



THE PREGNANCY TOXÆMIAS OR THE ENCYMONIC ATELOSITESSES

By

G. W. THEOBALD

M.A., M.D.(Cambridge), F.R.C.S.(Edin.), F.I.C.S., F.R.C.O.G., M.R.C.P.(Lond.).

Honorary Obstetrician and Gynæcologist to St. Luke's Maternity Hospital,
St. Luke's Hospital, and the Royal Infirmary, Bradford ;

Hon. Lecturer in Obstetrics and Gynæcology in the University of Leeds ;

Ex-Assistant Master, the Rotunda Hospital, Dublin ;

Formerly Visiting Professor of Obstetrics and Gynæcology in the
Chulalongkorn University, Bangkok, Siam.

Corresponding Member of the Société Française de Gynécologie, and of the
Österreichische Gesellschaft für Gynäkologie und Geburtshilfe.

With a Chapter on the Adrenal Cortex

by

JOHN DAWSON

M.B., Ch.B., M.Sc.(Leeds),

Lecturer in the Department of Biochemistry,
Leeds University.

WITH 56 ILLUSTRATIONS

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THE PREGNANCY TOXÆMIAS
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THIS BOOK IS DEDICATED WITH AFFECTION
TO MY WIFE WHO HAS SUFFERED MUCH
BECAUSE OF IT.

LARGE numbers of small pools are exposed by each receding tide and some are exquisitely beautiful both because of their inherent structure and because of the beauty of the plant life they sustain. Any significant change in the constitution of the sea water which bathes them would be incompatible with their continuance. These and all other forms of cellular life depend on the ability of the fluid by which they are surrounded to resist change, and this universal law may conceivably serve as a parable to illustrate the possible mode of genesis of eclampsia.

PREFACE

ECLAMPSIA is commonly characterized by convulsions, coma, hypertension, proteinuria, oliguria, and œdema, and is often preceded by epigastric pain, emesis, headache, and visual disturbances. It can, however, occur apart from any, or all of these manifestations ; and it is evident that there is no sign or symptom which is peculiar to eclampsia. The problem is to determine why so many different phenomena may manifest themselves in conjunction, and with such suddenness, during the third trimester of pregnancy. This intriguing problem is of the more significance because the pregnancy toxæmias now rank as the highest single cause both of maternal and of foetal deaths.

A breadth of vision and something of the Greek concept of " wholeness " must characterize the approach to this complex problem, and hypotheses incapable of accounting for *all* accredited clinical facts must either be discarded ruthlessly, or suitably modified.

The book is divided into four parts. The first, and longest, discusses the Pregnancy-Lactation syndrome, and the wider aspects of water metabolism, hypertension, proteinuria, oliguria, and œdema, and includes hitherto unpublished work. It also contains an informative chapter on the adrenal cortex by Dr. John Dawson, Lecturer in Biochemistry in the University of Leeds. The second part reports clinical facts, the third enumerates the eclamptic hypotheses, while the last is concerned with the prevention and treatment of both pre-eclampsia and eclampsia. The aim has been to make each chapter complete in itself, and this involves a certain amount of repetition.

Clinical facts form the only standard by which eclamptic hypotheses can be evaluated. During 1946 there were some three thousand confinements in St. Luke's Maternity Hospital and at the end of that year the medical staff consisted of one consultant obstetrician and gynæcologist, Mr. H. A. Rippiner, one obstetric officer, and one house surgeon, who were also responsible for the gynæcological department. The rapid development in the scope of the hospital clearly demanded an increased staff. Through the courtesy of my colleagues, Mr. Rippiner and Mr. G. A. Craig, most of the toxæmic cases which have occurred in the city, during the period under review, came under my care, while Mr. Craig undertook responsibility for most of the cases of antepartum hæmorrhage, unless they were associated with toxæmic symptoms. The figures in Chapter XV show the maternal and foetal mortality from eclampsia, hypertension and proteinuria, and from hypertension. They should be compared with those presented in Chapter XXXV, which show the improved results obtained from better antenatal care.

Paradoxically enough, the standard of antenatal care required "almost to eliminate" both eclampsia and pre-eclampsia increases the incidence of hypertension, and for two reasons. In the first place the blood pressure of each pregnant woman is taken more frequently, thus increasing the chances of obtaining more than one high reading, and in the second, some patients with hypertension are prevented from developing proteinuria.

The oral administration of one of the Rauwolfia compounds, either alone, or in conjunction with apresoline or one of the hexamethonium compounds, promises to be of value in the control of the hypertension of pregnancy and to relieve the pressure on antenatal beds. Either one of the newer veratrum preparations or the intravenous injection of apresoline may be of service in the treatment of the hypertension associated with pre-eclampsia, but the side effects of the latter drug, notably the tachycardia, may militate against its use in eclamptic patients.

The main conclusions presented are : that eclampsia is a generic term and that the syndrome can be provoked by more than one mechanism ; that eclampsia represents a failure of adequate adaptation to the pregnancy-lactation syndrome for which there are three main causes, (1) inherent defects in the expectant mother, (2) mechanical, and (3) nutritional factors : that the nutritional factor alone can be controlled adequately, hence the term pregnancy atelositeses or, more correctly, encymonic atelositeses ; that there is no satisfactory treatment for pre-eclampsia ; and that the secret of preventing both pre-eclampsia and eclampsia lies in preventing reversible changes from becoming irreversible, and this can only be done by obviating undesirable changes in the weight, blood pressure, and water balance of the expectant mother.

I fully realize my presumption in attempting to trespass on so wide a field of medicine and fear that there are probably not a few errors in the text. My friends Professor G. H. Bell, of Queen's College, St. Andrew's University, Professor Andrew Claye, of Leeds University, and Professor E. B. Verney, of Cambridge University, have most kindly read one or more of the chapters and saved me from gross errors. I thank them sincerely for their invaluable advice and hasten to add that they are in no way responsible for any view expressed in this book. I also acknowledge my deep gratitude to my colleague Dr. R. A. McInroy for so kindly undertaking the arduous task of reading the page proofs, and also for the photographs shown in Figs. 30 (a), 30 (b) and 41.

My grateful thanks are due to many : to the Editors of the *Journal of Experimental Physiology* for permission to reproduce Figs. 10, 10 (a), 11, 12, 13 and 14, and to the Editor of the *Journal of Pathology and Bacteriology* for allowing the reproduction of Figs. 34, 35, and 36 ; to the Director-General of the Royal Air Force Medical Services, and to the Office of the Surgeon-General of the United States of America, for material incorporated in Chapter XIII ; to Dr. John Douglas, Medical Officer of Health for Bradford, for figures presented in Chapter XXXV ; to

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Mr. Philip Wade, Librarian of the Royal Society of Medicine, has been kind enough to make the index. Every reader of this book will recognize his skill in this most difficult and important task, and I accord him my sincere thanks.

It is indeed a pleasure to conclude by expressing my grateful appreciation of the courtesy and consideration afforded me by my Publishers, Messrs. Henry Kimpton. I little knew what was involved in the making of such a book, and I have been overwhelmed by the way Mr. George E. Deed has admitted late material, pardoned repeated corrections, and met my every request.

G. W. THEOBALD.

June, 1955.

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PART I

THE PREGNANCY-LACTATION SYNDROME

THE CAPILLARIES

THE WATER METABOLISM OF THE BODY

ŒDEMA

THE POST-PITUITARY GLAND

THE ADRENAL CORTEX

THE LIVER

PROTEINURIA

HYPERTENSION, BOTH IN THE NON-PREGNANT
AND PREGNANT STATES

CHAPTER I

LE MILIEU INTÉRIEUR

“ La fixité du milieu intérieur est la condition de la vie libre.”

CLAUDE BERNARD.

A TYPHOID bacillus divides by binary fission and may give rise to a thousand million of its kind in a single day, each one of which will, as the result of enzyme activity, ingest its food, excrete its waste products, and behave in like manner, because each inherits the genes in the chromosomes of the parent bacterium. The study of cell life which commenced over a century ago has been remarkably intensified during the past two decades, and it is now recognized that all living cells are characterized more by similarity than by contrast. Each cell derives from another, each is dependent on the fluid in which it lives for its nourishment, each hands to the daughter cells characteristics locked up in the genes in its chromosomes.

Claude Bernard was the first to recognize that the billions of cells of which the body consists likewise depended on “la fixité du milieu intérieur.” The cells of the human body, like those in marine plants or bacteria, are dependent on a relatively stable fluid environment, enzyme activity, and, because of the division of labour, on hormones and nervous impulses. It follows that any significant changes in the osmotic pressure, or in the gaseous and other contents of the extracellular fluid could have sudden and serious consequences affecting the whole body, which might result in death.

Protoplasm, the stuff from which life is fashioned, is in essence a solution, or suspension in water of complex, and for the most part, colloid compounds. The energy of a living cell at any given time may be regarded as consisting of two main parts : (1) the total osmotic pressure of all the dissolved substances present in the cell ; and (2) the total energy which they will produce while undergoing complete oxidation. It is therefore clear that water is essential to the structure of protoplasm ; for the oxidative processes in the cell, for the osmotic pressure in and about the cell, as well for its nutrition, for there is no entry to a living cell save by way of solution. Water possesses many unique qualities, amongst which may be enumerated: its high specific heat; its solvent powers, unequalled by that of any other liquid; its ionizing power over salts; and the fact that it alone of all liquids expands when it freezes, and thus makes possible the survival of fish and other marine life in frozen waters. Its most unique quality is that it is essential to life and without it not even putrefaction can occur.

Selective Permeability of the Cell Membrane.

Each cell is bathed by the interstitial fluid and is protected by a "membrane" which ensures its privacy and integrity. The astonishing thing is that the contents of a cell match the interstitial fluid less by similarity than by contrast. Generally speaking potassium salts predominate in the cells and sodium salts in the interstitial fluid. Seeing that K salts ionize through artificial membranes with almost the same ease and rapidity as do Na salts, it is clear that this phenomenon of selective permeability provides one of the main riddles of life. In addition to osmotic factors, the integrity of the cell is conditioned by a complicated system of surface tensions and the operation of many enzymes, which would appear to act on an endless chain system. It is right that attempts should be made to explain biological facts in terms of physics and chemistry, for this attitude is conducive to progress. When pressed to a philosophy, however, it soon becomes apparent that the Mechanists have, so far, done little more than disprove the more absurd claims which have been postulated by the Vitalists.

The Clinician's Outlook.

It is passing difficult for the physician, encumbered as he is with the task of treating an endless stream of patients, of keeping abreast with the literature of his chosen subject, and living his ordinary social life, to ponder in his consciousness these fundamental facts which are impertinent to his professional life. The cardiologist concerned with diseased hearts, thickened arteries, and an elevated blood pressure, cannot often call to mind the fact that the main purpose of the circulatory system is to ensure a rapid transfer of fluids through capillaries which cannot be seen with the naked eye. Neither does it seem evident that these facts are stamped with vividness on the minds of medical students.

The successful clinician, be he physician or surgeon, depends more on art than on science, on technique than on physiology, and on experience than on knowledge. He knows, but does not often reflect on the fact that the intellectual and physical integrity of an individual, be he poet, philosopher, saint, or scientist, is entirely dependent on the ability of countless invisible cells to breathe, ingest nourishment, and excrete the waste products of metabolism in the privacy of their interstitial pools.

It will be suggested in the following chapters that the pregnancy-lactation syndrome affects the woman's organism so profoundly as to threaten the constancy of the extracellular fluid, and thus to make the onset of eclampsia possible.

CHAPTER II

THE PREGNANCY-LACTATION SYNDROME

NEWTON (1949), whose untimely death is a great loss as well to obstetrics as to physiology, devoted much of the latter years of his life to showing that pregnancy was characterized by the "maternal syndrome" and represented no haphazard improvisation to deal with a parasitic emergency. The term "Pregnancy-Lactation" has been substituted for "maternal," merely to stress the additional hazards involved in preparing for lactation.

He devised a method by which it was possible to destroy the foetuses in mice between the twelfth and fifteenth days of pregnancy, and to leave the placenta intact. These results led him to conclude that mice, in which the products of conception are reduced to placenta alone, are physiologically pregnant as judged by the following criteria :—

1. The occurrence of parturition at the normal time.
2. Maintenance of weight with loss at parturition.
3. Inhibition of oestrus.
4. Normal mammary development.
5. The appearance of a normal interpubic ligament.

It has further been shown that in some animals the healthy placenta may grow after foetal death, so long as it has been fully formed and the primary layers are present (Huggett and Pritchard, 1945 ; Pritchard and Huggett, 1947). If the doe (rat or mouse) be fed on a diet deficient in vitamin E, the foetuses will succumb at about the thirteenth day of pregnancy, but the placenta will continue to increase in size.

Selye, Collip and Thomson (1935), working with rats, obtained similar results and showed that if the foetuses were destroyed corpora lutea persisted until the placenta were delivered. Klein (1935) had already shown that after removal of the foetuses in rabbits the corpora lutea survived, so long as the placenta remained *in situ*. Deanesly and Newton (1940) demonstrated that the corpora lutea persisted in mice after destruction of the foetuses, even after the anterior pituitary gland had been extirpated. Indeed, in some animals, pregnancy continues undisturbed after this gland has been removed and the only function to be disturbed is lactation.

Klein (1933, 1935) also showed that mucification of the vagina occurred in pregnant rats and in hamsters in the absence of foetuses, and could indeed be induced in spayed females at will by the simultaneous injection of oestrone and progesterone.

Newton, therefore, added to the above criteria (6) maintenance of the corpora lutea of pregnancy ; and (7) mucification of the vagina.

It is thus evident that the corpus luteum enables the ovum to become embedded and that it in turn is enabled to survive because of the luteotrophic action of the placenta. In some animals, such as the guinea pig, horse, monkey and man, the ovaries may be removed after the products of gestation have reached a certain development, and the supposition is that the œstrogen and progesterone necessary for the maintenance of the pregnancy are supplied by the placenta.

It may, therefore, be concluded that the placenta is responsible for the maintenance of the corpus luteum of pregnancy and for the suppression of follicular development in the ovary and in consequence for the seven criteria of pregnancy described above.

Associated with these events a true hypertrophy occurs of the following structures: the uterus, the anterior pituitary gland (Compte, 1898; Launois and Mulin, 1904), the thyroid, and parathyroid glands, and the supra-renal cortex.

Pregnancy is characterized by an endocrine readjustment on the part of the mother, and recent work has clearly shown that in spite of species variation the story is fundamentally the same whatever animal is investigated. The importance of the placenta is becoming increasingly recognized while the part played by the foetus, the cause of all the bother, tends to decrease in significance. At this stage it will be convenient to confine our attention to man.

The Placenta.

It is not so very long ago that obstetricians regarded the placenta as a lump of meat, divided into from 14 to 20 cotyledons, and presenting two main surfaces. They envisaged it as a sort of sponge, holding blood from which the foetus met its requirements. Their chief concern was to see that it was delivered complete, and was decently interred. It must be confessed that primitive peoples, who hang the afterbirth from trees and perform other strange rites with it, have possessed a greater intuition concerning its mysteries. It may, however, be stated that obstetricians have known for over half a century that if the foetus dies the woman will preserve her contours and may not go into labour until her expected date. Not so long ago a woman re-entered St. Luke's Maternity Hospital suffering from toxæmic antepartum hæmorrhage. Her baby had died *in utero* some ten weeks previously and she had gone home and been in perfect health until the onset of the hæmorrhage, which occurred about the time she should have been delivered. It is now known that this mass of tissue, which develops in any part of the decidua, which becomes fully formed in twelve weeks, reaches maturity and commences to degenerate at or about the thirty-sixth week of pregnancy ; which possesses not a single nerve fibre and is in no way directly controlled by the central