a diminished output of urea, as for example in cirrhotic liver where the nitrogen in ammonia/

ammonia may rise to 20% and displaces the urea. (2) Formation of uric acid from breaking down of organic cells nuclei. The presence of leucin or tyrosin in the liver or spleen is probably derived from the breaking down of the cells of the organ. (3) Besides the liver cell has an antitoxic function.- (a) detoxicating: (b) decomposition: (c) simply stored. Therefore it is a protective agent against poison, so that structural or functional damage to the liver cells lead to accumulation of toxins in the body. In this connection Heger made some interesting experiments whereby he proved that indol and phenol are readily taken up by the liver cells more so than by cells of muscle or brain. But if the liver cells are damaged during life you have a very much reduced activity. Indol and phenol are oxidised by the liver and held in a transformed state - oxidised into indoxyl. The toxins of typhoid and tetanus suffer a great reduction in their toxic qualities because the liver is the seat of the most intense oxidative process in the whole body. It can decompose alcohol, acetic, formic and butyric acids and burn up citric and malic acid, etc. The indol after being oxidised into indoxyl unites with sulphuric acid from the cells and forms indoxyl potassium sulphate. If we summarize the work of the liver we might say that it revises the blood of the portal vein and is the sentry of the

systemic/

systemic system. Jaundice may be catarrhal, obstructive - haemoheptogenic - the latter being due to haemolysis due to toxins. The decreased supply of bile to the intestine leads to fat and proteid putrefaction. Haemoheptogenetic jaundice is associated with haemorrhage from nose, stomach, etc. Cholaemia is due to a reduction of the bile elements in the blood. The bile salts are haemolytic and delay coagulation and alter the blood vessels probably by paralysis and lead thus to haemorrhage. The normal function is by synthesis to form urea from the ammonia of the portal system and also the formation of methyl indol = skatol ~~and methyl~~. The formation of uric acid from the nuclei. Indol, phenol, etc., are oxidised and rendered inert. Various toxins are reduced in toxicity. But if toxic bodies enter the liver cells in sufficient strength, exceeds the physiological limits it leads to structural damage and inability to perform its proper function. It is probable that a cirrhotic liver is an attempt on the part of the hepatic organ to fix some poison absorbed into the portal system and which may be due to an enteritis. In the case of alcohol in excessive amount formed either by carbohydrate fermentation or ingested as such, it is not likely that the alcohol is the cause of the fibrous hyperplasia, but more like that it sets/

sets up a gastro-enteritis, defective assimilation and gastric fermentation and bowel putrefaction with the consequent absorption of putrefactive products beyond the physiological limits. The liver, in an endeavour to stem the flood of constant and excessive toxaemia fixes the toxin by means of the connective tissue cells which proliferate to meet the future requirements and thus the liver structure cells, ducts and vessels become squeezed and atrophied and give rise to obstructive jaundice, etc. In reference to a toxaemic cause it is curious to note that pyogenic cocci generally cause miliary abscesses in the kidney - settling in the capillaries of the kidney; while the infective granulomata generally - syphilis, glanders, tubercle, leprosy, actinomyces, all irritants of minor intensity the nodules are found in the spleen, the slow infection producing a connective tissue reaction.

Bilirubin.

Altered liver cells	Haemohepatogenous Jaundice.	Skin pigmentation
Diminished Urea		Urobilin.
Diminished Uric acid		Stereobilin
Accumulation of toxins		Defective fat absorption.
		Cholaemia { Bile Salts in urine. / Bile salts in blood.

Haemorrhage is due to change in the vessel wall leading to a greater permeability and a change in the serum whereby its coaguability time is lengthened. Such haemorrhages follow the injection of, e.g. diphtheria toxin or the poisons recin and aborin.

Haemolysis. Leucocytes:- There are bacteria which do not have a toxic protoplasm nor produce a soluble toxin in a fluid medium and yet produce effects it may be at a distance, e.g. b. anthracis. It is probable that these bacteria are only able to produce poisons in the living tissue. Again bacteria which produce toxins may in the living tissue more readily produce poisons and even may be of a different nature to those produced in an artificial media. In the living tissue, say in the bowel, you have a multiplicity of uncertainties which may curtail or increase the extra cellular or intra cellular toxins or give rise to a new toxin undeveloped in artificial media which is of known and measured quantities. These toxins are called aggressins and they are probably intracellular toxins. The important aspect is the recognition of toxins having an action on the leucocyte degeneration and death of these cells. Eisenberg records that in 'vitro' mixtures of leucocytes and cultures of the bacillus of anthrax, loss of motility and degeneration of the cell takes place. It is likely/

likely in human tissue as in animals, as shown by Grassberger and Shattenfrob, that there exists great differences in susceptibility both to the growth of bacteria, the formation of toxins and the effects of their absorption on the living tissue. This is often seen even in vegetable and especially in the ptomain poisons.

The destruction of the red blood corpuscle and the haemorrhages might be caused by the retention and accumulation in the blood stream of the bile salts which might be present owing to the haemohepatogenous jaundice. But as a rule these are not retained in the blood stream as they only appear in the urine for the first four days or so of jaundice. It is more likely that this is the formation of an immune body, it may be of the aggressin or other toxin acting upon the receptors of the blood corpuscles and thus allowing of their destruction by the ferment like complement which is a normal constituent of the serum.

Now Pfeiffer and Marx in the case of typhoid and Wassermann in cholers have shown that immune bodies are chiefly formed in the spleen, lymphatic glands and bone marrow. In the formation of immune bodies and complement, the large mononucleated and polymorphs take a large share. But in all probability the endothelium of the vascular system takes its part and probably/

probably is the cause of the increased permeability of the vessel walls and haemorrhages in this case in the spleen.

To make a short statement one might say the aggressins are the cause of the diminution of the white corpuscles and the destruction of the red corpuscles are due to the serum complement. While the associated haemorrhages are due to increased permeability of the vessel wall in part to cloudy swelling of the endothelium owing to hyperactivity and often detachment.

But it is known that substances of a definitely known chemical constitution, namely Lecithin, has the power of activating the haemolytic substance in cobra venom, in addition to the serum complement. The two apparently unite and form an actively toxic substance. This was demonstrated by Keyes and Sachs and corroborated by Fraser, while Flexner and Noguchi showed the same thing with normal serum.

Discussion.

Parkes Weber suggests that the spleen condition in Cirrhosis of the Liver may be due to a Toxaemia. Such a spleen has the following characters. Thickened capsule and trabeculae. Hyperplasia of fibrous tissue. Distention of veins. Malpighian corpuscles fibroid. The spaces are thickened and therefore smaller.

A/

A few lymphocytes. In chronic venous congestion from mechanical causes such as heart disease, emphysena, etc., you have the same pathological changes with obscuring of the cellular elements of the pulp. In both cases you have a hypertrophy of the muscular tissue of the capsule and trabeculae at first.

Between these conditions and the pathological changes in splenomegaly there is a very close resemblance. This hyperplasis comes into evidence again in cyanotic cirrhosis of the liver due to long standing engorgement of the hepatic veins, wherein you get a connective tissue increase in the immediate vicinity. It seems certain that a venous engorgement of liver or spleen from any cause will set up a fibrous hyperplasis in the neighbourhood of the engorged veins or sinuses. This engorgement may be set up by conditions so far apart as emphysena, mitral stenosis, portal obstruction. Further, cirrhosis of the liver, be it common cirrhosis, hypertrophic cirrhosis or syphilis, is always associated with a like condition in the spleen. All these conditions in the spleen are reflected as an engorgement of the venous sinuses. Now a venous engorgement by itself will not cause a connective tissue hyperplasia - a thickening of the fibrous network in trabeculae but the contained fluid must contain some chemical substance or element which acting/

acting upon the connective tissue cells causes them to proliferate it may be to add strength to the framework of the spaces or more likely to save themselves from destruction - or both. At all events it is clearly preservative.

On the other hand there is evidence that the spleen may be cirrhotic without the liver being so or that there is any known ground for a venous engorgement as, for example, in splenic anaemia. Yet the venous sinuses are distended and engorged with blood and in this case filled with leucocytes. It seems reasonable to suppose that this congestion is due to a regurgitation of blood from the portal vein into the venous sinuses. Mr Stiles in operating remarked upon the large size of the splenic tributaries in the pedicle, each of which admitted the little finger. If we remember that the blood in spleen is of very slow circulation, for reasons given, and that the blood pressure in the vessels therefore must be extremely low, and that the difference in level between the transverse fissure of the liver and the hilum of the spleen is about 2⅓ inches and further that the large veins of the portal system have no value. It seems certain that venous blood from the mesenteric veins must fall back into the spleen if poured into the portal vein faster than with which the liver can deal. It would seem likely that under normal/

normal conditions that this is the case, as five hours after a meal the spleen is engorged but only for a short time. It would seem that when the spleen becomes full, just as the auricle or ventricle become full, the nervous mechanism causes contraction of the splenic muscles and a widening of the venous sinuses of the liver with expulsion of the splenic blood. If for any reason this engorgement should continue, as for example from (a) liver incapacity to deal with the blood; (b) defective expulsion of the splenic blood; (c) or a venous congestion from too great a quantity of blood being regurgitated, then a connective tissue hyperplasia will begin. But connective tissue hyperplasia is not alone confined to the liver and spleen - it is also to be found in all organs of the body, especially in the kidney and the lung. Indeed in the former it would seem that a chronic interstitial nephritis is the analogy of liver and splenic cirrhosis. It is clear, therefore, that systemic blood will cause cirrhosis as well as portal blood, but the condition is perhaps more common in the portal than in the blood supplied by the systemic system and after all the condition may arise solely owing to the incapacity of the portal system to deal with the initial cause.

An obstruction in the portal system be it complete or/

or partial must cause a stasis in the mesenteric veins which means a slowing of absorption and of digestion which in turn will result in more or less further changes in the bowel contents, depending upon the completeness of obstruction. This can only mean that more or less proteid albumose of putrefactive origin will be absorbed along with the peptone. And it is probably this toxin which is the stimulating cause of connective tissue change. But a slightly different picture is presented by the regurgitation of portal blood in as much as you have no portal block partial or complete in an obstructive sense. You have a volume of blood entering the spleen which by right should enter the liver. That volume of blood causes an over-distention of the venous sinuses and fibrous hyperplasia. But in addition you have a primary putrefactive condition in the bowel. So that the blood entering the spleen is now heavily loaded with toxin molecules derived from the fermentative and putrefactive processes proceeding in the bowel. Hyperplasia of connective tissue is dependent upon a toxin of low intensity but constant presence. If the muscle fibres of the heart are continuously over-stretched the ventricles do not empty themselves but retain a certain amount of blood, depending upon the contractive quality of the involuntary muscle and thus in/

in time a block may be produced. And so with the splenic muscle. The first effect of over regurgitation is to multiply the strength of the capsular and trabecular muscle fibres by increase, which increase for a time meets the situation. But a time comes when these muscle fibres fail and gradually are no longer able to expel the spleen contents. It is during this period that hyperplasia takes place probably to increase the strength of the venous sinuses and the reticular framework. Moreover, besides being a toxin or toxins of low intensity and constant presence, it is destructive to red blood corpuscles and white blood corpuscles. And in this particular instance it is attractive to leucocytes, probably by chemiotaxis, as numerous leucocytes are seen in the spaces.

It would be an attractive hypothesis to suggest that alcohol was the cause of all these changes. In all splenomegaly cases gastro enteritis is a leading feature and it is not unlikely that a fairly large quantity of alcohol is formed from the carbohydrates. Further, it is undoubtedly the case that over indulgence in alcohol is the primary cause of liver and kidney cirrhosis. But liver and kidney cirrhosis can be present without any history of alcohol. And further that alcohol can be partaken in fairly heavy doses/

doses without causing cirrhosis, depending upon the susceptibility of the individual. To them all there is one common factor - fermentative changes in the stomach and putrefactive processes in the bowel. The alcohol, acetic, and butyric acids, etc., derived from the gastric fermentation (and especially the former which has a known capacity to do so) sets up not only an altered tryptic secretion but also intestinal by a process of catarrh of the lining endothelium of the bowel which of itself leads to bacterial Multiplication - stasis and increased putrefaction.

In this special case the urine showed no indican or other abnormal constituent excepting occasionally urates. There was no excess of uric acid or urea or bile salts or colouring matter. This goes to show that the liver was unaffected or if so it was able to perform its oxidative function effectively so far as the urine was concerned, excepting so far as its acidity was concerned which was hyperacid. Unfortunately the degree of acidity cannot be given nor the exact acid which which would explain exactly the cause of the frequent micturition. But it is likely as the condition progressed that abnormal constituents would be found in it. That there was an alteration in the viscosity of the bile ducts is shown by slight pigmentation.- the haemohepatogenous jaundice.

It/

It seems reasonable to suppose that rather than than alcohol that a toxin or more probably toxins are the casual factors. This would be in agreement with all that is known in respect of connective tissue hyperplasia and the train of symptoms attendant upon splenomegaly. These toxins must be derived from the bowel and further they must be developed from proteid putrefaction either from the putrefactive agent or the putrefactive process itself. From urinary reasons it is unlikely to be from the putrefactive process otherwise indications of this would be in the urine. It is therefore likely to be due to the agent. It is probable that the agent concerned in splenomegaly is a member or members of the typhoid group of bacilli. One is inclined towards this view because of (a) the the selection of the lymphoid tissue; (b) persistent diarrhoea; (c) enlargement of the spleen; (d) irregular pyrexia of a typhoid type. It may be that more than one kind of organism is concerned.As for example diarrhoea is a prevailing symptom in splenomegaly which diarrhoea may be due to the paratyphoid bacillus, whilst constipation might be due to the bacillus coli communis which seems improvable owing to the absence of indican in the urine. The probable truth maybe lies in a combination of both with the paratyphoid bacillus predominant.

What is true of bacteria in general is particularly/

particularly true of bacilli of the typhoid group, namely, that the formation of toxins in the living tissue is different to that in an artificial media. It is possible that an 'aggressin' which acting upon the leucocytes diminished their number, whilst the serum complement lyses the red corpuscles and causes a diminution in their number. It may be that the lecithin, a normal constituent in the spleen, activates the serum complement forming a very active toxic substance. Immune bodies are found in the spleen and it is likely that it is the first detoxicating influence which the portal blood meets after leaving the intestine. In the spleen the toxic body is neutralized - partially or wholly - and some of its constituents fixed by the connective tissue by some unknown chemical affinity. This affinity has been shown by Donitz and Heyman with tetanus and Wassermann Takaki in nerve tissue. The tissue which fixes the poison and thus neutralizes it is thus probably rendered inactive so that the organ is deprived of its influences and capacities: a constant and slow proliferation of tissue goes on since the stimulating influence is present in small amount and if so the demand is met with consequent enlargement of the spleen. The leucocytes in the splenic sinuses and the haemorrhages from the trabeculae both signify the presence of a toxin other than that fixed by the connective/

connective tissue cells. A probable explanation of these toxins is that into the portal system you have an absorption not alone of the extracellular toxins but the intracellular as well by lysis of the dead bacteria of the typhoid group.

Conclusion.

The primary cause of splenomegaly would seem to be a gastro-enteritis with repression of the glandular digestive activities. In many cases the gastro-enteritis is brought about by great mental strain. The changed stomach and bowel condition sets up fermentative and putrefactive processes giving rise to vomiting, flatulence, distention and colic pain, flatus, diarrhoea, frequent micturition. The putrefactive processes are set up by Bacilli of the typhoid group which are facultative anaerobic and thus will draw oxygen from the surrounding tissue such as haemoglobin and be thus the cause of a slight chlorosis. The intra and extra cellular toxins enter the portal vein and mixing with the portal blood enters the spleen. Some constituent is fixed by the connective tissue cells there and neutralized. The 'aggressin' element destroys the white blood corpuscle and the serum complement the red blood corpuscle.

The destruction of the red blood corpuscle alters the viscosity of the bile in the smaller bile ducts and/

and produces haemohepatogenous jaundice. The escape of the toxins into the general circulation alters the lining endothelium of the vessels and the coagulability of the serum of the blood so that you have haemorrhages especially from the ill-supported mucous membranes. The irregular pyrexia means an irregular toxaemia. The poisoning process may be repeated in the liver with atrophy of the liver cells and ultimately ascites from portal pressure.

Removal of the spleen throws into greater activity all lymphoid tissue of the body which may or may not increase. If it does not increase then in all likelihood this tissue is equal to the toxic qualities present. If it does increase it may be due to greater glandular capacity but more likely to a connective tissue hyperplasia such as is found in the spleen and liver and which brings splenomegaly in close similarity or proximity to Hodgkin's disease.

Finally. Idiopathic splenic enlargement. Banti's disease and splenic anaemia are one and the same disease, all being dependent upon a bowel toxaemia and differing only in the degree and intensity of the putrefactive processes in the bowel.