Chronic Nephritis, Accidental Hæmorrhage and Eclampsia.

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Chronic Nephritis and Eclampsia.

The conditions mentioned in the title of my paper are all inter-related. When a woman with chronic nephritis becomes pregnant, if abortion or miscarriage does not occur, she may eventually suffer from accidental hæmorrhage or may become eclamptic or uræmic; in accidental hæmorrhage, albuminuria may appear and eclampsi- arise, even when no evidence of previous renal aberration existed; in eclampsia, pure and simple, the urine often boils solid. In all three, the kidneys are implicated or may become implicated; and in all three, the renal state participates in the development of a toxæmia. While, however, the complications of pregnancy in women with chronic nephritis are naturally and rightly attributed largely, or mainly, to the state of the kidneys, a toxæmia following accidental hæmorrhage is imputed to a cause other than renal insufficiency; and the same is the case with eclampsia. In eclampsia, though renal lesions are common, they are so often out of proportion to the severity of the convulsive attacks that it is conceived that the renal state has no direct relation with the toxæmia. If eclampsia is dependent on renal insufficiency, the renal lesions, it is argued, should be commensurate with the clinical picture.

It is, however, clear that the kidneys are always implicated in eclampsia, and that their enforced inactivity plays a large part in the development of convulsions. Whatever the structural state of the kidney, oliguria or anuria always occurs with eclampsia, and this functional incapacity precedes the eclampsia. Though the convulsions may still further impair the kidneys and convert an oliguria into an anuria, a diminished output of urine always precedes the fits. The outstanding phenomenon of pre-eclampsia is a diminished output of urine; eclampsia and diuresis are incompatibles. Conversely, the basis of all treatment is to get the kidneys to act, all experience teaches that if this happen, the

patient will get well.* How, then, can deficient eliminating powers of the kidneys be dismissed as a cause of eclampsia?

Unhappily, the microscope has misled observers. The discovery post-mortem that the kidneys may show little cellular change is not evidence that the kidneys were working efficiently during the fatal illness; it simply demonstrates that the renal structure has not been greatly damaged. If an anuria be induced rapidly and if fits and early death ensue, how can one expect the kidneys to show evidence of marked disease? The microscope displays the dead or dying cells, it does not show the cells that were wounded or thrown out of action. In the same way, the (reputed) occasional absence of albuminuria is disconcerting, but the failure to find albumin does not indicate that the renal output is normal or sufficient. The existence of albumin in the urine of pregnant women *per se* is of little moment, it suggests that the kidneys are not normal—it indicates that a worse condition may arise, and is therefore important, but the point that matters is whether the kidneys are removing from the blood the waste products in sufficient amount per unit of time. If the woman is passing plenty of water, however much albumin it contain, we may suppose this is so. The diminution in the excretion, the passage of an insufficient quantity each twenty-four hours, not an albuminuria, is the great danger sign.

The fact that when chronic nephritics become pregnant, they rarely become eclamptic, re inforces the opinion that eclampsia depends on some other factor than inefficient kidneys, and this certainly is so. Eclampsia does not depend only on inefficient kidneys: it depends as well on an inefficient liver. Blockage of both ureters or removal of the only kidney does not produce eclampsia—nor does stasis in the renal veins. That the liver is gravely affected in eclampsia is admitted. If poisons from the intestinal tract get into the systemic blood unchanged, and if the kidneys cannot remove these poisons sufficiently quickly, eclampsia results. These are the essential factors con-

*Geipel reported a case, diagnosed clinically as eclampsia. On the seventh day, the excretion of the urine had become abundant, but the œdema remained unaltered, Cheyne-Stokes breathing appeared and the patient died. There had been only one fit, half an hour after delivery, and this had been followed by anuria for four days. Post-mortem: extensive necrosis of the renal cortices, and a peculiar necrosis of the spleen were found. The liver, apparently (macroscopically and microscopically) was normal.[10]

†The specific gravity of the urine in relation with the amount passed per day is obviously an important sign of renal efficiency: Fishberg regards it as a reliable test of renal function. "As is well known, the maximum specific gravity of the urine falls progressively as the kidney fails and forms a measure of the functional capacity."[7]

cerned in eclampsia. Other factors, possibly, come into play—such as the waste products produced peripherally, in the striated muscles, under certain conditions, but these are subsidiary, and may be neglected. If, then, in chronic nephritis the liver is normal or sufficiently normal, and the woman becomes pregnant and the liver remains adequate, why should eclampsia be expected?

Whether in chronic nephritis, apart from pregnancy, the liver is normal, I do not know; Saint-Blaise speaks of "la foie Brightique"[35]; but in most cases the organ seems adequate. In spite of that, chronic nephritics, when pregnant, occasion great concern. Not eclampsia—not an hepatic disability—however, is feared, but exaggeration of the renal condition and especially abortion or miscarriage. In order that term may be reached or a viable child be born, constant and careful supervision is necessary[43]. How different from this is the ordinary case of eclampsia—occurring as a rule in a young, previously healthy primigravida, who up to the attack has been busy, active, and running her house. If in the latter case, the manner of living—by restricting the blood flow through the liver and kidneys—is the cause of the eclampsia; in women with chronic nephritis, spending their days on a couch or in bed, the acute liver abnormality from such cause is prevented. Why, then, be surprised that such women escape eclampsia?

It is true such a woman may become "uræmic"—chronic nephritics, apart from pregnancy, become uræmic.* But if the

*It seems necessary here to attempt a definition of "uræmia." De Wesselow gives Volhard's classification[45]: (1) True Uræmia; (2) Pseudo-Uræmia; (3) Mixed Uræmia.

The symptoms of true uræmia are weakness and wasting, gastro-intestinal disturbances, liability to infection, motor-hyperexcitability, and hyperpnœa. "True uræmia is frequently a singularly undramatic condition, and is, in many instances, indistinguishable from the so-called latent uræmia which follows bilateral calculus suppression, or cortical necrosis of the kidneys." There is nitrogenous retention, and, de Wesselow adds, phosphate retention. The blood-pressure may be raised. The actual cause of death is unknown.

The symptoms of pseudo-uræmia, or "eclamptic pseudo-uræmia," are headache, vomiting, slow pulse-rate, and generalized convulsions. The patient may lapse into coma without preceding convulsions. "The symptoms of the condition, whether occurring in connexion with acute nephritis or with true eclampsia, are the same." The blood is dilute. "In contra-distinction to true uræmia, the blood-urea content is not appreciably increased, and phosphate retention is absent . . ."

Mixed uræmia is a mingling of these two. "In subacute nephritis the two types of uræmia may coexist, and this fact has, in the past led to considerable confusion." There are raised blood-pressure, hydræmia, convulsions, retention of nitrogenous waste products and phosphates. (de Wesselow[39]).

chronic nephritis is so bad as to render uræmia likely, pregnancy will scarcely occur, or, if it does, will not continue. If, then, a woman with chronic nephritis becomes pregnant and the pregnancy continues and she becomes convulsed, the convulsed state must be attributed to the pregnancy, and the nephritic state be regarded as a predisposing or even precipitating cause. From the clinical point of view, these cases differ not at all from eclampsia, and according to Whitridge Williams are to be treated "along the same general lines."[42] Possibly, efficient treatment before the fits—rest in bed and proper diet—such as we give in pre-eclampsia and should give in nephritic toxæmia[42]—would prevent the "uræmia." Clearly, if a patient with chronic nephritis and a good abdominal wall or a uterus larger than normal for the time of pregnancy (e.g., with twins), leads an active life, a liver defection may arise, as may an exaggeration of the renal difficulty. In such cases, the post-mortem shows not only signs of an old-standing nephritis, but also recent pathological changes identical with those found in eclampsia are present. Possibly liver changes occur, also in line. Necrotic changes may indeed be absent,[42] but it must be remembered that even in ordinary eclampsia, the liver lesions, like the renal, are variable. In a case of eclampsia complicating concealed accidental hæmorrhage reported by Couvelaire,[4] the liver was simply pale, and microscopically no lesion pathognomonic of eclampsia was found. Kehrer discussing Geipel's case of anuria, which also followed premature separation of the placenta but in which no eclamptic phenomena appeared, stated that cases of eclampsia occur without liver changes, the poison affecting especially the cerebral cortex.[15] Recovery of the liver is also a possibility, and seems to explain the apparent normality of the organ in Geipel's second case in which, seven days after the only fit, death occurred.[10]

The differentiation between eclampsia and uræmia clinically is a fine point, and often impossible. The progress of the patient after delivery may have to decide it. If the blood-pressure and urine become normal "by the end of the second or third week," the convulsions are imputed to have been eclamptic, otherwise, uræmia was the cause.[42] But if a pathological process result in changes which persist, how can it be considered as different in nature from a pathological process, producing an identical clinical picture and similar underlying changes from which complete recovery occurs? Does the fact that lesions in the one existed before the attack, while in the other they did not, affect the issue? But lesions which persist do not always seem to have existed prior to the illness. It is true that in eclampsia the kidneys frequently, perhaps usually, recover, but it is also

true that eclampsia may determine persistent renal changes with all their results (high blood-pressure),[13] so also, in chronic nephritis, pregnancy tends to leave the kidneys worse. Whitridge Williams states that if a pregnant woman with chronic nephritis is not seen "until after the onset of convulsions the condition is usually mistaken for eclampsia"; but the only proof he gives that the condition is not eclampsia is that after delivery the blood-pressure remains high, and albuminuria with casts continues. The occurrence of retinal hæmorrhages and albuminuric retinitis may indeed help in the differentiation, but "it is to be remembered that such lesions occur only in a fraction of the cases of nephritic toxæmia, so that a negative finding by no means precludes its existence."[42]

In the endeavour to distinguish between these two clinical states, emphasis has been laid on the state of the blood; and broadly speaking, we may say that the blood pictures are different. In eclampsia, the non-protein nitrogen of the blood is not greatly raised,* in uræmia, the increase is marked. And it is thought that because in eclampsia, the non-protein nitrogen of the blood is only slightly different from the normal that eclampsia is not a uræmia—is not due to an increase of waste products in the blood, and not due to a primary defect of the excretory organs. In chronic nephritis, it is argued, the non-protein nitrogen of the blood is greatly raised, but these patients more often abort than become eclamptic; in eclampsia, the non protein nitrogen of the blood is only slightly raised, yet convulsions appear and dominate the picture.

The non-protein nitrogen in the blood does not represent the sole waste product in the blood; the kidneys play an essential part in maintaining a sufficient alkalinity of the blood, and in doing this excrete various bodies. Apart from this, there are great differences between the woman already the subject of chronic nephritis who becomes pregnant, and the healthy young

*That the non-protein nitrogen in the blood in toxæmic pregnancy is raised seems certain: see Killian and Sherwin,[16] Caldwell and Lyle[3] and de Wesselow,[38] Mackenzie Wallis,[37] however, states that no striking deviations from normal pregnancy occur; Plass,[31] states that "these constituents are usually, but not invariably, increased above the normal pregnancy values, but less frequently exceed the commonly accepted standards for non-pregnant individuals . . ."

But if an individual is working and eating and the excretory organs are inefficient, an increase of the non-protein nitrogen in the blood would seem a reasonable expectation. "With few exceptions, defect of the urea excreting power of the kidneys appears to be the rule in cases of the toxæmias of pregnancy, . . ." (de Wesselow.[38])

woman, who being pregnant, becomes the subject of a pregnancy toxæmia. In the one, the non-protein nitrogen of the blood is already raised; in the other, the non-protein nitrogen of the blood is normal. In the one, the cerebral cells have already become accustomed to a raised percentage of the non-protein nitrogen in the blood; in the other, the cerebral cells are strange to such a rise. The question of adaptation plainly comes in here. An individual habituated to morphia, alcohol, or arsenic, is unaffected by doses of these poisons to which the unhabituated readily responds. The babe in arms, upset by food, becomes convulsed; the non-pregnant adult, upset by similar cause, usually suffers simple headache and malaise. In normal man, on an ordinary diet, the blood urea varies from 20 to 40 mg. per 100 c.cm. of blood; but in elderly people it may reach 50 mg. or more "without any definite evidence of renal disease apart from senile changes" (Maclean[18])—i.e., without apparent effect. And if the result of acute nephritis, e.g., from scarlet fever, is a "pseudo-uræmia"* (de Wesselow[39]), the non-protein nitrogen of the blood must be less than in cases of uræmia caused by chronic nephritis; but the convulsions in the former, according to de Wesselow, are more severe than those in the latter. Thus, the fact that the marked rise of non-protein nitrogen in the blood in pregnant nephritics is ineffective in producing convulsions, does not invalidate the conception that when pregnancy occurs in a healthy young and strong nullipara, a slight rise of the non-protein nitrogen in the blood may result in eclampsia.

Moreover, the non-protein nitrogen of the blood is not a homogeneous substance; it represents the nitrogen contained in several very different non-albuminous bodies. Some of these, such as urea, whatever their percentage in the blood, are perfectly harmless,† others (perhaps certain amino-acids, or other nitrogen-containing bodies), even in small doses are noxious.‡ The headache and malaise of bilious attacks and also those of pre-eclampsia show that some or other product of certain food-stuffs is

*See footnote p. 714.

†Increase of urea in the blood must affect the osmotic pressure of the blood (Gram, [12]), and thus have various influences. For example, it must increase the absorption of all sorts of bodies from the gut and thus tend to induce headache, malaise and even convulsions.

‡ " . . . there is no evidence that the nitrogenous waste-products exert any toxic influence upon the organism, . . . (Their) retention . . . is a useful guide to the degree of renal damage present, but in itself is apparently harmless; . . . "[39] But neither de Wesselow[39], nor Maclean[18] consider in this respect the effect of any other non-protein nitrogen body in the blood than urea.

noxious. If, then, the non-protein nitrogen in the blood is greatly raised, and if this rise is due to the accumulation of harmless bodies, such as urea, the patient naturally remains unaffected: but if the non-protein nitrogen in the blood is only slightly raised, but the increase is due to noxious bodies, the patient is not likely to remain unaffected. This seems to explain the apparent discrepancy between the increase of non-protein nitrogen in the blood and the reaction of the patient in these two types of case.

The noxious non-protein nitrogen bodies arise mostly in the gut and on absorption are destroyed by the liver, being converted by the liver into some harmless substance, possibly urea.[36] They also probably arise to some extent at least and under certain conditions in peripheral tissues, which tissues, apparently, however, have the power of destroying them, just as they have the power of converting unwanted amino-compounds, brought to them in the blood, into urea (Folin and Dennis[8]). In this respect, it is interesting to note that in such a low vertebrate as the frog, the products of the muscular activity of the hind limbs—those used in locomotion and thus on which the preservation of the animal depends—pass in part through the kidneys, but in part through the liver—by way of the renal-portal vein. Otherwise, they pass by lymphatics straight to the lungs. This indicates that muscular activity, in the absence of a good respiration, produces waste products inimical to the host; and thus, that the effect of peripheral metabolism in man must not be lost sight of in considering such a question as eclampsia. In warm-blooded vertebrates, the renal-portal vein does not exist, being unnecessary; the increased oxidation in the periphery doubtless was the cause of this disappearance, as it is probably the cause of the conversion of dangerous non-protein nitrogen products into urea or some other harmless body at the place where these bodies are formed. Possibly, during the fits of eclampsia, not only sarcolactic acid, but noxious nitrogen-containing products are let loose and enter the circulation, and play their part in the advance of the disease.

We are not considering the effect of eclampsia, however, but its cause; and the increase of non-protein nitrogen in the blood in relation with this. In chronic nephritis, the liver is, apparently, normal and the gut is the great source of noxious non-protein nitrogenous bodies, therefore since the liver converts these noxious bodies into harmless ones; a rise of non-protein nitrogen in the blood without convulsions, cannot be very surprising. In the pre-eclamptic state, the liver is not normal, it is not working as it should, and if noxious products from the gut get into the portal vein they stand a good chance of entering the systemic blood

unchanged—passing either through the liver itself or by way of anastomotic channels. If up to this moment, the kidneys have been working fairly well, but now also strike work, even a small rise of non-protein nitrogen in the blood may be effective in causing convulsions.

Personally, I believe that eclampsia is simply a uræmia. By "uræmia," I mean a pathological state, characterized by a rise, however slight, of some nitrogenous waste or by-product in the blood, due to impairment of the liver or kidneys or of both. The definition is unaffected by the variety of the waste or by-product, provided it come from protein, whether of endogenous or exogenous source, nor does its amount matter. The conception of uræmia at present held by most writers is simply that of the terminal stage of a long-lasting disease, but to recognize uræmia first at this stage helps no one. To-day's diagnosis of uræmia from its terminal symptoms and signs is comparable to diagnosing a case of carcinoma of the breast only after a large lump, fixed to the chest wall, with extensive lymph-gland involvement and with widespread metastases, is present; such a definition is worse than useless. Defective kidneys, plainly, must tend to produce uræmia, but uræmia frequently is prevented by prolongation of the renal activity at the lower level of efficiency, the incapacity for producing a highly concentrated urine being compensated for by a corresponding polyuria (Fishberg,[7]). Thus, the kidneys work overtime, when, if they were normal, they would be resting. In the pregnant woman, a curtailment of the renal activity, of which a diminution in the output of urine is an indication must result in uræmia. If the liver be healthy, it may matter little, but if the liver be inactive, then instead of harmless non-protein nitrogenous bodies accumulating in the blood and tissues, noxious ones enter the organism.

This opinion is based on what happens when a dog with an Eck's fistula is given meat,[29] and on the well-known effect of food as a precipitation of eclampsia.* The former, I think, shows that some non-protein nitrogenous body is responsible for the convulsions: the intoxication, apparently, is not simply an acidosis.[29] But whether the convulsions of pregnant women are due to a rise of this, or to an increase of some other

*It is interesting to find that Van Slyke, in his experiments on dogs, in which he injected a solution of amino-acids intravenously, found that an over-dose in one case produced a convulsion with subsequent death.[1] The heart weakened before the injection was finished. The dog was a female in the early stage of pregnancy and had been kept on a protein-free diet for nine days before the experiment.[36] (Exper. 4, p. 224).

waste product in the blood, does not greatly matter. The essential point is that eclampsia is caused by an inability of the liver and kidneys to function adequately, because these organs are compressed—during posture and during sleep at night,[24] and especially by movement to the extent that the blood-flow through them is impaired. This is the point that matters; for if it be true—if the facts fit—we become immediately masters of the situation; we can tell in which type of individual eclampsia is likely to occur, can warn predisposed individuals and more readily prevent the disease, and we shall know best how to treat it. In certain cases, no convulsions appear during the pregnancy; but the labour so further upsets the viscera that during the puerperium eclampsia is induced. How often in the early puerperium the administration of food precipitates the disaster, I do not know, but I know of one fatal case caused, in my opinion, by gruel. After labour, a woman requires rest, not food; and especially if there has been any suggestion of visceral difficulty or disorder.

I have already given some reason for this opinion. In 1913, I showed that the intra-abdominal pressure is increased in pregnancy, more especially in first pregnancies; and that this depends on the rapid enlargement of the uterus, and the response of the abdominal walls[24]; and in 1921, I showed that the incidence of eclampsia, the selection of cases by the pathological process, is in alignment with the idea—the facts fitting almost exactly[25]. The fate of the fat-laden connective tissue within the abdomen during pregnancy is confirmatory. The disappearance of the fat in the great omentum, in the peri-nephric tissues,* and in the pelvis (Veit, [44]), with the advance of pregnancy, as shown by the findings at Cæsarean section and by other inquiry, even in women who are not emaciated but on the contrary possess sub-cutaneous tissues well laden with fat, demonstrates that during pregnancy a force within the abdomen arises, producing in unessential tissues an atrophy and tending in others to prevent the hypertrophic response so necessary for the well-being of the individual. The regressive changes in the abdomen produced by pregnancy are not limited to the musculatures enclosing the visceral mass; at times, they occur also in the viscera themselves, and a metabolic upset, even the appearance of convulsions, is the natural result. So also we see that marked variations in size of the full-time child occur; in primigravidæ, the child from this cause is usually smaller than in multiparæ—successive new-born babes of any healthy woman tending to increase in size.

*Geipel refers to this particular in one case, thus: Fettkapsel mittelstark.[10] It is not supposed that a complete disappearance of fat always occurs: variations like those of the child's size are to be expected.

Nothing but an impediment to the circulation in the abdomen can explain these phenomena of atrophy, inhibition, and regression. No one of the specific toxæmic hypotheses of eclampsia does so, nor does any one of these hypotheses explain eclampsia. In this respect, the conception that the syncytium is inherently evil and that its descendants, living or dead, act perniciously in this way, is unjust, unwarranted and untenable; on the face of it, it is an absurd supposition. The idea that specific antibodies in pregnancy arise and prevent toxæmia has not been maintained; the supposition that the endocrine glands, including the breasts, by some aberration, occasion eclampsia has no basis in fact.* Although the milk-fever of cattle, on which the mammary conception of human eclampsia was founded, and which is an eclampsia or an eclamptic state or allied to eclampsia, is precipitated by a great mammary activity, yet is there no disease, no abnormality of the udder. The only feature is the enormous output of milk for which these beasts are bred. The milk-fever of cattle is explained by a deficiency in function of the excretory organs, of the liver and kidneys, occasioned by circulatory disturbances which the physical state of pregnancy and the great yield of milk after labour in these cattle successively determine[28].

That aberration in the circulation can occasion a toxæmia is plain. Valvular disease of the heart with loss of compensation presents a clear example. With failure of the central organ a toxæmia arises, obviously of purely mechanical origin. The toxæmia is due to inability of the body parts, especially of the liver and kidneys to function adequately. In the same way, an obstruction to the blood flow through visceral parts in pregnancy, however good be the heart, can produce a toxæmia. It also is due to failure of the excretory viscera. Truly, the two toxæmias are different, but so are the ways in which each patient lives. The one with failing heart is confined to bed and cannot eat; the woman pregnant, with her heart quite good or even hypertrophied but with viscera about to strike work, is busy and active and usually eats well. In fact, a good meal seems often to precipitate the disaster. In the same way, Matthews Duncan's criticism (1857)—so often repeated—that ovarian tumours and fibroids often grow as large or larger than the pregnant uterus, and seemingly must produce as great or greater pressure on the viscera yet do not produce eclampsia,[6] loses its strength. Manometric observations of the pressure in the rectum in these respective types, the condition of the abdominal wall in each, and the manner of living are

*Crook seems to think that possibly the toxæmia of pregnancy is related to or caused by aberrant action of endocrine glands affecting the water metabolism of the body.[5]

all different. Women with large ovarian cysts are not busy and active, anorexia is a common accompaniment.[20]

Moreover, there is another difference, the blood-pressure is not so raised. This certainly is so in cardiac cases, it holds also in the others, and makes a big difference. A concomitant, universal, in the eclamptic process is a raised blood-pressure*. That this is so has long been known. The older physicians applied ice to the head or even douched with cold water the head and bust of patients suffering from puerperal convulsions. They noticed the throbbing of the carotids and the suffused aspect of the face, and referred the effect of food, as a precipitant of puerperal convulsions, to its determining a marked flow of blood to the head. Blundell (1828) even showed that a great determination of blood to the head can produce convulsions, comparable in every way with those of the puerperal woman. He obstructed the aorta in the dog and found that convulsions occurred; but if he bled the animal first, convulsions were prevented.[1] He compared the convulsions of pregnant women with those of infants due to stomach upsets, and mentioned the value of the hot bath in both. The hot bath acts as a "diffusible stimulus"—it dilates peripheral vessels, and thus detracts blood from the head.[1] We may add that it also relaxes striated muscles—for instance, those of the abdomen, and if the blood-flow through the liver and kidneys is obstructed by undue contraction of the abdominal wall, the hot bath, by reducing muscular tonicity, must favour the blood flow through these viscera previously obstructed in this way, and facilitate their functioning. Venesection, perhaps, has more immediate effects in reducing blood-pressure, it also seems to act by reducing the "strength" of the patient—in which the tonic contraction of the abdominal muscles is a factor. Morphia, chloroform, veratrum viride, the lateral position, starvation and purgation, and emptying the uterus, all act in the same way. They do so either at once or in time, either directly or indirectly or in combined fashion. According to Barton Cooke Hirst, the best and quickest way of reducing the blood-pressure is by puncturing the membranes and letting out the liquor amnii.[14] Such an act, from Baudelocque's time to to-day, has been noticed to cut short the convulsions in eclampsia.

Thus, while a rise of the non-protein nitrogen in the blood of a pregnant woman may be the exciting cause of eclampsia, it acts only if the blood-pressure be raised. The compression of the abdominal visceral mass, the rise of waste products in the blood,

*" . . . cases of true eclampsia are said to occur without any definite rise in the blood-pressure. Further investigation is highly desirable."[39]

and the increase in volume of the blood, a concomitant of pregnancy[22], are all determinants of this increase. The blood, unable to traverse with ordinary facility the abdominal visceral mass, chooses channels more open to it—those of the limbs and the brain. Thus, the cerebral cells are impregnated with a vitiated blood under greater pressure than normal—and convulsions result. The relief of the abdominal compression, by yielding of the abdominal muscles, whether caused by the hot bath or the other remedies we have mentioned, diminishes the blood flow through the brain, thus, though the blood remain for the moment as vitiated as before, convulsions cease. But the reason that less blood traverses the brain is that more blood now passes through the abdominal viscera, including the excretory organs, for the difficulty existing before is diminished or removed. Thus does the blood tend to become immediately less vitiated.

Just as an interaction between the blood flow through the abdomen and that through the limbs and skull exists—as shown in the normal by the mechanics of "attention"; in normal pregnancy, by the improvement in physique and the brighter mentality; and, in eclamptic states, by the occasional bursting of blood vessels (cerebral hæmorrhage)—so between the several visceral parts within the abdomen is the same force in play. The idea that the blood supply to different parts is determined solely by vaso-motor control is erroneous. In "attention," there is an increased blood supply to the brain, but this is caused by a tightening up of all the muscles of the body, those of the limbs and of the abdomen, not by a contraction of arterioles other than those of the brain. The latter, if it occurred, would result in stagnation of blood in the capillaries and veins in the limbs and abdomen, and thus less blood than more would be sent to the brain. In the same way, Goll[11] found that by tying the branches of the abdominal aorta other than the renal, the output of urine was increased. This was caused not by the need of the animal, but by obstructing the blood-flow through other parts.

In the abdomen, the blood has only three possible paths—by way of the liver, by way of the kidneys, and by way of the uterus. Each of these has some peculiarity. The blood can reach the liver in several ways: by the gastro-intestinal path and portal vein, by the pancreatic path and portal vein, and by the spleen and portal vein. Blood can also reach the liver directly, by way of the hepatic artery; and according to Macleod and Pearce, in the dog," from 26 to 32 per cent. of the blood which flows through the liver is derived from the hepatic artery"[19]—an opinion which McMaster and Rous[21] tentatively accept. The arterial blood mixes with the venous portal blood in

the hepatic lobules, so that—if the conditions in the dog and in man may be regarded as comparable—"about one-third of the blood in the liver is arterial"[19]. The kidney receives only arterial blood, but in the organ the supplying renal branches divide into cortical and medullary arterioles—so that blood entering the organ has a choice of two paths. In the pregnant uterus, the placental supply, from its magnitude, distinguishes this path. The volume of blood passing at any one time through each of these three main paths depends for one thing on the several resistances—that is, on the resistance in the liver, on that in the kidneys, and on that in the uterus, all of which are conditioned not only by the calibre of the corresponding supplying arterioles (vaso-motor control), but also by the compression of the capillaries or sinuses into which these arterioles open.

Thus, although with diminution of the intra-abdominal pressure, the blood flow through the liver and kidneys is increased, the increase through each is proportional to the resistance offered to the passage of the blood through the other; and, moreover, to the resistance obtaining in the remaining possible tract (uterine). If the placental circulation should cease (intra-uterine death of child), more blood will go through the excretory organs and more blood will go through the liver or through the kidneys according to circumstances. If extensive areas of the renal cortices are necrosed, or the block preceding this states persist—so that blood cannot get through, more blood will traverse the hepatic tract than if the renal resistance were less. The blood will reach the liver in greater volume by one or other of the several ways, but more particularly by the hepatic artery, since the aortic pressure must be raised and the blood has not to traverse an intervening capillary bed (gastro-intestinal, pancreatic, splenic). In any case, more blood will go through the liver. We may thus suppose that waste amino-compounds or noxious nitrogen bodies, in the systemic blood, will be converted into urea—and at a greater speed than normal; but the urea, because of the renal state, will accumulate in the blood* If, on the other hand, the block to the blood flow in the kidneys is less, less blood will go through the liver and more through the kidneys. A lesser proportion of waste nitrogen-containing compounds in the blood will be converted into urea; but the kidneys will continue to get rid of all such bodies. If, however, a block in the liver, comparable with that in

*Compare the case of puerperal suppression of urine reported by Crook.[5] In spite of the apearance of urine, the urea in the blood rose to a great height but there were no convulsions. I believe I am right in saying that the mentality of these patients is fairly clear much more so than after eclampsia. And they do not get convulsions.

the kidneys with anuria should occur, the patient will die, for the kidneys alone cannot cope with the situation.* When the block is complete, neither blood from the portal vein nor from the hepatic artery can traverse the organ: acute yellow atrophy rapidly ensues and ends the scene. In this case, the vomiting, acting mechanically on a liver already seriously compressed by the pregnancy and in many cases further disturbed by the labour, seems to determine the disease. Vomiting, when persistent, renders hepatic activity difficult or impossible[26] and similarly militates against renal efficiency[27], so that even if the kidneys are good to start with and an hepatic block favours their supply, they rapidly become impaired.

In eclampsia, the block to the blood-flow through the excretory organs is usually not absolute, so that improvement is possible; and naturally, with the return of the circulation through these parts, they gradually begin to work again—and in a manner depending on the state of their cells. The liver, we are told, is capable of rapid regeneration[21, 23, 34], the kidney also is capable of recovery,[5] The return of these organs to the normal explains the patient's recovery—just as an incomplete return explains the persistence of ill-health. Under favourable conditions, the vitiated state of the blood tends to abate and ultimately to disappear. The return to the normal, however, is not uncomplicated. It has been shown that during early convalescence from toxæmic states the nitrogenous non-albuminous constituents of the blood rapidly increase but as rapidly fall[30], and that this happens particularly in cases with marked œdema[32]. Moreover, the more favourable

*Willcox lays stress on the "toxiphylactic function" of the liver, a function which, he says, "has not been sufficiently recognized.' "The liver is the organ which is mainly responsible for removing poisons, whether exogenous or endogenous, from the blood stream. It is the main protective organ of the body from poisons of all kinds, . . ."[41] If arsenic be taken by the mouth, it is found in the liver; if "arsenobenzol derivatives be given intravenously and death occurs within a few days, a large proportion of the poison will be found in the liver."[40]

The latter statement is interesting and seems to indicate that much more blood goes to the liver by the hepatic artery than is commonly imagined. Thus, with both kidneys out of play, the blood is still purified—which explains how it is that life may continue almost unaffected for several days (commonly about ten). But with both kidneys intact and the liver out of play, the whole picture is different: poisons rapidly accumulate in the blood, and the patient cannot live one day. "Quite recently, Mann and others[2] of the Mayo Clinic have succeeded in the operation of extirpation of the liver in dogs. A preparation lasting three months is required, and then when the operation of extirpation is completed, the animal only lives for twenty-four hours as a maximum, and probably much less, life being maintained for this short period by glucose injections." (Willcox[41]).

prognosis of eclampsia with œdema than in cases without œdema, has been commented on.[42]. While the latter has been supposed to indicate that something harmful is locked up in the œdema fluid, the former has been brought forward as an additional evidence against the visceral conception of eclampsia. But the rise of non-protein nitrogen in the blood with subsidence of the fits and an improvement in the patient no more shows that an impairment of the viscera is not the cause of eclampsia than do the other arguments advanced against this hypothesis which we have mentioned. In the normal, with the involution of the puerperal uterus, a similar but slighter rise of non-protein nitrogen in the blood occurs. Longridge at least has shown that the excretion of total nitrogen in the urine rises considerably on the fifth and sixth days of the puerperium, and continues so at a high level for some days; this he attributes to the involution of the uterus[17]. It seems a fair deduction to suppose that during this time the non-protein nitrogen of the blood is increased. In toxæmic cases, the question is whether during early convalescence chemically innocuous or noxious nitrogen-containing bodies are thrust into the circulation; and, if the latter, whether the liver can deal with them. But how after eclampsia the tissue cells react, and how œdema exerts an apparently favourable influence on toxæmic patients, wrapped up as these questions are with the cause of œdema and of its subsidence, are problems which for the moment may be left. What is certain is that if the blood pressure is falling or is normal, if the output of urine is increasing or is abundant, and if no sign of impairment of hepatic activity such as jaundice or vomiting exists, the patient presents a picture of continued improvement or is smiling and appears perfectly well.

The facts of chronic nephritis in pregnancy rather support this conception. The common observation that chronic nephritics more often abort or miscarry than become eclamptic shows at least that autolytic products arising in the placenta are not the cause of eclampsia—for if they were, chronic nephritics of all pregnant women should most often become eclamptic. The efficiency of the liver saves these patients from eclampsia; the insufficiency of the placenta, become hæmorrhagic and infarcted, explains the abortion or the miscarriage. The cause of such change in chronic nephritics is of easy explanation: the high blood-pressure in the systemic arteries is felt in the chorionic or placental sinuses, the walls of which, unable to meet such pressure, give way. In cases that go to term, we may suppose that the change in the kidneys is not very advanced, the rise of blood-pressure is not great, and perhaps that the walls of the placental sinuses are stronger than normal. Adherent placenta has yet to be explained. Possibly an explanation of it may be found in some such way as this.

BIBLIOGRAPHY

1. Blundell. "Lectures on Theory and Practice of Midwifery." *Lancet*, 1828, ii, 484, 513.
2. Bollmann, Mann and Magath. "Studies on the Physiology of the Liver : viii. Effect of Total Removal of the Liver on the Formation of Urea." *Amer. Journ. Physiol.*, 1924, lxix, 371—392.
3. Caldwell and Lyle. "The Blood Chemistry in Normal and Abnormal Pregnancy." *Amer. Journ. Obstet. and Gynæcol.*, 1921, ii, 17.
4. Couvelaire. "Deux Nouvelles Observations d'apoplexie utero-placentaire." *Annales de Gynécol.* 1912, ix, 486—495.
5. Crook. "Necrosis of the Cortex of the Kidney after Labour." *Proc. Roy. Soc. Med. Obstet. and Gynæcol. Sec.*, 1927, xx, 28.
6. Duncan, Matthews. "Uraemic Convulsions of Pregnancy, Parturition and Childbed." *Trans. from Braun*, 1857, 14.
7. Fishberg. "The Unitary Nature of Impairment of Renal Function." *Arch. Internat Med.*, 1926, xxxvi, 259.
8. Folin and Dennis. "Protein Metabolism from the Standpoint of Blood and Tissue Analysis. *Journ. Biol. Chem.*, 1912, xii, 141—162.
9. Geipel. "Ein Fall von totaler Anurie. "*Zentralb. f. Gynäkol.*, 1914, xxxviii, 517.
10. Geipel. "Nierenrindennekrose und Fleckmilz bei Eklampsie." *Arch. f. Gynäkol.*, 1925, cxxiv, 231.
11. Goll. "Ueber den Einfluss des Blutdruckes auf die Harnabsonderung." *Zeitschr. f. rat. Med.*, 1854, N.F., iv, 73.
12. Gram, H. C. "Observations on the Regulation of Osmotic Pressure (Conductivity, Chlorides, Freezing Point, and Proteins of Serum)." *Journ. Biol. Chem.*, 1923, lvi, 593—624.
13. Harris, J. W. "The After-Effects of the Late Toxæmias of Pregnancy." *Bull. Johns Hopkins Hosp.*, 1924, xxxv, 103—107.
14. Hirst, Barton Cooke. "Treatment of Eclampsia."*Amer. Journ. Obstet.*, 1910, 420.
15. Kehrer. "Discussion on Geipel's Case"9 *Zentralb. f. Gynäkol.*, 1914, xxxviii, 519.
16. Killian and Sherwin. "Some Chemical Studies in Normal and Abnormal Pregnancies. *Amer. Journ. Obstet. and Gynecol.*, 1921, ii, 6.
17. Longridge, C. N. "Excretion of Creatinin in Lying-In Women : with some remarks on Involution of the uterus. *Journ. Obstet. and Gynæcol. Brit. Emp.*, 1908, xiii, 420—429.
18. Maclean, Hugh. "The Prognosis and Treatment of Chronic Renal Disease. *Brit. Med. Journ.*, 1922, ii, 1067.
19. Macleod and Pearce. "The Outflow of Blood from the Liver as affected by Variations in the Condition of the Portal Vein and Hepatic Artery. *Amer. Journ, Physiol.*, 1914, xxxv, 87.
20. Malcolm and Gibb. "Over Five Hundred Gallons of Fluid removed from a Case of Ovarian Cyst." *Brit. Med. Journ.*, 1921, ii, 631
21. McMaster and Rous. "The Biliary Obstruction required to produce Jaundice." *Journ. Exper. Med.*, 1921, xxxiii, 731.
22. Miller, Keith and Rowntree. "Plasma and Blood Volume in Pregnancy." *Journ. Amer. Med. Assoc.*, 1915, lxv, 779—782.
23. Muir, R. "Discussion : Degenerative Diseases of the Liver." *Brit. Med. Journ.*, 1922, ii, 1064.

24. Paramore, R. H. "The Intra-Abdominal Pressure in Pregnancy." *Proc. Roy. Soc. Med., Obstet. and Gynecol. Sec.*, 1913, vi, 291.
25. Paramore, R. H. "Eclampsia and Its Incidence." *Lancet*, 1921, ii, 1147.
26. Paramore, R. H. "The Pernicious Vomiting of Pregnancy." *Lancet*, 1922, i, 867.
27. Paramore, R. H. "The Toxæmia of Acute Intestinal Obstruction : or Vomiting as a Pathological Force." London, 1923.
28. Paramore, R. H. "Eclampsia. A Refutation of Specific Toxæmic Hypotheses : Milk-Fever in Cattle Explained." Unpublished.
29. Pembrey and Ritchie. "General Pathology." London, 1913.
30. Plass, E. D. "Variations in the Distribution of the Non-Protein Nitrogenous Constituents of Whole Blood and Plasma during acute Retention and Elimination. *Journ. Biol. Chem.*, 1923, lvi, 17—29.
31. Plass, E. D. "Non-Protein Nitrogenous Constituents in the Blood in Eclampsia and Allied Conditions." *Journ. Amer. Med. Assoc.*, 1924, lxxxii, 266—269.
32. Plass, E. D. "Non-Protein Retention during Eclampsia and Allied Conditions." *Bull. Johns Hopkins Hosp.*, 1924, xxxv, 345—361.
33. Plass, E. D. and Bogert, L. J. "Plasma Protein Variations in Normal and Toxæmic Pregnancies." ibid. 361—367.
34. Rolleston, Sir Humphrey. "Degenerate Diseases of the Liver." *Brit. Med Journ.*, 1922, ii, 1055
35. Saint-Blaise. "Les Auto-Intoxications de la Grossesse." Paris, 1899, 42, 50.
36. Slyke, van, and Meyer, "The Fate of Protein Digestion Products in the Body." *Journ. Biol. Chem.*, 1913, xvi, 197—212; 213—229; 231—233.
37. Wallis, Mackenzie. "The Toxæmias of Pregnancy, with Special Reference to the Value of Certain Renal Function Tests in Diagnosis." *Journ. Obstet. and Gynæcol. Brit. Emp.*, 1921, xxviii, 3—22.
38. de Wesselow. "Some Chemical Observations on the Toxæmias of Pregnancy." *Journ. Obstet and Gynæcol. Brit, Emp.*, 1922, xxix, 21.
39. de Wesselow. "The Immediate Prognosis in Nephritis." *Lancet*, 1923, ii, 163.
40. Willcox, Sir William. "Degenerate Diseases of the Liver." *Brit. Med. Journ.*, 1922, ii, 1064.
41. Willcox, Sir William. "Jaundice." *Brit. Med Journ.*, 1924, ii, 500.
42. Williams, Whitridge. "Obstetrics." New York, 1923.
43. Williamson, Herbert. "The Induction of Premature Labour." *Journ. Obstet. and Gynæcol. Brit. Emp.* 1906, ix, 211
44. Veit. "Klinische Untersuchungen über den Vorfall der Scheide und der Gebärmutter." *Zeitschr. f. Geburtsh. u. Gynäkol.*, 1877, i, 146.
45. Volhard und Fahr. Die Bright'sche Nierenkrankheit. Berlin, 1914.

Chronic Nephritis, Accidental Hæmorrhage and Eclampsia.

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ACCIDENTAL HÆMORRHAGE.

Argument—

Accidental hæmorrhage is generally attributed to a toxæmia. The author considers that this view is wrong. He reviews the literature briefly, and points out fallacies in reasoning and deductions. He believes the rupture of placental sinuses is produced mechanically, and that all the consequences of accidental hæmorrhage are due to the bleeding. The factors in play are the general (aortic) blood-pressure, the pressure of the blood in the placental sinuses, and the pressure of the liquor amnii. He outlined his conception at Manchester (1927).[21] The argument boils down to a consideration of the placental circulation and of the factors causing variations in that circulation. Here the subject is introduced, and an argument developed from the general point of view which indicates that neither accidental hæmorrhage nor eclampsia is due to a specific toxæmia. When accidental hæmorrhage occurs in toxæmic states, it is not the toxæmia which causes the rupture of the placental sinuses, but the raised blood-pressure.

1. INTRODUCTION: ACCIDENTAL HÆMORRHAGE AND THE PREGNANCY TOXÆMIA.

The effect of chronic nephritis on the uterine contents leads us naturally to accidental hæmorrhage, for accidental hæmorrhage, however it affects the woman, is simply a hæmorrhagic state of the ovum on the grand scale. And there are other affinities. Thus, accidental hæmorrhage occurs in women the subject of chronic nephritis; indeed, according to some, chronic nephritis, in some degree or other, is always the cause of accidental hæmorrhage. In chronic nephritis the systemic blood-pressure is raised, and just as in early pregnancy a hæmorrhage about the chorionic villi from this cause may occur, so late in pregnancy may the walls of

the placental sinuses give way. But in many cases of accidental hæmorrhage there is no reason to suppose that a preceding renal aberration existed, not only may albuminuria be absent, but the patient presents none of the appearances of any toxæmia. Such cases usually arise in delicate women near term, and commonly the patients are multiparæ.

A case occurred before my eyes. The patient, a thin young woman, about five feet tall, with two children, had already been treated for general visceroptosis and asthenia. The right kidney had been stitched up (1924), a levator plastic operation performed (1925), and the stretched linea alba removed and the recti brought together (Feb. 1, 1926). On her discharge after that operation, the patient weighed six stones and eight pounds, and her general condition was much improved. Shortly after her return home, she became pregnant, and in November, 1926, being seven months gone, was admitted because it was thought labour was imminent. On December 22nd, she was re-admitted for the same reason—it having been stated that the membranes had ruptured. But this was an error. The patient presented no sign of labour, and none of toxæmia. Her general condition was fair, but the weakness of the flank muscles, made worse by the pregnancy, was manifest. At first she was kept in bed, but later allowed to get up and do light work in the ward. On January 10th, 1927, at midnight severe bleeding began. Next morning at seven, she was much worse. Cæsarean hysterectomy was performed. The child was dead. Convalescence was marred by headaches and depression, from which, however, the patient completely recovered. On May 31st, she looked well and said she felt well. On August 2nd, 1927, she was seen but not examined, she looked well, stated she was in the best of health and had gained two stones in weight. No albumin had ever been found in the urine.

Such experiences must be common. Certainly the literature indicates that accidental hæmorrhage, even of the concealed type, quite commonly occurs in women previously well. Goodell[8] writing on concealed accidental hæmorrhage, reporting a case of his own and adding 105 from the literature, does not ascribe the bleeding to a preceding state of ill-health. Though in some of these cases external bleeding occurred and even flooding—in 27 per cent. (Holmes,[14])—in the great majority, the bleeding was concealed. The great aetiological relationship, according to Goodell, is the number of confinements to which the woman has been subjected. And for Goodell, the great exciting cause is a disturbance produced by external or internal violence or even movement. "The circumstances leading to detachment of the

placenta," he says, "are various. In 26 cases, probably from irregular uterine contractions, it occurred during the process of labour; 37 cases could be traced to external violence or undue exertion; in seven the causes were purely emotional; and ten took place during sleep, the patient being aroused by the attendant pain." He gives the following as specified causes: blows received on the abdomen; missing a step; stepping over a gutter; lifting a pail of water; stooping over; falling down stairs; violent coitus. Thus, in 70 of his 106 cases, mechanical factors were in play—unless we exclude emotion, during which, however, the individual is not unmoved; while if movements during sleep or rest in bed, rather than purely chemical changes, were the cause, the number becomes 80—that is, 75 per cent.

Holmes, analysing 200 cases, takes rather a different view: he regards a pathological state of the uterine mucosa—an endometritis—as the great cause of accidental hæmorrhage. The reason seems to be that "multiparæ are more prone to endometrial disease than primiparæ, and ablatio placentæ is more frequent in the former than latter."[14] Although allowing that falls, jars, blows, violent exercise including walking, running, lifting heavy weights, and coitus; mental perturbation, as fear, anger, sorrow, and even excessive joy, and also a short cord, "unquestionably" may and do have some influence in producing a separation of the placenta; he believed that these causes *per se* "have been grossly exaggerated by all writers on this subject." "The trivial accidents attributed to the causation are not worthy of consideration." Even when injury is a cause, "some time usually intervenes" before the bleeding. The factors mentioned "are seldom of any consequence, unless there be a coincident pathologic change of the serotina"—the accident thus being but contributory.[14]

His opinion, founded apparently more on fantasy than fact, is not supported by the reports of his cases, which display a barrenness of "coincident pathologic change of the serotina." Holmes only found "endometritis and decidual metritis" given as the uterine change three times each; "scirrhus of the uterus, exudative myometritis, fatty degeneration of the decidua, 1 each." "Kidney changes were noted 20 times. Placental changes were mentioned in connection with kidney lesions in 9 cases." The kidney changes were thought to act by inducing an endometritis—a conception presumably erroneous in view of the commonness of albuminuria in pregnancy, and the relative rarity of accidental hæmorrhage. Moreover, if an endometritis is a predisposing cause of accidental hæmorrhage, it apparently presents no sign whereby we can distinguish it clinically—that is, whereby we can state whether

accidental hæmorrhage is likely in any particular individual. The only indication is a weak abdomen: though not universal, this occurs so often as to possess some significance. Since in old and decrepit people, the state of weakness predisposes to fracture of the neck of the femur, perhaps in women who have borne many children, the state of weakness of the "abdomen," rather than an imaginary endometritis, may predispose to accidental hæmorrhage. And possibly, just as a "trivial" movement—e.g., turning round rather abruptly while walking quietly in the garden may cause a fracture of the femur in the one case, so a trivial movement—e.g., turning round in bed— may cause a rupture of placental sinuses in the other.

However this may be, it is at least clear that many of the patients in Holmes' list, however weak, were in pretty good health up to the time of the bleeding. Thus trauma was said to be the cause in 67 cases. Such a statement would not have been made if any pathological condition likely to induce bleeding had existed in those cases—trauma can be assumed as a cause only in women reasonably well. Holmes says: "In my collection 67 had an accident as the cause; 27 had a pathological basis associated with accidents; 6 were supposed to have been due to short cords."[14] That is, in 50 per cent. of his cases, mechanical factors of some sort were considered as the important or determining ones; and in many of the others, mechanical factors were not ruled out.

Zweifel's testimony,[31] in spite of his dismissal of mechanical factors—since only one of his patients gave a history of trauma, of having fallen down stairs—also supports this conception. Of his 22 patients, all but one "were surprised by the bleeding when in a state of good health, a few even were in bed when the bleeding appeared."[7] He also, as we shall see, came to regard an endometrial change as causal of accidental hæmorrhage.

Many of Whitridge Williams'[26] patients, apparently, were also quite well. It is, however, difficult to substantiate the point: "in many instances an ante-partum examination was not possible, while in others it was made so long before the accident as to be devoid of significance." Of his 40 patients, two died "a few minutes after Cæsarean section, which was promptly performed after admission, and no urine could be obtained upon catheterisation, but in the remaining 38 patients more or less satisfactory observations were made." He divides them into groups according to the presence or absence of post-partum toxæmic symptoms (albuminuria). He says, "It seems fair to conclude that the women in the first group (no albumin—15 cases—40 per cent.) gave no evidence of suffering from any of the usual forms of toxæmia." In

the second group (a trace of albumin—14 cases), "such an association is debatable." Only in the last group, comprised of nine patients (26 per cent.) was marked albuminuria present: these "were the most seriously ill of the series," . . . and "three of the patients presented indubitable evidence of toxæmic conditions preceding the accident."

The patient, the subject of his paper, was in the ninth month of her third pregnancy, "and in good condition." "Eighteen days later," she complained of weakness, and on admission was found to be suffering from concealed accidental hæmorrhage. In another case cited (No. 13128), the woman was at term, and 30 hours before the accident, which was preceded by the onset of labour, the urine was free from albumin and the blood-pressure normal. It is reasonable to suppose that in both these patients, a toxæmia was absent before the bleeding; if this be disputed in the first case because of the 18 days which had elapsed between the examination and the accident, it is supported by the post-mortem . . . "the findings in the two fatal cases, which came to autopsy," . . . (of which the case referred to was one) . . . "showed no anatomical signs of toxæmia, and strangely enough, they were the two patients in whom no urine could be obtained upon catheterisation immediately before operation. The findings in one . . . have . . . been mentioned* . . . in the other . . . nothing was found but signs of pronounced anæmia."[26] The opinion that both these patients who died were perfectly well before the accident seems justified.

The same sort of evidence is obtained from other sources. The patient, whose case Goodell reported, was apparently well before the accident. A multipara at term, admitted because of previous difficult labours, passed six days in the ward "cheerfully" doing light work; and at one a.m. the following night was awakened by agonizing pain. It is true she had fallen down stairs the day before admission, and had since suffered from "a pain in her liver"—but this is not evidence of a toxæmia. In Richmond's[23] case—also one of concealed accidental hæmorrhage, indeed of utero-placental apoplexy—the author, referring to the patient, says: "Down to 18 hours before I saw her, she had enjoyed good health and the urine had been free from albumin." The observations of Young[29] are even more significant. "In two of our cases," says he, "an examination of the urine within a few hours of the bleeding was negative, whereas at a later examination

*"Microscopic examination showed that the various organs were normal except for slight parenchymatous changes in the epithelium of the convoluted tubules of the kidneys, but there were no signs of advanced toxæmia of pregnancy." (26 p. 260).

an albuminuria was revealed." Hewitt's[10] statement is final. "The patient, according to her own account, and to the reports of her relations and friends, was often quite healthy until the onset of the bleeding." The statement referred to concealed accidental hæmorrhage of the worst type.

But though many patients may have been quite well up to the accident, some have been otherwise. Some have presented "toxæmic" manifestations—such as headache and malaise, œdema and albuminuria—prior to the bleeding. In some cases, such symptoms have been of short duration. In Oldfield's[19] case the pregnancy was uneventful until a few days before the sudden onset of the illness, when the patient had noticed transient swelling of the feet and some abdominal pain. "She attached no importance to these symptoms and went about as usual, and was not seen until urgent abdominal pain began about 9.30 p.m. on June 16." The patient was 38, married nine years, and expected her first confinement on August 8. In other cases, the toxæmic state has been of much longer duration, for instance, dating from a previous "toxæmic" pregnancy—the sequence of eclampsia in one pregnancy and accidental hæmorrhage in some subsequent one being not uncommon (Young,[30]; FitzGibbon,[7]). In the former type of case we have the development of the pre-eclamptic state, preceding and presumably predisposing to accidental hæmorrhage; in the latter, we have chronic nephritis in play.

According to de Lee[16] accidental hæmorrhage, "in reality is an abortion at or near term." Young[30] is of the same opinion. From his studies, Young infers "that accidental hæmorrhage is really to be looked upon as an abortion occurring in the later months, and that it is caused by the same factors: in the same pregnancy there may be a threatened abortion at an early stage and accidental hæmorrhage at a later stage."[30] I think these authors are right. The cause of abortion in chronic nephritis, as I have urged, is the raised blood-pressure; if this is so, the cause of accidental hæmorrhage in chronic nephritics is the result of the same pathological change—a raised blood-pressure. And since in the pre-eclamptic cases, the same pathological phenomenon becomes dominant, being, indeed, the sign of impending disaster (eclampsia), the imputation of accidental hæmorrhage in such cases to this same cause seems warranted. If cerebral arteries are diseased, a raised blood-pressure may cause cerebral hæmorrhage in the non-pregnant, and also in pregnancy.[17] Similarly, if the placental sinuses are insufficiently supported, relatively or absolutely, the same factor may cause accidental hæmorrhage.

It is curious that a raised blood-pressure does not seem to have

been considered as a cause of accidental hæmorrhage. It is true that spiral arterioles intervene between the aorta and the placental sinuses, but there is reason to believe that the pressure of the blood in the latter channels varies with and depends, for one thing, on the blood-pressure in the aorta. The experimental work of Browne[3] seems to support this conception. Browne induced nephritis in pregnant rabbits by injecting oxalates, and then when the kidneys had become impaired, he injected more oxalates *plus* microorganisms and accidental hæmorrhage resulted. He believed the injections acted simply by damaging the kidneys, not that they directly caused the bleeding. He thought the bleeding was caused by endogenous poisons held up in the blood because of the impaired renal activity—the endogenous poisons act directly on the decidua and uterine muscle, and by affecting them cause the bleeding. He showed that the kidneys were impaired by determining the urea in the blood—which was greatly raised; but he omitted to consider whether any concomitant disturbance of the blood-pressure had been simultaneously produced. But to impute a laceration of the placental sinuses to toxins pure and simple, when these toxins are produced by a condition usually associated with a raised blood-pressure, does not seem sound logic. It is not unreasonable to suppose that besides the increase of urea in the blood, noxious nitrogenous bodies, the cause of an increased blood-pressure, were also produced in excess by the injections; and that the increased blood-pressure, rather than the toxins *per se*, was the cause of the bleeding.

An increase of blood-pressure, however, cannot be supposed to be operative as a cause of accidental hæmorrhage in women who up to the attack are perfectly well. Moreover, the occurrence of a pre-eclamptic state and of eclampsia which occasionally follow on the heels of an accidental hæmorrhage in such cases has to be explained. Thus has arisen a general muddle—for we seem to have no universal cause. The imputation of the pre-eclamptic state to a "specific" toxæmia—which Young even in 1927 repeats[30]—and the association of accidental hæmorrhage with this state, and especially the occurrence of utero-placental apoplexy, have naturally led to the conception that accidental hæmorrhage, in some of the cases at least, is the expression of a toxæmia. The commonness of albuminuria in accidental hæmorrhage has supported this conception. But opposed to this opinion is the fact that the "toxæmia" of pregnancy is more common in primigravidæ, accidental hæmorrhage more common in multiparæ. The incidence indicates that if accidental hæmorrhage is the expression of a toxæmia, the toxæmia is very different from the ordinary toxæmia of pregnancy

(Briggs,[1]). The toxæmia, as Eden[6] suggested, may be of a special kind, but if so, how can it occasion eclampsia? Are we to suppose that a toxin, specific for accidental hæmorrhage, can engender the reputed "specific" toxin of eclampsia; or that accidental hæmorrhage itself, in some way, by its effects or concomitants, can produce a specific toxin reputed to cause eclampsia? Such suppositions are supported neither by analogy nor inference. Young's conception[28,29] that it is the placental change which causes eclampsia is put out of court by many considerations, for instance, by the commonness of placental infarcts without "toxæmia" and the occurrence of marked toxæmia, even fulminating eclampsia, with out apparent placental change. Young's explanation of this latter —that it is due to the rapidity with which the disease occurs—in my opinion, is not valid. The placenta is not an organ related with the maternal metabolism: it does not play the same part as the maternal liver and kidneys play in the maternal metabolism. Placental inactivity or degeneration (without structural change) does not affect the maternal machine as inactivity or degeneration (without structural change) of the maternal liver and kidneys affects this machine.

The plea that placenta prævia is occasionally associated with albuminuria or even toxæmic manifestations does not show that placental degeneration is the cause of albuminuria or of a serious and important toxæmia, as Young asserts;[30] or that the bleeding in placenta prævia is or may be of toxæmic origin, an assumption which Browne[4] regards as justifiable. The albuminuria in these cases may be caused by distension of the uterus and the concomitant rise of intra-abdominal pressure, as in cases of concealed accidental hæmorrhage with the placenta normally situated—for occasionally, in placenta prævia, the bleeding to a large extent is concealed (Holland,[12] Browne,[4] Swayne,[25] Williamson.[27]). It is plain that the causes which determine bleeding when the placenta is normally situated may do so when the placenta is prævia. According to Johnstone,[15] "many cases of hæmorrhage associated with placenta prævia which occurred at or about the seventh month could not reasonably be explained by any expansion of the lower uterine segment. . . . he had always thought that these cases were really to be classed as accidental hæmorrhages occurring in a placenta which was anatomically prævia."[15] There is also the wonder whether in other cases when albuminuria is discovered, it may not be due to obstruction of the ureters. Obviously, if the placenta occupies the lower uterine segment, and a leg of the child is brought down and a weight is attached to it, a temporary obstruction of both ureters, with a resulting albuminuria may be induced.

However this may be, the inference from the incidence of these two separate states—accidental hæmorrhage and pre-eclampsia—which clearly under certain conditions tend to induce each other, is that the reputed cause of the one is not the reputed cause of the other, and does not cause that cause. The conclusion from this argument is that it is the effect of the one state (not its cause) which tends to induce the other state; it is the high blood-pressure of pre-eclampsia which tends to cause accidental hæmorrhage; it is the effect of accidental hæmorrhage in some cases on the woman (the increased intra-abdominal pressure—not a placental change) which at times in such cases produces pre-eclampsia or eclampsia.

Such an argument does not show that accidental hæmorrhage in the non-nephritic cases, without high blood-pressure, is not due to a toxin— the alternative to Eden's idea: but it may well be that there is no toxin causing accidental hæmorrhage even in these cases. And that this is so is indicated by several considerations. In the first place, the pre-eclamptic state itself, followed as it may be by eclampsia, is not due to a specific or any other kind of toxæmia—it is due to a visceral impairment which is primary and the cause of all the clinical and pathological manifestations—including the fits. In the second place, accidental hæmorrhage quite commonly occurs in women who up to the moment of the attack are perfectly well, and who throughout the illness may remain perfectly well—except in so far as the blood lost may effect them. Thus, it is stated that accidental hæmorrhage occurs from emotion, from fright, from mental stress—which according to Dawson[5] is associated with hyperpiesis. The accident—for it is an accident—may occur at term and the child be found well developed, even in cases of utero-placental apoplexy. In Whitridge Williams' case, the child weighed 3020 gms.: it is not always small as FitzGibbon states.[7] This puts out of court all toxæmic states of the blood and all visceral diseases as a precursor of accidental hæmorrhage.[20]

In the next place, accidental hæmorrhage, though it may recur in a subsequent pregnancy, very often does not. While return cases of eclampsia are not uncommon (Young[30]), in accidental hæmorrhage, a corresponding sequence is not stressed by observers, on the other hand it is opposed (Malan[18]). If accidental hæmorrhage *per se* is due to a toxin, comparable with the reputed toxin of eclampsia, the toxæmia or the concomitant visceral state should tend to persist and the bleeding to recur in subsequent pregnancies—that was not Malan's experience.[18] Accidental hæmorrhage should behave in this respect like eclampsia, and tend to leave its mark on the viscera. When accidental hæmorrhage

occurs in a woman, perfectly well up to the time of the bleeding, and causes eclampsia, the visceral lesions are slight and acute. If the patient recovers, the viscera recover, for the disease from its nature is brief. In other cases, the visceral mark is simply one of anæmia, general to the system. Only in cases in which chronic nephritis is present and has caused the accidental hæmorrhage does the renal state persist. Only if a pre-eclampsia has occasioned the bleeding, just in so far as the pre-eclamptic state has been in being, just in so far may a visceral impairment persist as in cases of pre-eclampsia uncomplicated by bleeding (Harris[9]). Cases even of utero-placental apoplexy, reputed to be evidence *par excellence* of a toxæmia, have been followed by natural pregnancies and labours at term, without any unnatural bleeding and the birth of well developed children, perfectly well (Eardley Holland[13]).

The repetition of the so-called "pregnancy toxæmia"[30] in this respect is especially interesting; it indicates the visceral basis of the disease, the effect of visceral lesions in the aetiology of accidental hæmorrhage and the effect of accidental hæmorrhage at times on the viscera. Sometimes it happens that in two successive pregnancies, albuminuria may exist, but be absent in between (Rivière): at other times, a pregnancy toxæmia may result in persistent albuminuria (Harris[9]). The persistence of the renal change points to the dependence of pre-eclampsia on a visceral disability which may end in a structural change or lesion. The idea that the pre-eclampsia causes the nephritis is erroneous: the very common occurrence of albuminuria in pregnancy without pre-eclampsia (or symptom or other sign of a toxæmia) and its exaggeration in pre-eclampsia, combined with the much more significant change—oliguria—which synchronously occurs, indicates that the visceral disability is primary. It is clear that pregnancy, as the result of certain physical conditions, may affect the viscera pathologically. Not all cases of persistent albuminuria after pregnancy occur in women in whom a scarlatinal or other nephritis developed long or shortly before the toxæmic pregnancy. That chronic nephritis may occur as a result of pregnancy and of pregnancy alone must be admitted.

Much more does the recurrence of a pregnancy toxæmia indicate a visceral basis for the disease. Especially is this so in cases in which albuminuria persists from a preceding pregnancy. It can be quite truly stated that if in the subsequent pregnancy, the viscera had been normal and remained normal, the "toxæmia" would not have developed. Indeed, we know quite well that very often the toxæmia does not recur in any subsequent pregnancy. So much has this been stressed that it has been imagined that

eclampsia produces an immunity against subsequent toxæmic pregnancies. But if the viscera remain affected and further pregnancies occur, the renal pathological state, which each pregnancy exaggerates, advances. In such cases, it is not surprising that ultimately a raised blood-pressure should ensue and that this should determine in some subsequent pregnancy accidental hæmorrhage. It is not surprising that eclampsia in one pregnancy should be followed by accidental hæmorrhage in the next. Fitz-Gibbon recalls three cases with a history of eclampsia in a first pregnancy and accidental hæmorrhage in the second or third pregnancy. He has recorded a case with eclampsia combined with accidental hæmorrhage in the second, third, and fourth pregnancies and accidental hæmorrhage in the fifth, each time occurring progressively earlier. He believes—and with reason— that severe toxæmia without eclampsia, such as calls for the termination of a pregnancy, is an even more potent cause than is eclampsia of accidental hæmorrhage in a subsequent pregnancy.

But the inverse sequence is not found—eclampsia, apart from another accidental hæmorrhage, does not tend to occur in women, otherwise well, who have suffered from an accidental hæmorrhage in some preceding pregnancy. It would only be likely to do so if twin pregnancy, hydramnios, hydatidiform mole, or concealed accidental hæmorrhage—all of which have the pecularity that the uterus is larger than it should be for the time of pregnancy—occurred. Even a severe toxæmia without eclampsia does not occur in such a case, unless the bleeding recur, and unless the blood be pent within the uterus. The reason is that accidental hæmorrhage *per se* does not tend to affect the viscera or leave them disabled by structural change. When the bleeding is external and free, it would be strange if it did. Venesection, as a treatment for eclampsia, acts only by affecting the blood flow through the viscera—it does not act by removing a poison; and venesection may quite reasonably be regarded as a prophylactic, acting in the same way. How, then, with bleeding can eclampsia occur? It can make no difference whether the blood comes from the median basilic vein or from placental sinuses. The occurrence of eclampsia on the heels of an accidental hæmorrhage itself shows that there is something peculiar about this bleeding. Only when the blood is not lost to the system (as shown by the effect on the pulse-rate), only when the blood remains pent within the uterus and thus affects the whole body of the woman, only then is eclampsia likely.

We shall come to the cause of the bleeding in women apparently well—without high blood-pressure, without pre-eclampsia, without chronic nephritis. Here it is to be noticed that the sequence

accidental hæmorrhage → pre-eclampsia (or eclampsia)

and the sequence

pre-eclampsia → accidental hæmorrhage,

from the aetiological point of view, are different, though the end picture of the two sequences may be the same. A scrutiny of both shows that neither for the pre-eclampsia in the first case, nor for the bleeding in the second, is the postulation of a preceding toxæmia, the play of a specific toxin, necessary. In the first case, the pre-eclampsia is produced just in the same way, by just the same mechanism, as it is produced in other cases without intra-uterine bleeding—for instance, by the wearing of tight corsets, combined with hard work, or by hydramnios under similar conditions. In the latter case the high blood-pressure of the woman is the determinant of the bleeding. The very reasonable conclusion—in fact, the only conclusion—is that the converse holds; that the accidental hæmorrhage in the first sequence, and the pre-eclampsia in the second, are not due to any toxæmia. The permutation of the factors referred to explains the various results met clinically. For example, a chronic nephritis, instead of ending in the nephritic toxæmia, may induce a genuine eclampsia. If a woman with chronic nephritis becomes pregnant and accidental hæmorrhage occurs, if the blood cannot escape from the uterus and the uterus thus becomes distended and the pressure within the abdomen rises, an undue compression of the liver becomes operative, and eclampsia as a complication of the bleeding is explained. If the bleeding is external and free, the uterus does not become distended and the liver remains unaffected, eclampsia not occurring. Thus it is that an accidental hæmorrhage may be unassociated with "toxæmia" in one pregnancy, while in a succeeding pregnancy with another accidental hæmorrhage a "toxæmia" may arise.

The imputation of a toxæmia, as the underlying cause of all the troubles of pregnancy, however, is very deep-rooted; and it is not surprising that accidental hæmorrhage should be attributed to such a cause. And in truth there is some reason for thinking of such a cause when we see a woman, up to the bleeding perfectly well, suddenly develop symptoms attributable by everyone to a toxæmia —headache, malaise, vomiting, albuminuria and even convulsions. The state of the uterus—the so-called utero-placental apoplexy—supports the conception. But the occurrence of accidental hæmorrhage in women who present none of these symptoms is disconcerting; and the existence of such, by some authors at least, is admitted. Two schools have arisen. The one believes that there

are two types of accidental hæmorrhage, the one type is simple, due perhaps to trauma, and is unassociated with any toxæmia; the other type is toxæmic from the start, the uterus is hæmorrhagic, and there are other changes (Portes[22]; FitzGibbon[7]). The other school believes that all accidental hæmorrhages are essentially toxæmic, and here again there are two divisions. Some believe the toxæmia is due to renal changes (Browne,[3]), others attribute it to the appearance of some subtle poison in the blood, apparently independent of the renal condition and even causing the renal aberration (Hofbauer[11]).

The latter view seems to have been largely adopted. The apparent dependence of accidental hæmorrhage on chronic nephritis, its appearance in the pre-eclamptic state, and especially the development in other cases of toxæmic symptoms secondary to the uterine disaster, seem to have obscured the very existence and the significance, of accidental hæmorrhage in women who are apparently well and who throughout the illness present no sign of any toxæmia. Even authors who recognize the occurrence of these cases refuse to admit their elemental relationship with the others. The toxæmic and the non-toxæmic cases have been regarded as types of two different diseases. But as Holmes truly pointed out, the "concealed cases" do not comprise the "whole subject": they are not in a separate category, possessing a different aetiology. Others have supposed that the complex explains the simple, instead of the other way round. Since the toxæmic cases are evidently due to a toxæmia, the simple cases—it is argued—must also be due to a toxæmia. Hence the conception that an ill-defined nephritis or some subtle blood change must explain an accidental hæmorrhage in women who before the accident were apparently quite well. "Toxæmia of pregnancy," it is stated, "is very frequently associated with the condition (the bleeding) and, as we all know, is undoubtedly one of the chief causes" (Broadhead[2]). The truth is we do not know this, we only suppose it, and we only suppose it because for the moment we see no other explanation.

In this paper another explanation is expounded. It is based on the conception that the simple, which always precedes in time the complex, must always explain it. Concealed accidental hæmorrhage is complex because the blood becomes pent in the uterus, only in this does it differ from simple accidental hæmorrhage. The failure of the blood to escape through the cervix, causes the complexity. If the bleeding is little (retro-placental hæmatoma), it may matter little, but if the bleeding is continuous, it may matter much. The pathological state of the uterus described as utero-placental apoplexy arises from this cause, and—as we have indicated—many other secondary phenomena.

REFERENCES.

1. Briggs, Henry. Remarks on "The pathology of utero-placental hæmorrhage." *Proc. Roy. Soc. Med., Obstet. & Gyn. Sec.*, 1921, xiv, 186.
2. Broadhead, G. L. "Accidental hæmorrhage, with a report of 34 cases." *New York State Journ. of Med.*, 1927, xxvii, 219.
3. Browne, F. J. "An experimental investigation into the etiology of accidental hæmorrhage and placental infarction." *Trans. Edin. Obstet. Soc.*, 1925-26, xlvi, 151-168. Also *Brit. Med. Journ.*, 1926, i, 683.
4. Browne, F. J. "A case of concealed hæmorrhage with placenta prævia." *Trans. Edin. Obstet. Soc.*, 1925-26, xlvi, 129-131.
5. Dawson, Lord. "Hyperpiesia." *Brit. Med. Journ.*, 1925, ii, 1161.
6. Eden, T. W. Remarks on "The pathology of utero-placental hæmorrhage," *Proc. Roy. Soc. Med., Obstet & Gyn. Sec.*, 1921, xiv, 185.
7. FitzGibbon, Gibbon. "A revised conception of ante-partum accidental hæmorrhage." *Proc. Roy. Soc. Med., Obstet. & Gyn. Sec.*, 1926, xiv, 80-94.
8. Goodell, W. "Concealed accidental hæmorrhage of the gravid uterus." *Amer. Journ. Obstet.*, 1870, ii, 281.
9. Harris, J. W. "The after-effects of the late toxæmias of pregnancy." *Bull. Johns Hopkins Hosp.*, 1924, xxxv, 103-107.
10. Hewitt, John. Remarks made in reply to discussion on "The clinical condition of the uterine wall in concealed accidental hæmorrhage." *Trans. Edin. Obstet. Soc.*, 1925-26, xlvi, 181.
11. Hofbauer, J. "Experimental studies on the toxæmias of pregnancy." *Amer. Journ. Obstet. & Gyn.*, 1926, xii, 159.
12. Holland, Eardley. "Case of combined antepartum hæmorrhage, placenta prævia and accidental hæmorrhage." *Proc. Roy. Soc. Med., Obstet. & Gyn. Sec.*, 1920, xiii, 132.
13. Holland, Eardley. Remarks on "Utero-placental (accidental hæmorrhage." *Ibid.*, 183.
14. Holmes, Rudolph Wieser. "Ablatio Placentæ." *Amer. Journ. Obstet.* 1901, xliv, 753-784.
15. Johnstone, R. W. Remarks on "A case of concealed hæmorrhage with placenta prævia." *Trans. Edin. Obstet. Soc.*, 1925-26, xlvi, 132.
16. de Lee, Joseph B. "The principles and practice of obstetrics." 1924.
17. Levant et L. Portes. "Hémorragies des centres nerveux au cours de l'éclampsie puerpérale." *Gyn. et Obst.*, Paris, 1923, vii, 332.
18. Malan, D. J. Remarks on "A revised conception of ante-partum accidental hæmorrhage." *Proc. Roy. Soc. Med., Obstet. & Gyn. Sec.* 1926, xix, 93.
19. Oldfield, C. and R. G. Hahn. "Acute toxæmia of pregnancy, with acute nephritis and accidental hæmorrhage; Cæsarean hysterectomy; Recovery. *Proc. Roy. Soc. Med., Obstet. & Gyn. Sec.*, 1917, x, 17-22.
20. Paramore, R. H. "Bacterial infection and accidental hæmorrhage." *Lancet*, 1926, i, 1064 (Correspondence).
21. Paramore, R. H. Remarks on "Late pregnancy toxæmia, etc." *Journ. Obstet. & Gyn., Brit. Emp.*, 1927, xxxiv, 395.

22. Portes, Louis. "Pathogénie et traitement de l'apoplexie utéro-placentaire." *Gyn. et Obstet.*, Paris, 1923, vii, 56-74.
23. Richmond, T. H. "Concealed accidental hæmorrhage." *Brit. Med. Journ.*, 1925, i, 154.
24. Rivière, "L'auto-intoxication éclamptique." Paris, 1888.
25. Swayne, Walter. "A case of toxæmia of pregnancy associated with bleeding." *Journ. Obstet. & Gyn. Brit. Emp.*, 1924, xxxi, 149.
26. Williams, Whitridge. "Further observations concerning premature separation of the normally implanted placenta." *Journ. Obstet. & Gyn. Brit. Emp.*, 1925, xxxii, 259.
27. Williamson, Herbert. Remarks on "Case of combined antepartum hæmorrhage." *Proc. Roy. Soc. Med., Obstet. & Gyn. Sec.*, 1920, xiii, 134.
28. Young, James. "The aetiology of eclampsia and albuminuria and their relation to accidental hæmorrhage." *Proc. Roy. Soc. Med., Obstet. & Gyn. Sec.*, 1914, vii, 307-348.
29. Young, James, and Douglas A. Miller. "Further observations on the aetiology of eclampsia and the pre eclamptic state." *Proc Roy. Soc. Med., Obst. & Gyn. Sec.*, 1921, xiv, 247.
30. Young, James. "Recurrent pregnancy toxæmia." *Journ. Obst. & Gyn. Brit. Emp.*, 1927, xxxiv, 279.
31. Zweifel, P. "Die vorzeitige Lösung der regelrecht sitzenden Nachgebert." *Monatschr. f. Geb. u. Gyn.*, 1912, xxxvi, (Ergänzh.), 55-68. (see esp., pp. 61 and 63).