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 endometrial 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.
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The types and morphology of cells encountered, the grouping of cells, the presence of mucus, leucocytes and erythrocytes, as well as the general aspect of the smears are considered. Others who have resorted to qualitative means of assessing the smears were SHORR (1940), BONIME (1949), BENSON and TRAUT (1950), BURGER and ROTH (1951), ROTH (1953) and LEMBERG and STAMM (1955).

SCHMITT (1953) graded the types of cells predominating in the smears. This author differentiated between parabasal cells, intermediate layer cells, cells from the inner layers of the superficial zone and cells from the outer layer of the superficial zone. Other 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 ALLENDE 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 acidophyllic index. (SALINGER et al., 1950, and others). The latter index is identical with the cornification index of DE ALLENDE 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 only found in keratinized epithelia. 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 indica-
tor 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 pyk-
notic 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 con-
form 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
and the smears assessed employing the criteria listed on the cytogram.

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 cytolo-

gical patterns may be encountered. Different degrees of ovarian activity
are responsible for the many smear types encountered during the meno-

opause. 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 meno-

pausal 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 meno-
pausal type in which parabasal cells are practically absent and interme-

diate and superficial layer cells predominate, the cells occurring in clus-
the criteria listed on the cytogram. The hydrogen-ion concentration was measured using a pH meter. The readings obtained by using oxyphen indigocarmin were employed more frequently. Cytology dealing with vaginal smears and the different phases of the menstrual cycle, with special reference to the vaginal smears, is reviewed. In addition to the descriptions of vaginal smears by Papanicolaou (1938), Bennett and De Alende (1943), and Hopman (1951) have published the results of experiments on the menstrual cycle, the readings obtained by using oxyphen indigocarmin were employed more frequently. The readings obtained by using oxyphen indigocarmin were employed more frequently.

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In addition to the descriptions of vaginal smears by Papanicolaou (1938), Bennett and De Alende (1943), and Hopman (1951) have published the results of experiments on the menstrual cycle, the readings obtained by using oxyphen indigocarmin were employed more frequently.

Period smears contain large numbers of leukocytes and many containing pyknotic nuclei, which reflect maternal oestrogenic influence. The period smears contain large numbers of leukocytes and many containing pyknotic nuclei, which reflect maternal oestrogenic influence.

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 period smears contain large numbers of leukocytes and many containing pyknotic nuclei, which reflect maternal oestrogenic influence.

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, with finally a preponderance of cornified superficial cells with pyknotic nuclei. The smears generally have a clean aspect, leukocytes 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 dimension and increase in leucocytosis and mucus content of the smears, with decreased acidophilia. Shorr (1940) from his experimental findings 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 Papanicolaou et al. (1948) maintain, but to the active influence of progesterone, 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).
For this hormone is luteotrophic and as HOPMAN (1951) obtained pregnancy with high dosages of vaginal epithelium was thought to LAOU, 1938, GEIST, 1940 and 1950) maintain to have obtained administration. SALMON (1941), SALINGER et al. (1950) effect to follow androgenic administer (1953) suggested that there normal menstrual cycle. PUNDEL suggest that whereas the individual vaginal epithelium giving rise to individual as well as combined changes in hormonal production that hormonal assays should be con- nal findings and in relationship to evidenced. It is impossible to associate nancy exclusively with alterations the entire maternal structure to the 17-ketosteroid excretion with two characteristic peaks during the first and last trimester of pregnancy. Of the different fractions it is said that the androgenic fractions are decreased in output while 11-hydroxycorticosterone and 11-hydroxyaethiochonalon, both thought to be metabolites of 11-oxy steroids are increased (DE WIED, 1955). VENNING (1946) and others have demonstrated an elevation of urinary glucocorticoid levels during pregnancy. 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 produc- duction. 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 toxemias.

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 the first 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 quanti-
tative analyses of vaginal smears during pregnancy, demonstrated an
increase in cells from the stratum spinosum superficiale with little varia-
tion 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. GAUDE-
FROY (1951) found an acidophilic index of 2% or less and a karyopyk-
notic 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 dif-
ferent 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 studies of squamous epithelium during pregnancy, demonstrated a quantitatively increased superficial cell layer with little variation among individuals. Subsequently, contributions to our knowledge of this topic were made by Hopman (1950), who reported a lucid account of changes in the vaginal epithelium during pregnancy, while influenced by physiological and hormonal activity appearing frayed, containing debris. Nieburgs (1957) found characteristic cloudy aggregations of intense cytoplasm during pregnancy, these “luteal” cells being present in smears after the 30th week of pregnancy. Pundel and van Meenestel (1951) and Wied (1954) classified a number of these categories into five different categories viz. the proliferation type, the pre-cornified type, the cornified type, the navicular type (the most common type) and the parabasal type. The latter was found during pregnancy, these “luteal” cells being present in smears after the 30th week of pregnancy. Pundel and van Meenestel (1951) and others determined acidophilic and pyknotic indices in pregnancy smears and stipulated a lower limit for normal pregnancy, GAUDE's index of 2.0 % or less and a karyopyknotic index of 1.0 % or less. In normal uncomplicated pregnancy this figure remained below 2, 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.

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 Meenestel (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.

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 leucocytes, 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.

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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
Incidence of Döderlein bacilli, these be-

trended to assume a shrunken ap-

type as described by Papanicolaou.

The latter authors which they regarded as signs of

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within 8 days. These findings suggest that determination of the regres-

rating has at least some value in forecasting the onset of labour.

In smears from 25 patients in whom pregnancy had proceeded be-

42 weeks, the acidophilic, pyknotic and cellular indices did not ap-

appear to differ significantly from those of the former groups. The regres-

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

imately continuing until delivery, commencing within 24 hours. Of these

atter 38 cases the smears of 35 showed regression ratings of 3 or

ore. Of the 38 in whom induction had failed, 5 had regression ratings

more. It was concluded that with assumed post-maturity, the

ression 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

pects of abortion, premature birth, foetal death, extra-uterine pregnancy

and hydatidiform mole. It is emphasised that whereas only a minor

portion of abortions and stillbirths are directly ascribable to endo-

crinal causes, alterations in hormone output may be secondary to tro-

phoblastic degeneration, and as such hormone estimation may be of prog-

nostic value.

The role of progesterone in the prevention of abortion and the

nostic value of pregnanediol excretion estimations in cases of

ated abortion are disputed. Results of therapeutic trials in which

rogesterone was administered to prevent habitual or threatened abortion

ave 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

stricted to those cases in which definite proof of its deficiency has

been obtained.

Since biological assays, and colorimetric and fluorometric methods

indicating the output of oestrogens are only of limited value during

the earlier months of pregnancy, little information is available relating

t o estrogen production in cases of abortion. On the assumption that

ilboestrol administration resulted in an increased production of prog-

esterone, following the observations of SMITH et al. (1941) and

SMITH et al. (1946), who claimed to have noticed an increased preg-

nanediol excretion following the administration of oestrogenic substances,

any 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
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-
vation might well have been due to, but not identical with sodium bicarbonate, are however also said to exert a favorable uterine vascularity and to play a role in the maintenance of the endometrium for nidation. During the second month, progesterone may serve as a reliable index of chorionic gonadotrophin for nidation. During the third month, chorionic gonadotrophin was usually found to be increased before a poor prognosis; conditions were said to preclude abortion. However, publications of results of hormonal tests active chorionic tissue remains controversial; it is considered that hormonal balance do not differ. The increase in chorionic gonadotrophin in cases of hydatidiform mole is known; oestrogen and progesterone were signified a poor prognosis, and is thought to preclude abortion. It is well known that it is considered that hormonal balance do not differ. The increase in chorionic gonadotrophin in cases of hydatidiform mole is known; oestrogen and progesterone were signified a poor prognosis; conditions were thought to preclude abortion. It is well known that it is considered that hormonal balance do not differ. The increase in chorionic gonadotrophin in cases of hydatidiform mole is known; oestrogen and progesterone were associated with amenorrhoea not associated with pregnancy. It seemed that although it was difficult to differentiate between hormonal and other causes of abortion the vaginal smear could be of some prognostic value and also be of help in assessing the effect of treatment. In the diagnosis of missed abortion, cytological examination proved valuable.

Smears from 212 cases admitted to the Groningen Clinic with clinical signs of disturbed pregnancy were compared. Clinically these cases were classified as follows:

- Threatened abortion with ultimate favourable course: 47 cases,
- Inevitable abortion: 42 cases,
- Incomplete abortion: 20 cases,
- Missed abortion: 12 cases,
- Threatened premature labour with ultimate favourable course: 22 cases,
- Premature birth: 27 cases,
- Dead foetus: 32 cases,
- Extra uterine pregnancy: 10 cases.

Of each smear the acidophilic, pyknotic and colpocytological indices was determined, while in addition the regression rating was estimated. The presence of erythrocytes, parabasal cells, basal cells, leucocytic rosettes, histiocytes, chorionic elements and foetal elements was also noted. Results are given on tables 17 and 18. It was seen that with this information differentiation between threatened abortion with an ultimate favourable course on the one hand and inevitable, incomplete and missed abortion on the other hand became possible, as did differentiation between clinically threatened premature delivery with favourable and unfavourable prognosis. A dead foetus was in 81% of 32 cases associated with a regression rating exceeding 2. Acidophilic, pyknotic and colpocytological indices were rather variable in cases of intra-uterine foetal death.

In every category the regression rating proved to be the most sensitive index. The cytological findings in cases of extra-uterine pregnancy were so varied that they should be regarded as entirely valueless. Recognition of erythrocytes, parabasal cells, basal cells, leucocytic clusters, histiocytes and chorionic and foetal elements appeared to be of doubtless
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 toxemia. They contended that this was due to syncitial degeneration and ascribed the toxemias 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 toxemias. The Smith's recommended the administration of large doses of stilboestrol to prevent syncytial degeneration in the prophylaxis of toxemia. 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 toxemia, 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 toxemia. ROUSSEL and HEROVICI (1952) found no gross alterations in the vaginal smears of cases with toxemia 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 toxemias. ANZISI (1953) likewise observed fewer superficial cells in his cases, the colpocytological index tending to be somewhat lower than in normal pregnancy.

From our own clinical material 142 smears from 50 toxemia 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 colpocytological indices do not vary greatly from those in normal pregnancy. The regression rating shows greater variation in the toxemic group, a considerable number of smears having a regression rating of over 3. This phenomenon would suggest that placental degeneration associated with severe toxemia
in many cases was associated with regressive 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 acidophilia.

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).