Vaginal smear examination in normal and pathological pregnancy
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SUMMARY

It was attempted to review some of the literature dealing with vaginal cytology during pregnancy. To this were added accounts of experience gained in the Groningen Obstetrical unit, by a systematic approach to the study of vaginal smear characteristics during normal and abnormal gestation.

A brief survey of the hormonal aspects of the conditions dealt with, a description of the histology of the epithelium of the normal and pregnant vagina and some reference to the cytological aspects of certain conditions, unassociated with pregnancy, are intended to serve as background for this study.

The introductory chapter provides a brief historical review of the subject. Reference is made to the publications of some of the earlier authors and of the better known authors who contributed to present day knowledge of vaginal cytology in fields other than cancer research during later years.

In Chapter II descriptions are given of the histology of the vaginal epithelium. Attention is paid to cyclical variations as well as to structural changes during pregnancy. The studies of histological variations during different phases of life, by CRUICKSHANK and SHARMAN (1934), and the epithelial changes resulting from the administration of hormones as described by DIERKS (1929), LEWIS (1933), PAPANICOLAOU and SHORR (1936), RAKOFF (1943) and others, illustrate the profound influence of hormonal changes upon the vaginal epithelium.

Accounts of pregnancy changes in the vaginal epithelium by STIEVE 1925, ADLER (1928), SMITH and BRUNNER (1934), DAVIS and PEARL (1938) and others, although differing in detail, are unanimous in that an active proliferation and growth of the cells, an increase in glycogen deposition and profuse desquamation of cells are characteristic features of gestation.

These histological changes observed during pregnancy explain some of the features of the gestational vaginal smear.

The cellular and other elements encountered in the vaginal smear are described fully in Chapter III. Familiarity with the morphology of these elements is essential for the study of vaginal cytology. Besides the cells derived from the different layers of the vaginal epithelium the significance of endocervical and endometrical cells encountered in the smears is mentioned. Reference is also made to the significance of erythrocytes, leucocytes and histiocytes as well as of mucus in vaginal smears.
Certain organisms which may be recognized in the vaginal smear profoundly influence its aspect. The vaginal bacillus of Döderlein is a common finding in the smears from sexually mature women with an actively proliferating vaginal epithelium. Bacterial cytolysis due to this latter organism makes diagnosis most difficult; actively proliferating cells are destroyed before they reach the cornification phase. Oestrogenic effect particularly is masked by this cytolysis. A large number of observers found a considerable proportion of pregnancy smears to be of the bacterial cytolytic type.

Pseudo acidophilism due to vaginal infection has been described particularly in association with streptococcal and with trichomonas infestation. Like bacterial cytolysis, pseudo-acidophilism may be reversed by locally applied anti-biotics and diagnostic possibilities may thus be improved.

The effect of trichomonas vaginalis on the vaginal smear is quite characteristic and TRAUT (1947), OSBORN (1953) and KEAN and DAY EMERSON (1954) recommended the Papanicolaou stained smear for the identification of this type of infection. Besides pseudo-acidophilism, the presence of leucocytes, mucus, clear spaces in the cytoplasm surrounding the nucleus (nuclear haloes) are features of the smears of trichomonas infested cases. Identification of degenerated forms of the protozoan in the stained smear, although often difficult, is regarded as necessary to establish the diagnosis although the general appearance and cellular changes are so characteristic that a probable diagnosis may often be made at the first glance. (KEAN and DAY EMERSON, 1954).

Monilia and leptothrix, other organisms that may occasionally be recognised in the smears, are briefly mentioned.

In Chapter IV results of investigations concerning cytological aspects of smears from the buccal mucosa and from urinary sediment and urethral mucosa are briefly reviewed.

The different techniques employed in obtaining material for the smears are mentioned. In the Groningen Clinic two cervical smears for cancer screening and two smears from the lateral vaginal wall for hormonal assessment are routinely made. The wooden spatula designed by Ayre is employed to obtain material. The smears are immediately fixed in equal parts 96% alcohol and ether and are stained by a modification of the technique described by PAPANICOLAOU (1942). Brief mention is made of simpler staining techniques and of the use of the phase-contrast microscope in cytological examination.

Hormonal assessment from vaginal smears and cytological diagnosis in pregnancy has been based on a variety of criteria. Qualitative methods of appraisal have been employed by Papanicolaou and his co-workers.
recognized in the vaginal smear of women at sexual maturity. The vaginal bacillus of Läderlein is a normal component of the vaginal flora. Bacterial cytolysis due to this bacillus can cause cytolysis in actively proliferating cells during the cornification phase. Oestrogenic influence may reverse the cytolysis. A large number of investigators have observed changes in the number of bacteria in the vaginal smear in pregnancy, suggesting that the normal flora may be altered.

Vaginal infection has been described in pregnancy, with the presence of mucus, leucocytes and erythrocytes, as well as the general aspect of the smear. Other methods of assessment include the Papanicolaou stained smear and the Wood's light examination. The smears are stained using modified techniques, allowing for qualitative means of assessing the smears. There are also semi-quantitative measures of grading the smear type whereby criteria as the morphology of the cells, nuclear pyknosis, the degree of cornification and the number of leucocytes are employed, are briefly mentioned.

A large number of investigators described quantitative means of assessing the smears. Murray (1938) enumerated the cellular elements present and also noted the presence of leucocytes, red blood cells and the amount of mucus. The term cornification index, the percentage of acidophilic cells, was defined by De Alende et al. (1943). Moracci (1949) determined the colpocytological index, being the ratio between the total number of superficial cells and the number of deep cells. Among other criteria based on enumeration of certain elements in the smears were the karyopyknotic index (Ferin, 1950), being the percentage of cells containing pyknotic nuclei, and the acidophylic index. The latter index is identical with the cornification index of De Alende et al. (1943).

Many authors, particularly the French, have employed these latter two indices in hormonal assessment.

In the Groningen Clinic cytograms have been employed on which cytological data can be recorded; an example of one of these appears on page 42.

For the purpose of our investigations concerning the cytological aspects during pregnancy, 400 cells were enumerated in each smear from at least four fields. For the differential cell count six types are considered: A the parabasal cells, B hypertrophic or glycogenic parabasal cells, mostly derived from the ecto-cervix, type C cells from the intermediate layer, type D cells from the stratum spinosum profundum, type E are cells from the cornified or squamous zone while type F are cells from the latter zone which have become keratinized and have lost their nuclei. This classification was after Papanicolaou et al. (1948).

From the differential cell count the colpocytological index may be determined. In addition the pyknotic and acidophilic indices are recorded.
and the smears assessed employing the criteria listed on the cytogram.

In a large number of cases the hydrogen-ion concentration was determined by means of the Electrofact pH meter. The readings obtained in this way compared well with those obtained by using oxyphen indicator strips, which for practical purposes were employed more frequently.

In Chapter V part of the literature dealing with vaginal smear aspects during various phases of life, different phases of the menstrual cycle and in some abnormal hormonal states, is reviewed. In addition publications dealing with the effect of hormones on vaginal smears are mentioned. FRAENKEL and PAPANICOLAOU (1938), BENNETT and RUSSEL (1941), PUNDEL (1950) and HOPMAN (1951) have illustrated that during the neonatal period smears contain large numbers of superficial cells, many being acidophilic and many containing pyknotic nuclei. These smear aspects reflect maternal oestrogenic influence. The oestrogenic effect gradually recedes and on about the 10th day post-partum (PUNDEL 1950), the smear assumes an atrophic aspect consisting almost entirely of parabasal cells. This condition obtains until the menarche when ovarian activity becomes evident in the smears and cyclical changes become manifest. Cyclical variations in the vaginal smear were described by PAPANICOLAOU (1933), RUBENSTEIN (1940), DE ALLENDE et al. (1943), SHORR (1945), BONIME (1948), PAPANICOLAOU et al. (1948) and others.

Cytological patterns at different stages of the menstrual cycle are recorded on page 58. These are from personal observations and conform with the descriptions of the authors mentioned. These variations reflect the interplay between oestrogenic and progesterational influences. Cyclical variations in acidophilic indices, karyopyknotic indices and cellular patterns after MURRAY (1938), DE ALLENDE et al. (1943), LICHTWITZ and FITOUSSI (1947), DE ALLENDE and ORIAS (1950), PUNDEL (1950) and others are referred to in this chapter.

After the climacterium has been reached a great variety of cytological patterns may be encountered. Different degrees of ovarian activity are responsible for the many smear types encountered during the menopause. A certain degree of rhythmical variability may remain visible in the vaginal smear for some time. PAPANICOLAOU (1933 and 1936) refers to a post-menopausal cycle. PAPANICOLAOU and SHORR (1936) recognised six different types of menopausal smears: the menopausal atrophic type, the intermediate type, the mucus type, the pre-menstrual type, the bacillus vaginalis type and the pseudo-leucopaenic type. PAPANICOLAOU and TRAUT (1943) mention the crowded menopausal type in which parabasal cells are practically absent and intermediate and superficial layer cells predominate, the cells occurring in clus-
the criteria listed on the cytogram. The hydrogen-ion concentration was
measured with a pH meter. The readings obtained by using oxyphen indica-
tors were employed more frequently. A literature dealing with vaginal smear
diagnosis, different phases of the menstrual cycle, and postmenopausal
states, is reviewed. In addition to hormones on vaginal smears are
employed, different phases of the menstrual cycle are
mentioned. These variations in vaginal smears are
SILCOOAU (1938), BENNETT and
HOPMAN (1951) have described. Some period smears contain large numbers
diphilic and many containing pyknotic nuclear index. The condition obtains
activity becomes evident in the smears in the last stages of the menstrual cycle are
individual variations may remain visible in PAPANICOLAOU (1933 and 1936)
and SHORR (1943), PAPANICOLAOU and SHORR (1943) mention the crowded meno-
proliferative effect to androgenic stimulation. This latter author as well as STOLL (1954) classified
the different menopausal smear types in almost the same manner as did
Papanicolaou.

During the phase of sexual activity variations from the cytological
patterns normally associated with the menstrual cycle may indicate some
hormonal disturbance. Ovarian agenesis and primary and secondary
ovarian deficiency are associated with cytological patterns similar to those
encountered in the prepubertal and the menopausal periods. The vaginal
smear may thus prove valuable in the investigation of cases of
amenorrhoea. In cases of anovulatory bleeding evidence of progesterone
effect remains absent from the smears although rhythmic variations in
ovestrogenic effect may be observed. LICHTWITZ and FITOUSSI (1947) in cases of amenorrhoea distinguish between ovarian and pituitary defi-
cency by injecting gonadotrophic hormone and observing its effect on
the vaginal smear. Only in the presence of functioning ovarian tissue will
an oestrogenic response be observed.

The nature of cytological changes due to the influence of oestrogens
on the vaginal mucosa have been described by GEIST and SALMON (1939), STODDARD and METZGER (1942), BROWN and BRADBURY (1949), PUNDEL (1950) and others. Most observers have described
this influence to manifest itself in an increase in superficial layer cells at the expense of the deeper cells, with finally a preponderance of cornified superficial cells with pyknotic nuclei. The smears generally have a clean aspect, leucocytes becoming relatively few in numbers. The cells are discrete.

The effect of progesterone administration upon the vaginal smear
was described by RUBENSTEIN (1940), SHORR (1940), BURGER
and ROTH (1951), HOPMAN (1951) and many others. Progesterone
produces increased desquamation with clumping and crowding of the
cells, curling and folding of the cellular edges, increase in nuclear di-
mension and increase in leucocytosis and mucus content of the smears,
with decreased acidophilia. SHORR (1940) from his experimental fin-
dings following the administration of progesterone, inferred that the
cytological changes encountered during the second half of the menstrual
cycle were not only due to diminished oestrogenic influence as PAPANI-
COLAOU et al. (1948) maintain, but to the active influence of pro-
gesterone, modifying the effect of oestrogens. The cytological descriptions
by Shorr following combined oestrogen-progesterone administration
strikingly resemble those of pregnancy smears.

The effect of chorionic gonadotrophin on the vaginal smear was
found by SHORR and PAPANICOLAOU (1939) to simulate that of follicular hormone. It is considered that this hormone is luteotrophic and not luteinizing. PLATE (1951) as well as HOPMAN (1951) obtained smears resembling those found in pregnancy with high dosages of pregnyl.

Initially androgenic effect on the vaginal epithelium was thought to be of an atrophic nature (PAPANICOLAOU, 1938, GEIST, 1940 and others). DE ALLENDE and ORIAS (1950) maintain to have obtained an atrophic effect due to androgenic administration. SALMON (1941), GREENBLATT (1943), RAKOFF (1943), SALINGER et al. (1950) and others have shown a proliferative effect to follow androgenic administration. LANGREDER and ZIMMERER (1953) suggested that there was an androgenic phase during the normal menstrual cycle. PUNDEL (1952) and WIED (1954) mentioned an androgenic proliferation type of vaginal smear encountered in the menopause.

The available evidence seems to suggest that whereas the individual sex hormones produce changes in the vaginal epithelium giving rise to distinctive cytological patterns, their individual as well as combined effect is that of mucosal proliferation.

In Chapter VI some views on the changes in hormonal production are given. VENNING (1955) stated that hormonal assays should be considered in conjunction with the clinical findings and in relationship to the limitations of the methods employed. It is impossible to associate colpocytological changes during pregnancy exclusively with alterations in the estimated production of specific hormones. They should rather be regarded as part of the response of the entire maternal structure to the effect of a changed hormonal balance adapting itself to the function of childbearing.

The experiments of BROWN and BRADBURY (1947) and PLATE (1951) suggest that chorionic gonadotrophin exerts a luteotrophic effect on the human ovary. Its production during pregnancy increases rapidly to reach a peak between the 50th and 70th day of gestation. During this period it is considered to stimulate the corpus luteum to produce greater quantities of oestrogen and progesterone. After the placenta has taken over the function of producing these hormones in increased amounts, chorionic gonadotrophin production appears to decline. Urinary excretion curves of total oestrogens and of pregnanediol follow a similar course with a steady increase up to the termination of pregnancy. Of the oestrogen fractions oestriol is excreted in far greater proportions towards the end of gestation. Oestrogens are said to sensitize the myometrium to oxytocics and are said to co-ordinate uterine contractions (REYNOLDS, 1949).
There appears to be no available evidence to indicate that oestrogen assays have thrown any light on the cause of the onset of normal labour, nor have they proved of value in predicting its time of onset. VENNING (1955) points out that during early pregnancy, pregnanediol excretion is maintained within rather narrow limits and although it is possible for pregnancy to develop normally with very low pregnanediol excretion during the earlier stages, progressive decline of pregnanediol output as well as negative findings on two or more occasions are indications of a poor prognosis. Many eminent workers, notably KNAUS (1929), REYNOLDS (1931, 1949) and others attributed an inhibitory effect on the myometrium to progesterone. Others (SCHULTZE, 1931, MOIR, 1934 and HENRY and BROWNE, 1943) disputed this theory and contended that it favoured uterine contractility. JEFFCOATE (1955) expressed the view that oestrogen and progesterone are complementary rather than antagonistic in their effect on the human uterus. LYON (1946), HECKEL (1946), PIGEAUD and DUBREUIL (1947) and RAK (1949) claimed to have noticed a decrease in pregnanediol excretion preceding parturition. VENNING (1948), KAUFMANN et al. (1951) and KAISER and WILL (1954) on the other hand found no difference in excretion of pregnanediol prior to the onset of labour. There is evidence to believe that there is an increased 17-ketosteroid excretion with two characteristic peaks during the first and last trimesters of pregnancy. Of the different fractions it is said that the androgenic fractions are decreased in output while 11-hydroxyandrosteren and 11-hydroxyaethiochonalon, both thought to be metabolites of 11-oxysteroids are increased (DE WIED, 1955). VENNING (1946) and others have demonstrated an elevation of urinary glucocorticoid levels during the first and third trimesters. The significance of these findings is not yet clearly understood, neither is known how much of the increased corticoid excretion is due to adrenal cortical and how much to placental production. Aldosterone was shown to be present in the urine of normal pregnant women in small amounts, in both free and conjugated forms, but particularly the latter, being increased in the toxaemias.

In the introductory portion of Chapter VII most of the literature dealing with the vaginal smear characteristics of normal pregnancy is reviewed. PAPANICOLAOU (1925) published a description of vaginal smear characteristics peculiar to intra- and extra-uterine pregnancy. In this and in a subsequent publication he emphasized the preponderance of the typical navicular cells during gestation. Other features characteristic of pregnancy, such as extreme clumping of the cells, abundance of Döderlein bacilli and the frequent occurrence of cytolytic changes were described by Papanicolaou. RAMIREZ (1928) provided descriptions similar
to those of Papanicolaou while MURRAY (1938), having made quantitative analyses of vaginal smears during pregnancy, demonstrated an increase in cells from the stratum spinosum superficiale with little variation in the curves. Several other authors subsequently contributed to our knowledge of this subject. BONIME (1949) provided a lucid account of the features which distinguish cells desquamated during pregnancy from others, stressing that cells desquamated while influenced by physiological activity appeared fresh and well preserved, while those shed during periods of involution or low levels of hormonal activity appeared frayed, shrunken, with their cytoplasm containing debris. HOPMAN (1950) emphasized the formation of characteristic cloudy aggregations of intensely cohesive cells during pregnancy, these aggregations assuming a purplish red colour particularly in the centre. NIEBURGS (1947) found an increase in intermediate layer cells during pregnancy, these "luteal" cells being almost exclusively found in smears after the 30th week of pregnancy.

KOLLER and ARTNER (1953) and WIED (1954) classified a large number of pregnancy smears into five different categories viz. the cornification or marked oestrogenic proliferation type, the pre-cornified or oestrogenic proliferation type, the navicular type (the most common finding), the cytolysis type and infective type. Table 6 page 93 represents figures for each of these smear types among the material described in these two publications, as well as among our own series of cases.

GAUDEFROY (1950, 1951), PUNDEL and VAN MEENSEL (1951), MULLER et al. (1951) and others determined acidophilic and karyopyknotic indices in series of pregnancy smears and stipulated which figures might be regarded compatible with normal pregnancy. GAUDEFROY (1951) found an acidophilic index of 2% or less and a karyopyknotic index of 30% or less necessary for the continuation of pregnancy after the 4th month. Most authors agree that the diagnosis of early pregnancy by means of the vaginal smear is extremely difficult, the characteristic appearances often only being obtained after the end of the first trimester. Smears from some of the amenorrhoeic states, which feature in the differential diagnosis of pregnancy, may be characteristic.

In our own series 582 vaginal smears from 126 women with normal uncomplicated pregnancies were examined. The smears were made at different stages of pregnancy. In 12.9% of these smears direct evidence of trichomonas infection was observed. Döderlein bacilli were encountered in 57.5% of the smears, although as mentioned 18.0% of the smears were of the cytolytic type.

The vaginal pH in the entire group varied between 3.9 and 6.6 and averaged 4.20.
RAY (1938), having made quantitative observations on the changes in the vaginal smear during pregnancy, demonstrated an increase in the number of squamous cells with little variation during pregnancy. Subsequently contributed to our understanding was the work of HOPMAN (1950), who provided a lucid account of the changes in the vaginal smear during pregnancy. These changes were influenced by physiological and hormonal activity, with the vaginal smear appearing frayed and containing debris. NIETBURGS (1947) found characteristic cloudy aggregations of intense pink color, these aggregations assuming a central position. HOPMAN (1950) and WIED (1954) classified these changes into five different categories, viz. the proliferation type, the pre-cornified navicular type (the most common type), the acidophilic and pyknotic index, and the cellular or colpocytological index.

Of each smear the readings were recorded on the cytogram and in each case the acidophilic, pyknotic and colpocytological indices were recorded. The degree of regressive change evident in each smear was determined by adding up a number of positive features of regression, viz. decreased cellular and nuclear diameter, poorly staining cytoplasm, indistinct cell membranes, diminished clumping, increased curling and folding, the presence of leukocytes, mucus and erythrocytes. These individual features added up are expressed as the regression rating. In normal uncomplicated pregnancy this figure remained below 3, in the vast majority of cases, only exceeding this figure shortly before the onset of labour. The regression rating proved to show less variation than the other indices mentioned.

The acidophilic index with few exceptions remained below 20 during the first and below 6 during the second and third trimesters. The pyknotic index remained below 20 in the vast majority of cases.

The cellular or colpocytological index varied between 0 and 1.0, in the majority of cases varying between 0 and 0.1.

In a group of 89 smears from normal pregnant women but with definite evidence of vaginal infection it appeared that the regression rating and the acidophilic index tended to be appreciably higher than in the former group, while the pyknotic and cellular indices appeared to be unchanged.

A few investigators attempted to utilize the vaginal smear in estimating the probable date of parturition and to diagnose post-maturity. Clinical and radiological methods thus far have proved to be of limited value in this respect while hormone assays have also been disappointing.

In Chapter VIII the literature dealing with colpocytological aspects of the later period of pregnancy and of post-maturity is reviewed. Although PAPANICOLAOU (1925) suggested that the approach of parturition might be revealed by certain characteristic vaginal smear changes, this author has never elaborated on this theory. PUNDEL and VAN MEENSEL (1951) observed 20 cases during the later phases of pregnancy and failed to observe any uniform cytological signs of imminent labour. They added however, that the subject merited further study. LABAT (1953) observed that preceding and during labour cells from the outer basal layer were augmented at the expense of navicular cells, and nuclear pyknosis tended to increase; the latter phenomenon being most marked. In cases of post-maturity in which decreased placental activity became evident an increase in outer basal layer cells with a relative decrease in navicular cells was likewise observed.

EZES (1953) in cases of post-maturity observed a decrease in
vaginal acidity, a change in the appearance of Döderlein bacilli, these becoming shorter, a decrease in number of navicular cells and a tendency for cells to be dispersed. The cells tended to assume a shrunken appearance and cells of the post-natal type as described by Papanicolaou increased in numbers. The acidophilic index did not change appreciably while there appeared to be some increase in the karyopyknotic index. Lemberg and Stamm (1955) failed to observe any alteration in acidophilic and karyopyknotic indices to precede labour, nor in their cases known to have reached post-maturity. The latter authors did however observe certain criteria which they regarded as signs of regression resulting from an alteration in hormonal equilibrium, associated with the termination of pregnancy. Poor staining of the cells, pale cells with indistinct protoplasmic borders, the presence of mucus, increased leucocytosis, fibrinous exudates and the presence of erythrocytes, diminished desquamation and decrease in the number of navicular cells are regarded by these authors as signs of regression. Utilizing these criteria, smears were graded into 3 categories viz. "normally progressing pregnancy", "type near term" and "type at term". Those classified as "type at term" usually delivered spontaneously within 1—2 days, those "near term" usually between 3—10 days while the remaining group as a rule did not deliver before 10 days.

The likelihood of success of medicinal induction in cases of alleged post-maturity was similarly related to the degree of regressive change, those classified as "at term" as a rule being successful and those designated "normally progressing pregnancy" usually failing to respond.

From our own cases 278 smears were made during the last 28 days preceding actual delivery. These were all obtained from women with uncomplicated pregnancies that delivered normally within 14 days of the estimated date by Naegle's rule. In each case the smears were assessed in the manner already described. It appeared that an acidophilic index of over 10, a pyknotic index of over 20 or a colpocytological index of over 0.5 with few exceptions seemed to be associated with delivery within 8 days. Indices below these levels did not preclude labour from following within this period. The regression rating appeared to be a more reliable guide in forecasting the time of delivery; a rating of 3 or more usually being indicative of labour following within 8 days, whereas a rating of less than 3 as a rule suggested that pregnancy was likely to continue for at least 8 days.

In another series of 213 patients one smear from each patient made from 1 to 28 days preceding spontaneous delivery was examined. Of 114 of these patients with a regression rating of 3 or more, 108 delivered within 8 days. Of 99 with a regression rating of less than 3, 23 delivered
In smears from 25 patients in whom pregnancy had proceeded beyond 42 weeks, the acidophilic, pyknotic and cellular indices did not appear to differ significantly from those of the former groups. The regression rating tended to be somewhat higher in the smears from the post-mature patients.

Of 76 patients assumed to have proceeded beyond the 42nd week of pregnancy, 38 medicinal inductions proved successful i.e. contractions ultimately continuing until delivery, commencing within 24 hours. Of these latter 38 cases the smears of 35 showed regression ratings of 3 or more. Of the 38 in whom induction had failed, 5 had regression ratings of 3 or more. It was concluded that with assumed post-maturity, the regression rating was a reasonably reliable guide in selecting cases in which induction of labour was indicated.

Chapter IX deals with some of the literature concerning hormonal aspects of abortion, premature birth, foetal death, extra-uterine pregnancy and hydatidiform mole. It is emphasised that whereas only a minor proportion of abortions and stillbirths are directly ascribable to endocrinal causes, alterations in hormone output may be secondary to trophoblastic degeneration, and as such hormone estimation may be of prognostic value.

The role of progesterone in the prevention of abortion and the prognostic value of pregnanediol excretion estimations in cases of threatened abortion are disputed. Results of therapeutic trials in which progesterone was administered to prevent habitual or threatened abortion have also been variable. Certain authors believe that progesterone administration might accelerate abortion, (RUNGE, 1942, BENDER, 1947 and 1948). Bender maintains that progesterone therapy should be restricted to those cases in which definite proof of its deficiency has been obtained.

Since biological assays, and colorimetric and fluorometric methods of estimating the output of oestrogens are only of limited value during the earlier months of pregnancy, little information is available relating to oestrogen production in cases of abortion. On the assumption that stilboestrol administration resulted in an increased production of progesterone, following the observations of SMITH et al. (1941) and SMITH et al. (1946), who claimed to have noticed an increased pregnanediol excretion following the administration of oestrogenic substances, many workers have prescribed stilboestrol for cases of threatened or habitual abortion, and have claimed reasonable success. SOMMERVILLE et al. (1949) contended that the apparent rise in pregnanediol excretion

within 8 days. These findings suggest that determination of the regression rating has at least some value in forecasting the onset of labour.
following diethylstilboestrol administration might well have been due to the excretion of substances related to, but not identical with sodium pregnanediol glucuronidate. Oestrogens are however also said to exert a trophic effect on the uterus, to improve uterine vascularity and to play a part in the preparation of the endometrium for nidation. During the later months of pregnancy oestriol excretion may serve as a reliable index of placental function.

It is generally held that the enormous amount of chorionic gonadotrophin produced in early pregnancy is responsible for the maintenance of and the continued production by the corpus luteum and in this manner it indirectly influences the production of progesterone and oestrogen. (VAUX and RAKOFF, 1945, VENNING, 1955). The majority of authors agree that diminished excretion of chorionic gonadotrophin was usually secondary to trophoblastic regression and signified a poor prognosis; conversely high chorionic excretion levels are thought to preclude abortion.

For obvious reasons there are no publications of results of hormonal assays in ectopic pregnancy. As long as active chorionic tissue remains in contact with the maternal circulation it is considered that hormonologically extra- and intra-uterine pregnancy do not differ. The increase in urinary and serum chorionic gonadotrophin in cases of hydatidiform mole and chorion epithelioma is well known; oestrogen and progesterone are on the other hand markedly diminished (HINGLAIS and HINGLAIS 1949).

In Chapter X the vaginal smear characteristics of abortion, premature birth, foetal death, extra-uterine pregnancy, the haemorrhages of pregnancy and hydatidiform mole are dealt with.

PAPANICOLAOU (1925) expressed the view that the threat of abortion could possibly be revealed in certain smear changes. FLETCHER (1940) stressed the importance of finding outer basal cells in incomplete abortion. PAPANICOLAOU and TRAUT (1943) described as common characteristics of vaginal smears in abortion, the increase in acidophilic cells, increase in nuclear pyknosis, blood and mucus. According to these authors leucocytes were as a rule increased, appearing in clumps and with the histiocytes exhibiting phagocytic activity. BENSON and TRAUT (1950) differentiated between normal pregnancy threatened, complete, incomplete, tubal and missed abortion as well as secondary amenorrhoea, using as criteria the presence and nature of pregnancy cells, abortion cells, deep cells, erythrocytes, leucocytes, histiocytes, bacteria, mucus and detritus in the smears. Several authors regarded the vaginal smear as a valuable guide in the diagnosis and treatment of abortion, and utilized the acidophilic and pyknotic indices as criteria of assessment of the hormonal status (GAUDEFROY, 1949, PUNDEL, 1952 and others). LEM-
...might well have been due to, but not identical with sodium Locke, but not identical with sodium Locke, but not identical with sodium Locke, but not identical with sodium Locke, but not identical with sodium Locke, but not identical with sodium Locke, but not identical with sodium Locke, but not identical with sodium Locke, but not identical with sodium Locke, but not identical with sodium Locke, but not identical with sodium Locke, but not identical with sodium Locke, but not identical with sodium Locke, but not identical with sodium Locke, but not identical with sodium Locke, but not identical with sodium Locke, but not identical with sodium Locke, but not identical with sodium Locke, but not identical with sodium Locke, but not identical with sodium Locke, but not identical with sodium Locke, but not identical with sodium Locke, but not identical with sodium Locke, but not identical with sodium Locke, but not identical with sodium Locke, but not identical with sodium Locke, but 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diagnostic significance. None of these elements however appeared to be constant features of any of the conditions mentioned.

In Chapter XI brief reference is made to the literature dealing with the hormonal aspect of the gestoses.

It is generally accepted that in the majority of cases severe pre-eclampsia is associated with increased chorionic gonadotrophin blood and urine levels. This is not considered to be due to greater production of this hormone but to decreased utilization for stimulating the production of oestrogen and progesterone (SMITH, 1955).

SMITH and SMITH (1948), summing up the results of their many investigations, concluded that they had proved that oestrogen and progesterone were liberated in diminished quantities preceding the onset of clinical features of toxæemia. They contended that this was due to syncitial degeneration and ascribed the toxæemias to a toxic metabolite of this process. This toxic substance (euglobulin), by causing vasoconstriction, was said to cause further syncytial necrosis. PAGE (1948) demonstrated that diminished placental oxygen saturation was associated with the toxæemias. The Smith's recommended the administration of large doses of stilboestrol to prevent syncytial degeneration in the prophylaxis of toxæemia. It has been said that gravimetric sodium pregnanediol glucuronidate estimations have been shown to either fail, to rise or to drop prior to the onset of symptoms of toxæemia, but that if in the same patient pregnanediol were measured no constant change would be noticed (SMITH, 1955). Besides diminished total oestrogen excretion, the proportion between the fractions appeared to be altered, there being a slight rise in oestradiol and a marked drop in oestriol excretion.

PARVIAINEN and SOIVA (1950) encountered an increase in deeper cells in the vaginal smears from cases of severe toxæemia. ROUSSEL and HEROVICI (1952) found no gross alterations in the vaginal smears of cases with toxæemia of pregnancy; the acidophilic and pyknotic indices tended to be subnormal in their experience. MUSSI and FALCOFF (1953) observed fewer superficial layer cells in the toxæemias. ANZISI (1953) likewise observed fewer superficial cells in his cases, the colpocytoplogical index tending to be somewhat lower than in normal pregnancy. From our own clinical material 142 smears from 50 toxæemia patients with varying degrees of severity were assessed in a similar way to all other smears. Comparing these with a group of normal pregnancy smears, it appears that the acidophilic, pyknotic and colpocytoplogical indices do not vary greatly from those in normal pregnancy. The regression rating shows greater variation in the toxæemic group, a considerable number of smears having a regression rating of over 3. This phenomenon would suggest that placental denegation associated with severe toxæemia
In many cases was associated with regresional changes in the vaginal epithelium.

In Hyperemesis gravidarum a number of authors have observed increased urinary chorionic gonadotrophin excretion (ANSELMINO, 1936, SCHOENECK, 1936, BRANDSTRUP 1939 and others).

Some conflicting reports have been published with regard to oestrogen and pregnanediol excretion in this condition. HAIN (1942) confirmed the findings of BROWNE et al. (1938) that no hormonal abnormality is found in hyperemesis gravidarum.

Very little has been published with regard to colpocytological findings in hyperemesis. PUNDEL and VAN MEENSEL (1951) described two cases in which the cytological patterns were similar to those encountered in normal pregnancy. LEDESMA (1948) found an increase in acidoophilia.

In 8 cases of severe hyperemesis observed by us, the cytological findings did not differ from those in normal pregnancy.

In 51 patients with varying degrees of toxaemia comparison between urinary oestriol assays and vaginal smear findings reveals some correlation. Results are tabulated (table 20).