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THE CAUSES OF THROMBOSIS OF THE PELVIC VEINS IN PUERPERAE.

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by

John Tennant, M.A., M.B., C.M.

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HISTORICAL.

The literature of this subject begins in the latter part of the eighteenth century. Before that "white swelling" can hardly be said to have been recognised as a distinct disease but was included with the dropsies of cardiac and renal origin in the current classifications of disease. By Smellie[1], in his text book, it is not mentioned at all among puerperal diseases but already in his day the outlines of the disease in question were coming into view among the misty distances of pathology. Although Davis[2] in 1823 first clearly explained the condition, as early as in 1753 Zinn had given a good description of its clinical course, recognised it as a distinct entity and had just missed its pathology almost by an accident. I propose to quote Zinn's description of his case, which is a model of clearness and insight, and before doing so bring forward a fragment of a lecture by Hunter[4] which has been preserved (White) and which illustrates the views prevalent at Zinn's time and for forty years after it. "They have imputed the swelled limb that happens after lying in to a Depôt de Lait, but it is not; for something is wrong in the constitution; the patient is seized first with pain in the groin, the pulse becomes smart and the part becomes tender, this pain and tenderness get gradually lower down and the muscles/

muscles are stiffened into hard lumps and an oedema gradually succeeds the inflammatory swelling. It is generally called a cold, but it is not. In some it is over in a short time. In others it will last some months. It generally does well." Puzot (quoted by White) in a posthumous work published in 1759 describes the disorder accurately under Article "Depôt laiteux sur la Cuiffe". To return to Zinn - his observation was published in 1753 in the Commentaries of the Royal Society of Sciences at Gottingen, Vol. 2, p.364, Gottf. Zinni, Sodalis extraordinarii, observationes in corporibus morbosis - observatio 1 - Oedema pedis ex pressa vena crurali:- "A woman, nearly 30 years of age, after a difficult labour and in consequence of careless conduct, suffered much disturbance of her lochia. Her right leg was seized with an oedematous swelling which extended from the groin to the heel and enlarged the right labium pudendi. At the same time she was seized with loss of appetite.

Every possible means afforded by the art of healing was used to remove the swelling, but without success. Neither diaphoretics nor purgation nor diuretics gave any relief and fomentations and friction excited the most violent pain. An incision was made through the cutis of the thigh that the water might be drawn off by an issue, but only a few small drops were discharged by it. The serum in the cellular membrane assumed in some sort the nature of a tremulous gelatine, all the more/

more fluid part of it being resorbed. At the end of two months the patient died asthmatic".

This was evidently a case of femoral thrombosis with pulmonary embolism.

At the end of the eighteenth and beginning of the nineteenth century two English physicians made attempts to elucidate the disease, which show a critical understanding of pathology and anatomy and cannot fail to commend themselves to modern students. Unfortunately neither of these ingenious writers had an opportunity of verifying their hypothesis by dissections and so both missed the essential element in the explanation.

White[5], after discussing the previous literature, including Zinn's case, described fourteen cases which had come under his observation in the Manchester Lying-in Hospital or in private practice, of which thirteen were typical cases of white swelling, two having also pulmonary embolism and another severe constitutional symptoms suggesting pyaemia. He then discusses its diagnosis from sciatica, rheumatism, phlegmon, erysipelas and abscess, and shows that it does not come from defect of lochia nor redundancy or deposit of milk or metastasis of matter, and reaches the following conclusions:- "(1) That the proximate cause is an obstruction, detention or accumulation of lymph in the limb: (2) that the lymphatics are obstructed as high at least as where they enter the pelvis/

pelvis under Poupart's or Fallopian's ligament, since every part is much swelled to which the lymphatics which are beneath that part extend, as the groin, labium pudendi, thigh, leg and foot of one side, and every conglomerate gland is painful, such as those in the groin, hams and back of the leg: (3) that the lymph so obstructed is in a sound state: (4) as the disorder happens only to lying-in women and affects the lower extremity only, we may conclude that this obstruction is occasioned by some accident happening at the time of labour or from some state peculiar to child-bed. Though the proximate cause appears very evident, perhaps the remote cause may not be so clear and probably will not be precisely ascertained till it be proved by dissection." He then discusses the anatomy of the lymphatics of the lower limb, of which he gives illustrative engravings, and dismisses the conjecture that the swelling is due to pressure of the child's head on the pelvic lymphatics or that it is due to rupture of the peritoneum or Poupart's ligament with cicatricial contraction and pressure on the lymphatics "as they would likewise compress the crural veins which does not appear to be the fact" and adopts the explanation that supposing the lymphatic vessels to be obstructed by the pressure of the child's head during labour, "while the lymph is driven on through the valves by the pulsatile contractions of the coats of its vessels, by the great exertions of the muscle and the strong vibrations of the inguinal/

inguinal artery, which are greatly increased by the labour pains, the lymphatic vessel - - - must at last burst", and be subsequently obstructed by the cicatrix in its wall. "If the above hypothesis be true, the disponent cause may in all probability be a weakness of the coats of the lymphatics in such subjects as have the main vessels formed into one principal trunk under Poupart's ligament."

White wrote another pamphlet on the subject in 1807, principally for the purpose of replying to various criticisms, to which task he brought greater animation than is usually displayed in the search for scientific truth of the present generation. In addition to polemics, this second paper contains a number of interesting clinical reports and a statement that out of 8000 women delivered under his observation at Manchester Lying-in Hospital or in their own homes, four had phlegmasia dolens, that is 0.06%: Junge[6], ~~wr~~ writing statistics for various German speaking cliniques, gives 55 cases of thrombosis of any sort in 89,317 labours = 0.06%. Junge's figures of course include slight cases which produced no swelling. Boissard[48] in 1901 reported 16 cases of phlegmasia in 4000 labours. In 1792, Charles Brandon Tyre[7] put forward another hypothesis that the condition is due to pressure on the iliac vein by swollen and inflamed lymphatic glands, and described a number of cases.

Davis/

Davis[2] published his views in 1823. After discussing current views on the pathology of the disease he proceeds:- "It shall be my object to prove that the proximate cause of the disease called Phlegmasia Dolens is a violent inflammation of one or more of the principal veins within or in the immediate neighbourhood of the pelvis, producing an increased thickness of their coats, the formation of false membranes on their internal surfaces and gradual coagulation of their contents, and occasionally distinct suppuration of their whole textures, in consequence of which the diameter of the cavities of these important vessels become so greatly diminished, sometimes totally obstructed, as to be rendered mechanically incompetent to carry forward into their corresponding trunks the venous blood brought to them by their inferior contributory branches". He then gives the clinical histories and post mortem appearances of three cases, all sufficiently typical, of which I shall give a resume of the first.

Case 1. Delivered February 7th, died March 4th with swollen left leg and thigh; death preceded by ingravescent symptoms of general infection. Post mortem appearances noted by Mr. Lawrence. "Left lower extremity presented a uniform and oedematous enlargement, without any external discolouration, from the hip to the foot ..... The inguinal glands were a little enlarged ..... The femoral vein, from the ham upwards/

upwards, the external iliac and the common iliac veins, as far as the junction of the latter with the corresponding trunk of the other side, were distended and firmly plugged with what appeared externally to be a coagulum of blood. The femoral portion of the vein, slightly thickened in its coat and of deep red colour, was filled with a firm red coagulum closely adhering to the sides of the tube, so that it could not be drawn out..... the trunk of the profunda was distended in the same way as the femoral vein, but the saphena and its branches were empty and healthy. The substance filling the external iliac and common iliac portions of the vein was like the laminated coagulum of an aururismal sac, at least with a very slight admixture of red particles.....but in its centre was about a teaspoonful of thick fluid of the consistence of pus, of a light brownish tint and pultaceous appearance".

Davis's explanation is "All the parts liable to much pressure or to enlargement of diameter during pregnancy appear to be more or less predisposed to inflammation upon the sudden removal of these agencies by the consummation of the act of parturition. Hence the predisposition especially to hysteritis and peritonitis during the first week after labour and to swelled leg and mammary abscess at a later period". The next advance was made by Robert Lee[8]. In his paper he described five cases of Phlegmasia Alba Dolens, in all of which he diagnosed femoral and iliac phlebitis, and/

and the dissection in ~~the~~ a case where death ensued at a subsequent labour fourteen months after the onset of the phlebitis. Here he found that the femoral and iliac veins were converted into a ligamentous cord and the entrance of the internal iliac was completely closed. On the fly leaf of the copy of the pamphlet in the library of the Royal College of Physicians of Edinburgh is a manuscript note signed by Robert Lee, and dated June 27th, 1829, "I have ascertained beyond a doubt that the disease commences in the uterine branch of the hypogastric or internal iliac veins and extends from thence to the iliac and the great venous trunks of the lower extremities. Uterine phlebitis and Phlegmasia Alba Dolens are therefore modifications of the same disease. From two cases which have occurred since the publication of the preceding memoir and where an opportunity was afforded me of examining the parts after death".

In the following year (1829) he published another paper showing conclusively that Phlegmasia Alba Dolens is a phlebitis arising in the uterine veins and extending into the iliac. He quotes a dissection which is of so great interest in connection with pelvic thrombosis that I take this opportunity to transcribe it:- "A case of obliteration of the vena cava and its principal branches after parturition, has been recorded by Mr. Wilson, where the inflammation which had produced the morbid state must have arisen in the uterine veins/

veins. The coats of the emulgent veins and of their branches were thickened and their cavities obliterated completely, as were the primary iliac veins until they had nearly reached the groin, and the internal iliac veins with most of their branches, particularly those which returned the blood from the uterus. The uterus was much larger than usual, the coats of its principal veins were thickened and their cavities practically obliterated. The small branches, both in its substance and in its internal surface, were very numerous and much distended with blood. The vessels of the lower extremeties were in a perfectly healthy condition; no accumulation of the blood had taken place in the veins nor had any watery fluid collected in the cellular membrane. The anastomosing branches of the veins on the sides and back parts of the pelvis were much enlarged, as were also those between the saphena major and the branches accompanying the deep seated arteries passing through the foramen magnum ischii and the great sciatic notch. Large communications existed between the venae pudicae externae and the lower branches of the inferior mesenteric vein, which was enlarged to treble its natural size; the veins coming from the sinuses of the dura mater, in the vertebral canal, the sinuses themselves and the communications between them and the sacral and lumbar veins were, by the blood contained in them, rendered very apparent. The lumbar veins anastomosed with the vena azygos, which was three

times/

times its natural size." In this case there was no swelling. James Hope[9], writing in 1841, adopted and amplified the views of Lee, of whose papers and illustrations in fact he made very free use. "Inflammation of the veins or uterine phlebitis, when its frequency as well as its destructiveness is considered, may be regarded as one of the most formidable affections of the puerperal state. Coagula of the fibrin of the blood, often extending a considerable distance into the uterine veins, are found in the orifices of these vessels after every labour, and are the principal means employed by nature for the permanent suppression of uterine hemorrhage..... Now when the placenta is detached and the coagula first form, the veins are in the same relative circumstances as the stump after amputation; in the same way, therefore, there extremities may inflame and the inflammation may be propagated upwards. Some have supposed that exposure to the air is the cause of softening ..... But a more powerful cause is certainly to be found in the exposure of the lacerated ends of the veins to the putrid matter formed by decomposition of blood or fragments of the placenta. Inflammation, once established in the uterine veins, is seldom confined to them but runs along their continuous membrane to the spermatic and hypogastric veins, involving the Fallopian tubes, the ovaria and the broad ligaments in its effects. Thence it may extend to the vena cava/

cava itself, to its principal branches returning blood from the lower extremities and occasionally even to the veins and substance of the kidney..... The anatomical characters of uterine phlebitis are as follows. The coats of the veins are thickened and the cellular tissue investingthem becomes hypertrophied and greatly condensed. Sometimes the muscular tissue immediately around a vein, participating in the inflammation, is infiltrated with deep red or with chocolate coloured blood and is greatly softened..... On opening the vein we find the following succession of degrees of phlebitis which, in the opinion of Cru Gurveilhier, are constant in every case. (1) Concretions of pure blood adhering to the venous parietes: (2) concretions more or less discoloured, the centre of which contains pus, at first sanious afterwards laudable; when the layer of concretion is thin, it has the appearance of false membrane lining the tube: (3)absence of all concretions, and pus, either sanious or laudable is in immediate contact with the thickened and wrinkled vein: (4) erosion and laceration of the venous parietes allowing the pus to escape around and present the appearance of an ordinary abscess in which the lacerated vein can with difficulty be detected.

The cause of this series admits of a simple and satisfactory explanation. When a vein inflames, the first effect is coagulation of blood in the affected portion. If resolution takes place, which is by no means/

means uncommon, the coagulum is absorbed and the calibre of the vessel is either reopened or it remains permanently obliterated. But, if suppuration is established..... so long as the pus is retained in the interior of the concretion, the symptoms are local, but when by the destruction of the concretion the pus comes in immediate contact with the vein, one of two things happens. Either the pus remains isolated by means of sanguineous concretions plugging the two ends of the inflamed portion of the vein - in which case the pus is sometimes absorbed and the vein obliterated and sometimes it progressively accumulates, distends the vein and causes erosion and rupture of its walls; or, the portions of concretion which acted as plugs are slowly undermined by absorption and at length carried away by the torrent of the surrounding liquids. The pus is then intermingled with the blood and simultaneously appear typhoid and fatal symptoms."

Various forms of the lymphatic theory still found supporters after this date (e.g. Kiwisch von Rotheraw[10] "Die Krankheiten der Wöchnerinnen" Prag. 1840, W.A. Freund[11] "Gynak Klinik", Strassburg, 1885). Indeed many most recent writers are careful not to abandon it entirely (Olshausen[12]). But Hope's handbook not only completed, but stamped as official, the theory of Davis. Practically no further advance in the knowledge of pelvic phlebitis was made until the study of lacteria was instituted.

In/

In this thesis I propose to discuss puerperal thrombosis, but chiefly from the pathological standpoint. The clinical side of the subject presents many important problems, notably the question of prophylaxis, but these can be dealt with most advantageously by clinicians who have a large mass of material to draw conclusions from. Pathological interest in the subject has increased of recent years since many obstetricians, on the suggestion of Trendelenberg[13], have adopted surgical measures for the treatment of pyaemic phelbitis in puerperae and the question of the parasitic or mechanical causation of benign thrombosis has attracted notice of very many investigators, both clinicians and pathologists. The mechanical conditions of blood circulation in the pelvis, and particularly in the uterus, are influenced by anatomical considerations which are not found in other parts of the body and I wish to give an account of these before discussing the other aspects of the subject.

ANATOMICAL.

The pelvic veins generally have recently been the subject of a special illustrated monogram by Konatski[14], and those of the uterus and bladder respectively have been dealt with by Fenwick and Nagel[15]. The intramural veins of the uterus have been injected and described, among others, by William Hunter[16], Hyrtl[17] and Nagel[15]. The pelvic visceral veins differ from those of other viscera in that they all communicate with the veins of the perineum and with those of the adjoining organs. Thus the veins of the bladder form a plexus with the dorsal vein of the clitoris in front and with the vaginal veins behind, while they drain into the uterine veins. In the same way the haemorrhoidal veins anastomose with those in the posterior wall of the vagina and also with the plexus in front of the sacrum, and the blood from the vagina and rectum drains both downwards into the perineum and upwards into the pelvis. As the intra pelvic veins are devoid of valves this arrangement appears to be a generous provision for the drainage of viscera whose proper veins are thrombosed.

Apart from small anastomotic channels such as the chain of veins along the ureters, the following routes present themselves for the passage of blood upwards from the true pelvis.

1. The obturator vein receives twigs from the pudendal plexus and communicates freely with either the external iliac or the inferior epigastric vein.

2./

2. The ovarian veins.

3. The hypogastric vein.

4. The superior haemorrhoidal vein.

5. The anterior sacral venous plexus.

It is not usual to find a definite venous trunk corresponding to the lateral sacral artery. I have found, as a fairly constant arrangement, that accompanying on its right side the medial sacral artery is a small vein which opens above into the Inferior Vena Cava. Its rootlets form a plexus of fine twigs in front of the bone which communicates with the haemorrhoidal veins and with two large branches which pass from the gluteal vein through the 2nd and 3rd anterior sacral foramina. These branches establish a free communication between the pelvic veins and the intra spinal and posterior spinal venous plexuses. The higher of these two branches joins the gluteal vein on its posterior border at the same level as the inferior uterine vein joins it in front, and in cases where the uterine and hypogastric and common iliac veins are blocked on one or both sides, these communications appear to be of the greatest importance. A case of the kind was described by Wilson (see page 8) where evidently these vessels and the superior haemorrhoidal had become large enough to convey most of the blood from the pelvis and lower limb. In all cases of obstruction of the internal iliac vein on one side, these vessels seem the readiest/

readiest channel for all the parietal pelvic veins; in the viscera the venous anastomoses are so free that the blood may be readily conveyed to the other side of the pelvis. In order to make the matter as clear as possible, I have appended a drawing of these veins, which are constantly present (Fig.1). In some cases a third communicating branch passes through the first anterior sacral foramen. So free is this anastomosis, that in a pelvis which has been removed from the body, fluid injected into the large veins at the brim of the pelvis spirts out of the veins in the vertebral canal. Konatski remarks that he has seen the pelvic veins filled with injection introduced peripherally into the internal jugular vein which had travelled by this route.

Uterine veins. I have injected and dissected those veins in five adults and five foetuses and growing children. They are not quite constant in their distribution and relations.

The blood vessels of the pelvis lie in the sub-peritoneal tissue, a fibrous tissue containing, in fat persons, a moderate amount of fat. In the upper and anterior part of the pelvis this tissue is loose and easily torn and has no strong bony attachments. But in the lower and hinder part it is developed into a very strong and well defined fibrous layer which is strongly attached to the border of the sacrum. The utero sacral ligaments are part of this tissue but are not any stronger than the surrounding sheet. This fascia/

fascia is quite distinct and readily separated from the pelvic fascia proper, from which it is separated by the blood vessels. It is a subperitoneal fascia. In front of the ureter it is much weaker. It is continued upwards with the inferior uterine vein into the neighbourhood of the cervix uteri and to the broad ligament, adjacent to the side of the uterus. The outer part of the broad ligament is occupied by the bladder, when it is distended, and contains a very loose and feebly developed fascia. In the absence of fat there is practically nothing but two layers of peritoneum. The extremely dense connective tissue in the inner part of the broad ligament, which may also contain fat, is continuous with the walls of the uterus and cervix and it is quite impossible in dissection to say where one stops and the other begins. In it lies the broad ligament plexus of veins, called by Spalteholtz and Konatski the utero vaginal plexus. It does not, as Spalteholtz says, surround the ureter but lies internally to and behind it, though one of its efferents, the superior uterine vein, lies in front of the ureter. There is no difficulty in separating the plexus from the ureter, which is only bound to the cervix by the loosest of connective tissue. The parametrial veins are very difficult to separate from one another and from the lateral margin of the uterus. They constitute a mass of tortuous, freely anastomosing veins closely matted together by strong fibrous tissue. In the pelvis/

pelvis of a woman, aged 59, I found these somewhat simpler in their arrangement, but in another, aged 57, they were quite complicated and I have not had an opportunity of making a comparative study of them at different ages. In foetuses and young children there is no plexus but one or two venous trunks ascending at the border of the uterus from which they receive a series of straight branches, and terminating in the ovarian vein; the fibrous tissue is not so well developed. The veins which drain this plexus are three, the ovarian and superior and inferior uterine.

Ovarian vein. It must be clearly understood that this vein and the inferior uterine vein form one continuous channel. For convenience the ovarian vein is described as starting near the upper cornu of the uterus. It is formed by the junction of two stems, one, the outermost member of the parametric plexus, opens below into the inferior uterine vein, ascends for about an inch receiving branches from the broad and round ligaments and uterine wall, and unites just behind the insertion of the round ligament with a large vein which passes horizontally out of the uterine wall behind the uterine tube and amastomoses very freely with the corresponding vein on the other side (injection passes directly across from one ovarian vein to the other). The stem thus formed passes outwards for about an inch to the hilus of the ovary, close to which it divides into an upper and lower branch. These two branches/

branches as a rule both receive branches from the ovary, short stems, four to six in number, with which they form a loose plexus. In some cases the upper branch alone drains the ovary. The upper branch receives several twigs from a vein which arches along the mesosalpinx and communicates at its extremities with the uterine and ovarian veins. The ovarian veins lie directly behind the ovary. Thence they pass upwards and over the brim of the pelvis as two or three trunks which unite into one before entering the renal vein or inferior vena cava.

Superior uterine vein. This vessel is rather inconstant. In two out of five adult pelves I have found it absent and in all of them it is much smaller than the inferior uterine vein. It commences near the lateral margin of the neck of the uterus by the union of a large branch from the vesico-vaginal plexus with a branch of the inferior uterine vein. It runs outwards and upwards in company with the uterine artery, receiving small tributaries from the side of the bladder and from the ureter which it crosses in front. It accompanies the uterine artery as far as the internal iliac artery, passes backwards behind the latter and opens into the internal iliac vein near the level of the first anterior sacral foramen.

Inferior uterine vein. Commences opposite the isthmus uteri by the confluence of a number of branches. Three or four large trunks issue from the side of the uterus between/

between the levels of the round ligament and the internal os and with the inferior root of the ovarian vein form the plexus I have described, which occupies chiefly the concavity formed by the isthmus uteri. The uterine vein passes outwards and downwards behind the ureter and receives branches from the back of the cervix and vagina and one from the vesico-vaginal plexus; these both ascend by the side of the cervix. It also communicates near the cervix with the anterior uterine vein. After coursing across the pelvic floor downwards, backwards and outwards, it opens into the internal iliac vein between the levels of the second and third anterior sacral foramina.

The vesico-vaginal plexus may also send branches directly to the internal iliac vein which they enter below the uterine veins. There may also be separate branches from the vagina and bowel (vaginal and middle haemorrhoidal veins). One or more of the vesical, vaginal and middle haemorrhoidal veins may be absent.

The distribution of the intramural veins of the uterus is difficult to ascertain by ordinary dissection methods. The vessels do not run in septa of connective tissue, but their coats are incorporated with the fibres of the uterus and can hardly be separated from them. The vessels of the puerperal uterus cannot be injected, as the injection runs out at the placental side.

Several anatomists have written descriptions of these/

these veins. They are divided into three layers, an outer or subperitoneal layer of small vessels, an inner submucous layer also of small vessels, and in the muscular wall the ~~layer~~ larger parenchymatous veins. The anastomoses of the uterine arteries are very abundant. Hyrtl[17] says of them "There is no organ in the human body in which there is so rich a supply of anastomoses to provide a uniform distribution of the blood to all parts. The same might be said of its veins." William Hunter[16] describes the veins of the pregnant uterus in the following words:- "The veins of the uterus would appear to be still more enlarged in proportion than the arteries. The spermatic and hypogastric veins in general follow the course of the arteries and, like them, anastomose on the side of the uterus. From thence they ramify through the substance of the uterus, running deeper and deeper as they go on without following precisely the course of the arterial branches. They form a plexus of the largest and most frequent communication which we know of among the vessels of the human body. And this they have in common with the arteries, that their larger branches go to or rather come from that part of the uterus to which the placenta adheres, so that when the venous system of the uterus is well injected it is evident that that part is the chief source of the returning blood. Here, too, both the large and the small veins are continued from the placenta to the uterus and are always/

always necessarily broken upon the separation of these two parts. The veins are without valves and are therefore easily injected. In injecting we observe that at first they become turgid and project on the surface of the uterus, but in proportion as we throw a greater quantity of wax into these vessels, they grow more flat and obscure because the uterus itself becomes more filled and tense, which has the effect of compressing the veins that run in its substance".

In this connection I noted in a foetus whose uterine veins I injected, that that organ was swelled to twice its natural size and yet on microscopic examination many veins were seen into which the injection had not penetrated.

Hyrtl publishes a beautiful drawing of a dissection of injected veins in a pregnant uterus prepared by corrosion with hydrochloric acid. The larger branches run transversely. The veins are so abundant as to appear everywhere in contact with one another. He says that two "colossal" veins run down the lateral border of the uterus, their diameters being 4 and 5 c.m. respectively, and unite below into one trunk. They divide irregularly into a number of coarse penetrating vessels, which ramify with tortuous anastomosing channels in the middle layer of the uterus, and quite obscure the arteries. In the mucosa the plexus is of smaller vessels, even at the placental site. The veins run for the most part transversely in the uterine wall.

In/

In view of the measurements he gives of the parametrial veins, it is noteworthy that he finds the uterine arteries in pregnancy increased to double their diameter, that is four times their capacity. Comparing Hyrtl's measurements of the lateral veins in pregnancy with my own observations of the same in the resting uterus, I should say the diameter of the latter is increased three times and therefore their capacity not less than nine times. Hyrtl also calls attention to folds and grooves on the surfaces of the veins which he takes to be an indication of valves which he thinks do not functionate.

Nagel presents a greatly reduced drawing of injected veins in a pregnant uterus. Those which he exposes all run vertically from the fundus towards the isthmus, where they emerge. They present numerous transverse anastomoses. Hyrtl's figure is of the veins as seen from behind, Nagel's from the side, which may account for the differences in their distribution. Nagel also represents grooves on the surfaces of the veins.

Both authors state emphatically that the veins, when injected, are flattened horizontally, ribbon like, not rounded. Nagel does not represent the parametric veins as so large as Hyrtl found them, nor those in the parenchyma as so abundant.

The veins which Hyrtl represents in the parametrium of the gravid uterus are straight, but of course in the/

the puerperal condition will be tortuous.

Finally, all writers are agreed as to the absence of competent valves in all the pelvic veins. In a recent paper Clarke[18] discusses the veins of the uterus. He examined microscopically a large number of uteri from foetuses, children and adults, and also those of animals. He considers the mesometrium so vascular as to constitute an erectile tissue like that of the corpora cavernosa. I give some of his conclusions in his own words:-

3. During infancy a cavernous condition exists in the mesometrium and by arterial invasion of the venous spaces the condition of the adult uterus is attained.

5. The cavernous tissue of the mesometrium is similar to that which exists in erectile tissues, e.g. corpora cavernosa, also to the spongework in the foetal heart of man and the adult heart of some amphibians.

6. The venous spaces in the cavernous tissue of the human uterus are not obliterated but remain as potential rather than actual spaces. They have a delicate endothelial lining and external to this is a fibrous connective tissue layer. They are concerned in erection of the uterus and in the formation of maternal blood sinuses during pregnancy.

The anatomical points concerning the intrauterine and parametric veins to which I wish particularly to call attention are their large size as compared with the arteries and with the veins they drain, the great number/

number of the channels and their abundant anastomoses and tortuosities, all of which are factors leading to slowness of circulation or actual stagnation in parts of the network.

Most important observations on the condition of the parietal pelvic veins in the puerperium are made by Webster[19]. He gives a series of drawings of frozen sections of the upper part of the pelvis in the earlier stage of the puerperium. During the first four days the uterus is represented as moulded all round to the contour of the bony pelvis. It seems to fit it like a cork in a bottle. The broad ligament is invisible and its plexus of veins must be subject to pressure. The ovarian veins are raised out of the pelvis and free. The internal iliac vein is flattened. Webster says "In a pelvis of average size at the beginning of the puerperium, the uterus fills the greater part of the pelvic cavity and compresses the extra uterine tissues. This compression is specially marked between the uterus and the bony wall, and to a much less extent inferiorly owing to the softening and relaxation of the fascial and muscular tissues of the pelvic floor. In consequence of this condition of the parts, the intra-pelvic parts have their blood circulation interfered with to a considerable extent, those parts of the pelvic floor which are least interfered with, viz., the sub-pubic tissues, vaginal walls and perineum, being congested/

congested, the tissues between the uterus and the pelvic wall, however, being anaemic, having their vessels closed or nearly closed." Evidently during the early puerperium there is a great mechanical hindrance to the escape of blood from the lower part of the broad ligament plexus and from the veins in the floor and side of the pelvis. In the drawings of the pelvis after the fourth day the close apposition between the sides of the uterus and the wall of the pelvis is no longer evident."

PATHOLOGICAL.

It is necessary to preface the discussion of puerperal thrombosis by an account of the views of pathologists on intra-vascular clotting generally; when a general agreement exists, a short restatement will be enough, but on some parts of the subject divergencies of opinion exist and here more detailed consideration appears to be called for.

Many haemolytic and destructive agents pròduce conglutination or precipitation of the elements of the blood, but these processes are mostly artificial and are not directly related to the present question, for which there exist two kinds of coagula, the white and the red. I have thought it better to avoid the expression hyaline in this connection, as authors use it in different senses.

Red blood clot consists of all the solid elements of the blood entangled in a network of fibrin filaments. Of course the essential element in its development is the formation of fibrin, an insoluble proteid which does not exist as such in the blood. When clotting occurs, fibrin separates from the plasma in threads which entangle the corpuscles. If the corpuscles are kept in rapid motion during fibrin formation (as by whipping the blood) most of them remain free from the clot and float in the serum. It is believed that the blood/

blood normally contains a substance prothrombin which is "fibrin ferment" in an inactive condition. The prothrombin is derived from the white blood corpuscles, possibly from platelets. The substance which activates it is thrombo-kinase which is also a product of the disintegration of leucocytes and perhaps of platelets. When both these substances are present, thrombin or fibrin ferment is formed and converts the fibrinogen of the plasma into fibrin. This reaction only occurs when calcium salts are also present. It is obvious that thrombokinase must be constantly forming in the blood or entering it in consequence of the death of leucocytes and such traces of it are neutralized by an antithrombin which enters the blood from the liver. Clotting of the circulating blood is quickly effected by injecting a considerable dose of ferment containing fluid into a blood vessel, but a small dose is rapidly brought into contact with antithrombin by the circulation and so neutralized. Thrombokinase, or a body which exerts the same action, has been prepared from many other tissues, and some writers speak of it as a disintegration product of practically all cells.

Red clot does not form in circulating blood, except experimentally, on account of the presence of antithrombin, but the supposition of Virchow, that stasis alone is a cause of clotting, was controverted by Lister and Baumgarten, who, independently, proved that a vein could be ligatured in two places without coagulation/

coagulation occurring for many days in the isolated mass of blood, provided the dissection was carried out aseptically and without seriously interfering with the nutrition of the vein. Bardeleben[20], however, found that if the ligatures are applied so as to have the vessel wall stretched by the contained blood, coagulation sets in in a day or thereabouts. It is supposed that the thrombokinase is liberated from cells in the wall of the vein damaged by pressure. The present opinion is that intravascular formation of red clot only occurs in stagnant or greatly retarded blood and only in the presence of thrombokinase. It is a strictly chemical process.

On the other hand, the formation of white clot is by many distinguished as a strictly mechanical process with which fibrin formation has in the first instance nothing to do. This aspect of the matter is dwelt on with insistence by recent German writers (Aschoff[21], Ferge[22], Klein[23], Zurhelle[24] and others), while it is a distinction which is treated with great reserve by some English-speaking authorities (Welch[25] and Boycott[26]). The first point upon which there is a general agree~~argu~~ment is that thrombosis does not occur so long as the vascular endothelium is intact.

The true nature of white clots was first made clear by Bizzozero[27]. His researches have been followed by many others, notably those of Eberth and Schimmelbusch[28] and/

and recently by Aschoff[21] and his pupils in Freiburg. The latter describe the formation of a thrombus roughly as follows:- It is a branching structure, compared by Aschoff to coral or resembling in its arrangement a villous polypus; it adheres by its thickest part to the vessel wall while its round tapering filaments float freely in the blood-stream. These filaments are attached to all sides of the main stem and in their turn give origin to secondary branches. This part consists entirely of blood platelets by the further accretion of which the filaments become longer and thicker. Between the filaments the blood continues to flow until they are so closely matted together as to obstruct its passage. Leucocytes may adhere to these but Aschoff does not consider them an essential nor an early part of the process. This, which Aschoff calls the head part of the thrombus, at a later stage becomes consolidated and shrinks into a granular mass in which the component platelets are indistinguishable. When the blood stream is partly obstructed by the head, threads of fibrin begin to be separated out and entangle blood corpuscles and a mixed thrombus of white and red parts is formed (the "neck part" of Aschoff). Finally, when the lumen of the vessel is quite blocked, a red clot forms and grows backwards along the vein to the next membrane (Aschoff's "tail"). Beyond the clot, centrally, the vessel may be found empty or again a red clot may form as far as the next branch. In disease, particularly/

particularly when the blood pressure is low, the clot frequently continues to extend in both directions and with extraordinary rapidity. The mechanism is as follows:- The stagnant blood beyond the thrombus coagulates centrally up to the next junction where the conical extremity of the clot is in contact with the sluggish blood stream and becomes covered with platelets until the vein is blocked. More red clot then forms centrally up to the next junction of veins when platelets are again deposited on it and so the process goes on. Aschoff, and all the recent German writers whose works I have consulted, constantly insists that the blood platelets are the one essential element of a white clot. On the other hand, as recently as 1909, W. H. Welch[25], who has made a special study of the subject, and Rolleston maintain that at a very early stage leucocytes and fibrin and even red blood corpuscles may be added, though the platelets constitute the primary deposit. The platelet masses are usually surrounded by a ring of fibrin, the thrombokinase having its origin from decaying platelets or leucocytes. "Does the recognition of the described mode of development of a thrombus necessitate a radical break such as that made by Eberth and Schimmelbusch with the old and still common conception that a thrombus is still essentially a blood coagulum? This question applies only to the first stage of the formation of a white thrombus/

thrombus for the completed thrombus is still essentially a blood coagulum. It is, however, both of scientific and practical interest to inquire whether the coagulation phenomena usher in the process of thrombosis or are merely secondary. A decisive answer to this question cannot be given until we are better informed than at present concerning the chemistry and morphology of conglutination processes and the sources and properties of the granular material constituting the youngest thrombi." "Leucocytes, though they do not usher in the process of ordinary thrombosis, make their appearance at an early stage and often accumulate in such numbers as to constitute a ~~layer~~ large part of a thrombus." "Intravascular plugs occur which are made up wholly or predominantly of polynuclear leucocytes. These are formed mainly in small vessels in acutely inflamed regions where they are to be regarded as inflammatory and probably chemiotactic in origin. Boycott[26], as recently as 1912 when Aschoff's work was all published, says "We may take as an example the case where thrombosis of a large vein occurs in consequence of a local injury to the endothelial lining. The first change appears to be a local accumulation of particles resembling platelets at the seat of injury..... Leucocytes are soon added to the mass and fibrin then becomes recognizable. By the further accumulation of leucocytes and separation of fibrin the thrombus quickly grows..... The more rapid the process the more red cells will be entangled/

entangled." "The essential abnormality which underlies the conditions which favour the occurrence of thrombosis is in all probability an excess of thrombokinase at some point in the circulation. The common way in which the excess is produced is an injury to the vessel wall. This injury can be produced in a variety of ways..... Bacterial poison can produce the same effect. Vessels, especially veins which are involved in an area of acute inflammation, often become thrombosed in sequence to the invasion of the vessel walls by the causative organisms, and destructive inflammation of the cardiac valves by the rheumococcus is regularly followed by the deposition of thrombus at the site of injury..... The rapidity of the blood flow is not of itself a causative factor though it may be of considerable accessory importance..... It is not improbable that there are general changes in the thrombogenetic apparatus which make clotting more easy, of a kind parallel to those which in haemophilia produce the reverse effect."

In a passage in the same chapter, the author suggests that the movements of the corpuscles in the blood stream past the fibrin filaments, which ex hypothesi are forming the thrombus, causes them to escape entanglement in it and accounts for its white colour in the same way as the movement given to forming fibrin in whipped blood prevents it catching the corpuscles. In the former case the blood corpuscles are/

are being carried past the fibrin network and so escape, in the latter the fibrin is being carried past the corpuscles by the glass rod or other instrument used to whip the blood; in both the result is escape of the corpuscles and formation of a white clot. But if one considers the pace at which corpuscles are microscopically observed to be travelling in the vein of a frog's tongue, such as is sometimes used for these observations, it will be obvious no comparison can be made between that and the rapidity with which blood is whipped in defibrination. The general sense of Boycott's reservations appears to be sufficiently met by observations of thrombosis in blood which was rendered incapable of yielding its fibrinogen in the form of fibrin. Among others, Schimmelbusch[29] was able to produce platelet thrombus in blood rendered incoagulable by albumose. In Schwalbe's experiment with blood to which luch extract had been added, Sahli and Egnet[30] failed to obtain thrombosis, but Derewinke[31], repeating it, found that thrombosis could be obtained in blood containing just enough luch extract to render it incoagulable but that if an excess of the extract was added the platelets no longer adhered.

Adami and Nicholls[32] appear to accept the view of Eberth and Schimmelbusch. They say "Pure platelet thrombosis - as first shewn by Eberth and Schimmelbusch, if a needle or other foreign body be introduced through the walls of a blood vessel, a thrombus becomes formed. Microscopic/

Microscopic examination shows such a thrombus to be finely granular in appearance. Higher powers resolve the granules into blood platelets. Here and there a leucocyte may be enclosed but the mass consists essentially of blood platelets. Almost insensibly the new granular parts of such a thrombus may pass into a completely fused hyaline mass. There can be no doubt that the majority of white parietal thrombi in the heart and large blood vessels originate thus by an accumulation of platelets."

Welch[25] in 1909, in spite of his own numerous experiments, still thought further observations necessary on the chemistry and morphology of conglutination processes and the sources and properties of the granular material constituting the youngest thrombi. Some of Aschoff's and Ferge's work was published in the same year and a summary of the whole of it in 1912. In 1910 a new and laborious investigation was published by Zurhelle.[23] His method was aseptically and avoiding the use of chemical antiseptics to expose the jugular vein of a rabbit and transfix it with a fine round needle carrying a silk thread (No.00) which was cut short and left in the vein; the wound was then closed and after a varying period the vein was again exposed, doubly ligatured and transferred straight into fixing fluid. The length of the experiment varied from 5, 10 or 20 minutes to one or several days. The vein was embedded in paraffin and serial sections examined. In all cases Zurhelle/

Zurhelle found more or less thrombosis. The earliest traces adhered to the endothelium where the thread passed through it. The thrombi in all cases consisted of platelets and no stainable fibrin was present except in advanced cases. The lacunae between the bars of the thrombus were filled with red cells unaltered, or only very exceptionally showing trivial changes which could be accounted for by pressure. No alterations whatsoever were to be found in leucocytes: "A careful examination of my numerous preparations never showed a trace of breaking down of leucocytes. Nuclei and granules both looked natural and stained well. Leucocytes, when present, were always on the surface of the thrombus bars, not enclosed in the hyaloid masses of fused blood platelets". He insists particularly on the integrity of all the cells, red and white, in the young thrombi, in order to combat the suggested origin of platelets from the disintegration of one or other of them and also the possibility of fibrino-kinase being set free from them. He does not of course deny the participation of fibrin in older thrombi.

These writers appear to make out a good case and I think what they call the purely mechanical theory of thrombosis may be accepted as a working hypothesis. The essential elements of it are a slow blood current and a change in the endothelium of the vessel wall. The obvious illustration of the former is the preponderance of venous over arterial thrombosis (77.5% Lubarsch[34]) in/

in spite of the admittedly greater liability of arteries to disease. In fact in the aorta it is not uncommon to find rough and calcified areas of the inner wall with no recognisable thrombus attached. Numerous arguments in favour of retarded blood stream as an aetiological factor have been adduced but there is no occasion to recapitulate them as no one denies it. The interruption of the axial character of the blood stream by an eddy behind a valve or by a sharp turn has the same effect as general retardation. The explanation of this factor is as follows. The axial stream in any tube is of course the fastest and the rapidity of the current falls towards the edges where, in an infinitely thin layer, it reaches zero. In blood vessels normally the axial stream carries the red corpuscles and platelets while the lighter leucocytes move more slowly in the periphery. Eberth and Schimmelbusch[35] calculated the rapidity of the centre stream as twenty times that of the edge. In this condition, even if the wall of the vessel is rough, platelets will not to any great extent come into contact and adhere to it. If the current is considerably retarded the platelets are also thrown to the periphery and come incontact with any diseased endothelium which may present itself. If the movement ceases altogether, then, it is no longer possible for a constant series of platelets to be carried to the seat of thrombosis and deposited, and the process is interrupted. The second factor, equally

essential/

essential, is a change in the endothelium which may either be shed, leaving a rough surface, or become sticky or rough. Zahn found that a smooth glass rod introduced into the blood current had no effect but that if its surface was roughened it was covered with blood plates. Aschoff did not admit the fatty degeneration of endothelium which occurs for example in anaemia and fever as a cause of thrombosis, but others, such as Ponfick[36], think such endothelium may be swept away as a detritus in the blood current and have a point of thrombosis. Such changes of course are produced artificially by mechanical, chemical and thermal agencies. One of the chief questions at issue is under what conditions may they be produced by bacteria or bacterial poisons.

Other possible factors besides the blood velocity and the condition of the walls are the physical and chemical properties of the plasma and the condition of the blood cells, particularly the platelets.

With reference to the condition of the plasma, the relation of thrombosis to fibrin formation has already been discussed; it is true that fibrinogen is more abundant in the blood in the puerperium, but there is no evidence that this excess is a primary factor in the production of thrombi, though it is readily credible that it will accelerate their extension. Fibrin formation is influenced also by the venosity and the calcium content of the blood. A recent research on the/

the subject of calcium and thrombosis has been published by Brooks and Curwell[37]. They ascertained that they could diminish the coagulation time by one half or lengthen it by one third by giving calcium lactate or citric acid to the animal. Having ascertained the doses and methods of administration which produced this effect regularly, they used in each experiment three rabbits, a control, an animal to which citric acid was fed and one which received calcium lactate.

Experiments:- (a) A length of 3 c.m. of distended marginal ear veins was isolated by compression between artery forceps and compressed and lacerated by toothed forceps for five minutes, when much haemorrhagic extravasation along its course was visible. The forceps were then removed, and in all the animals the circulation was immediately resotred and no thrombosis occurred.

(c) A segment of 2 c.m. of marginal ear vein was isolated and clamped with paper clips for twelve hours, the anastomosing circulation being at the same time prevented. After removal of the clips the circulation was immediately restored in all the animals. After three days, a firm thrombus was found in the calcium lactate rabbit but not in the citric acid rabbit nor in the control.

(d) A virulent culture of pneumococcus was injected in the neighbourhood of the vein so as to compress it. No thrombosis took place in any of the animals.

(e) Five drops of 5% solution of silver nitrate were injected/

injected into the perivenous tissue. Immediate and permanent thrombosis followed in all the animals.
(f) Three drops of turpentine were injected between the branches of the median vein. Within two hours the ear was swollen and inflamed and showed thrombosis of all its veins. The thrombosis was notably more extensive and resolution slower in the calcium than in the control rabbit and in the latter than in the citric animal. The same results followed the use of 5% solution of turpentine in an inert oil.

Experiment (f) only proves that coagulation is more extensive when the coagulation time is reduced by excess of calcium in the blood. Experiment (c) is not conclusive in the absence of a microscopic examination of the veins a few hours after the removal of the clips. The same criticism applies to experiment (a).

The viscosity of the blood has been investigated in relation to thrombosis by Bachmann[38] and by Determann[39]. Bachmann found it increased in pneumonia and tuberculosis, but decreased in typhoid fever. In all these diseases alike thrombosis is common. Determann found the viscosity to vary within wide physiological limits according to diet and exercise, but that there was no relation between it and thrombosis.

On the other hand leucocytosis does appear to favour thrombosis. Franz[40] produced leucocytosis experimentally in animals by the injection of nucleic acid/

acid and then clamped the femoral vein for a few minutes. Thrombosis occurred, but none in the controls.

Beyond these few observations we have no knowledge of how the physical and chemical properties of the blood influence thrombosis.

After a clot, whether red or white or mixed, has formed in a blood vessel certain changes occur. A small mural thrombus may simply be disintegrated and washed away if the conditions cease to be such as conduce to its continued growth, or it may cease to grow and become calcified. Larger thrombi contract and become drier and at an early period adhere to the vessel wall wherever they are in contact with it. This is perhaps attributable to degeneration of the latter consequent on asphyxia and starvation. The subsequent changes depend partly on whether the clot, which may be regarded as a necrotic tissue, is also the seat of microbial growth. If it is not infected, it may be calcified. More commonly it is organized by the growth into it of blood vessels and connective tissue. These adventitious vessels often communicate with the lumen of the obstructed vein before and behind the clot, in other cases spaces formed in the latter by contraction appear to acquire an endothelial lining. In either of these ways the obstructed vessel may reacquire its lumen and be restored to something like its original condition. In other examples organisation only leads to the formation of cicatricial tissue and the final result/

result is a fibrous cord. When organisation is retarded, from any local or constitutional cause, the clot softens in the centre and is converted by what is called an autolytic process into a creamy material. The peripheral part of the clot which is in contact with living blood or other living tissue does not undrop this fermentation owing, it is supposed, to the presence of antilytic substances in the blood. Such a softened clot is of course a possible source of emboli. If a clot is infected organisation does not proceed normally, but it is liquified by the bacteria and at the same time invaded by leucocytes and so results a purulent debris which of course tends to enter the blood stream as larger or smaller infective particles.

EXPERIMENTAL.

A good many attempts have been made to illustrate thrombosis by bacteriological experiments, both in vitro and in vivo. They have been generally unsuccessful. In fact the subacute inflammatory processes of human disease are not easily reproduced in short-lived animals like rodents, which generally either rapidly recover from inoculation or develop a quickly fatal septicaemia. The test tube experiments have consisted in examining the products of bacterial metabolism for blood coagulating substances.

Loeb[41] experimented with plasma obtained by inserting a cannula into a vein of a goose and centrifuging. He diluted the plasma with nine parts of 0.8% salt solution which he found by controls made no difference to the result. To 3 c.c. of this mixture he added a few drops of a culture of the bacillus examined. The culture was always several days old and the medium free from peptone. The mixture was placed in a shallow dish and examined at intervals, being kept either at room temperature or in an incubator. His results were fairly constant. The Staphylococcus Pyogenes Aureus was found to have greatest coagulating power. It frequently caused coagulation of the plasma in from four to six hours. B. Diphtheriae, B. Zerosis, B. Typhosus, B. Tuberculosis and Streptococcus Pyog. had no marked power. B. Coli, B. Pyocy. and B. Prodig. had/

had a little power. He does not regard his tests of B. Tuberc. and Streptococcus Pyog. as satisfactory and suggests that a more virulent culture of the latter might be more active. A sterilized culture of staphylococcus Aureus had lost the greater part of its effect. By controls he satisfied himself that the coagulation was not due to the contact effect of the bacteria as a finely divided foreign body. He considers that there is no fallacy in applying his results to mammals as it is unlikely that the coagulating substance is specific for one animal or group of animals. Finally, he thinks that the substance in question is an enzyme and that this property of bacteria is directly concerned in producing thrombosis in sepsis. Granting that Loeb's interpretation of his experiments is correct, his very wide inferences are much more than the premises will carry. But he does not prove that the coagulum was fibrin at all. Its microscopic and chemical characters are not described. If a ferment was present, then a drop of serum from a successful experiment should have produced a rapid coagulation in another specimen of plasma. This experiment was not tried. I have discussed Loeb's experiments at some length because they are constantly quoted by writers on puerperal thrombosis. The argument is that the soluble products of bacteria tend to coagulate the blood and this argument is handed on from one commentator to another with this paper as a reference. In fact/

fact, in puerperal sepsis, streptococci which Loeb found inert are the chief microbes concerned. This is the only experiment on the subject in vitro.

Talke[42] injected staphylococci not into a vein but into its immediate neighbourhood, and removed the vein at varying intervals for examination. Platelet thrombosis occurred in some cases after eight hours or more. The coccus was never found in the youngest thrombi but in those of twenty or more hours duration. He concluded that the thrombosis was caused not by the cocci directly but by the changes caused in the vessel wall by different products.

Somewhat similar experiments were performed by Lubarsch[34]. He loosely ligatured the jugular vein in two places so as to impede but not to stop the current. Two to four hours later the animal was inoculated with a small dose of bacteria in a vein or a larger dose in the peritoneum. Recent humanized cultures were used in all cases. Thrombosis occurred in 9 out of 18 experiments with staphylococcus pyogenes aureus, much less frequently with streptococci, pneumococci, B.coli and B. Diphtheriae. Controls with dead or filtered cultures were mostly negative. On the other hand, Lubarsch in human pathology observes that where thrombosis occurs in the middle of a septic area, it often takes place before the microbes have reached the endothelium of the thrombosed vessel and must be attributed to diffused toxins. Klein remarks that Lubarsch's/

Lubarsch's experiments were not properly controlled and the thrombosis may have commenced before the inoculation was performed.

Talke's experiment was repeated by Bardeleben with streptococcus pyogenes, which is more germane to the present subject, and no thrombosis was obtained.

Brooks and Curvell injected a suspension of a virulent pneumococcus about a vein, so as to compress it. No local lesion followed. They injected ten drops of a virulent 24 hours culture of B. Typhosus into a vein without producingany venous lesion.

Fromme[43], experimenting on rabbits, introduced silk threads into the jugular vein and found that if the thread were infected a thrombus formed but not if they were sterile. Zurhelle[24], repeating those experiments, found that the thrombus formed whether the threads were sterile or septic. Jakowski[44] performed certain experiments a propos of two cases of thrombosis following appendicitis and volvulus. He used suspensions in salt solution of cultures of B. coli communis of human origin which had been grown artificially one generation.

Experiments:-

1 and 2. 0.25 c.c. of suspension injected into a vein. Another vein exposed and gently squeezed with forceps. No thrombosis after four days but a septic clot in the heart.

3 and 4. 0.5 c.c. of suspension injected subcutaneously; elastic ligatures placed round one or both hind limbs/

limbs for 24 hours. After three or four days thrombi, consisting of fibrin and blood corpuscles, were present in veins of hind limbs. In these experiments the purpose was to simulate sluggish venous circulation.

5 and 6. Rabbit injected in left ear vein with 0.5 c.c. of broth culture. Right ear vein pinched with forceps and ear surrounded by an elastic ligature. The animal was killed on the third day and a large slightly discoloured and septic clot was found in its right ear vein.

The value of these experiments is greatly reduced by the severity of the primary lesions. The ligature was in all cases tight enough to cause great swelling and discolouration of the distal part of the limb or ear; and in some of the post mortem dissections was found to have lacerated the tissues. The clots formed in the leg veins were ordinary red coagula. The experiments simply show the difficulty of producing thrombosis by bacterial inoculations.

The only microbe which has been proved to have any specific coagulating actifity is B. Mallei. Duval and White[45], after injection of this bacillus, or its killed culture, or its filtered products into the ear of a rabbit, invariably found spreading coagulation in the veins and arteries, the ear often sloughed. If the injection was intraperitoneal, the same lesions occurred in the mesenteric and omental vessels.

So far, beyond Talke's experiments with staphylococci/

staphylococci, there is very little experimental proof that any of the pyogenic organisms or their products are concerned with the production of thrombi or coagula in rabbits or guinea pigs. Landois[46], however, says "From the investigations of Alexander Schmidt it has been shown that even healthy functionating blood contains some fibrin ferment from the destruction of white blood corpuscles normally undergoing dissolution, and in greater amount in venous than in arterial blood. The fact is, however, particularly noteworthy that the amount of fibrin present in the blood in cases of septic fever may increase to such a degree that spontaneous coagulation thrombosis may take place and even terminate fatally."

Bardeleben[20] carried out a special research for the purpose of seeing whether phenomena resembling puerperal thrombosis could be produced experimentally in rabbits by means of cultures of streptococcus. He divides clinical thrombosis into two forms - a rapidly fatal form with steady high temperature, and generalized sepsis and a slow form with intermittent rigors and signs of pyaemia. He wishes to determine the cause of the difference and quotes various writers who attribute it to the ability or inability of the streptococcus to multiply in the blood, or to the amount of toxin they produce (in the absence of which they are rapidly destroyed); or generally to the degree of their virulence. These appear to be different expressions/

expressions for the same thing - or to the mass of the initial dose. Variations of the resistance of the host is an important factor in man, but insignificant in small rodents and must be represented by using cultures of various degrees of virulence. Another factor is the port of entry of the virus which may pass immediately into the blood stream, say through an open vein in the placental site, or may enter the blood indirectly from other tissues. A condition which he could not reproduce is the sluggish flow of blood which may be assumed to occur in the veins of the uterine wall and neighbourhood after child birth. This was represented by putting a temporary or permanent ligature on a vein.

The first experiments he relates were directed to infecting the wall of a vein, which he effected by injecting a suspension of streptococci into the tunica adventitia or tunica media. He used varying doses of virulent cultures. In no case did any thrombosis occur. He finally obtained thrombosis in the vein by infecting a collodion capsule with a highly virulent culture and folding it round the vein. But on the whole his experimental attempts to obtain penetration of a vein from without by microbes was unsuccessful. He concludes that the wall of the vessel offers greater resistance than other tissues and only very virulent cocci can invade it.

The remainder of his experiments were by intravenous inoculation/

inoculation. In one case he found wide spread thrombosis in veins on both sides of the body. This was a rabbit of 1050 g. which received 10 c.c. of virulent culture in a vein. This was at least 10,000 lethal doses and was as if an ordinary human adult had a pound and a half of culture of highly virulent streptococci introduced into a vein. It is impossible to argue from such an experiment to anything in human pathology. But injection into a doubly ligatured segment of a vein of one tenth volume of culture material was followed by a slow coagulation beginning in about 12 hours or later if the culture was of feeble virulence. A similar injection of sterile broth or of boiled culture did not cause clotting. In these experiments, if the streptococcus was a virulent one, the clotting spread in a few days to the facial vein and thence to the innominate vein and the right side of the heart. Bardeleben gives no indication as to whether these clots were white or red and no histological report as to the state of the walls of the veins. The animals had septicaemia, of course, and died in a few days. If the culture was one of slight virulence, clotting occurred slowly in the ligatured segment of vein and the animal was ill for a day or two, but recovered. The contents of the ligatured vein were sterile after a few days, the cocci having died out. Bardeleben adds that in no case did these less virulent cocci penetrate through the wall of the vein, but he does not say how

he/

he found that out. It is rather important, as one of his conclusions at the end of the paper is that streptococci of moderate virulence in a clot are not likely to cause a general infection. He had an interesting series of experiments on injecting a small dose of virulent cocci into a vein between two ligatures.

Group A. 1. Ligatures left on vein - animal died after 48 - 50 hours.

2. Ligature removed after 24 hours - animal died after 36 hours.

3. Ligature removed after 24 hours - animal died after 30 hours.

Group B. Ear amputated after 36 hours.
One animal survived four days, the other died after 48 - 50 hours.

From these experiments he infers that the presence of the ligatures postponed death decidedly and as effectively as amputation of the ear after 36 hours. And they certainly support his opinion that the wall of a vein is a distinct obstacle to the spread of infection either from without to within the vein, or vice versa, and that such spread can only occur with a highly virulent infection. Of course the difficulty with rabbits is that according to the virulence of the germs, death or recovery of the animal occurs as a rule in a few days and the subacute or chronic infections do not occur.

His general conclusions are:-

1. When streptococci pass directly into the blood (through a gaping vein at the placental site), thrombosis/

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thrombosis will occur whether the virulence is high or low, provided the blood in the infected vessel is at or near a stand still. But if the blood is flowing freely, bacteriaemia will follow if the microbe is virulent, if avirulent, it will die in the blood.

2. Cocci may infect the wall of a vein from the surrounding tissues and pass through it and cause clotting without previous stasis, but this will only occur experimentally if the cocci are in a virulent condition.

He considers that in the puerperal condition, according to the virulence of the cocci, there may be a slight local thrombosis with rapid generalization of the poison, and death, or a spreading thrombo-phlebitis leading to pyaemia, or a less extensive thrombo-phlebitis which stops and resolves as the cocci soon die out. He does not think that clotting spreads beyond the inner part of the wall of the uterus in the absence of infection.

CLINICAL.

In the study of clinical records on this subject, one is immediately confronted with the difficulty that these records consist either of isolated cases collected from periodical literature, of which examples are appended, or of statistical tables. The former give no indication of the frequency of the disease and in the latter in most cases all puerperal thromboses, whether of the pelvic veins, the femoral or the superficial veins of the leg are recorded together.

The following table is compiled from various German lying-in Hospitals by Junge[6].

Junge recorded	81	thromboses in 10,056	labours = 0.8%
Hoffmeier	12	10,000	0.12%
Neu	35	3,014	0.16%
Lang	34	7,805	0.48%
Wenczel	34	9,251	0.36%
Schauta	47	32,000	0.15%
Esser	35	3,014	1.2%
Klein	76	34,951	0.2%

Hoffmeier's[47] figure, which is the lowest, is derived from a service where the patients were advised to get up on the second day and he adduces it to illustrate the beneficial influence of this treatment; but altogether the figures appear to me extraordinarily low. I have not found any figures relating to obstetric practice in England or America or France, but I think/

think that thrombosis, if all superficial cases are included, is much commoner in this country. In my practice, speaking from memory, it has exceeded 1% and may easily have been more. Boissard[48] at Tenous had 16 cases of phlegmasia alba dolens in 4000 labours which is equivalent to about 120 cases of thrombosis all told, or 3%. One is tempted to suggest that some of the German figures refer to thrombosis of large veins but Junge at least says that his own figures include every trivial case of clotting in the veins of the leg. I cannot produce any large series of figures dividing the cases into thromboses of femoral veins, superficial veins and pelvic veins. Of Junge's cases 53 (65.5%) involved the saphenous veins alone, which in 90% of the cases were varicose; on the other hand, varicosity was only present in 26.8% of the total of mothers. This latter is a smaller figure than experience in this country would lead one to expect. It might be suggested that the small number of thromboses in the table I have given finds its explanation in a relative rarity of varices in German women, but this is contradicted by Christofoletti[49], who found them in two thirds of pregnant women, and by Hell[50], who declares they are present in practically all pregnant women between the ages of 25 and 40.

Before passing from the subject of frequency, I wish to refer to statistics of thrombosis after abdominal section. It is notable that this complication is commoner/

commoner after abdominal than other operations. Cordier[51] collected 232 cases of post operation thrombosis, of which 200 followed abdominal sections. Clark[52] reported 35 cases of thrombosis after 3000 laparotomies, 1.17%. Albanus[53] collected 53 instances after 1140 laparotomies, 4.6%, while after operation for disease of the vermiform appendix, thrombosis of veins occurred in 29 out of 3334 cases collected by Haward[54] from various London hospitals.

In gynaecological operations thrombosis of veins is somewhat commoner than in abdominal operations generally, but that is due to the frequency of the complication after operations on the uterus. I shall discuss this in detail presently. The important fact is that after abdominal and particularly gynaecological operations, venous thrombosis takes place in from 1% to 4% or even more of cases. This is of course a much larger percentage than that after child birth as indicated by the figures above. The disease has also, as will be seen, a different distribution, but the two conditions present practically the same problems of causation. The age distribution of puerperal thrombosis is exemplified in the following table from Schneider[55]:-

Age	Number of mothers.	Percentage.	Number of cases of thrombosis.	Percentage.
15-20	241	10.4	0	0
21-25	584	25.2	8	17.4
26-30	545	23.5	3	6.5
31-35	451	19.4	15	32.6
36-41	351	15.1	12	26.1
41-45	125	5.4	8	17.0
46-50	19	0.01	0	0

These/

These figures suggest that women in the latter part of reproductive age are more liable than those in the earlier part. Of the mothers, 40% were above 30 years of age, and among these occurred 75.7% of the thromboses 20.6% were above 35 years and accounted for 48.1% of the disease. Junge does not supply so elaborate data on this point but of his cases of thrombosis only 40% were over 30 years of age, 50% were between 20 and 30 and 9% were under 20.

With reference to multiparity, Schneider[55] found that primiparae supplied 36.6% of the total material but only 8.6 of the thromboses. Junge, on the other hand, reports 26% of his cases of thrombosis among primiparae, and Wenczel 76%, but these authors do not give the total proportion of primiparae delivered. It appears, however, that no influence on the incidence of thrombosis can be certainly ascribed to either age or multiparity.

Information is also available concerning other diseases preceding or accompanying and possibly accounting for thrombosis. Klein[23] records 76 cases, of which 31 (40.7%) had normal and 45 (59.2%) had pathological or operative labour. In Schneider's series 33.5% of all the labours were operative and 43.5% of the thrombosis followed operative delivery. Junge had the same percentage (43%) of operative delivery among his cases of thrombosis. Wenczel had a percentage of 65, Klein/

Klein of 59.3.

Among the predisposing causes, Schneider places placenta praevia first. In his 2316 cases were 1.8% of placentae praeviae and of those no less than 20% had thromboses of veins during convalescence, just ten times the normal proportion. Of Esser's[56] 35 cases, four had placenta praevia. Of Schneider's cases of manual separation of the placenta, 6.8% developed thrombosis. These of course are both conditions in which an extraordinary liability to haemorrhage and sepsis occurs. Thrombosis also occurred in 5.3% of Schneider's cases of extraperitoneal Caesarean section. He thinks the operation involves bruising of the pelvic veins.

Junge, after deducting cases of abortion and cases where the notes were imperfect, found that in 75% of the thrombotic cases the second stage had lasted 15 minutes or longer and in 39% its duration was from 40 minutes to three hours, cardiac complications were present in 15% and some haemorrhage in 21%.

As regards sepsis, 27 (58.6%) of Schneider's cases had no rise of temperature and he expresses the opinion that infection as a cause in them can be excluded. Esser records in 3014 labours 35 cases of which 17 were free from fever. Hulle[57], out of 21 cases of thrombosis, had six whose temperature did not exceed 36.8°C. Heideman[58] records 10 out of 27 cases as fever free, Jahn[59] 5 out of 26, Sänger[60] 12 out of 25, Hoffmeier

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3 out of 12, Neu 17 out of 35. Junge regarded 58 out of his 81 cases as free from infection. Putting these figures together, we find 155 out of 312 recorded as free from septic infection - 50%. Of Klein's 76 cases, he regards infection as certainly the cause in 35. Of the remaining 41, 9 had anaemia, 9 atonic post partum haemorrhage, 8 severe varix, in 5 serum was injected into the thigh and in 2 electrargol into a vein and he regards these as possible causes. Of contributory causes, the other 8 he thinks may be accounted for by meteorism (3), jaundice (1), phthisis (1), trauma in labour (2) and ~~vari~~narcosis (1).

We have therefore certain definite predisposing causes of puerperal thrombosis, viz:- operative delivery, haemorrhage and sepsis; the long second stage is also a predisposing cause, but may be so only by involving one of the above conditions.

Another question that may be discussed at this stage is the time of onset of thrombosis. This can be determined exactly in the case of superficial veins and usually also in the case of the femoral or popliteal trunk, where the signs are unequivocal. With regard to the pelvic veins it is different and the first definite sign of disease in them is either an embolism of the pulmonary artery or extension ~~of~~ to the veins of the thigh. Heideman and others lay stress on tenderness of the side of the true pelvis and in the region of Poupart's ligament as early signs. Mahler[62] considers/

considers a slight daily increase in the pulse rate (Kletterpuls) without rise of temperature pathognomonic of the condition in the absence of anything else to account for it. He states that at the acme of the thrombotic process there is frequently an evanescent rise of temperature after which the accelerated pulse persists, and attributes the symptom to the increase of venous blood pressure pending the establishment of a collateral venous circulation. Michaelis[63], in an inquiry into the premonitory symptoms of thrombosis and embolism, says that if careful observations are made in most cases a subfebrile temperature supervening on normal will be observed for a few days before the physical signs come into evidence; the latter, at this stage, are slight and inconstant, particularly where the ovarian veins are concerned. Richter[64] ascribes them both, when present, to slight repeated pulmonary embolisms.

But in general both of these observations have been received with scepticism. Krämer[65], for example, analysing 51 cases finds Mahler's sign present in 2, absent in 41, and doubtful in 8; and that of Michaelis present in 3, absent in 40 and doubtful in 8. A similar conclusion from the examination of a large number of cases was reached by Kuster and by Von Herff. It may be granted therefore that the diagnosis of pelvic thrombosis in its early stages is difficult and not usually carried out, and that figures relating to/

to the date of onset are only to be accepted with that caution.

In a small number of cases, thrombosis of the surface veins of the leg is present before labour. Esser found it so in 5 out of the 35 cases he analysed, but it has not been so common in the experience of others; it occurred before birth in three of Schneider's ~~six~~46 cases. It must also be borne in mind that most writers consider some extent of antipartum clotting in the uterine veins a physiological phenomenon (Williams). Of 43 post partum cases of Schneider's, 30 occurred in the first eight days, 7 from the 9th to the 12th, 4 from the 13th to the 19th, 1 on the 20th and 1 on the 40th. Of Wenczel's[66] 34 cases, 14 occurred in the first week, 11 in the second, and 9 in the third. These figures do not discrimminate between pelvic and extra-pelvic thrombosis. Junge's experience was that the period from the second to the sixth day was the commonest time of onset and included nearly all the cases of thrombosis of varicose saphenous veins, that the femoral cases began from the 7th day (the latest on the 31st), and the pelvic cases a little later. Most writers agree that thrombosis of the pelvic veins tends to have an earlier onset than that of the femoral vein which, of course, is often affected consecutively. Boissard[48], in 16 cases of Phlegmasia Alba Dolens, found that it began in 6 from the 3rd to the 8th day and in 10 from the/

the 12th to the 21st.

As to the site of the disease, in most cases it commences in the superficial veins of the thigh or leg and does not spread to the femoral or pelvic veins. Of Junge's 81 cases, 53 (61%) were of the saphenous veins, 17 (21.4%) of the pelvic and 11 (13.6%) of the femoral. Junge does not refer to the probability of the pelvic veins being also involved in many of the last. The figures of course include cases of septic phlebitis. On the other hand, of 51 post operative cases only 7 involved the saphenous vein (13.8%), and 25 (49%) the femoral; the remainder presumably were in the pelvic veins though he does not say so.

Klein[23] quotes several authors on the question of the side of the body involved in puerperal thrombosis.

	Right Side.	Left side.	Both sides.
	31	48	18
In his own puerperal cases	18	26	30
In his own surgical cases	13	28	21
Totals	62	102	69

In respect of the preponderance of left sided thrombosis the surgical cases do not differ from the puerperal, but there is a great difference with regard to the veins affected. The preponderance of thrombosis in the saphenous veins is peculiar to the puerperal state, just as their varicosity is pre-eminently a disease of pregnancy. It usually commences within two/

two or three days of childbirth and is unconnected with disease in the pelvic or femoral veins.

Thrombosis of the saphenous veins appearing in the second or third week nearly always means that the pelvic or femoral veins are already attacked.

With reference to femoral thrombosis in the puerperium, it must first be noted that the femoral and popleteal veins, especially on the left side, are a site of election for this disease. Lubarsch, in his note on 584 cases of thrombosis, found it in the femoral vein in 241. In the thrombosis which sometimes occurs during convalescence from typhoid fever, the femoral vein occupies the place of honour. Thayer[67] out of 42 such cases found the femoral vein involved in 21, the popleteal in 5, the iliac in 5, veins of calf in 5, internal saphenous in 3, the pulmonary artery, pulmonary, common iliac and axillary veins each in 1. In reference to the puerperal condition, Krönig[68] lays stress on the occurrence of femoral thrombosis independently of the pelvic veins and from the figures of Junge it does appear to occur, though less frequently than after operations. In this connection Latzko[69] says that out of 48 cases of femoral thrombosis in puerperae he was able during life to trace the process to the pelvic veins in 38 and in two others the connection was established at the post mortem examination. He considers that 80% of puerperal/femoral thromboses are associated with pelvic

thromboses/

thromboses and that in most cases the former arises from the latter. Williams[70] says "Thrombosis occurring in the crural, popliteal or saphenous veins - Phlegmasia Alba Dolens - is usually a manifestation of puerperal infection and follows the direct extension of a thrombotic process from the pelvic veins".

Postoperative thrombosis is relatively commoner than puerperal thrombosis and is incidental particularly to abdominal operations. Klein collected the records of about 17,000 operations, of which about one fourth were gynaecological caeliotomies and found that venous thrombosis followed in 1.3% of them. In 12973 abdominal sections he found 270 cases of thrombosis - 2.1%. These were largely gynaecological operations. Clark reported thrombotic sequelae after 35 out of 3000 laparotomies (1.2%) and Haward ~~Smith~~ after 29 out of 3334 operations for disease of the appendix. Albanas[53], on the other hand, collected as many as 53 cases of thrombosis in 1140 laparotomies. The general impression appears to be that venous thrombosis may be expected after 1 to 1.5% of abdominal operations. Operations on the pelvic organs give rather worse figures. The following table from Klein gives very fully the incidence of this complication. The figures are from Schauta's Klinik.

Nature of operation		Number of operations.	Number of thromboses.	Percentage.	Emboliems
Laparotomy		1953	39	2	0.9
Vaginal caetiotomy		1106	18	1.6	0.4
Various other operations		2792	13	0.5	0.1
		5851	70	1.2	
Myoma Operations	Abdominal Hysterectomy	360	15	4.1	2.0
	Vaginal Hysterectomy	282	7	2.5	0.7
	Enucleations Lapar.	16	1	6.25	0.5
	Enucleations Vaginal	72	1	1.4	1.3
		88	2		
Cancer	Lapar.	191	10	5.2	0.5
	Vaginal	229	6	2.6	1.3
		420	16	3.8	
Op. on Annexa		845	9	1	0.6
Cancer of External genitals		421	6	1.4	0.23
Prolapse and retroflexion		633	3	0.3	0.14
Various other		1881	7	0.37	0.26

The operations most important in connection with thrombosis are those for myoma and for uterine cancer. In the former class Klein's percentage for vaginal hysterectomies is 2.5 and for abdominal hysterectomies 4. In cases of myoma, Hoffmeier[47] reports 1.7% of thromboses in 170 abdominal hysterectomies, and 3.4% in 59 cases of vaginal hysterectomy, 59 abdominal and vaginal myomectomies without any thrombosis and one case/

case of castration followed by thrombosis. Burchardt[71] reports 12 cases of thrombosis in 236 operations for myoma (5%), 6 being fatal cases of pulmonary embolism. Bland Sutton[72] gives statistics of fatal embolism after hysterectomy for fibroids from his own experience and that of Olshausen, Spencer, Lyle, Noble and Baldy. The total is 26 fatal cases in 1089, 2.3%. Zurhelle[73] had 2.75% of thrombosis after abdominal hysterectomy for myoma and only 0.7% after removal of inflamed appendages.

The results of abdominal hysterectomy for cancer are rather worse. In explorations of cases of cancer Zurhelle had 3.75% of thrombosis, Wertheim in his last 500 cases had only 10, 2%, of thrombosis; in the same period his figures in 921 operations for displacement and 845 operations for disease of the appendages were 5 (0.5%) and 9 (1.1%). He attributes his better results to early rising of the patient. The general figures of surgeons are worse. Klein gives 5.2 as against 2.6 for the vaginal operation.

From those figures it appears that uterine operations are especially prone to lead to venous complications, that the latter are more common after abdominal than vaginal incisions, and that the extension of the operation for cancer of the cervix associated with the name of Wertheim is the most dangerous of all in this respect and is closely followed by hysterectomy for myoma. Zweifel[74] found thrombosis less frequent after the/

the supravaginal operation than after panhysterectomy, but this is not the universal experience. Schanta[75], discussing the frequency of thrombosis after the abdominal and vaginal operations on myomatous uteri, states that it is more common after the abdominal operation and that this is not accounted for by any difference in the gravity of the cases submitted to the different procedures in his practice. He suggests that it is caused by the earlier rising and more rapid convalescence in the vaginal cases. It is to be noted that thrombosis occurs much less often after myomectomy than after hysterectomy.

In forming deductions from those operative results three their aetiological factors have to be considered, sepsis, absorption of products of tissue necrosis and pre-existing vices of the circulation.

With reference to sepsis, a great many surgeons unhesitatingly ascribe all these cases to infection with bacteria, which are not necessarily pyogenic. Bland Sutton[73], for example, thinks post operative thrombosis in the saphenous vein is caused by such infection travelling along the superficial abdominal veins and condemns buried sutures. Goodrich[76] ascribes post operative femoral phlebitis to infection of the blood clot in or about the veins of the abdominal incision by attenuated bacteria. Grant[77] wrote to about twenty prominent surgeons and pathologists in America, of whom about half attribute the thrombosis to

a/

a mild infection. Willie Meyer[78] says the condition is always infective, though the infection is not necessarily from the field of operation. Sauson[79] expresses himself in a like sense. Schrotter[80] maintains emphatically that all thrombi are evidence of bacterial activity. Schanta, Bumm, Fränkel, Mendel, Latzko and Fromme among German writers put down these cases as practically always septic.

A strong argument for this opinion is founded on the greater frequency of thrombosis after hysterectomy, when a mucous canal is opened, than after myomectomy or ovariotomy. In Wertheim's operation, which gives the largest incidence of thrombosis, there is an exceptional liability to septic infection. On the other hand, supra vaginal hysterectomy for fibroid disease does not present nearly the same opportunities for infecting the wound.

On the other hand, Edebohls[84] refers to 10 cases in his practice, none of which he considers septic. J. G. Clark[52] says it originates from a primary thrombosis of the deep epigastric veins which is slowly propagated along these vessels until it reaches the external iliac and is non infective. Von Beck[81] argues strongly against regarding these cases as necessarily infective. Krönig[68], in presenting the same view, offers a minute examination of the results of more elaborate recent antiseptic methods. He discusses particularly the statistics of post operative thrombosis/

thrombosis in various kliniks before and after the introduction of indiarubber gloves, and finds no difference; he reasons that the gloves are particularly adapted for the exclusion of the attenuated infection which is often postulated in those cases and appears to make out a very strong case. A proportion of these cases is by every one admitted to be septic, but the assertion that the remainder, in which no other evidence of infection is present, is caused by an attenuated virus which eventually dies out, begs the whole question and is not supported by any large body of pathological or experimental evidence. The same assumption is made with regard to puerperal thrombosis and will be discussed in relation to it. Interesting in this connection is the relative rarity of thrombosis after operations for the extirpation of inflamed ovaries and tubes, where an attenuated virus and a local tissue immunity are often present.

The second possible factor is the absorption of morbid products from tissues that have become necrotic or been strangulated by ligatures. It is of course a well established fact that a thrombokinase is present in the extractions of most tissues. It was first demonstrated in highly cellular tissues such as the thymus and lymphatic glands, but it is also present in muscular and connective tissue and Bernheim[82] found it exceptionally active in extracts of the coats of blood vessels. Such substances absorbed from a wound into the blood may cause progressive clotting in neighbouring/

neighbouring veins in which the current is sluggish. Such absorption is likely to occur after the application of mass ligatures and the latter, on account of the abundance and inaccessibility of the vessels, are employed in pelvic surgery more than in any other part of the body; they are used especially in Wertheim's operation, which is most commonly followed by thrombosis. But here again we are confronted by the facts that removal of appendages, for which mass ligatures are usually used, do not lead to so many thromboses, and hysterectomy for fibroids, in which mass ligature is less frequently employed, is almost as conducive to thrombosis as is Wertheim's operation. Mention may be made in this connection, of the experiences of Bumm and Zweifel, related by Krönig.. The former abandoned mass ligatures in myohysterectomy from fear of infection of the stump and consequent phlebitis, the latter abandoned ligature of individual vessels in the floor of the pelvis and adopted mass ligatures because he feared that the veins which did not bleed and ~~source~~ were left open might prove to be a portal of phlebitic infection. But in neither case did the alteration of technique lead to an altered incidence of post ~~partum~~ operative thrombosis.

The frequency of thrombosis after abdominal hysterectomy for cancer may also be attributed in part to the dissections of lymphatic glands in which the very veins which subsequently become thrombotic are exposed/

exposed; too much emphasis must not be laid on this consideration in view of the experience of surgeons after the dissection of the axilla for cancer. In these cases axillary thrombosis is almost unknown, but femoral thrombosis not uncommon, which clearly points to a local factor in the pelvis and lower limb.

The third causal element in post operative thrombosis is a pre-existing vitiation of the circulation or of the blood itself. It has been shown by Strassman and Lehman[83] that in a third of women suffering from the effects of myoma, the heart is atrophic; in addition, the chronic septic intoxication which is present in many cases of both myoma and cancer, exercises a detrimental influence upon the heart and the general nutrition, as well as on the blood itself. Lubarsch lays great stress upon this factor in accelerating the coagulation of the blood; the frequent and severe haemorrhages which are common in both of these classes of cases, and indeed often constitute the indication for operation, produce anaemia with degeneration of the heart and of the inner coats of blood vessels. Haemorrhage has also an influence in increasing the coagulability of the blood, though this is probably only temporary.

Finally, some authorities seek to explain their post operative thromboses by means of a specific dyscrasia of the blood, the exact nature of which

(Clark[52]/

(Clark[52], see also Mendel[104] on Thrombophilia) still awaits investigation.

Examination of all those data leads to the conclusion that while a proportion of cases of post operative thromboses is caused by local or general infection, there is probably a large residue of cases not directly caused by infection but attributable to anaemia, haemorrhage, trauma, cachexia, cardiac weakness and perhaps prolonged recumbency.

POST MORTEM APPEARANCES.

Post mortem examinations do not convey any idea of the frequency of puerperal thrombosis, because while the pyaemic cases die, the benign cases nearly always recover. They are generally recorded in tabular or statistical form which is for the present purpose of less value than a detailed account of individual cases. Trendelenberg[15], in the post mortem examination of 43 puerperae who died of septic diseases, found pyaemic thrombi in 21 (accompanied in four by lymphatic infection), bilateral in 14, unilateral in 7. In about one third of the cases the thrombi did not extend beyond the parametrium, while in the remainder large trunks were involved.

Grossman[85], in 51 autopsies, found pure thrombophlebitis in 14 and thrombophlebitis along with lymphangitis in 13 - total 27. Leuhartz[86] found pyaemia in 50% of his cases.

These figures are enough to show the large part which infection of veins plays in puerperal fever, being responsible for about half of the fatal cases. They throw no light on the frequency and cause of bland thrombosis which, however, is well illustrated by clinical statistics.

I have selected from the records a number of post mortem examinations, in which interesting clinical and pathological details are supplied, and which illustrate the/

the pathology of both conditions. Sperling[87] in 1893 published a number of records in order to illustrate the anatomical conditions present in pulmonary embolism, with special reference to prophylaxis.

Case 1. (Charcot and Ball, 1858) Normal labour, sixth day pain in left iliac region, fluctuating swelling, left sided Phlegmasia alba dolens; the swelling abated in the following days; sudden attack of dyspnoea and death on tenth day.

Post-mortem. In left parametrium an abscess as large as a pullet's egg. Uterus healthy and its sinuses free from clots; the left femoral, iliac and hypogastric veins converted into hard cords in their whole length; their lumina fully occupied with fibrous clots as also the common iliac vein to within 3 c.m. of its termination, that is as far as the suppuration extended: the vena saphena also blocked: the clots were for the most part attached to the thickened and wrinkled walls of the veins. Here and there they contained yellow pus. The clot was yellowish white with brown streaks. In the common iliac vein was a conical thrombus with scalloped free border. In the peripheral parts of the veins the clots were dark brown, soft and only lightly adherent, etc., etc. Here is evidently a case of septic phlebitis and thrombosis secondary to suppurative cellulitis, the intramural parts of the uterine veins being free from infection.

Case/

Case 2. (Paulsen, 1860) Multipara admitted to hospital four weeks after a tedious but natural labour with free haemorrhage in the third stage; lochia somewhat abundant, mixed with blood, odourless. For three days she had felt a pain in the right side passing down into the leg, which was swollen. Skin felt natural: pulse 90: no headache: poor appetite: bowels confined: micturition natural: abdomen much distended, especially about umbilicus, everywhere tender and soft: right leg swollen from foot to groin: femoral vessels tender below the inguinal fold, but no induration noted: skin of natural colour and temperature, lungs and heart normal. After ten days expectant treatment the fever disappeared, appetite returned and the swelling and tenderness of lower limb were abolished. She then died very suddenly. Post-mortem. In both pulmonary arteries were clots consisting of a central yellowish white part surrounded by soft dark clot. The crural vein contained a clot which in places was dark throughout and in places consisted of a whitey-yellow, more or less friable core surrounded by a layer of dark coagulum. The wall of the vessel looked quite healthy inside. The central fibrinous clot was readily separable from the dark surrounding layer. There was no trace of central softening or suppuration. The thrombus reached into the vena cava 1 c.m. beyond its commencement and ended with/

with a broken point. Above it, in the wall of the vena cava, was a faintly projecting ledge of fibrin giving the contour of the embolus that had broken off.

This case was one of benign thrombosis starting in the femoral or iliac vein without involvement, apparently, of uterine and hypogastric vessels, although the presence after four weeks of abundant bloody lochia suggests that the latter may have been the starting point of the trouble. At any rate, it is a typical case of white leg without any evidence of infection. It is notable that there was excessive bleeding in labour.

Cases 3 and 4, (O.V.Franqué, 1868) are those of women who died in the third week of the puerperium, having exhibited no signs of illness except pain over the femoral vein. One of them had had placenta praevia. At the post mortem in both was found embolism of the pulmonary artery and extensive clotting in the veins of the thigh. No other veins are mentioned and there is no suggestion of any other lesion, both appear to be like case 2 - benign primary femoral thrombosis.

Case 5. (F. Frankenhäuser, no date) Bleeding four weeks before labour, placenta praevia; soon after labour, air hunger, etc., death 24 hours after labour. Post-mortem. An old coloured clot which started from the placental site, filled the whole of the right uterine vein, the hypogastric and a part of the iliac vein/

vein. Embolism of the pulmonary artery by a similar clot which came from the iliac vein. This is a very important case. There had been bleeding from the placental site four weeks before; consequent clotting had spread as far as the iliac vein. There is nothing in the case to suggest sepsis; the clot was red throughout apparently. Sperling, in commenting on it, suggests that uterine contraction in the third stage of labour had pushed an old clot in the wall of the uterus into a more central permeable vein, which had become an embolus. Examination of the text, however, makes it clear that at the time of labour clotting was present up to the iliac vein.

Case 6. (Frankenhäuser) / Attempted artificial induction of labour by a catheter passed between the uterus and membranes; the placenta was wounded and considerable haemorrhage followed. After six weeks the patient was delivered with forceps and died of pulmonary embolism at the conclusion of the operation. The post mortem report does not say what was found in the pelvis.

Case 7, (Cohn, no date) is similar. Haemorrhage three weeks before labour, pulmonary embolism at end of labour. No details post mortem.

I have narrated cases 5, 6 and 7 to illustrate the possibility of dangerous thrombosis occurring before/

before labour in cases of haemorrhage during the last part of pregnancy. It is a contingency which many writers ignore. Sperling draws attention to the danger of such clots being squeezed out of the uterine wall in the third stage and set free in the circulation.

Case 8 is related by Richter.[88] V-para aged 29. Transverse presentation, version. Quite well and free from pain and swelling until the evening of the 4th day, when a pulmonary embolism occurred. A second and fatal attack took place on the 8th day.
Post-mortem examination showed fresh red clots in the right tubo-ovarian ligament, thrombosis of right iliac vein, inferior vena cava and renal veins. This case illustrates the rapidity with which clotting may spread in the large veins.

Case 9. (Martin, quoted by Sperling) Normal labour. Persistent bleeding for four weeks after. Two days later sudden death.
Post-mortem. Both branches of pulmonary artery embolized. Thrombosis of the iliac veins extending into the broad ligaments. Uterus retro-flexed. On its anterior wall a placental polypus showing microscopically calcified villi.

A case of white leg by extension of thrombosis from the uterine veins without infection.

Widal[89] in his dissertation on puerperal infection described/

described the post mortem appearances found in a number of cases, of which the following two are of interest:-

Case 10. Rosa B., aged 36, 1-para. Delivered with forceps April 10th, 1888. April 12th, rigor. Temperature continued elevated until her death on April 30th - the 20th day.

Post mortem. Diphtheritic endometritis. False membranes were also observed on the surfaces of portio, vagina and vulva. On section of the uterus, the veins appeared full of pale clots. By pressure on it one could squeeze out everywhere moulds of fibrin. Utero-ovarian veins were filled with fibrino-cruentous clots. In the large uterine sinuses, these exactly resembled those seen in phlegmasia alba dolens, being adherent to the walls and consisting of a fibrinous or fibrino-leucocytic core with a cruoric periphery in places. Microscopic examination of the veins that contained red-clot showed no bacteria, but in those which contained mixed clot chains of cocci were observed in great abundance on the endothelium. In very few places were cocci observed in the lymphatic spaces.

The patient had septicaemia and pneumonia. Streptococci were grown in pure culture from the interior of the uterus, from the clots, the uterine muscle and the blood.

Case 11. A woman with fibroids and metrorrhagia took ill with a classical phlegmasia alba dolens and at the same/

same time with erysipelas of the face which afterwards attacked the perineum. She died on the 7th day of the phlegmasia.

Post-mortem. Ulcerated myoma. Left utero-ovarian and iliac veins thrombosed. Some of the clots were red and some white or mixed. That in the iliac veins was purulent in its interior and full of streptococci.

In these two cases Widal maintains that the mixed clots were caused by the streptococci growing along the interior of the vein, and the red ones were of mechanical origin. From these two cases and from certain clinical evidence, he draws the conclusion that "phlegmasia alba dolens is of an infective nature". From that he infers that discontinuous puerperal thrombosis, as in the crural or saphenous veins, is produced by the bacteria which have entered the circulation and are deposited and grow on the endothelium behind a valve or in a varicose pouch. I shall return to the discussion of this point later. Widal's cases illustrate the proposition that streptococci growing on the endothelium may cause thrombosis, but do not lead us any further.

Along with them may be taken some interesting cases related by Krämer[90].

Case 12. A.C.H., aged 24, was feverish when admitted to the hospital and was delivered by forceps, April 11th. A pure culture of streptococcus pyogenes was obtained from the uterine secretion at that time.

10th/

10th day, infiltration of left parametrium, pain in left leg, cough.

16th day, hard cord felt in left parametrium.

20th day, swelling of left leg, systolic precardial murmur.

28th day, right leg also swollen and swelling extending up abdominal walls.

48th day, swelling reached the level of 8th dorsal vertibra. Death.

Post-mortem. Embolic pneumonia of right lower lobe; purulent thrombophlebitis of inferior vena cava, pelvic and femoral veins on both sides. The thrombi in the femoral veins were fresh, those in the uterine veins were old and retrogressing. Streptococci were demonstrated in the clots.

The following case is given in more detail and is of greater pathological interest.

Case 13. Seven months pregnancy complicated by cancer of the cervix. Delivered by "hysterotomia anterior" and perforation. Free haemorrhage necessitated tamponage of uterus and vagina for 24 hours: 50 c.c. of antistreptococcic serum were injected prophylactically. When the tampon was removed, the temperature fell to normal and remained normal for ten days. On the 11th day a slight rise of temperature occurred and the patient complained of pain in her back. On the 22nd day there was pain in the left leg from the groin to the ankle and swelling of the thigh, which extended to the leg and foot. Five days later,

another/

another slight rise of temperature occurred, with swelling of the right labium and right leg. By the 40th day the swelling had so far abated that the patient was allowed to sit up in bed, and a week later under lumbar anaesthesia the extended abdominal operation for cancer was performed. The uterine and spermatic veins were found thrombosed; a portion of the thrombus from the right uterine vein was examined culturally and microscopically and found sterile. On the fifth day after the hysterectomy, an abscess of the abdominal wall was opened, and four days later the patient died.

The case is so far of peculiar interest. The uterus was infected at the time of delivery but the puerperium ran a normal course, with the exception of a slight rise of temperature on the 11th day, until the 22nd day when clotting became evident in the veins of the left lower limb. This spread to the other side five days later with a moderate (39.2°C) and temporary rise of temperature. This is a very typical instance of the class of cases of white leg which many regard as independent of infection, but the fever was slighter and of less duration than is often observed. The evidence is not conclusive that the phlebitis was not of infective origin (Widal, for example, found infection in parenchymatous veins of the uterus where the more peripheral veins were sterile) but both the clinical course of the case and the bacteriological/

bacteriological investigation strongly support it. The findings at the post mortem are of the greatest importance.

Post-mortem. The right external iliac and femoral veins are filled with a clot of a fresh reddish colour, which extends into the cava. The pelvic veins are all thrombosed and the left external iliac filled with an old grey-red clot which at the edges showed traces of commencing recanalization. On the left side the connective tissue in the floor and wall of the pelvis is infiltrated and inflamed, the exudation containing cocci and bacteria in great abundance. Microscopic examination of the iliac and femoral veins showed recent changes on the right side and canalization on the left. In the section of the left iliac vein, penetration of the outer part of the thrombus by bacteria is evident. The pathologist, Orth, who did not know the clinical history, remarked that this case showed an old thrombosis and a recent cellulitis.

Here we have a quite convincing evidence of secondary septic phlebitis in an already thrombosed vein, caused by septic cellulitis. The case is illustrated by low power microscopic drawings.

In the description, unfortunately, in one passage the author speaks of the clot examined at the time of the operation as coming from the right uterine artery, and in another passage as coming from a vein, but the context makes it clear that vein instead of artery should/

should be written in the first passage.

Pourtalès[91] relates some cases which illustrate the different processes of venous infection.

Case 14. VI-para. Severe haemorrhage in the third stage and manual removal of the placenta. Temperature rose on the following day and continued feverish until the 10th day when, after vaginal douching, it fell to normal. On the 14th day a slight rise of temperature occurred, and the patient was examined. A piece of placenta was removed and the uterine cavity was irrigated with ten litres of sterilized water. The uterine secretion was examined and Pourtalès was satisfied that no streptococci were present. Two hours later there was a rigor. On the 22nd day streptococci were found in the discharge from the uterus and on the 26th the patient died.

Post mortem. Small abscess in left parametrium, 300 c.c. of pus in pelvic cavity; peritonitis quite recent. Thrombi were found in the uterine walls, parametria, both hypogastric veins, both spermatic veins and left renal; left kidney was gangrenous.

On microscopic examination it was found that the thrombi in the veins in the uterine wall were infected with streptococci, which formed large colonies in the middle of them. Sections of the venous plexus in the parametria showed most of the large veins thrombosed. In many the thrombi consisted of layers of hard/

hard fibrin, free from bacteria; others showed in the central part of the clot softening and leucocytic invasion and chains of streptococci. Along with the latter were also clusters of staphylococci and bacteria (Pourtalès claims that this is the first case where a staphylococcic or putrid infection of puerperal clots has been demonstrated although mixed infection has been found in secondary embolic abscesses). The microbes did not generally penetrate far from the softened central area of the clot into its peripheral parts. Only in a few places was the liquefaction so far progressed that the vessel wall had only a few shreds of fibrin left adherent to it. In those places the microbes were seen in these fibrinous remnants and also penetrating the coat of the vein which showed enormous leucocytic invasion. The same appearances were present in both spermatic veins. The clot in the renal vein was not infected.

In this most interesting case, there may have been from the first a putrid infection of the endometrium, but Pourtalès is satisfied that no streptococci were present till the 14th day, when the operation took place and he considers it a clear case of primary thrombosis, followed by a streptococcic infection which involved the parametria and peritoneum and also travelled along the thrombosed veins. The thrombosis in the renal vein had proceeded further than the infection. There is a contrast between the microscopic appearances in/

in this case and in the following, and those of Duffek who found the cocci only in the peripheral layers of the clot and between the endothelial cells in cases which he regarded as a primary septic endophlebitis with secondary thrombosis. Pourtalès' view in this case is that the infection progressed in a preformed clot by tunneling and liquefaction of the central part of it. The patient lived 14 days after the onset of the infection.

Case 15. A IX-parous woman died on the 9th day of the puerperium. There was swelling of the right lower limb and thickening over its vein.

Post-mortem. Adherent thrombi in right crural vein. Iliac vein was reddened but not thrombosed. Surroundings of both veins were swollen and infiltrated with gelatinous fluid. Left veins normal.

Microscopically the uterine wall in a few places showed streptococcic invasion without a marked leucocytic zone. At the placental site streptococci were present in the superficial layer, the arteries and some of the veins were empty and not invaded by bacteria; other veins were thrombosed up to their open mouths, these contained abundant streptococci and showed no softening of the clots. The cocci were chiefly in the peripheral parts of the thrombi but a few were seen in the central parts. Where they were most abundant the endothelium was swollen, detached and necrotic and the underlying/

underlying tissues showed round cell invasion. Tubes and ovaries normal. Parametria showed numerous veins, some of which contained fluid blood and had intact walls, while thin chains of cocci were seen in contact with the swollen endothelium of others. In these situations the veins were more or less thrombosed and their walls were infiltrated with round cells, though free from bacteria. The same appearances were seen in the crural vein, the thrombus being crowded with streptococci at its periphery but not at its centre, and showing no softening. Many places showed a growth of cocci along the endothelium with little or no thrombosis, the latter being preceded by swelling and necrosis of the endothelial cells.

This case illustrates primary phlebitis (Bumm's Endophlebitis streptococcica) with secondary thrombosis, the infection being chiefly of the interior of the veins where it appears to have spread as rapidly as erysipelas does in the skin, the patient having died on the 9th day.

Case 16. Patient confined May 2nd, with severe post partum haemorrhage. May 3rd fever; May 8th hysterectomy and death. At placental site were many thrombi projecting into the uterus, some of which were infected with streptococci which were propagating themselves along the walls of the veins and between the endothelia. Section of the broad ligament showed some/

some of the veins thrombosed and similarly infected. Here also the inner surface of the vein is the chief site of the microbes, they are scarce in the deeper parts of the thrombus.

Case 17. Case of placenta praevia delivered by turning, August 24th. On September 10th temperature was 38°C and swelling set in in both limbs and labia, the left leg being the worst. There were numerous tender varices. For two months the temperature never exceeded 38°C and was nearly always 37°C. The swelling spread to the abdominal wall and buttock and the left arm swelled up to the shoulder. Poikilocytosis was present. Pernicious anaemia was diagnosed and she was transferred to another ward. On November 25th, two and a half months after the commencement of white leg, the temperature rose to 38.7°C and she died on November 27th.

Post-mortem. Uterus - small area of anterior wall covered with false membrane. There was an old localised fibrous peritonitis, nephritis, fatty liver and heart, recent endocarditis in a retracted mitral valve. Veins - both femorals, iliacs, hypogastrics and lower part of inferior vena cava closed with grey adherent thrombus. In the veins and some capillaries of the uterine wall are streptococci which were no where observed to have penetrated the vessel wall through the endothelium. The thrombus in the left crural vein/

vein was largely organised and vascularised, but in lymphatic-like spaces in it were numerous long chains of streptococci. Streptococci were present in the mitral valve.

In this case the cocci in the thrombi remained above for two and a half months without spreading into the surrounding tissues, and at the end of that period set up septicaemia and ulcerative endocarditis.

Case 18. Hoehne[93] so recently as 1912 described a case of puerperal pyaemia in a primipara of 21 years. On the 24th day after 12 rigors the abdomen was opened. The left hypogastric vein was tied and the left spermatic resected. In removing it an abscess extending into the psoas muscle was discovered. The broad ligament was infiltrated but not suppurating. The patient recovered. In this case the infection was staphylococcal and Hoehne considers the phlebitis the primary disease and the psoas abscess secondary. This is a very exceptional case.

It will be observed that Pourtalès described two forms of septic infection of veins, one in which the streptococci grow along the axis of the clot in a saprophytic manner and cause softening of its interior, and the other, in which the growth is a progressive invasion of the endothelium followed by thrombosis. In both cases he regards the mouths of the veins at the placental site as the portal of entry of infection. He describes an inflammatory reaction of the wall of the/

the vein and of the surrounding tissues, but the bacteria show little tendency to invade the latter, in the manner described in Hoehne's case.

The histological appearances described by Bumm[92] are very similar. Bumm was one of the first writers who gave a detailed account of the minute anatomy of puerperal septic metritis. His first paper, written in 1891, is founded on material obtained from five cases of fatal puerperal sepsis. He dwelt on the difference between lymphatic and venous infection and superficial putrid infection and on the significance of the presence or absence of the leucocytic zone. He compared the living tissues to a filter keeping out the less pathogenic micro-organisms. Two of his cases were of venous infection. In both of them there was a septic and putrid endometrial infection, and the surface of the uterus was necrotic and had a greyish greasy appearance. Microscopically, everywhere there was a superficial necrotic zone teeming with bacteria and streptococci and separated by a layer of small round cells from healthy muscle underneath. In the placental site no traces of placenta were seen but there were numerous thrombosed veins which could be readily traced both to the surface and to the broad ligament. The arteries were empty and not infected, but in the thrombosed veins all stages of infection were recognisable. One of his figures shows how the microbes/

microbes have grown into a clot which projects from the surface of the endometrium. The clot has the usual structure of red clot. In the most superficial part of it are seen rods as well as cocci, deeper are cocci only. Bumm speaks of red clot as unorganized tissue which presents a locus minoris resistentiae, but not as dead. There is a foot note that this exclusion of saprophytes is universal in lymphatic infection but is not always observed in venous infection. The penetration of the cocci is in the axis of the thrombus in which situation their growth can always be detected if they are present at all. From the axis they grow towards the periphery and the wall of the vein. Their growth is accompanied by crumbling and breaking down of the clot. In the early stages of the process the wall of the vein appears normal, but as the cocci grow towards it, it is more and more invaded by round cells. The latter wander into the vessel which finally contains a detritus consisting of remnants of clot, round cells and micrococci. In a few veins invasion of the wall by the cocci appears to be commencing. The appearance of the endothelium suggested that it became necrotic with the advancing infection. The veins in both broad ligaments and the spermatic veins presented the same appearances.

Bumm adds that in these phlebitic cases the cellular tissues showed a good and effective tissue reaction and/

and appears to think that they were cases where the cocci were not virulent enought to penetrate except through thrombus, at least in the early stages of the process.

The microscopic findings in these cases resemble those of the case by Pourtalès narrated above (case 14) and suggest that the cocci growing along the axis of the clot were the cause of further depositions. Bumm does not actually express this view and some years later[95] expresses himself as follows on phlegmasia alba dolens:- "I see every year about a dozen cases, mostly after operation, where the leg swells and becomes white and shiny and that, I believe, is the condition called phlegmasia alba dolens. Tenderness in the region of the swelling and the swollen appearance have given origin to the name. It has nothing to do with a phlegmon in the sense of suppuration. But there is a streptococcus infection proceeding from the uterine veins, creeping along the endothelium in the large veins and proceeding in retrograde fashion to the femoral vein. The tender point is the femoral vein under Poupart's ligament and the tenderness precedes the swelling and thrombosis". "Phlegmasia alba dolens is caused by no connective tissue infection but by the creeping infection along the veins - hence the spread to the other side. Its proper name is endophlebitis streptococcica." This appears to correspond to the description of case 15 by Pourtalis.

An/

An important contribution has recently been made to the subject by Duffek[94]. He first describes septic thrombosis of the femoral vein in three cases, erysipelas, pyaemia after streptococcic infection of the skin, and purulent parametritis. The thrombi were all alike. They consisted of a nucleus of platelet thrombus with layers of leucocytic or mixed thrombus superposed. In addition, separating the proper thrombus from the wall of the vein was a broad leucocyte zone where many of the cells were disintegrated. The cocci were present only in the core. The vessel walls showed inflammation which was more extensive than the thrombosis. In all these cases he regards the thrombosis as having been formed at a distance from the site of infection from various causes and the cocci as having been enclosed in it. In no case was there evidence of infection of the wall of the vein or of the surrounding tissues.

Before proceeding to discuss puerperal thrombosis he examined two uteri, one removed by Porro's operation and the other at a post mortem after caesarean section. He concluded that the veins in the inner third of the uterine wall are always closed by clots after labour because in this part the muscle elements have been injured by the trophoblast and the vessel walls are degenerated so that closure by contraction is impossible, but that in the outer two thirds they are emptied when the/

~~the~~ the uterus contracts and clotting does not occur normally. The clot in the inner layer is a red stagnation clot of course. A certain part of the clotting occurs anti-partum and is associated with alterations in the foetal elements and in the decidua. Examining infected uteri he found cocci penetrating the clots deeply and small cell reaction around the invaded vessels. In older cases the veins of the middle and outer layers were involved and filled with purulent masses in the middle of which were cocci. He does not regard it as properly a thrombosis, but as a "purulent endophlebitis". He looks on any extension of thrombus beyond the inner third of the uterine wall as pathological.

He made a number of unsuccessful attempts to reproduce those appearances by the experimental infection of the uteri of pregnant rabbits.

Finally, cases have been recorded of thrombosis produced by invasion of the wall of a vein by microbes circulating in the blood, that is invasion from its lumen, not from the vasa vasorum. This condition is very exceptional and is entirely denied by some writers. Widal[89] refers to a case observed by himself and Chantemesse, where tubercle bacilli had been deposited in this fashion. This is the only evidence he produces in favour of his explanation of femoral thrombosis occurring in discontinuity with thrombosis of the uterine veins. Welch[25] says "Vaquez found the tubercle/

tubercle bacillus alone in a thrombus of the femoral and profunda veins, both in the thrombus and the adjoining interna. Tubercular endophlebitis had been found in the superior vena cava by Banti and in the inferior vena cava by Guffon." Discussing marantic thrombus he says "In a case which I examined of multiple venous thrombosis complicating leucocythaemia, there was a primary mycotic endophlebitis with secondary thrombosis. There was a secondary streptococcic infection. In the intima of the thrombosed vessels were numerous scattered foci in which large numbers of streptococci were present. In these areas there was necrosis of endothelial and other intimal cells with proliferation of surrounding cells and many multinucleated leucocytes. These foci formed little whitish elevations capped with platelets, fibrin and leucocytes, the whole presenting an appearance similar to that of endocardial vegetations. There was marked nuclear fragmentation both in the intima and in the thrombi. Fresh mixed thrombi containing fewer streptococci were connected with these phlebitic vegetations. Although the vasa vasorum were hyperaemic and were the seat of a moderate emigration of leucocytes, streptococci were absent from the adventitia and the appearances decidedly pointed to the direct penetration of the streptococci from the circulating blood into the intima. I have examined three similar cases. A similar form of mycotic endophlebitis has been described by Vaquez."

S U M M A R Y.

Writers on puerperal thrombosis divide themselves immediately into three classes, those who maintain that all the cases are infective, the upholders of the mechanical theory, and a small number who are inclined to emphasise certain chemical factors in the causation of the disease. These, however, cannot be described as three different schools of thought, as the members of the first class quite recognise the importance of the local mechanical conditions as a contributory cause, and those of the second and third classes do not deny that many cases are of mycotic origin but maintain that the disease also occurs in the absence of infection.

The actual sequence of events in the undoubtedly infective cases is a matter on which opinions differ, and is probably variable. Many cases, where a virulent micro-organism is present, exhibit a lymphatic as well as a phlebitic infection. To this category belong, for example, 17 out of 27 cases reported by Heideman, 13 out of 27 by Grossman, and 4 out of 21 by Trendelenberg. Altogether about 50% of the septic cases. These are rapidly fatal cases in which the phlebitis plays a subsidiary part and is masked by the symptoms of generalised sepsis. There is a second rarer variety, of which case 1 above is an example, where septic thrombosis occurs in consequence of phlegmonous or suppurative inflammation of the surrounding/

surrounding tissues. To a phlebitis of this nature in the iliac or femoral vein Olshausen[12] restricts the term Phlegmasia Alba Dolens. It is quite comparable to sinus thrombosis in otitis media. The latter is attributed by surgeons either to a phlebitis spreading up to the lateral sinus from small tributaries in the ear or mastoid bone or to direct invasion of the sinus wall from an extradural abscess, and the pathological events in the pelvis are doubtless similar. In the great majority of cases, however, the disease commences by microbic invasion of a torn vein at the site of the placenta.

Bumm, Bardeleben, and many others suggest that relaxation of the uterus by permitting imperfect closure of these veins is an important predisposing cause. Bardeleben's experiments lead him to certain definite conclusions. He says that a very virulent micrococcus may invade the uterine wall by way of an empty vein, but that if its virulence is small it will meet with the same obstacles as in lymphatic invasion, and perish. On the other hand, if there is blood in a vein which is so invaded, a highly virulent coccus will produce septicaemia, one of less virulence a progressive thrombosis and pyaemia, while a very mild infection will cause thrombosis but rapidly die out. The same idea of the pathogenesis of puerperal thrombosis is expressed in more picturesque language by Leith Murray[96]. "In the/

the case of infection of the placental sinuses, the local reaction results in a thrombosis of the vessel, a markedly protective reaction and one likely to be successful. If, however, the infection traverses this clot, the thrombosis will also extend and barrier after barrier will be raised and demolished till the infection reaches the iliac veins and finally the femoral. This must take some time and in the majority of cases the organisms are now considerably attenuated, so that the body can cope with them. The result is phlegmasia alba dolens. But, it may be asked, if this is the course of events, why does the temperature rise rather suddenly with the appearance of thrombosis in the thigh? The explanation probably is that the exacerbation is caused by the greater tendency for autoinoculation to come as the result of movements of the thigh."

Instances in human pathology where this course of events has been observed are few. Two such cases are described by Lenhartz[97] where streptococci were observed microscopically in the clot, but failed to grow artificially and were supposed to be dead.

On the other hand, numerous bacteriological investigations with negative results are recorded. Lubarsch[34] investigated microscopically 215 cases of bland thrombosis (i.e. where no local septic complications followed) and culturally 28, and only discovered bacteria 20 times in the former and 8 times in the latter. These were not puerperal cases but were cases in the great majority of/

of which acute or chronic infective disease was present elsewhere in the body, as it usually is at death. Systematic observations of this kind on cases of puerperal thrombosis apart from pyaemia are wanting, possibly from absence of opportunities, and writers chiefly form conclusions from collateral circumstances. One negative observation by Pourtalès I have referred to (Case 14). Hulles[57] records another fatal case of pulmonary embolism where no bacteria were found in the clots. Von Bèck[81], referring to post operative thrombosis says that in cases where the field of operation was aseptic he has always found thrombi aseptic, but does not give details.

A fallacy that must be avoided in bacteriological observations is that the clotting tends to be more extensive in infective conditions of veins than the actual infection. Latzko[98] for example says "Infection of the venous wall rather than of the blood stream is the cause of thrombosis and, given a small area of such infection, the thrombus may spread widely. I have seen cases where histological examination revealed little or no change in widely spread venous thrombosis, while a phlebitis in the placental site was present and in such cases the centrally growing thrombus is sterile ..... of course stasis and other factors do play a part, but only a secondary part". Both Pourtalès and Widal relate cases where some of the thrombosed veins contained/

contained bacteria and others did not and Latzko, in the above passage, calls attention to the same fallacy about cultural and microscopic tests for bacteria that the clotting may progress both centrally and peripherally into veins which are not infected. So that in the present state of our knowledge a wide series of observations on cases in which post mortem examinations are rare is required to prove that puerperal thrombosis occurs without infection. Nevertheless I think that many circumstances point to this conclusion.

There is first of all the clinical course of the disease. I have already given figures indicating that about 50% of the cases show no other evidence of infection. This argument must be accepted with great caution in view of the case I have cited above of Pourtales' (case 17) where endometritis and infective thrombosis existed for two and a half months and the case was finally diagnosed as one of pernicious anaemia.

Heideman[58] advanced a new theory to account for those apparently aseptic cases. After discussing various anatomical and chemical contributory causes, he states his opinion that these cases are caused by a specific infection. "On careful review, I think all my cases without exception were caused by infection. Jahn found 21 out of 26 cases inflammatory, Singer 23 out of 35 certainly inflammatory. I should get a similar figure if I used pulse and temperature alone as indications, but I prefer to follow the general symptoms/

symptoms, including headache, disturbed sleep, restlessness and weakness of the heart, all of which I regard as incubation symptoms of thrombosis, the incubation period being about seven days. Localised prodromata are spontaneous pain or tenderness at the side of the uterus and tenderness above Poupart's ligament. These symptoms are as characteristic of thrombosis as bronchitis is of measles or angina of scarlet fever. My chief reason for thinking it infectious is that the cases do not come singly but in series, and one finds the same in the literature. I think it a special form of wound infection. In four cases in particular in which I determined the site of the placenta during labour, within 24 hours tenderness of that side of the pelvis set in and above Poupart's ligament, and femoral thrombosis declared itself in due course..... The same infection causes meteorism and weakness of the heart by its injurious effect on muscle. Shortness of breath is an early symptom..... At birth through the placental site the blood vessels are invaded by the microbes which increase its coagulability. The character of the disease depends on the grade of the infection. With slight infection it is limited to the neighbourhood of the point of infection - the immediate vicinity of the uterus - or limits itself to the situations where the increase of the poison has the best opportunities - namely, varices. If the infection is/

is severe, the clotting spreads widely. The infection alone and the fibrin ferment it sets free would not be enough without an undamaged circulation to cause wide thrombosis - the ferment would be diluted. But with poor circulation a local excess of ferment exists and thrombosis follows. The circulation of course fails immediately post partum owing to diminished abdominal pressure."

This theory of course has no pathological evidence behind it and is contradicted by bacterial experiments (Loeb and others), but is interesting as showing the straits to which upholders of the infective theory are reduced in attempting to account for all cases.

Another argument against the theory that all these cases are due to local infection may be founded on such cases as 5, 6 and 7 above, where thrombosis spread widely in the pelvic veins in consequence of partial detachment of the placenta before labour and where no question of infection appears to arise.

The supposition that the thromboses in question are a result of injury to endothelium caused by pathogenic bacteria or soluble bacterial poisons in the blood assisted by local mechanical factors and general low blood pressure is contradicted by the fact that severe cases of puerperal sepsis are not specially prone to thrombosis and in cases of typhoid fever and pneumonia the thrombosis occurs much later than the maximum of toxaemia.

The/

The great difficulty in the way of accepting the infection theory for all thromboses is that this theory itself is not understood; it is not a satisfactory explanation of the phenomena. How does the infective process bring about the thrombosis or clotting? This question must be separately discussed in relation to local and distant thrombosis. With reference to local thrombosis, in the first place in man we do not know what the early changes are. Pourtalès described streptococci growing in the axis of a thrombus and thrombosis advancing in front of them in one case, in another he finds the cocci growing along the endothelium and so causing an advancing thrombosis. Duffek described the same appearance. Bumm also records both of these phenomena. In other cases the explanation is that the thrombosis has resulted from degeneration of endothelium caused by the products of bacteria growing in or about the wall of the vein and the thrombus has undergone a secondary infection. The existence of these phenomena is of course undeniable, but their interpretations are quite conjectural and receive very little support from experimental work. These interpretations are further strained to explain "bland thrombosis". Bumm found that a streptococcus which did not penetrate the lymphatic spaces of the uterine wall, being delimited by a barrier of round cells, was still capable of colonizing/

colonizing a clot in a placental vein and causing it to be propagated to the side of the pelvis and producing pyaemia. The microscopic appearances support this explanation; but the further assumption that a less virulent coccus can produce a progressive thrombosis, the emboli from which act as non-irritative foreign bodies, and gradually become extinct, is merely a surmise. The experiments of Von Lengelsheim[99] and Walthard[100] and some of Bardeleben's rather indicate that under the circumstances the pathogenicity of the virus should be enhanced. Von Lingelsheim produced stagnation in a rabbit's ear by encircling it with plaster, and found that a small injection of streptococci, formerly indifferent, now produced severe inflammation or death. Walthard, performing similar experiments with indifferent streptococci from the vaginal secretions of pregnant women, got the same result. If we consider, in the second place, discontinuous thrombosis, as in the femoral or popliteal vein after labour or operation, the difficulties in the way of the infection theory are equally great. We have first of all the statistics of Lubarsch who by microscopic examination found infection in 9.3%, and culturally found it in 28.6. If infection is the cause either it must have been conveyed in the vasa vasorum, which is possible, as in a case recorded by Welch (p.93), but so rare as to be practically unknown, or the microbes must have been deposited on the endothelium from/

from the circulating blood and there set up changes which led to thrombosis (as Widal, for example, suggested). In fact, according to Aschoff, when such a thrombus is infected the microbes are not usually found on the vessel wall but in the interior of the thrombus, where they have been entangled and deposited from the circulating blood. However Aschoff, like Lubarsch, found the great majority of such thrombi not infected even in cases where a septic infection existed. Thus the evidence from human pathology is against the infection theory in the case of autochthonous thrombi while of course experimental work gives it no support.

The mechanical and chemical factors which may be concerned now demand consideration. It must be premised that the pelvic veins are more liable than any others to thrombosis. Lubarsch, in the passage I have referred to, says that in the examination of 1932 bodies he found venous thrombosis in 584 (30.1%) and in these the pelvic veins (chiefly prostatic, uterine, vaginal and haemorrhoidal plexuses) were involved in 383 and the femoral in 241. Hall Edwards[101], in a recent paper, after referring to the frequency with which phleboliths are detected in radiographic examinations, says "I have taken, or supervised the taking of, over 20,000 radiographs and so far have failed to obtain the image of a phlebolith outside the pelvic area". This peculiar liability of these veins to stagnation and thrombosis is attributable to the following causes:-

(1)/

(1) the constant opposition of gravity, (2) the absence of valves and of muscular pressure which are important auxiliaries to the circulation in the limbs, (3) the multiplicity of the channels by which the blood may be conveyed from a given viscus, a circumstance which leads to stagnation in those which at a given moment are not in use, or to a reduced current in them all.

If we consider in this light the conditions obtaining in the uterine veins in puerperae, we shall see that the factors favouring stagnation are greatly exaggerated. The broad ligament veins are always tortuous, but this tortuosity must be increased in the puerperium owing to the recent contraction of the space they occupy; the veins, as I have estimated from Hyrtl's drawings, are of nine times their normal capacity per unit of length, whereas the capacity of the arteries is only multiplied by four; therefore the venous current must be correspondingly slowed. It is, however, believed that early in the puerperium owing to the tonic contraction of its muscular walls the uterus receives very little arterial blood, so that in these large and tortuous veins the blood current must be maintained largely by the flow from the broad ligament, bladder and vagina. Another factor obstructing the outflow, to which attention has not hitherto been directed in this connection, is the compression of the hypogastric veins on the one hand and the broad ligament plexus on the other between the puerperal uterus and the/

the pelvic brim which is demonstrated in Webster's sections. This pressure must greatly impede the flow of blood from the large veins in the part of the broad ligament adjacent to the isthmus of the uterus, but does not of course affect the ovarian veins.

The intramural veins of the pregnant uterus form a network of very large and numerous vessels which, in the early part of the puerperium, are empty and flattened spaces owing to the pressure exercised upon them by the uterine muscle and to the deficiency of arterial blood. In the lower intrapelvic part of the uterus these are probably more or less congested as Webster found the cervix and vagina to be.

Another circumstance favouring venous enlargement of the pelvis during the puerperium is the relaxation of the abdominal wall which tends also to prevent the veins from being properly emptied during inspiration.

These anatomical conditions, which are present in all puerperae, and appear to render blood stagnation in the pelvis inevitable, are not alone sufficient to bring about thrombosis. In discussing the clinical aspects of the question, I have shown that in puerperal cases prolonged second stage, haemorrhage, operative labour and sepsis are such common antecedents of thrombosis as to make a causal connection very probable. These four conditions are not mutually exclusive, but in fact overlap one another so much that they can probably be reduced to two, namely, haemorrhage and sepsis. In relation/

relation to post operative thrombosis, it has also been shown that haemorrhage and sepsis are the most important antecedents. Sepsis as the direct cause of thrombophlebitis has already been discussed. As an indirect cause it may be influential by injuring the inner coat of the veins and by increasing the coagulability of the blood, but the evidence on those points is conflicting and reasons have been adduced for believing that their importance is exaggerated. It is also detrimental to the blood pressure both by direct poisoning of the heart and by the diminution of muscular activity to which it leads. Similarly recent haemorrhage leads to a temporary increase of the coagulability of the blood and chronic anaemia is injurious both to endothelium and to heart muscle. So that a place in the causation of thrombosis may with good reasons be assigned to those two constitutional factors. There are many cases in which they are both absent.

The chemical details of puerperal involution of the uterus are unknown. But a large amount of material is absorbed from its wall; there is first the decidua which, according to Wormser[102], a few days after labour is divided into two layers of which the inner necroses and is cast off; here is a possible source of thrombokinase. The shrinkage of the uterus has been measured. According to Williams, at the end of labour the whole organ weighs 1000 g., one week later 500 g., two weeks later/

later 375g., and at the end of five or six weeks 40 to 60 g. Webster says its length is reduced in 15 days from $7\frac{7}{8}$ inches to $3\frac{3}{4}$ inches. Senger estimates the average length of a fibre in the full time uterus at 208.7 microns and five weeks after labour at 24.4 microns. It is supposed that the excess disappears by a digestive process which is favoured by the anaemia and by the presence of fatigue products, especially lactic acid. Some of the resulting substances are probably lost in the lochia but in fact the urine contains from 30 to 50% excess of nitrogen, so that much must be absorbed. In this great and rapid catabolism of muscular tissue a second possible source of thrombokinase must be recognised.

As shown by Franz[103], the presence of leucocytosis at the termination of labour both in the blood generally and in the internal genitals is another factor favouring clotting.

There does not, however, appear to be normally any diminution in the coagulation time of the peripheral blood in puerperae in spite of the presence of an excess of fibrinogen, although Jacobi[105] describes a case of femoral thrombosis where the coagulation was reduced to 45 seconds (40% of normal) and which rapidly cleared up after the exhibition of citric acid. Normally, however, calcium in the blood is diminished after labour. On the other hand, as has been seen, haemorrhage is a very frequent/

frequent precursor of thrombosis which may be due to the cardiac weakness or to the increased coagulability of the blood which it causes.

Another circumstance of importance is the presence of coagula in the veins torn at the placental site. These do not normally extend deeply into the uterus, but it may be suggested that in the absence of tonic contraction of the uterus they might do so and spread to the broad ligament either by continuity or in consequence of the expression of the clot or its serum by uterine contractions. In fact atonic bleeding has been frequently noted as a precursor of pelvic thrombosis.

Many writers are inclined to invoke some unknown chemical element to explain puerperal thrombosis. As I have mentioned, Grant wrote to about twenty authorities in America for their opinions as to the cause of post operative thrombosis, and several of these suggested some unknown blood dyscrasia. Mendel[104] believes there is a disease which he calls "Thrombophilia" and which is hereditary. Hertz and Haunequin[108] speak of a similar affection which they attribute to "une localization de l'arthritisme sur le tissue veineux". Keim[107] attributes many cases to intoxication of the liver from constipation or mucomembranous enteritis which impairs the antithermobotic function of the liver. He believes it is often an aseptic extension from antipartum clotting. He also speaks/

speaks of phlebitic heredity.

Among recent theories on the subject, the most interesting is that of Filbner[108]. He found that after removal of the blood a very powerful thrombokinase could be obtained from foetal membranes, placenta, uterine or intestinal muscle simply by macerating for a few hours in saline solution. He found such an extract very effective in stopping sinus bleeding in cranial operations, and that quite a small dose injected into the vein of an animal caused rapid death with coagulation. He made attempts to immunize animals against such an extract of uterus, but unsuccessfully. In the course of his experiments he found pregnant bitches were susceptible to the poison, but that for about six weeks after giving birth to a litter they were immune to ten times a lethal dose. Filbner is of opinion that after labour and after operations this substance is absorbed into the blood and that an antibody exists during the puerperium and that puerperal thrombosis is due to deficiency of the antibody or to excessive absorption of this thrombokinase. This very plausible suggestion has not been confined nor, so far as I know, contradicted.

CONCLUSIONS.

About half of the cases of pelvic thrombosis in puerperae are caused by septic infection.

The residue do not give clinical or pathological evidence/

evidence of sepsis and are probably due to the action on stagnating blood in the uterine or parametric veins of thrombo-kinetic substances absorbed from the interior or walls of the uterus. Liability to this accident is increased where sepsis, anaemia or cardiac weakness is present.

EXPLANATION OF FIGURES.

Figure 1. Sacrum and adjacent parts of innominate bone of a female child aged 2. The ureters and middle sacral artery have been removed leaving exposed the venous plexus in front of the sacrum and the branches which penetrate the anterior sacral foramina.

Figure 2. Uterus and broad ligaments of a woman of 47, seen from behind. Part of the posterior layer of peritoneum and the arteries have been removed. The left ureter is exposed. There has been peritonitis at the extremities of both tubes.

Figure 3. Uterus and broad ligaments of a woman of 49, seen from the front. Part of the anterior layer of peritoneum has been removed. The veins have been dissected on the right but not on the left side. The right ureter is exposed. The right superior uterine vein is absent.

Figure 4. Section of the pelvis of a woman of 59; it passes 7 mm. above second posterior sacral foramen and 8 mm. above lower border of symphysis pubis. The uterus is retroverted and pushed to the left by distension of the lower rectum. Part of the anterior layer of the broad ligament has been removed to expose the parametric veins, which appear somewhat atrophied. The uterus is nearly normal in size.

I am greatly indebted to Professor Arthur Robinson for kindly allowing me to make dissections in a room in his department, to Drs. Theodore Shennan, Carnegie Dickson, Haig Ferguson and James Young for anatomical material, to Mr. Andrew A. Gamley for the drawings, and to the President and Council of the Royal College of Physicians of Edinburgh for permission to read in the library.

Fig. 1.

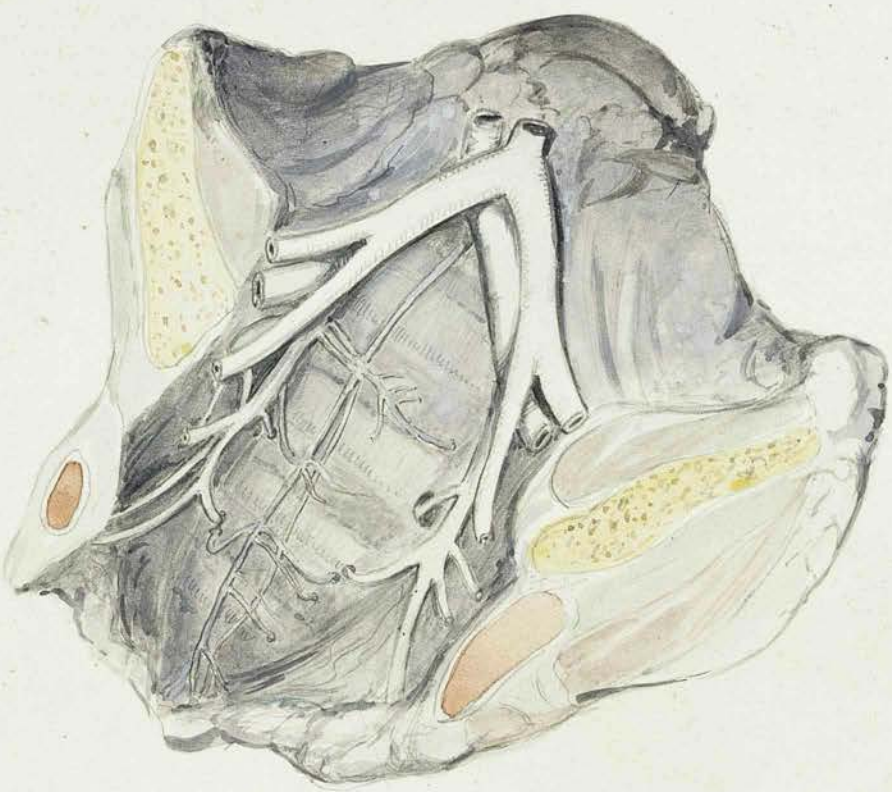

Fig 2

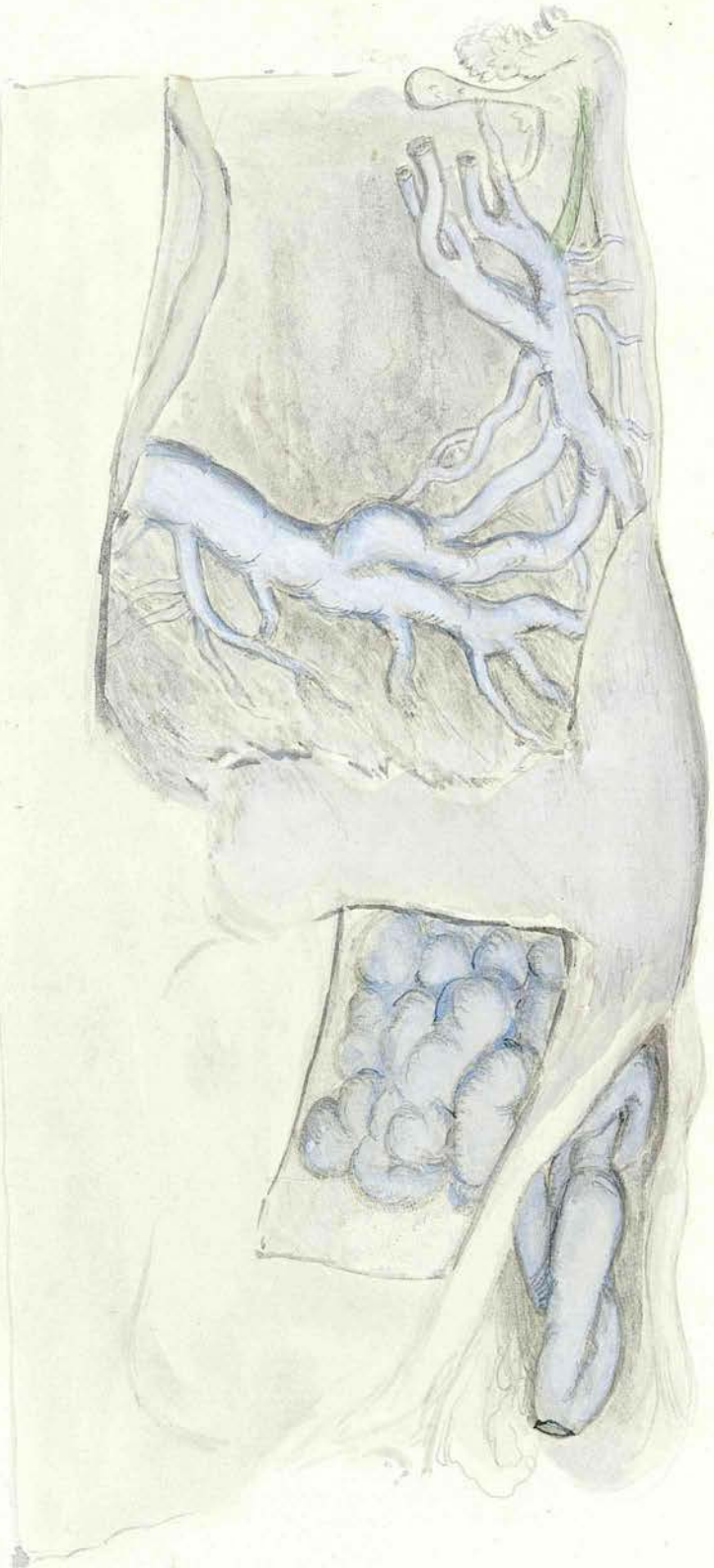

Fig. 8.

Fig 4.

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