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Recent advances in the etiology of pre-eclampsia and eclampsia

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"RECENT ADVANCES IN THE ETIOLOGY
OF PRE-ECLAMPSIA AND ECLAMPSIA"

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CONTENTS

1. INTRODUCTION
2. CLASSIFICATION
3. HYPERTENSION
 - a. Liver
 - b. Kidney
 - c. Eye Grounds
 - d. Angiospasm in Other Tissues
4. ALBUMINURIA
5. COMMON FACTOR
 - a. Physiology
6. PITUITARY PRESSOR-ANTIDIURETIC SUBSTANCE
7. LIVER PITUITARY RELATIONSHIP
8. PLACENTAL THEORY
 - a. Syncytial Degeneration
 - b. Effect of Placental Products
 - c. Placental Metabolic Products
 - d. Placental Endocrine Disturbances
9. ENDOCRINOPATHY
10. CONCLUSIONS

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INTRODUCTION

The present conception of preeclampsia and eclampsia is that they are one and the same disease, the only essential difference being that the preeclamptic patient has no convulsions. Preeclampsia should then always be a precursor of eclampsia.

There have been few attempts to approach the subject of etiology of eclampsia and preeclampsia from the standpoint of pathology. The various theorists have preferred to fit the manifestations of the disease into their own preconceived notions of its etiology rather than to take as a point of departure the demonstrable changes produced in the human body, and to find therein a common factor for all the signs and symptoms.

The term toxemia is now regarded as of poor descriptive value since no toxin has been isolated in eclampsia, nor is the blood of eclamptic patients more poisonous than that of other pregnant women.

CLASSIFICATION

Kellog divides the disease into two main groups:

1. Those showing evidence of disease independent of pregnancy, including essential hypertension, glomerulonephritis, pyelonephritis, and degenerate nephropathies.
2. Those showing no evidence of disease. The latter being divided into three sub groups, the first includes those patients with no evidence of the disease except hypertension and albuminuria, the second includes all of sub group one, plus the rest of the findings including headache, spots before the eyes, nervousness etc. The third sub group includes sub groups one and two with convulsions added.

It is with those patients showing no evidence of disease with which this paper will be concerned.

Gibberd states that a first toxemia may affect a previously healthy woman in one of three ways:

1. It may give rise to an obvious chronic nephritis.
2. It may be followed by a more or less habitual recurrence of toxemia with subsequent pregnancies, with apparantly normal kidneys in the intervals, or
3. Leave the patient absolutely normal.

HYPERTENSION

One of the two most common findings in this disease is an elevation of the blood pressure. Reinberger and Russell classify the toxemias into three groups according to the elevation of blood pressure.

1. Mild toxemia—slight elevation of blood pressure 130/60.
2. Moderate toxemia—above 130/60 to 150/80.
3. Severe—from 150/80 to 200/100 and above.

Irving observed the blood pressure on both arms at the same time and found that not infrequently a variation of as much as 20mm. Hg. was present. This strongly suggests vascular spasm effecting at the same time different vessels unequally. The blood pressure is determined by the minute output of the heart, force of contraction, viscosity of the blood, and peripheral resistance. Since none of the others are found to be altered, peripheral resistance must be the deciding factor. This resistance due to spasm in the kidney, or generally, is a protective mechanism to maintain adequate filtration pressure.

Schwarz states that a hypertension, unless due to some intercurrent disease must always be considered as ominous. Even when no other symptoms are present it must be regarded as a definite preeclampsia.

Zangemeister has shown that preeclampsia can be distinguished from other types of hypertension by the fact that in the former there is the definite oscillation of the readings, whereas, in the latter the readings are constant. The degree of hypertension is never an indication of the degree of danger present, for sometimes a slight but persistent hypertension with occasional periods of marked hypertension is of more significance than a persistent and marked hypertension.

Liver

Changes in the liver are less extensive and have lost their place of prime importance. Schmorl in 1893, in a monograph based upon the autopsy findings of 17 women dead of eclampsia, stated that he found in every case lesions of the liver which he believed were so characteristic that their presence justified the diagnosis of eclampsia without further knowledge of the history of the case.

Bouffe de Saint Blaise demonstrated such lesions in the livers of 42 consecutive cases and in 1902 Schmorl reported finding them in 71 of 73 autopsied cases of eclampsia. The remaining 2 showed fresh complete thrombosis of the portal vein.

The characteristic lesion was found at the periphery of the lobule and consisted of fibrous thrombosis in the capillaries, hemorrhage, and necrosis of the liver cells.

Fatty degeneration was less common. Thrombosis of the radicles of the portal vein may be found. This periportal hemorrhagic necrosis with similar though less marked changes in the intracapsular tissue has all the characteristics of a severe infarction and is confined to those areas supplied by the hepatic artery. Although these pathological lesions in the liver are only irregularly found and seem quite unrelated to the clinical syndrome, it is quite possible that the condition when found is a result of constriction of the hepatic arteries.

Acosta-Sison reports that the main changes found in the liver were disturbances in its circulation ranging from congestion, petechial hemorrhage, to large discrete hemorrhagic patches varying in size from a few millimeters to two centimeters in diameter. The parenchyma varies from a mere cloudy swelling and fatty degeneration to focal necrosis.

Hoffbauer regarded this periportal necrosis of the lobules as the characteristic lesion of the liver in eclampsia. Necrosis is said to be produced by pressure from extravasated blood that has escaped through the portal capillaries. Hoffbauer maintains that the lesion may affect any part of the lobule and is not confined to any definite area.

Teel and Reed state that there is marked narrowing of

the arterioles of the liver, leading to ischemia, hemorrhage, and not infrequently thrombosis. In such an organ as the kidney or liver, thrombosis of the afferent arteriole would lead to destruction of the unit involved. Similarly, prolonged ischemia, as a result of the arteriolar spasm, might conceivably lead to permanent damage to the functional unit supplied.

Kidney

Histiological evidence that there is spasm of the glomeruli has been found by numerous observers including 2,3, 12, 16, 27, 28, 36, 37, 43. According to Addis, the essential lesion of the kidney is dilatation of the afferent vas and glomerular capillary, with well marked ischemia of the tuft. The whole tuft is swollen and completely fills Bowman's capsule.

Fahr, in 1924, found an increase in the size of the glomeruli due to swelling of the capillary wall and a relative absence of blood cells in the capillary lumina which produced marked ischemia.

Weir measured the diameter in microns of the glomeruli. In five of seven eclamptic patients the average was greater than normal, one showed a slight increase, and one a slight decrease. Fahr considered these changes to be due to spasm of the afferent arterioles and believed that they were accompanied by swelling of the vessel walls.

Irving states the tubules exhibit albuminous degeneration which may advance to hyaline formation and fatty changes.

Study indicates that not all glomeruli are involved and some may escape entirely.

Eye Grounds

Further evidence that there is spasm of the vessels is found in the observations of the eye grounds, 16, 22, 28, 30, 32, 38, 49, 50, 53. Wagener states that the first visible sign is a narrowing of the arterioles of the retina which may affect any or all branches of the central artery. This narrowing is often accompanied by irregular constriction of the arteriolar lumen, usually first or more marked in the smaller nasal branches. Later, as the narrowing and constriction becomes more fixed, individual cotton-wool patches and hemorrhagic areas may appear in the retina, and finally diffuse retinitis of the albuminuric type may develop. Wagener concludes that although the occurrence of retinitis does not justify the diagnosis of serious glomerular nephritis, it obviously indicates the probability of serious involvement of the renal arterioles along with the systemic arterioles, and probable persistence after pregnancy of kidney damage.

These spastic lesions, according to Hardin, McIlroy and Huggins, account in part for the transient blindness, occasional dizziness, and specks before the eyes. This intermittent vasospastic phenomena of the retinal vessels with or without perivascular exudation, are common

occurrences in eclampsia and preeclampsia. According to Kellog and others, persistence of the angiospasm for a longer period of time may result in retinitis or detachment of the retina. Klasten says "The detachment of the retina is an indication for the termination of pregnancy.

Angiospasm In Other Tissues

As further evidence of spasm Irving states that the adrenals and spleen both frequently exhibit vascular lesions and may be the seat of hemorrhage. In the adrenals the extravasation of the blood in the cortex is accompanied in some instances by engorgement of the capillaries.

According to Eastman and Irving changes are found in the smaller vessels of the nail fold consisting of alterations in the size of the arterioles with evidence of spasm producing alternate regions of contraction and dilatation, together with elongation of the capillary loops and more or less capillary stasis.

Mussey has studied histiologically small sections of muscle taken from preeclamptic patients and has found alterations in the arterioles identical with those just described.

In 1927 Jaffe' reported that in cases of death from eclampsia the cerebral vessels showed extensive changes,

varying from slight swelling and poor staining nuclei to an actual hyalinization of the vessel walls with disappearance of the nuclei. In his opinion the media was first involved, and later the intima. He agrees with Hinselmann in concluding that the injury to the vessel walls is due to spasm of the arterioles which finally results in necrosis of the smaller branches.

ALBUMINURIA

There have been numerous attempts to correlate the hypertension with the lesions of the kidney. Some maintain that the renal damage is due to hypertension and others that the hypertension is due to the renal damage.

de Snoo (12,13) states that in many cases of eclampsia the renal function is entirely normal before the onset of the convulsions. The effect of the convulsions upon the kidney is not specific because the same effect may be observed in patients without convulsions. These findings are upheld by Wagener who believes that the pregnant woman reacts according to a distinct vascular pattern to vascular and renal insults. Therefore, de Snoo claims that the renal disturbances are dependent upon vasomotor abnormalities especially spasm of the blood vessels.

In order to explain the albuminuria a brief resume of kidney function is necessary. According to Cushny's theory, which is at present accepted, after the urine

has passed through the capillary loops of the glomeruli into Bowman's capsule it becomes the glomerular filtrate and is identical in composition with the blood plasma except that it contains no protein. Albumin, therefore, is not a normal constituent of the glomerular filtrate. This filtrate is forced out of the glomeruli under the direct head of the blood pressure which is about 120mm. of Mercury. Opposed to this force is the osmotic pressure of the plasma proteins which remain in the blood stream and exert a force in the opposite direction of 40mm. Mercury. The glomerular filtrate contains substances which are of use to the body and hence are completely or almost completely reabsorbed as they pass down the tubules. These Cushman calls high threshold bodies and are sugar, sodium, and bicarbonate. Sugar will be excreted if its concentration in the blood exceeds 0.18%. This may be brought about if the patient is given intravenously over 2 grams of glucose per kilo. of body weight. An artificial diabetes is engendered since water will pass into the glomerular filtrate to lower an increased osmotic pressure produced by the excess sugar. This is the physiological basis behind the intravenous use of concentrated glucose to stimulate urinary secretion.

Sodium, calcium, and chlorides are not completely reabsorbed, only enough to maintain a physiological

concentration in the blood.

Creatinine and sulfates have no thresholds. In grave kidney impairment creatinine is the last substance to be accumulated in the blood. The amount of creatinine retained has some prognostic importance since it is said that over 5 mg per 100cc. indicated recovery to be hopeless.

According to Irving, vascular spasms of the afferent vessels produces anoxemia of the glomerular loops which results in their increased permeability so that albumin is allowed to pass. This capillary circulation is controlled by the Rouget cells, a layer of unstriated muscle encircling the vessel walls, reticulated to allow transudation of fluid. The basis of the albuminuria may be explained by the experiment of Eastman in which clamping of the renal artery produced immediate and marked albuminuria as soon as the constriction was released. This may be explained by the fact that clamping of the artery results in ischemia, according to Teel and Reed, which in turn injures the Rouget cells and the permeability of the capillaries is increased. Due to this anoxemia of the glomerular loops, albumin is allowed to pass. Oliguria may be accounted for in the same way. The more severe the spasm the less urine that passes through the glomeruli.

Casts are found in the tubules as a result of the solidification of albuminous material in absence of sufficient

fluid to hold it in solution.

Hematuria may result from stagnation of blood in the branches of the afferent arterioles which supply the tubules and may rupture into them, due to the sudden release of pressure.

COMMON FACTOR

Granting that it has been established that arterial spasm is the common factor in eclampsia and preeclampsia the next question concerns the cause of this phenomena.

Physiology.

Constriction and dilatation of the blood vessels is controlled by the vasomotor center which is situated in the floor of the fourth ventricle at the level of the calcanus scriptorius. Any substance which will stimulate the vasoconstrictor fibers may be expected to cause contraction of the terminal arterioles. No such substance has been found. The same effect might be produced by the action of some substance such as pituitary extract upon the vessel walls.

PITUITARY PRESSOR-ANTIDIURETIC SUBSTANCE

Hoffman, Anselmino, and Kennedy were the first to prepare an ultrafiltrate from the blood of eclamptic and preeclamptic patients. They injected this substance into rabbits and found that it would cause anuria, retention

of chlorides, and elevation of blood pressure. Comparing this with those of the autacoid of the posterior pituitary, the chemical and physical properties were found to be identical. In their quantitative determinations of the autacoid they found that the amount present ran parallel to the severity of the symptoms.

This theory of the pituitary source of pregnancy toxemias and eclampsia is not new. It was first suggested by Hoffman in 1918 but contentions were not widely discussed as it was not possible to adduce experimental proof.

Kellog performed the same experiment as Hoffman using dogs instead of rabbits and noticed a phenomena which closely parallels the condition found in actual eclampsia and preeclampsia. In these experimental studies, hyperglycemia, increased lactic acid formation, lowering of carbon dioxide combining power, and increase in inorganic phosphates was found. As an obvious parallel, uncompensated acidosis, hyperglycemia, and increase in inorganic phosphates are well established biochemical phenomena in eclamptic women.

Further evidence that the pituitary is at least in part responsible for the edema and blood pressure is substantiated by Fauvet who was able to produce all of the symptoms of eclampsia except the convulsions by the administration of posterior pituitary extract of animals.

Dieckmann found that the injection of pituitrin into preeclamptic patients caused a very abrupt and marked increase in both systolic and diastolic blood pressure and a marked decrease in the volume of urine. In one case oliguria became so marked that an acute pulmonary edema developed. No difference was noticed between the effect of pitressin and pitocin.

Edmunds and Gunn found that when the extract was injected slowly, intravenously, there was a rather slow rise in blood pressure which remained elevated for some time. They found this rise in pressure to be due to constriction of the peripheral arterioles as was shown by the lessened volume of the organs.

Cushing reported in eclampsia a massive basophilic invasion of the posterior lobe of the hypophysis. These basophilic elements are traced up the stalk of the pituitary, in favorably fixed tissues, to the region of the tuberal nuclei, the stimulation of which cause posterior pituitary substances to appear in the cerebrospinal fluid.

Irving, Hurwitz, Bullock, and Melville were unable to find pressor and antidiuretic substances in patients with toxemias of pregnancy.

LIVER-PITUITARY RELATIONSHIP

Hartman and Trendelenburg have, in their research,

recently brought into association with the activity of the liver and of the capillaries the absorption or inactivation of the pressor principle of the pituitary.

Grollman, Himwich, and Geiling found that pituitary extracts interfere in some unknown manner with the utilization of oxygen by the tissues. The cells become anaerobic in their activity and go into oxygen debt, as evidenced by the fact that the arterio-venous difference is markedly reduced. This reflection of lowered oxygen consumption by the tissues is analogous to that found in actual eclampsia.

This inhibition of oxidation is recognized as having an injurious effect upon living cells, particularly those of the liver. This effect, according to Kellog, is principally upon the peripheral cells of the liver lobule. Under such conditions, glycogen disappears and autolysis occurs in these areas, bringing in its train the deleterious effects of histamine-like substances upon the liver. Upon reduction of normal hepatic tissue, the functional capacity of the liver to destroy toxic substances and to inactivate pituitary extract is further diminished. In other words, the oxygen want favors the development of focal necrosis, and a vicious cycle is induced by the coincident vascular phenomena. Constriction of the ramifications of the hepatic artery and portal vein occurring

as a response to pituitary extract and the constrictions of the hepatic veins in response to histamine-like substances, and hemorrhage due to both the resulting venous engorgement and the damage of the endothelium due to oxygen lack, is the result of a complexity of conditions of the liver, dependent upon a combination of events.

According to Kurzrok, the liver glycogen is converted into glucose and a small amount of lactic acid. When the liver is already poor in glycogen due to the action of the pituitary extract, the muscle glycogen is converted into lactic acid and a small amount of glucose. This may be the explanation for the increase of lactic acid found in the eclamptic patient.

PLACENTAL THEORY

The placental theory regarding the etiology of eclampsia has, in late years, received considerable attention.

Syncytial Degeneration

Tenney made a study of the placentals of 17 eclamptic and 10 preeclamptic patients and found that syncytial degeneration was markedly increased both in severity and in total area involved. This was accompanied by a thickening of the basement membranes of the villi in preeclamptic and eclamptic patients and was found to be due to a definite increase in the number of collagen

fibers. The thickening was not uniform and some parts were much thicker than others. Irregular projections of the membrane between the syncytial cells seemed to be more marked. Tenney also found a fairly accurate correlation between severity of toxemia and the extent of placental area involved. He counted villi to determine the amount of destruction and found they were degenerate in proportion to the severity. A moderate amount was found in all placentas.

Bartholomew (6) studying the size of infarcts in the placenta found that they had a definite relationship to the severity of the toxemia. He thought that the location of the infarct determined to a considerable extent whether the toxemia would be manifest as eclampsia or as abruptio placenta, stating that those infarcts located within the placenta were associated with eclampsia while those at the periphery were associated with abruptio placenta.

Colvin attempted to produce infarcts in the placentas of pregnant bitches by injection of hot oil or saline, hoping to cause infarction. In one case convulsions occurred in a bitch during labor several days after injection, but in a majority of cases, the animal aborted within one or two days before toxemia could develop.

Goodall found that the shorter the duration of the toxemia the less the amount of placental changes found.

In over 500 of 750 placentas examined by him definite macroscopic evidence was found of hemorrhage and infarction.

It is well known that infarction is followed by necrosis and autolysis, thereby liberating poisonous protein split products such as peptone, histamine, tyramine, and guanidine.

Experimental evidence is found that prolonged spasm of the umbilical vessels can be readily elicited by histamine. Kellogg states "the origin of placental infarcts, particularly of the hemorrhagic type, frequently encountered in placentals of preeclamptic and eclamptic patients, is readily traceable to such substances passing through the placental barrier." In other words, placental pathology in eclampsia has the same pathogenesis as the abnormalities found in other organs and should not be considered as having causal relationship to toxemia of pregnancy.

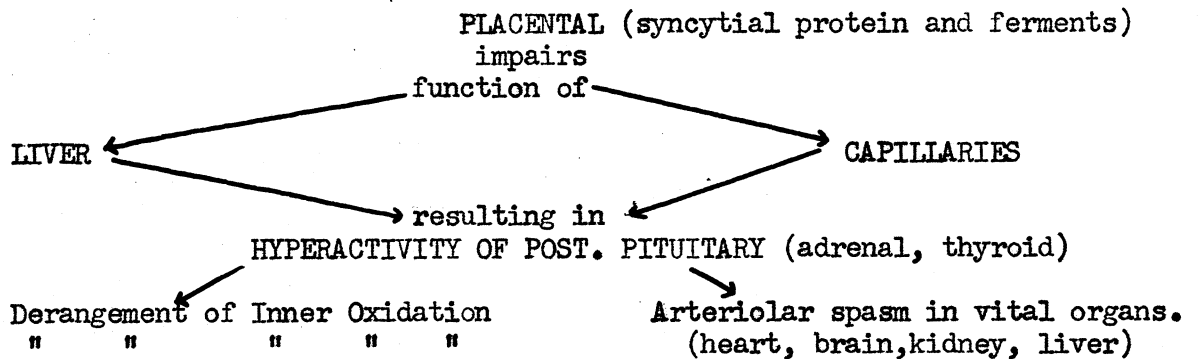
Effect of Placental Products

According to Kellogg, during all period of pregnancy, varying amounts of syncytial buds, fetal ectoderm, are being thrown off from the large area of chorionic villi whose exposed surfaces at term equal 6.5 meters. These syncytial substances are eventually broken down and dissolved in the maternal blood. It is therefore understandable that the pregnant organism is under the constant influence of blood foreign proteins. Berblinger maintains that such

proteins serve as messengers to the pituitary, thyroid, and adrenals, which structures respond by hyperplasia and hypertrophy.

The increased permeability of the capillaries during the last few weeks of pregnancy has been established by the research of Benda who claims this is due to placental split protein products.

According to this theory



v. Bergman attempting to prove that liver damage was due to split protein products, injected synthetic bilirubin, 1mg/kilo in 15cc. of 0.5% Na_2CO_3 . In the normal, the total amount was excreted in 2 to 4 hours and up to the fifth lunar month of pregnancy, normal figures were obtained. Taking as indicative of damage, 10% retention or more, during the second half of gestation, 40% were found to have functional deficiency of the liver. These findings were substantiated by Gibberd, Picardi, and also Brown who says the liver fails to act as a barrier between portal

and systemic circulation, allowing these protein substances to pass unchanged into the systemic circulation producing their effect upon the various organs. Falls upholds this view.

Placental Metabolic Products

Bartholomew and Titus found that placental tissue contains double the amount of arginine present in any other tissue. They hold that guanidine is derived from a series of oxidation and reduction reactions and that placental tissue is capable of liberating sufficient guanidine to cause convulsive seizures.

The arginine, which is normally derived from protein digestion in the intestinal tract, is carried to the liver, where the special enzyme, arginase, found mainly in the liver and kidneys, breaks it up into urea and ornithine. If, however, acute infarction occurs in the placenta, the absence of the special enzyme, arginase, may possibly allow the decomposition of arginine to begin at the carboxyl end of the chain and finally liberate guanidine by the oxidation process. Bartholomew claims that guanidine increases the excitability of the motor nerve endings to the constant electric current. That the muscles of preeclamptic and eclamptic patients are rendered hypersensitive, in some similar way, is suggested by the frequency of the twitchings and the ease with which convulsions are often precipitated by sudden noises and disturbances.

Wedon succeeded in producing eclamptic convulsions by the injection of guanidine. He found the same changes in acid base equilibrium of the blood as occurred in eclampsia and maintains alteration in the metabolism of guanidine plays an important role in the etiology of eclampsia.

Theobald used eclamptic blood, oxydates, and guanidine in intravenous injections but was unable to produce convulsions or to substantiate Wedon's findings.

Bartholomew and Kracke injected a Berkefeld filtrate of artificially autolyzed normal placental tissue into guinea pigs and found that it produced stupor, convulsions, and death. The pathological changes in the kidney and liver were similar to those found in eclampsia.

The relationship between placental infarcts and the liberation of excess guanidine into the maternal blood is not yet understood.

Placental Endocrine Disturbances

In the toxemias of pregnancy we are dealing with the addition of a gland of internal secretion, the placenta, to an equilibrated system. Certain changes will occur in the pregnant woman, due, first to the addition of the placental hormones, prolactin, estrone, progesterone, and possibly others, and second, to the loss of equilibrium of the remaining glands of internal secretion. The

response of the remaining glands in the endocrine chain will in part depend upon their inherent stability.

Unstable systems, or those previously compromised by hormonal disturbances, will be amenable to the greatest variation in response, and such response may be hyperfunction of the posterior pituitary, insufficiency of the adrenal cortex, thyrotoxicosis, hypothyroidism, or instability of the autonomic nervous system.

That there is an abnormal function of the placenta is pointed out by Smith and Smith. They made assays for prolactin and estrin in the blood and urine of 65 pregnant women and 26 placentas. Of this group, 38% were normal, 20% were preeclamptic, and 42% were mild to severe eclamptics. Their results indicated that excessive amounts of prolactin and a tendency toward low levels of estrin were characteristic of toxemias and that this abnormality was of placental origin. In late pregnancy toxemias the abnormal rise in serum prolactin was found to precede the clinical manifestations of the disease by at least six weeks which of course means that the toxemia can be diagnosed and treated four to six weeks before the clinical manifestations are present and before the disease has caused damage to the liver and other organs.

Bickenback and Fromme were unable to find an increase in follicular hormone in the urine and blood of eclamptic women.

Fevold found that the anterior pituitary body was stimulated by estrin to cause an increase in the leutenizine hormone.

Hardin found the estrogenic hormone to exert a depressant effect on the anterior pituitary, and claims that excesses of estrogenic substances may override the effect of progesterin in animals.

Here, as elsewhere, the exact relationship of the findings to the disease are not well understood. It is possible that with further research along this line a definite relationship can be established.

ENDOCRINOPATHY

Anselmino, Hoffman, and Kennedy maintain that pregnancy produces a condition of hyperactivity throughout the system of ductless glands, but in contraindication to endocrinopathies a harmonious balance is still maintained thus securing the well regulated course of life processes with objective and subjective well being of the woman.

It is Bevil's belief that endocrine dysfunction is the essential cause of late toxemias of pregnancy. He says that all glands hypersecrete with stimulation and that pregnancy adds the necessary stimulus. These contentions

are upheld by Kurzrok. According to this theory, the excess secretion of pituitary, thyroid, adrenal and pancreas produce the toxic symptoms.

Experimental and clinical observations strongly suggest that the anterior pituitary is necessary for controlling the activities of the other endocrine glands. In fact, the pituitary has been called the moderator of the endocrine system. Ablation of the pituitary gland causes involution of the thymus and atrophy of the thyroid. Control of the sex glands has been amply demonstrated. An interrelation with the adrenal function is indicated by the observation that ablation of the pituitary body causes atrophy of the adrenals, particularly the cortex.

Stander states that the thyroid gland in pregnancy undergoes a change, becoming more vascular and showing a definite hypertrophy. The parathyroids likewise undergo a marked change during pregnancy. The chromophil cells multiply in number and are better outlined, from which one may infer that their function is increased during pregnancy. There is always hypertrophy of the hypophysis, however, it is the anterior lobe which regularly undergoes hypertrophy. The posterior lobe does not, although it is well established that it is

this part of the pituitary which is connected with stimulation of uterine contractions.

It is well known that thyroxine increases the blood pressure and pulse rate and is toxic to the nervous system. (3) were able to prove that thyroid secretion in toxemias was increased above normal. However, in Vorzimer's series, 35% of which were toxemias, 68% were below plus 10 which is the accepted lower limits of normal pregnancy. This may be explained, according to Kurzrek, by the fact that there is a thyrotrophic hormone, which if injected slowly over a number of days, causes the metabolic rate to drop below normal.

Harlow claims the basal metabolic rate is affected by the ovarian hormone. Women with faulty ovarian functions are likely to have a low basal metabolic rate due to the production of the antithyrotrophic hormone which inhibits the thyrotrophic hormone produced by the pituitary.

(48s) observations on a series of toxemias and controls gave the following results:

Hair Distribution:

1. An increase in the amount with a tendency to male distribution on the legs, thighs, abdomen, face and chest.

2. Decrease in hair, and sometimes almost absent, especially on the pubic regions and axilla.

Both were present with equal frequency in 75% of the cases with toxemia and only 9% of the controls.

Stature:

There was more tendency to stocky build in 65.8% of the toxemia patients as compared to 21% of the normal controls.

Giant pelves were frequently found.

Facies:

The most common finding was an enlarged nose. The patients looked older than their stated age. 55% of the toxemia patients showed some change of facies as compared to 5% on the normal controls.

Of the 120 patients with toxemia as compared to the same number of controls, 98% of the toxemia patients revealed evidence of one or more endocrine stigmas and in a large majority there were two or more. (48) concludes that about 30% of the women with these evidence of endocrine dysfunctions will develop toxemias.

Renal function as determined by non protein nitrogen and concentration tests was not impaired in any of these 120 patients.

- Hardin concluded from a series of cases that in more

than 85% of the patients with recorded histories, that eclampsia is observed in individuals who are underheight and overweight. The calvarium is, as a rule, thick in those patients coming to autopsy. The malar bones are prominent. The nose tends to broaden at the alae. The nasofrontal ridge is flattened, the mandible is prominent, and the lips are coarse.

These findings are similar to those found in acromegalic persons. According to Wiggers, "there is an overgrowth of bone affecting first the lower jaw, as well as the malar bones. This causes separation of the teeth and a broad prognathic jaw. The supra-orbital ridges are hypertrophied."

CONCLUSIONS

1. Eclampsia and preeclampsia are one and the same disease, the only essential difference being one of degree.
2. Angiospasm is the common factor in producing albuminuria and hypertension.
3. The angiospasm may be due to a pituitary pressor-antidiuretic substance present due to:
 - a. Syncytial degeneration
 - b. Placental infarcts.

- c. Histamine-like substances.
 - d. Placental endocrine disturbances.
4. The entire endocrine system may have lost its equilibrium due to the addition of the placenta and its numerous hormones.

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