SOME OBSERVATIONS ON THE TOXAEMIC CONDITIONS OF PREGNANCY.

Part, 1, Ocular Changes.

Part, 2, On the Nature of the Toxin.

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April, 1919.

Part One.

Ocular Changes.

The Observations contained in the following paper were commenced prior to the War, in the wards of Dr Jardine at the Glasgow Royal Maternity and Womens' Hospital, and the work done there is comprised in the section dealing with the ophthalmic changes found in the toxaemic states of pregnancy. The remainder of the paper is based partly on the the literature of the subject, and partly onobservations carried out in private practice among my own patients. The theory I have evolved with regard to eclampsia I have not seen advanced previously: while it cannot lay claim to any great merit on the score of originality, since it is only the piecing together of the work of others, nevertheless the theory seems to fit the case and coordinate the various facts, which without this coordination are only isolated pieces of information.

I am greatly indebted to Dr Jardine for his kindness in permitting me to examine his patients and to make use of the naterial thus gained. The ocular changes herein described were all found in his cases.

While toxaemic cases are met with frequently in lying-in hospitals, they are comparatively rare in general practice. I have only met with one case of eclampsia in general practice and that unfortunately before it had occured to me to examine the eyes of these cases, and this too was one of the specially rare cases where eclampsia occurs without albuminuria.

The thesis shows that retinitis and optic neuritis may occur in these cases, and that the ocular condition is due to a toxin and not to other conditions, such as nephritis etc., which are usually adduced as the etiological factor in these pathological changes in the eye.

The theory on eclampsia, while largely speculative,

seems to provide a suitable working basis on which to regard the disease. The present-day treatment of eclampsia, for example, copious bleeding, must have a decided effect in reducing the sum total of the poisoning of the liver, since about one fourth of the total blood in the body is present in the liver at any given moment. The undoubted utility of this mode of treatment is an additional point in favour of my theory. On the basis of the theory, it is essential that as soon as a diagnosis of "toxaemia" of whatever variety can be made, that protein should be withdrawn from the diet. So far I have not had an opportunity of putting this idea into practice in cases of toxaemia of pregnancy, but I have done so in cases of acute Bright's disease, a disease which is, in many ways, distinctly analogous to eclampsia gravidorum.

In these cases I now withhold all protein as far as is practicable. The diet I find quite suitable and

and at the same time most convenient is that consisting of ordinary bread and butter, and for fluids, tea, lemonade etc., milk is withheld since it contains too much protein. That milk, or at all events its products of digestion, exerts a toxic action on the kidney is shown by the fact that in cases of acute nephritis it is possible to vary the amount of albumen in the urine at will, by the administration and the withholding of milk. By experiments in these cases I have found that with a bread and butter diet, there is only a trace of albumen at the end of a week. If now milk is prescribed for a day, it will be found that the urine, on the day following, is densely laden with albumen. If the milk be withdrawn, the urine will be practically clear again in 24 hours. The exhibition of milk will again cause the albumen to appear.

These dietetic experiments show with some certainty that the primary lesion in nephritis is

not necessarily the kidneys, but that it is in the liver, since toxic alimentary products pass through the liver, reach the kidney, poison it, and so permit serum albumen and serum globulin to pass from the blood into the urine. In acute nephritis the liver is found at autopsy to be in a state of cloudy swelling, which meansthat, as in eclampsia, its function was impaired during life.

There would seem to be little doubt that a certain degree of toxaemia occurs in all cases of pregnancy, in some cases so slightly as to be of little moment, inothers again it is a matter of very serious import.

OPHTHALMOSCOPIC APPEARANCES IN ECLAMPSIA GRAVIDORUM.

Six cases of characteristic eclampsia were examined, of these four had definite ocular changes, while two had nothing abnormal to be seen in the fundus oculi. The appearance of the fundus in the four cases was fairly typical of the four and corresponded to a certain extent to the findings in albuminuric retinitis.

The retinae showed white patches of various sizes some of them large; one case showed a patch larger than the optic disc, but mostly they were about one third of the diameter of the di sc. The number of patches in each eye varied from one to six. The distribution, irregular throughout the retina, did not have the

macular relationship characteristic of retinitis albuminurica. The retinae were somewhat "hazy" in appearance, the vessels were engorged and it was always difficult to distinguish the macula lutea.

The optic disc varied in appearance, one case showed no alteration, two showed signs of commencing optic neuritis, while the fourth presented a well marked optic neuritis. This last case is so interesting not only on account of the severe eye condition present, but also on account of the confusion of diagnosis which arose with regard to it on the part of the doctor who sent it to hospital, that I give some further particulars concerning it.

Mrs. A., was sent to the Glasgow Royal Maternity and Womens' Hospital as a case of cerebral tumour, since she was pregnant and exhibited the classical "tripod" of symptoms, headache, vomiting and optic neuritis.

Her history was, that about seven days before admission to hospital she began to complain

of failing vision together with headache and vomiting. She subsequently called in her doctor, who, having examined her eyes, diagnosed cerebral tumour and sent her to hospital as a case of such.

On examination at the Hospital, I found her to be in a somewhat foggy mental state, but she was able to answer simple questions. She was seven months pregnant and fairly well advanced in labour.

A catheter specimen of urine was copiously laden with albumen; it contained no sugar or pus. Microscopic examination of the sediment revealed the presence of numerous blood casts and red blood corpuscles.

Ophthalmoscopic Examination:- Both discs were choked, both sides were equally affected. Some small white patches were present on the retina, distributed irregularly over its surface. The patches were more numerous on the right side. The

patient had a few slight convulsions and delivered herself shortly afterwards, spontaneously.

During the puerperium the patient improved rapidly, after a fortnight the ocular changes had disappeared, and only a faint trace of albumen was present in the urine.

It is noteworthy in regard to this case which had the most severe ocular changes of the series, that it was not a severe case of eclampsia, inasmuch as the convulsions were only slight. One severe case had only slight optical changes, and this case proved fatal. Another fatal case had no changes whatever, which shows that the severity of the eye condition is not necessarily related to the degree of the eclampsia.

Whether the presence of these eye changes is frequent and the incidence ratio of four to six would hold over a larger series, I am unable to say. My series may be exceptional, but it is quite

possible these lesions occur with some frequency, and a knowledge of them is lacking for two reasons, firstly, because the ophthalmoscope is not a usual component of the obstetrical armamentarium, and secondly, the ophthalmologist does not as a rule come in contact with cases of this category.

Notes on cases apart from Eclampsia.

Pernicious Vomiting.

Mrs G... In this case the woman was emaciated and afflicted with severe and pernicious vomiting. As she failed to respond to other modes of treatment, labour was induced at six months. The urine contained no albumen or sugar.

Ophthalmoscopic Examination:- Both fundi were of the fair complexion type. The discs showed slight optic neuritis; no retinal changes were detected. Three weeks after delivery the discs were normal in appearance.

Albuminuria.

Mrs D... This woman was six months pregnant. The legs and abdomen were oedematous and she complained of sickness of four weeks duration. On admission the urine was densely laden with albumen.
Ophthalmoscopic Examination:- The discs were slightly choked. Three weeks after admission, she had responded so well to treatment that her symptoms subsided without the necessity of inducing labour. Only a trace of albumen remained in the urine and the optic discs were normal in appearance.

Mania.

Mrs. S... This case showed well marked signs in the retina, corresponding somewhat to retinitis albuminurica. Elongated white patches were present in the macular region, roughly oval in shape with irregular edges.
Urine:- No albumen or sugar.

After delivery she became so violent that she had to be removed to a mental hospital. I have no

knowledge of her subsequent history.

These cases show definitely that alterations may occur in the retina and optic nerve in the toxaemic conditions of pregnancy, and that they are apparently peculiar to this condition, and not to any underlying cause such as nephritis, diabetes or cerebral tumour. The case of Mrs D., (Albuminuria) shows that the optical changes are due to the toxic cause, and not to the kidney condition, since the eye change clears up, while the nephritis condition remains.

With the exception of that of de Lee, the more recent text-books give no description corresponding to the above findings. The eye changes are evidently part of the profound alteration induced by the toxaemic state, which gives rise to many other symptoms indicating a marked disturbance of the nervous system.

The literature on this on this subject is scarce, and so far I have been able to find few references to eye changes of any description occuring in the toxaemic states of pregnancy. there is so little that I am able to qucte what I have culled in a few lines. Haab 1) gives a very excellent illustration in his book, of a case of hoemorrhagic retinitis in a pregnant woman. The plate shows congestion of the veins, large patches of hoemorrhage, white patches situated round the optic disc, with smaller patches round the macula lutea, as in retinitis albuminurica. Optic neuritis is present.

I translate his remarks.

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1) HAAB, Handatlas und Grundriss der Ophthalmoscopie und ophthalmocopischen Diagnostik, fig63.

"Retinitis bei Gravidität".

"In spite of the white spots in the macular region, no albumen was found in the urine in this case after frequent attempts. After delivery at term the whole severe disease of the left eye healed completely within three weeks, and nothing remained of the large patches of blood and the white degenerative foci, although the woman was highly anaemic before and especially after the confinement. The right eye was not affected."

"Perhaps this is a partial stoppage of the central vein, (the vessels are not completely occluded)".

The Above case has a distinct resemblance to what I have found, especially in the fact that the changes disappear after delivery. My cases however showed bilateral changes, not unilateral as in this.

The best account I have met with, in connexion with the ocular changes in pregnancy and in toxaemia is that of de Lee 2) who says that amaurosis may occur without ophthalmoscopic change, and is caused by poisoning of the ganglia and optic nerves, the toxin having a special selective action for them: he goes on to state that pregnancy seems to dispose to the occurence of neuroretinitis, with a tendency to hoemorrhages and exudate. Posey and Hirst are quoted as believing that optic neuritis and retinitis, due to the toxaemia of pregnancy, may indicate basal trouble before changes show in the urine. De Lee is the only author who mentions the occurence of neuroretinitis in these cases of toxaemia, and he believes that they result in permanent damage to the eye. My experience has

2) de Lee, Principles and Practice of Obstetrics, 1913.

so far, been contrary to this.

Williams 3) mentions some ocular changes with regard to eclampsia in his book. As a rare condition he states that Hemianopsia may occur as a result of the cerebral lesions incident to eclampsia, I have no personal experience of this condition, which is very rare. He also states, I quote verbatim,

> "Oedema of retina causes disturbance of vision during the latter part of pregnancy. In other cases the visual disturbance is unattended by demonstrable changes in the retina or optic nerve..... As was shown in the section on nephritic toxaemia, albumin-

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3) Williams, Obstetrics, Ed. 1917.

uric retinitis is a complication of chronic nephritis, but not of pre-eclamptic toxaemia or eclampsia. Accordingly the outcome is dependant upon the further course of the underlying disease."

My cases serve to show that changes can be demonstrated not only in eclampsia, but also in other toxaemic states of pregnancy, and further even if a kidney lesion be present, the ocular lesion may be recovered from, (Case of Mrs D.).

Webster 4) writes that there may be amaurosis, colour blindness, photophobia, diplopia and strabismus. Edgar 5) mentions amaurosis, but neither of these two authors make any reference to the internal changes of the eye, but merely record the symptoms as stated.

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4) Webster, A TextBook of Obstetrics, p. 372.

5) Edgar, Practice of Obstetrics.

Berkeley 6) states with reference to eye changes,

> "Patient complains of puffiness of eye-lids etc., she may become blind suddenly, and this may occur without any other sign. The eyes show no changes except intense oedema and sometimes partial detachment of the retina. Retinal hoemorrhages are not common and they totally disappear if the patient recovers."

I have no experience of retinal detachment in this connexion, it is however mentioned by deLee. There is certainly oedema of the retina in certain cases, but it is not a general feature, as the above paragraph might lead one to infer.

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6) Berkeley, Fairbairn, Russell Andrews, etc., Text-Book, 1917.

The condition as I have found it, resembles largely albuminuric retinitis, excepting of course the optic neuritis, which, should it make an appearance in Bright's disease, is usually found in the later stages. The white patches of albuminuric retinitis are due to fatty degeneratio of the nerve fibres of the retina, (Swanzy 7/), whereas the patches I have found are not permanent, and accordingly must be of an exudative nature, since they clear away so rapidly with the recovery of the patient, leaving no apparent visual defect. The process of disappearance of these patches can be watched, and it is found the edges of the patch become crenated, the whole patch shrinks from day to day until it is no longer visible. In the case of choked disc, the neuritis gradually fades, and every day the intensity is less, until the disc

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7/ Swanzy and Werner, Diseases of the Eye, 1907.

returns to normal.

The resemblance of this condition to albuminuric retinitis fades with the disappearance of the plaques of exudate. Retinitis albuminurica is a permanent condition as usually discovered, it is, however, possible that in the early stages it might resemble the retinitis of toxaemia. As far as it is possible to judge meantime, the two conditions are distinct.

Experimental Retinitis.

Fuchs 8) quoting Zur Nedden, mentions that retinitis albuminurica can be produced experimentally. The method consists of injecting kidney substance of one animal, into an animal of a different species.

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8)Fuchs, Ophthalmology, Trans. Duane, 1917.

The serum of the second animal developes a lysin which is lytic to the kidney substance of the first. If this "nephrolytic" serum be injected into an animal of the first species, retinitis and nephritis are produced. Fuchs does not state whether this condition is transitory, permanent or immediately fatal. I am inclined to think that were the dose not immediately fatal, the retinitis would resemble the toxaemic type, that is to say it would clear up with the recovery of the animal. Unfortunately, however, no further information is given on this subject by Fuchs. This experiment is an attempt to prove that a substance having a specific action on the kidney is also specific to the retina. There is however greater likelihood of the retinal changes being caused by the the toxic material resulting from the destruction of the kidney substance. As will be shown later, toxins derived from the destruction

of protein by cleavage, like other toxins, produce the maximum effect on the most highly organised and specialised tissues. There seems to be no reason to believe that the ocular changes of Zur Nedden's experiment would not be produced by a lysin specific to a different organ from the kidney.

Later it will be shown that the toxins of eclampsia are in all probability the products of protein cleavage by lysins. These substances have a most decided action on the different systems of the body, and will produce their effect on the retinal epithelium. An abnormal condition of the endothelium of the retinal capillaries will permit of the extravasation of lymph through the capillary walls, and with the coagulation of portions of this, to the formation of retinitic patches.

The cause of optic neuritis is obscure. In cases of intra-cranial tumour optic neuritis is

caused by the increase of of the intra-thecal pressure. The increase of pressure in the cerebra-spinal fluid has been reported to be as high as 410 m.m., of mercury, as against the normal 120 m.m., and Purves Stewart 9) states that improvement follows the withdrawal of cerebra-spinal fluid by lumbar puncture in eclampsia.

Fuchs states that optic neuritis may occur in pregnant women during pregnancy and lactation, while he mentions the probable cause as toxic, he makes no suggestion as to the nature of the toxin. De Lee suggests that the neuritis may be a part of the polyneuritis which may occur in pregnancy.

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9) Article in Eden and Lockyer's New System of Gynecology, 1914.

Part Two.

On the Nature of the Toxin.

The Question as to the nature and the mode of action of the toxin of pregnancy is by no means settled, and, while the idea of the presence of a toxin meets with general acceptance, opinion is conflicting with regard to its true or presumable nature. In the literature dealing with eclampsia, there is a considerable mass of information available concerning the altered metabolic state in pregnancy and in the toxaemic conditions of pregnancy: also certain pathological changes have been found, more or less constant, according to the different authorities. While these facts are well known, they do not seem to have been properly correlated.

I do not purpose dealing with the numerous theories of eclampsia and toxaemia already advanced, most of these deal only with one aspect of the situation, and take little notice of the metabolic question involved, moreover, they are usually dealt with in the text-books, where their shortcomings are indicated.

The minor symptoms of pregnancy have, as I shall

endeavour to show, a very definite relation to the graver morbid states of pregnancy, and, on considering the symptomatology of pregnancy, that is to say, the accessory symptoms apart from those induced by change in size of the uterus by the growing organism, and the changes in the breasts, which while not properly understood are nevertheless physiological, the conclusion is forced on one that the symptoms of various kinds, alimentary, nervous and cardiac etc., are all of toxic origin. A truly normal pregnancy, that is to say one where none of these accessory symptoms are present, is really remarkably uncommon. Some of the symptoms may become so exaggerated as to form diseases in themselves, for example, sickness may become pernicious vomiting, while anaemia may develope into pernicious anaemia.

Brief consideration of the more common symptoms shows that they mostly point to alteration in the alimentary systems, less frequently other systems may be involved in the disturbance, for example the nervous system, the skin (chloasma), the cardiovascular

system, (palpitation and fainting), even the osseous system may be involved, as is exemplified by the rare condition of osteomalachia. I have two cases under observation meantime, where one of the first symptoms to arise in successive pregnancies has been an attack of asthma, which only affects these patients during gestation. I have another patient who assures me that she always knows when she is pregnant by a slight cough and spit which comes on in the first month of pregnancy. While in a case of this sort a patient's unsupported statement is always somewhat open to doubt, the two asthmatic cases show with some certainty that the respiratory system may become affected as a result of pregnancy.

The nature of the toxin in ordinary pregnancy is bound up with the problem as to that in the more generally recognised toxaemic conditions. As stated above, a truly normal pregnancy is a somewhat uncommon

event, and morning sickness, constipation and nervous symptoms, which may take the form of irritability or depression, are all so common as to be regarded generally as more or less normal and inseparable from the usual parous state.

Sickness may assume various degrees of severity in the same and in different women, and may vary from slight morning sickness through all gradations until it assumes the pernicious type, where the patients life is in danger, either through the underlying toxaemic condition, through malnutrition, or through a combination of both. We can hardly assume that the different degrees of severity can have different causes, accordingly it would seem that the cause of a mild case of sickness and a severe case would be the same, except for the difference in quantity of the toxin present.

Constipation as a symptom is variable, and women, who never have had any suggestion of alimentary

stasis, may become affected with this early in pregnancy, and it may prove most intractable and unresponsive to drugs throughout the whole course of gestation.

Nervous symptoms may exhibit a variety of manifestations both in character and in intensity, from the slight depression or irritability, which are so common, we may have symptoms ranging in severity to actual insanity. An example of the alteration in the nervous system would seem to be the feeling of increased well-being which occurs in certain women, some of whom say they never felt better in their lives, may be a process of mental exaltation. Pica and bulimia have also, doubtless toxic origin. The peripheral nerves may be involved in toxic changes.

Pregnancy produces definite changes in the metabolism of the mother from the commencement, and, apart from the symptoms mentioned above, these changes

are also manifested by the altered state of the blood and of the urine.

The fact that as rule in ordinary pregnancy the symptoms tend to abate as the pregnancy advances, and that these are, generally, of less frequent occurence and severity in multiparae, points to the establishment of some defensive mechanism: as will be shown later this mechanism is mostlikely a proteolytic ferment, relative or absolute failure in the production of which will lead to the onset of untoward symptoms.

Pathological Findings.

Liver.

Definite degenerative changes are found in the liver in the toxaemic conditions of pregnancy, and these are generally well described in the text-books on midwifery. Hofbauer describes degenerative changes occuring in the liver of normal pregnancy, but this is contradicted by Opitz, (Williams).

Blood.

Blood.

In pregnancy there is a diminution of the glycogenic content of the blood, the urea content is also diminished, (Howell 10/). In eclampsia this diminution is found to be intensified, (Williams). Associated with the diminution of urea, there is an increase in the ammonia content of the blood. Amino acids (Howell) and carbamic acid (Ludwig and Savor) 11) have also been demonstrated in the blood of pregnancy. Lactic acid has also been shown to be present in the blood of normal and toxic pregnancy, (Leathes) 12) . Certain products of foetal origin are to be found in the maternal blood stream, these are, syncitial cells and pieces of chorionic villi, (Schmorl 13/),

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10/ Howell, Text-Book of Physiology.

11) Ludwig and Savor, quoted by Williams.

12) Leathes, Acidosis in Pregnancy. Proc. Royal Society of Medicine, Pathological Section, March, 1908.

13/ Schmorl, quoted by Abderhalden.

Abderhalden 14) mentions other substances of a protein nature, which are most likely serum albumin and serum globulin and these he has demonstrated in the blood of the mare.

Urine.

Urea is present in lessened amount from the normal, and there is a marked increase in the amount of the ammonia present. This is shown by analysis, and one frequently observes the strong ammoniacal odour in specimens of urine from expectant mothers.

So far I have seen no connection traced between the above substances present in the blood,

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14) Abderhalden, Defensive Ferments of the Animal Organism, trans. Gavronsky, 1914.

with the changes in the liver or with the symptoms of pregnancy and the symptoms of toxaemic pregnancy. A few physiological considerations will show that there is a very intimate connection and that in all probability the liver changes and the symptoms are the direct result of the presence of these abnormal constituents of the blood.

The introduction of protein, foreign to an animals economy, such as red blood corpuscles or blood serum from an animal of a different species, will give rise to the formation of a lysin which has the power of producing hydrolytic cleavage of the protein molecules into the soluble end products, amino acids etc. Abderhalden has utilised this principle in devising his serum diagnostic test for pregnancy. His test demonstrates the presence of a lysin in the maternal blood, specific to the foetal elements in the blood. This is shown by the development of amino acids from placental tissue or placental peptone, when acted

upon, in vitro, by the serum of a pregnant woman. We see then, in addition to the other abnormal constituents of the blood, the presence of a lysin specific to the foetal elements which gain entrance to it. Amino acids will be formed from these foetal elements by cleavage: carbamic acid is believed to be a stage in the further reduction of these substances to urea.(Luciani 15)) From the Eck 16) operation, it will be seen that carbamic acid is highly toxic, especially in the systemic circulation, so that it is highly probable this substance plays an important part in producing the toxaemic condition. Amino acids, with the exception of tyrosin and tryptophane (Combe)17) do not appear to be specially toxic, and even these two substances are only

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15) Luciani, Human Physiology, Vol. II, trans. by Welby.

16) Vide post.

17) Combe, Gastro-Intestinal Auto-Intoxication, 1908.

moderately so. Phenol derivatives are however, toxic, and possibly these substances have some action. It may be added, that possibly some of the polypeptides, comprising groups of two or three amino acids might have a toxic action, before they are finally resolved into the component amino acids.

Manifestations of Liver Changes.

Hofbauer, already quoted, claims that changes in the liver can be detected post-mortem even in normal cases of pregnancy, but this is denied by another author, unfortunately I have been unable so far, to obtain the original papers in order to examine their respective claims thoroughly. However, from the other information available, chemical and clinical, it can be readily shown that the liver is

changed in its function, even if the post-mortem appearance should be unaltered.

In the deficiency of urea and of glycogen in the blood, we have definite evidence that the normal function of the liver is upset, since the liver is the seat of formation of these substances. In the Eck operation it is found that the liver substance is degenerated, the cause of this must be toxic, since the nutrition of the liver should be adequately maintained by the blood reaching it via the hepatic artery, which is the nutrient artery of the liver. The toxic substances in this case are proteolytic end products derived from food, so here there is direct proof that these end products can exert a toxic action on the hepatic protoplasm. In pregnancy the effect of the end products derived from foetla elements will at first be slight, since they are not present in any considerable quantity, but later through their continued action and because of the increase in amount due to the growth of the placenta,

the effect will be more marked. Resistance is established as a general rule in pregnancy, except in the cases in the cases which pass into the toxaemic states, most probably by an enzyme which can cause the rapid conversion of the amino acids and carbamic acid to ammonia, which is not toxic unless in large amount.

Reference has been made to the operation of Eck's fistula, which would seem to have a very definite bearing on the problem of toxaemia.

In physiological experiments dealing with the absorption of the products of food digestion, Pavloff found that, when the portal vein was directed into the systemic circulation by means of Eck's operation a definite series of changes arose. Luciani's account of these of these is as follows:-

> "Sensory and motor disturbance which developed into clonic and tetanic convulsions recurring in spasms. The excitatory phenomena were succeeded by a comatose period in which

some animals died, while others recovered comparative health. Careful observation showed that those attacks occured in the dogs that had eaten most meat. Pavloff and Massen induced similar attacks in operated dogs by feeding with an excessive quantity of nitrogenous foods.

"When Nencki and Hahn (who took charge of the chemical part of the work) discovered a large amount of carbamic acid in the urine of the operated dogs, it occured to Pavloff and Massen to see whether the phenomena of autointoxication were due to this abnormal product, which would under normal conditions be converted by the liver. On injecting carbamate of soda or calcium to an amount of 0.25 grm. per kilo of the body weight, into the veins of a normal dog, they noted nervous disturbances similar to those seen in dogs

with Eck's fistula, while the same salt introduced into the alimentary canal was innocuous, even in larger doses. They noted further, that the administration of sodium carbamate by the mouth, even in smaller doses, in dogs with Eck's fistula, produced a similar poisoning to that obtained with a flesh diet..... By this they concluded that the toxic agent which produces the spasms of auto-intoxication in the operated dogs is represented by the carbamic acid, which is normally neutralised by the hepatic cells, and gives rise to the formation of urea, carbonic acid and water, according to Drechsel's theory. The Russian experimenters confirmed this conclusion by excising a large part of the liver in dogs with Eck's fistula, and tying the hepatic artery, when a comatose state was at once produced,

followed by strong convulsions which lead to death after 6--12 hours.

"The liver in animals with Eck's fistula was found to be atrophied, with partial degeneration of the epitheilia, due to accumulation in the blood of waste products.

"The urea in the operated dogs' urine was distinctly reduced, and this reduction was associated with a constant increase of uric acid and ammonia."

I have quoted the above description at length on account of the important bearing this experiment has on the subject of toxaemia of pregnancy.

Luciani states that these experiments have been confirmed by de "Filippi. The close resemblance of the symptoms of a dog with Eck's fistula and of a case of eclampsia is indeed remarkable, not only are the symptoms equivalent, but the changes in the

blood, liver and kidneys are also similar.

The question arises as to why substances are toxic to the liver when they reach it via the hepatic artery and innocuous when they reach it via the portal vein. No explanation on this point is given by the physiologists, but it is a possible hypothesis that substances in the portal capillaries are converted there to urea, without having the intimate contact with the liver cells, which substances arriving by the hepatic artery would have, and it may be that the endothelium of the portal capillaries has a protective function towards the liver cells.

The fact remains that the changes which occur in the liver cells are due to the toxic action of the end products of protein digestion, in the case of the Eck operation; in the toxaemic conditions of pregnancy , there is no reason to suppose that the end products of protein cleavage, derived from the foetal

elements will not have a similar effect to that found in the operated dogs, and give rise to degenerative changes, or at all events, impairment in function of the liver.

Alimentary Symptoms in relation to the Liver.

The symptoms of hepatic disturbance are not well marked, and, with the exception of pain in the region of the gall bladder and of jaundice, we have no symptom pointing definitely to the liver as the seat of any abnormality. Sickness is a common enough symptom of liver involvement, and the onset of a simple attack of catarrhal jaundice, before the actual appearance of icterus, is frequently an attack of vomiting.

In pregnancy as I have already mentioned, there are chemical changes in the blood which point to a disturbance in the normal hepatic function, and it would seem that the alimentary symptoms arising in pregnancy are due to the altered function of that organ.

Morning sickness is usually accompanied by nausea, and most probably this symptom is referable to the alteration in the liver. As will be mentioned later, the toxin has a decided effect on the nervous system, accordingly the sickness might be due to stimulation of the cerebrla vomiting centre. Sickness of the cerebral type, however, is usually stated to be free from nausea, it is unlikely therefore, that morning sickness is generally of this type, although it might conceivably occur. Reflex stimulation of the vomiting centre due to the presence of a foreign body in the pelvis might also be a cause of the vomiting. If this were the case, then any foreign body in the pelvis would cause sickness, but it is possible to have large fibroids etc., without any symptoms whatever, so that we can hardly regard this as an adequate explanation of such a common symptom as morning sickness: and further as the uterus grows in pregnancy the sickness generally ceases, if the pelvic reflex playeda part in the causation of the

sickness, we might expect to become the symptoms to become increasingly severe as pregnancy advances, but this does not happen.

Hepatic Tenderness.

This may occur in the vomiting of pregnancy. As a rule,women are not in the habit of seeking advice with regard to the simpler forms of sickness. In the more severe forms, I have found this sign occasionally. These patients complain of pain in the region of the liver, and there is very definite tenderness here and along the costal margin of the right side. I have had a case where the whole of this region was exquisitely tender,--- a young primipara--- and continued to be so, throughout the whole term of gestation.

In the absence of other signs of disease, pleurisy, cancer, pleurodynia etc., we can only conclude that this tenderness is of hepatic origin. The area of cutaneous tenderness in the above case corresponded to that supplied by the 7th, 8th¾,9th and

10th thoracic nerves. The nerve supply of the liver is derived from the same spinal segments via the great splanchnic nerve and the semilunar ganglion.

I have not seen this symptom mentioned as occuring in connection with morning, although de Lee draws attention to it in connection with eclampsia. It can only be regarded as affording clinical evidence that there may be decidedly hepatic involvement in morning sickness.

Constipation.

This is of frquent occurence in pregnancy, and offers another presumable indication of the disturbed activity of the liver. The diminution in the formation of urea and glycogen is definite evidence that the secretions of the liver are altered, it is a justifiable assumption therefore, that there will be a deficiency of the external secretion of the liver, bile, with a corresponding decrease in the bile salts and pigments which are known to be very necessary for the proper

for the proper function of the gut to proceed.

Nervous Symptoms.

Toxins produce their effects first of all on the most highly developed and specialised tissues of the body. An example of this is seen in the liver. In the same way it would be expected that nerve cells would be affected by the toxin. The nerve cells would come under the influence of the toxin and the manifold symptoms of this involvement are evinced in many cases of pregnancy.

Kidney Changes.

In the toxaemic conditions of pregnancy, the toxin is present in much larger amount than in ordinary pregnancy. The renal epithelium is a delicate structure, and is accordingly liable to be affected by the toxin. Renal involvement is, therefore, a secondary change following on the presence of the

the toxin in the blood.

Ocular Changes.

As stated in the first part of this paper, with regard to experimental retinitis, the nephrolytic serum would produce end products from the destruction of the kidney substance. These end products would act probably similarly to the toxins of pregnancy in producing retinitis.

Eclampsia.

While there is abundant evidence that a toxin exists in most cases of pregnancy, it is necessary to find what relation this condition has to those known as the toxaemias of pregnancy. From the foregoing it is seen that changes occur in most cases of pregnancy. The changes in the toxaemic conditions are simply more profound than are those encountered in the ordinary cases of pregnancy, where the symptoms are slight and generally pass of towards the middle of term, whereas

in the toxaemic conditions, the symptoms and signs are usually manifested in the latter half of pregnancy, although they may supervene much earlier. From this it would appear that the primary toxic condition passes into a grave pathological state, and there is evidently a failure, relative or absolute, in the defensive mechanism, which permits of this. The increase in the amount of the toxin will produce marked effects on the liver, and with the liver partially out of action, a state of affairs will arise, strictly comparable to that existing in a dog with Eck's fistula. The products of the digestive tract will now make their way into the general circulation and increase the toxaemia, and also the extent of the liver lesion, with the result that a vicious circle will be established between the liver, portal and general circulations, which will ultimately give rise to the profound toxaemia causing the eclamptic seizures. Ffom this it would seem that

the results of the Eck operation in a dog represent more than any other condition, experimental eclampsia.

Post-Partum Eclampsia.

Eden 18) casts doubt on the idea of the presence of a toxin derived from the uterus, since eclampsia may occur post-partum. The above theory overcomes this objection, since the direct cause of the eclamptic state is probably not derived from the uterus directly, but is caused by alimentary products, i.e., it is a secondary toxaemia caused by the removal of the liver bloc. The liver might be affected sufficiently for this some days before the onset of actual eclampsia, which will only ensue when the toxaemia

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18) Eden, Text-Book of Midwifery.

has reached the intensity necessary to produce the symptoms. If alimentary products are actually the cause of the convulsions, there is no reason why the eclampsia should not arise after delivery, since the hepatic tissue will not return to normal for some days after the withdrawal of the primary toxins. Further in the Eck operation convulsive symptoms do not arise until about ten days after the fistula is established.

SUMMARY.

1. In most cases of pregnancy, there is a toxic state, which gives rise to the varied symptoms of pregnancy.

2. The toxin of pregnancy has a marked effect on the liver, which causes definite effects on the metabolism of the mother.

3. The toxin is most likely the cleavage products of the foetal elements, chorionic villi, syncitial cells etc.,which find their way into the maternal blood.

4. The toxaemic conditions of pregnancy are

secondary, caused by the breakdown of the liver which allows the passage of alimentary products into the general blood stream.