Thesis for M. D. Glasgow

THE TOXÆMIA OF PREGNANCY,

WITH SPECIAL REFERENCE TO

THE ÆTIOLOGY AND TREATMENT OF PUERPERAL ECLAMPSIA

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THE ÆTIOLOGY AND TREATMENT OF PUERPERAL ECLAMPSIA

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TOXÆMIA OF PREGNANCY

THE various explanations as to the origin of toxic material that not infrequently jeopardizes the life of mother and child are not as yet accurately described. Retained as they are under certain conditions in the blood-stream, they naturally act as powerful irritants to delicate structures, such as nerve tissue, glomeruli of the kidneys, and fundus of the eyes, producing hæmorrhages, congestion, and œdema; or, in other words, manifestations of a general toxæmia, and, as a consequence, symptoms in the pregnant patient which are specially addressed to the nervous system.

Ætiology.—So many theories have been advanced that this condition has been described by several writers as a 'disease of theories,' some maintaining that it is simply a disorder of the nervous system peculiar to pregnancy. Its asso-

ciation with uræmia has been conclusively demonstrated to have no foundation, urea as such not circulating in the blood. Spiegelberg advanced the theory that the circulation of **ammonium carbonate** was responsible. Chemical analysis does not support this view. Bacterial invasion of the blood-stream has been advocated as being the cause, but blood and urine cultures have failed to adduce evidence substantiating the **bacterial** nature of eclampsia. The origin has been further described as being due to **fœtal** causes. Many other theories have from time to time been advanced, but there is still one to which I must allude—the **pressure** or mechanical theory, which is exerted on the renal vessels and other organs, producing disturbance of function, which I shall endeavour to explain is a very potent element in the production of this disease.

It is a universal rule that each part of the body does not merely do its own special work, but is concerned in the great cycle of changes which is called general metabolism, and interference with any organ upsets not only its specific function, but causes disturbances through the body generally.

To my mind the foregoing explanations as to the cause of eclampsia are not (so far as I have been able to investigate) in the very least supported clinically, but I am convinced that the true ætiology is to be found in the direction that the condition is a **disease** of **metabolism** and nutrition, resulting in **auto-intoxication,** by acid products interfering with the oxygen-carrying power and alkalinity of normal blood. Abnormal accumulation of acids can occur by acid excretion being **reduced,** or, on the other hand, the acids may be **increased,** while at the same time their elimination is interfered with. For example, an acute attack of gout illustrates a reduction in the output of uric acid; but where you have increase of acids with defective elimination, the results, pathologically speaking, are much more important. It must be remembered in this type of case that the maternal organism is sometimes unable to accommodate itself to the increased work necessary for the elimination of the acids, it having to deal with the maternal as well as the fœtal excretory products; and from this inability or disturbance of kidney function you have **renal insufficiency** established,

with retention in the blood-stream of injurious products.

Many organic acids have been described and grouped, but the acids which have particular bearing on this subject, viz., **β-oxybutric** acid, **diacetic** acid, and **acetone,** which chemically are closely related to one another—have now been given the common name **acetone bodies.**

The **sources** of these acetone bodies and where they are formed has now to be considered.

Acetone (C_3H_6O) has been detected in very minute traces in normal urine (physiological acetonuria), but it is maintained by some that it is only found in healthy urine after some indiscretion in diet, such as alcohol ($C_2H_6O_6$); but the presence of **diacetic acid** ($C_6H_{10}O_3$) is pathologic, and is now looked upon as a serious symptom, its presence in urine being the result of some perversion of oxidation.

In a dietary consisting exclusively of meats and fat you can produce acetonuria, and it is a remarkable fact that the addition of carbohydrates to the diet causes the acetonuria to disappear. This leads one to believe that there must be some inter-

relationship between absence of carbohydrates from the diet and perversions of oxidation. To tissue combustion and respiration carbohydrates are in a measure essential, their absence interfering with oxidation, and the resulting acetonuria ultimately destroying the red blood corpuscles, thus depriving the organism of the vehicle through which oxygen is carried to the various tissue cells. In short, the absence of sufficient carbohydrate metabolism would be perverted in such a way that **acetone bodies** would be produced as new bodies—*i.e.*, as abnormal products of metabolism. According to the oldest views, acetone and diacetic acid are formed in the **intestinal** tract from a decomposition of the carbohydrates, probably preceded by their defective treatment on the part of the liver and pancreas, which from one or other cause may not for the time being be functionally active or the seat of pathological change. It is well known that **intestinal sepsis** or decomposition plays an important part in the production and aggravation of disease, and that it is the aim of every physician to render, by the use of judicious intestinal antiseptics, the evacuations as inoffensive

as possible, as in the treatment of typhoid fever, the summer diarrhœa of children, and other allied disorders; and when this is obtained, the manner in which distressing symptoms abate, or at least are ameliorated, is most satisfactory, this factor in the treatment of these conditions being essential to their successful management, intestinal septic absorption having no limits to the constitutional disturbance which may be produced through this medium. But this is by the way. Returning to where these acetone bodies are found, I have already mentioned their detection in the intestine, but at the same time the proportion is small compared with the quantity circulating in the blood, which suggests that these bodies have **other sources,** pointing to an intracellular process. In support of this, acetonuria is present in advanced malignant disease and in diabetes, the loss in weight being brought about by the destruction probably of the carbohydrates in the body, which would account for the acetone bodies being detected in the urine in these cases. Until recently the idea was generally prevalent that the **proteids** were the source of the

acetone bodies. The chief argument against this view, however, was the fact that they were also frequently excreted when the metabolism of the proteids was normal, or even abnormally low. Another idea—namely, that acetonuria was the result of the degradation of the body proteids—was advanced at one time, but had to be abandoned as soon as careful metabolic studies were made in diabetic subjects, in whom it was found that proteids might be retained, while acetone bodies could be continuously excreted in the urine.

It is impossible to determine whether or not all the organs of the body participate in this intracellular process. Magnus-Levy, however, discovered that some of these bodies were a product of the autolysis of the liver and pancreas, and his observations may therefore be considered an argument in favour of the view that these organs have something to do with the formation of acetone bodies, just as we find in myxœdema disturbances of the thyroid function, which is the primary cause in the production of this disease.

In pregnant patients disturbance of one or more functions is frequently met with. There are those

of the circulatory system, the nervous system, or the particular specific function of one or more organs, these at first being simply functional—that is, without organic change—and generally disappear at the termination of gestation; but, on the other hand, if they be prolonged and unduly severe, they lead to more active changes in the form of pathological conditions, such as eclampsia, or resulting in the premature termination of an abnormal pregnancy.

In the early stages of gestation eclampsia is not met with; the earliest recorded case, so far as my knowledge goes, was at six months. In the cases which I have carefully observed the condition developed within six weeks of the full term, at a time when the pressure effects were greatest, and more apt to set up disturbances of the blood-supply in the various organs.

I have already stated that some of the acetone bodies were the product of a functionally-deranged liver (in the first instance) and pancreas, and it must be borne in mind that the functions of these organs play a prominent part in the general metabolism of the body, but particularly so in connec-

tion with the **metabolism** of **carbohydrates,** and let me repeat that a dietary consisting entirely of meat and fats will lead to the formation of acetone bodies, but whenever carbohydrates are added to the food the acetonuria disappears. In connection with the functions of the liver, it is necessary to remember how certain **toxic** principles are collected to cleanse the blood (these elements are gradually turned into blood, or excreted as bile), also to transform other poisonous foreign bodies in a similar manner, and through the **antiseptic** properties of the bile to moderate the intensity of intestinal decomposition or fermentation.

In the cases of eclampsia which I have investigated **acetonuria** was present in all, suggesting that one primary cause is to be found in disturbance of **carbohydrate metabolism,** which implicates the two organs chiefly concerned in this process—namely, the **liver** and **pancreas;** and an explanation of this perversion of function is to be found in **mechanical pressure** interfering with the blood and nerve supply, or possibly in the presence of some pre-existing disease of the gland itself, producing defective carbohydrate assimilation.

Acetone bodies are also detected in the urine of diabetics, the presence of diabetic acid being of grave import in the prognosis, and in this connection it is interesting to note the influence that disturbance of pancreatic function has in the production of diabetes. It has been noticed that after surgical operations on this gland, or experimental removal of the pancreas from animals, diabetes results, the urine containing sugar, diacetic acid, and a considerable quantity of acetone; and it is a matter of the greatest interest as to how far the pancreas participates in the pathology of diabetes. May the explanation not lie here rather than be attributed entirely to the liver, or to the fact that the disease is essentially a neurosis? At least it would explain the actual cause in a large proportion of the cases, and would suggest that there are possible dangers, after what I have stated with regard to carbohydrates in relation to acetonuria, in dieting diabetics too strictly. I merely mention these points with reference to diabetes (pancreatic), as they have very much in common clinically, as, for example, you have in both **acetonuria** and

other lesions not far removed, such as retinal changes, symptoms referable to the nervous system and changes in the kidneys. And, further, I venture to suggest that the ætiology of the two conditions is to be found in an acid **auto-intoxication**; and be it noted that in pregnant women there is a tendency to the increased production of toxic elements, and, by favouring organic insufficiency, producing a **predisposition** to an auto-intoxication.

With regard to the **urine,** in the cases on which I have notes albumin was always present, varying in amount in some, the urine becoming almost solid on boiling. Although in one or two cases the amount was comparatively small, urinary flow was scanty; but I noticed this seemed to be increased after a convulsion for a short period. Urea in every case was diminished, in some cases as low as 1 per cent. Furthermore, in the majority of cases there was a distinct reaction to Fehling's solution; acetone bodies were also present. In connection with the tests employed for their detection, there are one or two points which must be carefully noted, otherwise mistakes are

sure to occur. **Legal's** test, which is, perhaps, not very sensitive, is easy of application. I observed that if the red coloration did not appear at once, by setting the tube aside for a few hours it was obtained, even to a dark purple. A more delicate test, and one capable of detecting a trace of acetone, is **Lieben's** test, the resulting precipitant being iodoform, which is readily recognised by its odour. Diacetic acid was found in all cases. The test employed was that suggested by **Von Jaksch**, and in connection with this test it is of the greatest importance that the specimen of urine to be examined should be fresh, for if decomposition has begun, the diacetic acid takes up a molecule of water and splits into acetone, alcohol, and carbon dioxide. Again, it is to be remembered that the claret-red coloration obtained with this test is also met with in patients taking certain medicinal remedies—*e.g.*, salicylic acid, carbolic acid, antipyrine, etc.; but you distinguish diacetic acid by the fact that if the urine be previously boiled diacetic does not give the red ferric chloride reaction, while the other substances do. Further, salicylic acid, carbolic

acid, etc., are not extracted from the urine by ether, whereas diacetic acid is soluble in this substance.

I have never had the opportunity to perform an autopsy where death was the result of eclampsia, nor have I observed such; but on consulting a large amount of literature to find what **pathological evidence** there was in support of the idea that this disease is one of a special metabolism, produced through some derangement of function, or by pathological change in the liver and pancreas, I find that, with few exceptions, the general statement is made that the most characteristic lesions are to be found in the **liver,** some pathologists stating liver and **pancreas.** These changes are described as being small multiple **hæmorrhages,** in which **necrosis** has begun, giving the liver, to the naked eye, a mottled appearance. Schmorl attributes this to degenerative changes following **thrombotic** processes in the smaller portal vessels, and he further considers that these changes in the liver were pathognomonic of eclampsia. Hæmorrhages have also been detected in the pancreas, central nervous

system, and serous surfaces. The changes in the kidneys are evidently not of any great moment—at least, not sufficient to explain such a condition as eclampsia. All that is mentioned in pathological reports is simply that they were found to be hyperæmic. To determine the permeability of the kidneys, Guénard administered methylene blue, and it was found that the drug could always be demonstrated in the urine a short time after the administration, which proved that the renal function was not impaired, even though anatomical or pathological lesions might be present.

The **clinical manifestations** are various, and some are only occasionally met with. There are sometimes certain **premonitory** signs in cases of eclampsia which enable you at once to make a correct diagnosis; but frequently, on the other hand, the condition is never suspected until a convulsive seizure has actually taken place.

I will only remark on symptoms in the cases with which I have come in contact. It is not a well-established fact that œdema, either in the face, legs, or hands, is the first symptom to attract attention; possibly that may be so, but the patient

probably thinks that it is one of the discomforts she has to look for, and therefore seeks no advice. Frequently the earliest complaint is failing **vision,** with **vertigo** and **headache,** this latter particularly so in the morning on getting out of bed. My association with an ophthalmic institution may explain why I have met with eye difficulty as an early premonitory sign in these cases. Again, on several occasions I noticed that the discomfort was **epigastric pain,** and given a case where frequent requests are made for the relief of this pain during the latter weeks of gestation, it is undoubtedly a symptom which should put one on the alert, and institute a thorough investigation, as I believe this is often the precursor of a seizure.

Again, **drowsiness** and defective memory are sometimes met with as a premonitory sign; furthermore, headache, associated with most obstinate **vomiting,** is often an early symptom, **swelling** in the hands and feet, or on rising in the morning the patient observes that her face is swollen. **Primiparous** women seem to be the most liable. In some a prominent early symptom has been profuse and persistent **diarrhœa,** with offensive

evacuations, indicating intestinal sepsis or decomposition; and on one or two occasions **jaundice** has been seen, involving, as this does, the **liver function.** But one or more of these early symptoms are often absent, the first sign indicative of the toxæmia of pregnancy being a fit, which may or may not be ushered in with the commencement of labour. In one case the first convulsion came on while I was making a vaginal digital examination. There had been no previous complaint on the part of the patient; she had always expressed herself as feeling well. You may have repeated **convulsions** without starting labour, but I have only seen two cases where they were prolonged beyond six hours **after** child-birth. There is no special feature to notice in the paroxysms themselves, more than that they seem to vary in severity and duration and period of interval. The resulting coma is often most profound; doubtless this depends on the quantity of toxic matter circulating in the blood-stream, so that the severity of the seizure would be in proportion to the degree of **toxæmia** present. These convulsions are said sometimes to be confounded with those of epilepsy or hystero-epilepsy,

but a differential diagnosis should not be a difficult problem. The **pulse** is, as a rule, one of high tension, particularly in the plethoric type of case, while in the anæmic it is rapid and weak. This feature is not unlike the acute nephritic pulse, but the quality is explained as the result of a contraction in the arterioles throughout the body, or irritation of the vaso-motor centre by the toxic material in the blood.

In reference to **treatment** of eclampsia, one has not often the opportunity to initiate **prophylactic** measures, but in this direction a great deal can be accomplished; for example, after the statements I have made, the importance of rendering the intestinal tract free from fermentative processes cannot be over-estimated when one remembers the large surface there is for absorption of toxines into the blood. The **antiseptics** employed for this purpose must be mild and non-irritating, your aim being to **disintoxicate** poisonous acids and prevent, as far as you possibly can, their accumulation in the blood-stream. **Alkalies** possess this power.

Sulpho-carbolate of soda (alkaline and antiseptic), combined with the bicarbonate, I have

found serves this purpose admirably, or that excellent preparation **glyco-thymoline,** which is most suitable, also, in the relief of distressing dyspepsia. To my mind this treatment of the intestinal tract is the most **important prophylactic** help we have. A watchful eye on the urine is, of course, paramount. Ascertain the amount of urea, test for ferric chloride reaction (acetone bodies), and if eliminative processes are at fault, employ means to correct this. Diet should consist of ample liquid and light nutritious food, and if acetonuria is found to exist, a sufficient quantity of carbohydrates must be taken, for reasons already mentioned.

Promote a healthy action of the skin by hot-packs and other means. By the employment of these prophylactic remedies you are attending to the channels from which you look for assistance in preventing the development of eclampsia—namely, the **bowels, kidneys,** and the **skin.**

If the child is dead, which is frequent, and provided some of the premonitory signs are present, the uterus should be emptied without **delay.** But not infrequently the first time we see a case

of eclampsia is when the paroxysms have actually taken place. We then endeavour to adopt **curative** measures, and it will depend upon the **promptness** and **thoroughness** of the treatment employed what amount of success will be attained in the saving of life. I will only mention the remedies I have employed, as I have no experience of the many other methods of treatment. These comprise chloroform, venesection, opium, and the injection subcutaneously of normal saline solution.

The first time I came in contact with a case of eclampsia produced an impression on my mind which will never be obliterated. During my student life I never saw such a case, but a few years after having started practice I was one afternoon on my way to make a call at a considerable distance in the country, when on passing a farmhouse I was requested to visit the farmer's daughter, who was said to be seriously ill. I found a young woman in violent convulsions, and the history was that these had continued since ten o'clock that morning, with but short intervals, and at these periods she was never conscious. She had been seen shortly after the

first fit by a medical man, who diagnosed the condition as one of simple hysteria. I was more fortunate by seeing the patient actually in a seizure. Abdominally and otherwise I had no difficulty in ascertaining that she was pregnant, although the mother had never suspected this, as the girl seemed always in good health, and performed her usual duties until going to bed the previous evening; but later I learned from the patient that frequently she had had morning headache, which generally passed away as the day advanced.

I felt myself in a somewhat awkward plight, from the fact that I had no appliances or medicinal remedies with me. I consequently began to consider what best I could do under the circumstances. A vaginal examination showed that labour had not developed, and, so far as I could determine, the child was dead. The emptying of the uterus as quickly as possible suggested to me the first indication. I therefore sterilized a long stocking-wire, passed it through the cervix, and punctured the membranes, thereby diminishing the contents of the uterus; and in

the hope that this procedure would bring about uterine contractions, I further sterilized my pocket-knife, and opened her median basilic vein, and bled her to the extent of 10 ounces. And, most remarkable to relate, before I had closed the wound her twitchings ceased, and within fifteen minutes she was conscious. The external os had now begun to dilate, and, with pains of exceptional expulsive power, the dead child was born. Urinary flow, which I learned had been most defective, was quickly re-established. She never took a post-partum fit, but made an excellent recovery.

The blood which was removed was extremely dark in colour, this doubtless being caused by the amount of toxines present, and from the fact that there is for a time a degree of asphyxiation during the seizure. Since this experience I have frequently resorted to **venesection,** with most gratifying results, and I have not confined this to the plethoric type of case, but have employed such treatment where the pulse has been rapid and weak with equal success; by so doing you simply lessen the dose of poison in the blood-stream. Return of consciousness I have witnessed on several

occasions after blood-letting, and have repeated the operation on the same patient.

The **cardinal points** in the treatment of eclampsia are:

(*a*) To control the convulsions;

(*b*) Stimulate elimination;

(*c*) Empty the uterus as quickly as possible.

Before remarking on any points which occur to one under these headings, there is one class of case where, from my experience, there is no time to delay. The type I refer to is where a pregnant patient consults you about her **eyesight**, and on making an ophthalmoscopic examination you detect small hæmorrhages situated chiefly around the macula and course of the blood-vessels, blurring of the disc—in short, symptoms of albuminuric and neuro-retinitis. The treatment in these cases is to induce premature labour without delay. I have had many opportunities to investigate these cases before and after delivery, and I have no hesitation in stating that immediate action is necessary, because, be it remembered, you have to deal with a **toxic retinitis**, a symptom of a general toxæmia which will in time partially,

if not totally, destroy vision. The minute clots of blood in the retina will be absorbed, and subsequent atrophy, degeneration of nerve fibres, with fatty infiltration of the granular layer and associated pigmentation, and hyperplasia of connective tissue with fatty degeneration, will occur if the patient is not relieved; and surely sufficient damage has already taken place without subjecting the patient to the risk of having next to useless sight.

With regard to the control of the fits, **chloroform** is the universal help. **Morphia** in these cases is of undoubted value, although I am aware that it is not held in high esteem by competent observers. Frequently in other hands it has failed because the dose administered is too **small.** Eclamptics seem to me to be almost proof against any toxic consequences. I never give less than $\frac{1}{2}$ grain hypodermically, and have repeated this dose within two hours. I have administered $1\frac{1}{2}$ grains in less than five hours, with excellent results. The morphia does not retard elimination; its use prevents the paroxysms, which is all-important, because I believe the greater the

number, the more the patient's life becomes endangered.

In cases where the weakness is extreme, the breathing low and shallow, requiring the use of strychnine, digitaline, and ether, morphia, if used, must be so with a cautious hand, because in these cases you do not wish to depress the respiratory centre further.

In our endeavours to stimulate **elimination** in an unconscious patient we find our means rather limited. Lavage of the intestine with warm saline solution and a minim of croton oil in butter placed on the pharynx will produce free purgation, and give eliminative assistance so far as can be obtained from this channel; hot-packs should be used to promote diaphoresis. But beyond doubt the principal and invaluable therapeutic agent we possess is the **injection of normal saline solution,** whereby you dilute the blood and consequently the poison; further, the patient is stimulated, which is important, because there is naturally considerable shock after such fits, and you also promote **diuresis.** It is truly wonderful how rapidly this will sometimes develop, and in patients collapsed and with

weak, rapid pulses the manner in which this treatment revives them is equally striking. But to my mind the **greatest** value in this line of treatment, and one which cannot be over-estimated, lies in the fact that this physiological salt solution **disintoxicates acetone bodies, limiting** their **formation** by favouring their **oxidation, acetonuria** having been known to disappear in a few hours after treatment. Sterilized normal saline solution is conveniently put up in hermetically-sealed tubes by Martindale of London; they are dependable and always ready for use. All you require is the addition of a pint of sterile water. This is an important matter, because one never knows when such an agent may be urgently required for this and other purposes; and by the use of these tubes you avoid the risk of introducing a fluid which is not sterile, thus preventing the development of abscess or cellulitis.

The indication to **empty** the **uterus** as soon as possible with due regard to safety is the right line of treatment, and this is supported by **statistics** as regards the maternal mortality in these cases, because in the majority the child

is dead or will probably die; and remembering that, as a rule, with the completion of the labour you have **cessation of the fits,** these are cogent reasons why this procedure should be undertaken as a justifiable one; in short, where the child is dead, and albuminuric retinitis is present, or the death of the mother is imminent, there must be no hesitation in resorting to operative interference.

There are many methods to promote the induction of premature labour. I have no experience of Bossi's dilator, but depend on the ordinary Hegar type until dilatation is so far advanced that Champetier de Ribes's bag can be introduced; but great advantage is to be gained, where there is no attempt on the part of the os to dilate, by rupturing the membranes, thereby exciting strong contraction in the uterus, which is much more powerful than in normal labour. It is true that by this means I lose the dilating help of the liquor amnii, but this is counterbalanced by the powerful expulsive pains produced by diminishing the contents of the uterus; then, by employing version or by application of the forceps, delivery can be

rapidly completed. In cases of pelvic deformity and where the child is viable the question of Cæsarean section would require to be considered. Of course, by so doing the risk to the mother is much increased. All lacerations should receive immediate attention, because in these cases the liability to septic infection is greatly increased. The third stage should not be hastened. A moderate loss of blood should be encouraged rather than arrested.

In the remarks I have made I have endeavoured to throw some light on the true cause of puerperal eclampsia, using what pathological evidence I could obtain, and clinically by observing a considerable number of cases in connection with the out-patient department of King's College Hospital and the Hospital for Diseases of Women, London, and those I have treated in private practice, with the result that these investigations, for reasons which I have expressed in this monograph, lead me to assert the view that the condition is an acid **auto-intoxication** dependent on errors of a special metabolism, in which the liver and pancreas are chiefly implicated. I have

also indicated a few most important points in the treatment of the disease in the premonitory stage, the best prophylactic and curative measures to adopt, and wherein lies the real therapeutic value of the saline solution treatment.

PAISLEY,
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