It is suggested that the following diagram adequately depicts the tissue phase of schizogony as it occurs in malignant tertian malaria in man:

Comment and Conclusions

At the beginning of the present century the life cycle of the malaria parasite in man appeared to be completely known. It is a matter of considerable interest that, nearly half a century later, hiatuses in precise knowledge of the subject still exist. Despite the brilliant work of Shortt and his colleagues, only the pre-erythrocytic stage in *P. vivax* has so far been demonstrated in man. The technical difficulties associated with the production of hyperinfection in man and the demonstration of tissue schizonts in the liver have been overcome. No suitable laboratory animal is known which can be experimentally infected with any of the human species of malaria parasite, and in these circumstances the various problems concerning tissue forms are unlikely to be solved finally without the use of experimentally infected volunteers.

In the meantime the following tentative conclusions based mainly on indirect evidence are put forward regarding the tissue phase of the three species of malaria plasmodia commonly affecting man.

1. In benign tertian and quartan malaria there are both pre-erythrocytic and exo-erythrocytic stages of schizogony similar to those now known to occur in cynomolgus malaria in monkeys.
2. In vivax malaria characterized by short-term relapses such as are produced by the New Guinea or Chisson strains, normal exo-erythrocytic schizogony is maintained throughout the whole course of the disease and erythrocytic merozoites reach the circulating blood with regularity. Relapses cease when solid immunity and tolerance have developed or radical cure has been established.
3. In vivax infections characterized by long-term latency before relapse, such as is seen in infections with the St. Elizabeth, Madagascar, and Dutch strains, parasitaemia and immunity fail to become established during this initial latent period. As a working hypothesis it is suggested that during latency the exo-erythrocytic cycle is atypical, inasmuch as schizogony is switched over to the exclusive production of liver-invading merozoites, so that no erythrocytic merozoites reach the circulation. Latency ends when there is a reversion to normal exo-erythrocytic schizogony; this is indicated by the close relapse pattern which supervenes after the long period of latency has terminated in an overt malaria attack.
4. In malignant tertian malaria, after the pre-erythrocytic schizonts have ruptured and discharged their erythrocytic merozoites into the circulation on the seventh and possibly the eighth and ninth days as well, they disappear without giving rise to late exo-erythrocytic forms. The subsequent course of the disease will be determined solely by erythrocytic schizogony, and if parasitaemia is eradicated radical cure will result.

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CLINICAL VALUE OF PREGNANEDIOL ASSAYS*

BY

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A laboratory technique such as pregnanediol assay may lay claim to clinical value if it can be shown that its results yield information about diagnosis, prognosis, or treatment which will supplement that gained by unaided clinical examination. In assessing the clinical value of a given technique various factors must be considered and given due weight. The accuracy of the method, for example, is not of primary importance, though its ability to give unequivocal answers to the clinical questions posed is clearly a first requirement. Ease and speed of performance are significant considerations, and the nature and quantity of the clinical specimens required deserve attention. If to these we add the uniqueness of the information yielded by the technique, it should be possible to form an opinion of its value to the clinician in comparison with other laboratory procedures. In this paper the attempt is made to evaluate the position of pregnanediol assay, as judged by the above criteria and using the data that I have myself obtained.

A large number of different procedures for the assay of urinary pregnanediol have been described, some undoubtedly being far more accurate than others. I shall not attempt a comparative discussion of these rival methods, but certain general remarks are warranted. In the first place, methods requiring three or four days and many man-hours to complete are of little potential clinical value, no matter what their excellence as purely research techniques may be. Secondly, since by the nature of the clinical problems concerned repeated assays may be necessary, it becomes a matter of urgency to avoid, if at all possible, urine-collection requirements which would limit the application to in-patients only.

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Clearly, few out-patients would co-operate to the extent of producing a weekly or fortnightly 24-hour urine collection, while the completeness of such collections as might be forthcoming would always be open to grave doubt. Great practical advantage would therefore be derived from the possibility of using first morning urine specimens rather than 24-hour collections, and it seemed reasonable to investigate such a possibility even though the variations in the results so obtained would be expected to be larger than those from 24-hour collections. With few exceptions, therefore, first morning specimens have been the rule throughout this investigation.

A final remark under this general heading may be made concerning the disadvantage, for clinical use, of methods which determine sodium pregnanediol glucuronide, as compared with those which determine free pregnanediol. Any bacterial contamination may lead to hydrolysis of the glucuronide and so give a spurious low value for the assay, and since in the hurly-burly of clinical medicine such contamination would be difficult to control, it seems wiser to avoid this potential cause of inaccuracy and to employ methods the results of which would not be vitiated in this way.

Considerations such as those outlined above led to the adoption, first of a modification of the Guterman (1944) technique (method I), and later of that described by Sommerville, Marrian, and Kellar (1948) (method II) after it had been shown (Swyer, 1949, wherein the details of the modification of the Guterman technique are described) that the method of Sommerville *et al.* was by almost all criteria the more preferable. Using these methods, an attempt has been made to study the clinical value of pregnanediol assay from the following points of view: (1) as a diagnostic test for pregnancy; (2) as a prognostic test in threatened abortion; (3) as a prognostic test for the likelihood of the initiation of labour by induction procedures; and (4) as a diagnostic aid in complications of pregnancy.

1. General Consideration of Results

For the purposes of this communication the results of a total of 858 pregnanediol assays are available for consideration. The details of these are set out in Table I, and the

TABLE I.—Broad Details of 858 Pregnanediol Assays

Method	No. of Assays Performed		Totals
	Non-pregnant	Pregnant	
Modified Guterman	146	456	602
Sommerville, Marrian, and Kellar	49	207	256
Totals	195	663	858

distribution of the values obtained is shown in the form of histograms in Fig. 1. The most striking feature of the latter is the considerable degree of overlap of values for pregnant and non-pregnant urines as obtained by both methods. The mode is shifted to the right in the case of method II, but apparently more so for pregnant than for non-pregnant urines. This is what would have been expected from the observations previously reported (Swyer, 1949), and is borne out by comparison of the two methods as pregnancy diagnosis tests (recorded below). The point which may be stressed is that, judging from the results as a whole, it cannot be expected that differentiation between pregnant and non-pregnant urines on the basis of their pregnanediol content will always be possible, so that the results in section 2 may be regarded as a fair sample of the overall results.

FIG. 1.—The distribution of 858 urinary pregnanediol assays.

2. Pregnanediol Assay as a Diagnostic Test for Pregnancy

The utilization of urinary pregnanediol assay as a basis for the diagnosis of pregnancy was first proposed by Guterman (1944, 1945), for which purpose he devised his rapid technique, which he did not, however, claim to be more than semi-quantitative. The high degree of accuracy for pregnancy diagnosis which Guterman found has not been uniformly achieved by other investigators (see discussion), and it was because of this that it was felt that yet another series might be desirable, especially one in which some other pregnancy diagnosis test of generally accepted validity was performed concomitantly with the pregnanediol assay on the same specimen of urine. For this purpose the Friedman test was selected, a standard quantity of 10 ml. of filtered urine being injected intravenously followed 48 hours later by sacrifice of the rabbit and examination of the ovaries for corpora lutea. All the specimens used in this series were actually sent for pregnancy diagnosis, so that in all cases there was some degree of clinical uncertainty. The subsequent fate of each was checked, and only those cases in which it was ascertainable have been included in the series.

For the first group of patients the modified Guterman procedure was used in 110 cases, and the results compared with the Friedman test are shown in Table II. In deciding

TABLE II.—Concomitant Friedman Tests and Pregnanediol Assays (Method I) on 110 Urines Sent for Pregnancy Diagnosis (6 mg./litre Regarded as Minimal Value for Pregnancy)

	Total	Friedman Test		Pregnanediol (Method I)	
		Correct	Incorrect	Correct	Incorrect
Pregnant ..	63	57 (90.5%)	6	26 (41%)	37
Non-pregnant ..	47	43 (91.5%)	4	44 (94%)	3
Totals ..	110	100 (91%)	10	70 (63.5%)	40

whether the pregnanediol value was indicative of pregnancy or not, some level had to be chosen rather arbitrarily as the dividing-line. As a guide, assays were performed on the urines from 30 patients known to be non-pregnant, and

since the highest value found was 5 mg./litre, it was decided to regard 6 mg./litre as the minimal level for the diagnosis of pregnancy. Objections to this procedure could be cited, and because Guterman regards the "positive" colour in his test to be given by about 4 mg./litre of pregnanediol, the results have been recalculated on the basis of 4 mg./litre being the minimal level for pregnancy diagnosis (Table III). There is a slight improvement, but it is not sufficient for escape from the conclusion that, while false positives in non-pregnancy are rare, false negative pregnanediol values in pregnancy are so frequent as to condemn the test as an aid to pregnancy diagnosis.

TABLE III.—*The Results of Pregnanediol Assays (Method I), Previously shown in Table II, Recomputed on the Basis of 4 mg./litre as Minimal Value for Pregnancy*

	Total	Pregnanediol (Method I)	
		Correct	Incorrect
Pregnant	63	31 (49%)	32
Non-pregnant	47	43 (91.5%)	4
Totals	110	74 (67.3%)	36

Attention may be drawn to some of the cases in which discrepant results were obtained. There were two cases of proved hydatidiform mole, in both of which the Friedman test was positive (even when diluted 1/100, only 0.1 ml. of urine being injected); for the purposes of this comparison, these were interpreted as "false positive" Friedman tests, without any aspersions being cast upon the technical reliability of the test. In these cases the pregnanediol excretion was *nil* and 1 mg./litre respectively. Two other cases were clinically suspected as being those of hydatidiform mole; in one, in which the Friedman test was positive (though not on dilution) and the pregnanediol excretion was *nil*, subsequent events showed the case to be that of normal pregnancy; in the other, in which the Friedman test was negative and the pregnanediol excretion also was *nil*, no evidence either of pregnancy or of hydatidiform mole was obtained when the uterine contents were examined.

A specimen from a pregnant woman, when the period was only three days overdue, gave a negative Friedman test and contained 3 mg. of pregnanediol per litre; eight days later the Friedman test was still negative but the pregnanediol content had risen to 6 mg./litre. In a case which was subsequently proved to be that of ectopic pregnancy the Friedman test was negative and the pregnanediol excretion 4 mg./litre. In two cases of missed abortion the Friedman test was positive and the pregnanediol excretion 9.5 and 5 mg./litre. In neither case was a foetus found on evacuating the uterus. In three other cases "false negative" Friedman tests were obtained in cases of pregnancy; these must be regarded as technical faults. The corresponding pregnanediol levels were *nil* in two cases and 15 mg./litre in the third.

For the second group of patients, the procedure of Sommerville *et al.* (method II) was used in 101 cases, and the results, compared with the corresponding Friedman tests, are shown in Table IV. Once again 6 mg./litre is

taken as the lowest permissible value for a "positive" pregnancy diagnosis, and it can be seen that the overall pregnanediol test results are considerably improved (82% correct) as compared with those in the previous series (63.5 or 67.3% according to the criterion of a "positive" value); that the reliability in pregnant cases is much greater (82.5 compared with 41 or 49%); but that a considerably larger number of "false positives" has now been produced (18.25% compared with 6%).

In this series there were three cases of missed or incomplete abortion; the Friedman test was positive in one, the pregnanediol value being 1 mg./litre, and negative in the other two, in which the pregnanediol values were 6 and 18 mg./litre respectively. There were, in addition, two cases of threatened abortion in which the diagnosis of pregnancy was uncertain at the time of testing; in one the Friedman test was negative, the pregnanediol value being 8 mg./litre and the patient aborted; in the other the Friedman test was positive, the pregnanediol value being 19 mg./litre and the pregnancy continued. A case of salpingitis which was considered clinically to have been possibly that of ectopic pregnancy had a pregnanediol excretion of 24 mg./litre; the Friedman test was negative.

3. Pregnanediol Assay as a Prognostic Test in Threatened Abortion

There have been several reports of the relation between pregnanediol excretion in cases of threatened abortion and the fate of the pregnancy (e.g., Hamblen, Cuyler, and Baptist, 1942; Guterman, 1946; Bender, 1947, 1948). The present series of cases is small compared with those of some previous authors, but the numbers are nevertheless sufficient for conclusions to be drawn which are not altogether in agreement with earlier reports.

FIG. 2.—The distribution of 56 urinary pregnanediol assays from cases of threatened abortion.

Forty cases of threatened abortion have provided a total of 56 urine specimens for pregnanediol assay; the distribution of the values is shown in Fig. 2, where the cases are grouped into those that aborted and those that did not. The distributions are clearly different, but the overlap is

TABLE IV.—*Concomitant Friedman Tests and Pregnanediol Assays (Method II) on 101 Urines Sent for Pregnancy Diagnosis*

	Total	Friedman Test		Pregnanediol Assay	
		Correct	Incorrect	Correct	Incorrect
Pregnant	63	62 (98.5%)	1	52 (82.5%)	11
Non-pregnant	38	37 (97.5%)	1	31 (81.75%)	7
Totals	101	99 (98%)	2	83 (82%)	18

quite obvious. When the mean values for the two groups are compared by the *t* test, the following result is obtained:

Mean value for abortion group . . . 8.733 mg./litre
 " " non-abortion group . . . 12.4 " "
 $n=54$; $t=2.579$ ($P<0.02>0.01$)

It may therefore be concluded that the pregnanediol values in cases of threatened abortion are, in general, higher when the pregnancy is going to continue than when it is going to terminate, and that the chances of a difference between the means such as that observed occurring on a purely random sampling basis from a homogeneous population are more than 1 in 50 though less than 1 in 100 against.

The clinician, however, is more interested in individual cases than in the behaviour of patients with threatened abortion in general, and it is therefore of importance to consider the ability of the test to predict the outcome in individual cases. A pregnanediol value of 6 mg./litre has again been taken as the minimum for predicting continuation of the pregnancy, and the findings are set out in Table V, both on the basis of the first reading and, where

TABLE V.—*Prediction of the Fate of Cases of Threatened Abortion on the Basis of Pregnanediol Excretion*

	First Reading			Final Assessment		
	Pregnancy Continued	Aborted	Total	Pregnancy Continued	Aborted	Total
Correct	12	14	26	14	15	29
Incorrect	5	9	14	3	8	11
Totals	17	23	40	17	23	40

more than one assay was performed, on the basis of the final assessment, a rising pregnanediol titre being taken as indicative of continuation of pregnancy. The correct prediction was given in 29 out of 40 cases in the final assessment (72.5%). Of the 40 cases, 57.5% aborted; of those that did not, 14 out of 17 had satisfactory or rising pregnanediol titres, but of the 23 patients who aborted, eight also had satisfactory pregnanediol titres.

4. Pregnanediol Assay as a Prognostic Test for the Likelihood of the Initiation of Labour by Induction Procedures

Since most observers agree that the spontaneous onset of labour is ordinarily preceded by a pronounced fall in the pregnanediol excretion, it seemed worth while to investigate the excretion in patients in whom, for various clinical reasons, it was desired to induce labour and to see what correlation, if any, existed between the amount of pregnanediol excreted and the effect of the induction procedure. This has been done in 10 patients, the results being shown in Table VI, in which the cases are recorded in ascending order of pregnanediol excretion.

TABLE VI.—*Pregnanediol Assays in Patients on whom Induction Procedures were Performed or Contemplated and the Results of Those Procedures*

Case No.	Pregnanediol	Mode of Induction	Result
1	10.5 mg./24 hrs.	O.B.E.	Delivery
2	19.4 "	Spontaneous delivery	Delivery
3	23 mg./litre	High puncture	Delivery
4	25.2 mg./24 hrs.	O.B.E.	"
5	41 "	Spontaneous delivery	"
6	49 "	O.B.E.	Delivery
7	49.7 "	O.B.E.	Nil
8	55.5 "	O.B.E.	Delivery
9	56 "	O.B.E.	Nil
10	57 "	Repeated 2 days later	Delivery
		Spontaneous delivery	

O.B.E. = Induction by castor oil, bath, and enema.

It is interesting to note that in three cases spontaneous labour began *before* the induction procedure was started, with pregnanediol excretions ranging from 19.4 to 57 mg. in the preceding 24 hours. On the other hand, the excretions in the two failures were both high—49.7 and 56 mg./24 hours respectively. It would seem, therefore, that, although induction is less likely to succeed at high levels of pregnanediol excretion, the prediction of the fate of a given case cannot be accurately made on the basis of pregnanediol assay.

5. Pregnanediol Assay as a Diagnostic Aid in Complications of Pregnancy

With a view to investigating the possible value of pregnanediol assay as a diagnostic aid in various complications of pregnancy 41 such assays were carried out on specimens obtained from 17 patients with various complications. The details are set out in Table VII, and the following comments seem justifiable: in cases of missed abortion variable values may be found, some "positive" and others "negative";

TABLE VII.—*Pregnanediol Assays in Various Complications of Pregnancy*

Case No.	Diagnosis	Pregnanediol mg./litre	Remarks
1	Missed abortion	9, 4, 3, 0	Friedman test positive. Curettage showed surviving placental tissue but no embryo
2	" "	0, 5	Friedman test positive; no embryo found on curettage
3	" "	8	Friedman positive; pregnancy continued
4	" "	8	
5	? Incomplete abortion	10	Confirmed by curettage
6	Hydatidiform mole	0	Friedman test positive undiluted only; normal pregnancy
7	" "	0, 1	
8	? Hydatidiform mole	11	Friedman test negative; "non-pregnant"
9	" "	0	
10	" "	0	Daily pregnanediol assays; pregnancy went to term
11	Ante-partum haemorrhage at 35 weeks	43, 38, 60, 23, 45	
12	Ante-partum haemorrhage at 37 weeks	60, 69, 51, 54, 16	Pregnancy continued
13	Pyelitis at 29 weeks	34	
14	Ectopic pregnancy	4	Friedman test negative; confirmed at laparotomy
15	Double uterus	33	Daily pregnanediol assays; pregnancy continued
16	Polycystic ovary; punctured at 8 weeks	0, 5, 10, 31, 10, 9, 7, 9, 10	
17	Dystocia dystrophica	92, 128, 78, 154	Daily pregnanediol assays at full term

the Friedman test may also be positive or negative, and it cannot be claimed that either test, or the two in combination, enables a definite diagnosis to be reached.

In both cases of proved hydatidiform mole the pregnanediol excretion was trivial, while chorionic gonadotropin was present in the usual large amounts. On the other hand, Case 8, clinically considered to be one of hydatidiform mole, was found to have both Friedman test and pregnanediol assay within the limits of normal pregnancy, and such it eventually proved to be. In Cases 9 and 10 hydatidiform mole was again suspected clinically; pregnanediol excretion was *nil* in both cases, but in one the Friedman test was positive undiluted only and normal pregnancy was the eventual conclusion, while in the other the Friedman test was negative and no further evidence of pregnancy was forthcoming.

The two cases of ante-partum haemorrhage showed pregnanediol excretions within normal limits for the periods of gestation, and the same applies to the case of pyelitis at the 29th week of gestation. In the case of ectopic pregnancy, both the Friedman test and the pregnanediol assay was misleading. The pregnanediol excretion in Case 16—that of polycystic ovary punctured at 8th week

of gestation—showed that the operation had not interfered with progesterone production and, accordingly, the pregnancy proceeded normally. In the last case—that of dystocia dystrophica—the pregnanediol excretion seemed to be excessive in view of the fact that labour, albeit of an ineffective type, had already begun.

Discussion

Before discussing the results reported above, it would seem desirable to point out why no mention has so far been made of the use of pregnanediol assay as a means of detecting ovulation in non-pregnant women. Sufficient studies have been made by various workers (e.g., Venning and Browne, 1937a, 1937b; Stover and Pratt, 1939; Hamblen, Cuyler, and Baptist, 1942, etc.) of the pregnanediol excretion during the luteal phase of the menstrual cycle to make it abundantly clear that the total excretion is so variable, and may be so small in apparently normal cycles, that only accurate techniques employed on complete collections of urine extending over several days (even the complete luteal phase) could hope to give indubitable evidence of corpus luteum activity. These requirements place the method entirely outside the realms of clinical practicability, and when it is granted that the basal body temperature record and the endometrial biopsy can give highly reliable results with very little effort, it must be conceded that pregnanediol assay can have no clinical value for this purpose.

The advantages claimed for pregnanediol assay as a diagnostic test for pregnancy were its rapidity (some three hours only are required for the Guterman method) and that it eliminates the inconvenience and expense of animal tests. The accuracy claimed by Guterman (1945) was 92.7% for 248 cases, the Friedman test in 201 of these being only 87.1% correct. Apart from McCormack (1946), who found complete agreement between pregnanediol assays and Friedman tests in 266 cases, no other observers seem to have achieved results at all comparable with these.

It is instructive to compare the published figures of the above authors with those of Reinhart and Barnes (1946) and Merivale (1948); this is done in Table VIII, which

TABLE VIII.—*Comparison of the Published Results of Various Authors with Pregnanediol Assay as a Pregnancy Diagnosis Test*

Author	No. of Patients	Percentage Accuracy	
		Pregnanediol Test	Friedman Test
Guterman	248	92.7	87.1
McCormack* ..	266	99.0	99.0
Reinhart and Barnes ..	130	69.2	—
Merivale	105	63.8	—
Swyer, Series I ..	110	67.5	91.0
„ „ II	101	82.0	98.0

* Omitting 30 cases of threatened abortion, all with negative pregnanediol and positive Friedman tests.

gives the overall accuracy figures. It is evident at once that there is close agreement between the results of Reinhart and Barnes, Merivale, and the first series reported in this communication, and gross disagreement of these findings with those of Guterman and of McCormack. Guterman (1945) has pointed out that his test should be restricted to patients with amenorrhoea who have not received progesterone therapy, but, as Reinhart and Barnes observe, the elimination of patients with vaginal bleeding or those who have received progesterone therapy materially limits the value of the test for routine clinical use.

Although in most of the published series the proportion of false positives is relatively low (that of Reinhart and

Barnes is an exception), such results can be obtained in a variety of conditions—for example, the luteal phase of the menstrual cycle, which, if prolonged by a lengthened proliferative phase, might well lead to the clinical suspicion of pregnancy; corpus luteum cysts (Guterman, 1945; McCormack, 1946; Bender, 1948); arrhenoblastoma; a case of amenorrhoea with uterine enlargement due to metastatic carcinoma; and a case of salpingitis diagnosed clinically as ectopic pregnancy (Morrow and Benua, 1946). This last case is interesting in so far as it compares with a somewhat similar case reported in this paper, also with a “positive” pregnanediol excretion (24 mg./litre).

When all the available evidence is considered it seems impossible to escape the conclusion that the reliability of pregnanediol excretion is insufficient to warrant its use as a clinical method for pregnancy diagnosis. In its main claim, that of rapidity and convenience, it bears no comparison with the male-toad test, and, provided a supply of suitable animals can be assured, this test, or one of its modifications, would seem to fulfil all the requirements for clinical use.

Regarding the prediction of the fate of threatened abortion, once again the accuracy reported in the present series is far less than that claimed by Guterman (1946) (72.5% correct for 40 cases as compared with 93% for 73 cases). Bender (1948), however, has produced evidence that, using the Guterman test to differentiate cases of threatened abortion with high pregnanediol excretion from those with low outputs, and reserving treatment with progesterone for the latter only, a statistically significant increase in the salvage rate can be obtained; on the other hand, progesterone given to patients with threatened abortion with positive Guterman tests increased the likelihood of abortion. If this work can be substantiated, it would seem to be a really valid clinical application of pregnanediol assay. It is right, however, to point out that the administrative difficulty of obtaining the result of the test promptly, together with the necessity to wait for the first morning urine sample, may lead to delay in the exhibition of progesterone in those cases that warrant it, the abortion perhaps becoming inevitable as a result.

In the diagnosis of complications of pregnancy, the results presented do not suggest that pregnanediol assays are likely to prove of much value except in the case of hydatidiform mole, in which pregnanediol seems to be absent from the urine. It is true that it would be impertinent to attempt to generalize from the findings in two cases only, but on this point confirmatory support is to be obtained from other sources: Guterman (1945) found negative tests in three cases of hydatidiform mole, while McCormack (1946) reported the same results in two other cases. On the basis of seven cases, therefore, it would seem reasonable to suggest that absence of urinary pregnanediol in a case clinically suspected as being hydatidiform mole and giving a positive test for chorionic gonadotropin in high dilution, very substantially supports the diagnosis.* Such a confirmation may be of great value at about the twelfth week of gestation, or in the case of multiple pregnancy, in both of which conditions the gonadotropin excretion may normally be so high as to give a positive Friedman test at 1/100 dilution.

If now the clinical value of pregnanediol assay is judged from the evidence presented on the basis of the criteria laid down in the introduction to this paper, it must be con-

* Since reading the proofs of this paper, the author has had a third case of hydatidiform mole with a positive Friedman test at 1/100 dilution and absence of urinary pregnanediol. Dr. S. Bender, however, has encountered two out of three cases of hydatidiform mole with “positive” pregnanediol excretions.

cluded that, in general, it has little to offer the practising clinician. It seems doubtful whether the relative inaccuracy of the methods suitable for clinical application can be held completely responsible for this state of affairs; rather should one ascribe it to the inherent variability of pregnanediol excretion both in the same and in different patients. Consideration of the factors responsible for this variability is beyond the scope of the present discussion, but it does seem permissible to observe that there are no solid grounds for believing that pregnanediol excretion reflects at all closely the progesterone levels of the blood, and undoubtedly the latter are of far the greater physiological significance. Simple direct means of assessing the blood progesterone would surely supply evidence of much more clinical value than could ever be expected from the pregnanediol excretion in the urine.

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VESICO-BULLOUS DISEASES AFFECTING THE EYE*

BY

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There are few skin diseases which may not at some time involve the eye and its appendages. It is impossible to consider all of them here, even in the most summary way. I propose instead to survey a single group—the vesico-bullous diseases of internal origin—affecting the skin and mucous membranes. Even with this restriction the survey must necessarily be a brief one.

The more one considers the vesico-bullous diseases the more one is struck not by their clinical differences but rather by their essential similarities. A common factor seems to operate in all of them, producing a particular type of cell reaction. It is this which makes a study of the group of special interest. In some diseases a virus, in others an unknown toxin, exercises a destructive action on the mucosae or on the deeper cells of the epidermis, with resultant cellular liquefaction. This seems to release a physico-chemical force, which in turn increases capillary permeability and attracts the filtrate as well as the local tissue

fluid to the injured area. In this way a vesicle is formed. When the hydrostatic pressure within the vesicle has reached a certain point the movement of the fluid is checked. Whether the vesicle breaks down to form an oozing erosion or not depends largely on the thickness of its roof. Naturally, in the conjunctivae and other mucous membranes the covering is thin and the vesicles are correspondingly transient, so that the clinical picture is a raw oozing surface, whereas the skin may still show intact vesicles. But though the distribution and clinical appearance in the different diseases of this group are varied and characteristic, histologically we can distinguish only grades of severity in an essentially similar reaction.

Percival and Hannay (1949) have published an excellent study of the pathology of bullous formation, from which the following interesting sentence is taken: "To state the problem differently, it can be asked why the exudate remains in the dermis in urticaria, becomes localized at the dermo-epidermic junction in dermatitis herpetiformis, in the rete mucosum in eczema, and under the stratum corneum in pemphigus foliaceus, when the mechanism which made the exudate available is common to all four conditions, and is in all probability initiated by a common factor."

The diseases of this group which affect the eye are: herpes simplex; herpes zoster; erythema multiforme, including the severe form known as the Stevens-Johnson syndrome; foot-and-mouth disease; Touraine's aphthosis; dermatitis herpetiformis; and pemphigus. (Conjunctival scarring is associated with other skin diseases, such as bullous eruptions following vaccination, erythroderma ichthyosiforme of Brocq in its bullous form, epidermolysis bullosa dystrophica acquisita, and congenital syphilis, but these conditions do not belong to the group under consideration.)

Herpes Simplex

This well-known disease is characterized by the often-repeated occurrence of little groups of blisters on a base of oedema and redness. Its virus origin is amply proved, and corneal inoculation of a rabbit gives positive results. In contrast with what occurs in many virus diseases the host develops no immunity. On the contrary, a local hypersensitivity often causes the same small patch to respond on each occasion. The lips and face are most frequently affected, but lids, conjunctiva, or cornea may suffer instead.

The evidence suggests that the virus is a saprophyte living in happy matrimony with the tissues until a *tertium quid* disturbs the harmony. This may be any one of a variety of agents which include cold, heat, sunlight, food, drugs, and bodily upsets. The injured cell then goes through the processes of liquefaction and vesicle formation already described. Individual eruptions heal easily and need only to be kept clean. But to prevent recurrence is a difficult matter. Irradiation of the affected area of skin with x rays may produce an alteration which increases local immunity, or repeated inoculations with smallpox vaccine may raise the general resistance, but disappointing results are common.

Herpes Zoster

This complaint is not transmissible by inoculation. But as specific antibodies have been found in the blood, and inclusion bodies have been demonstrated in the vesicles, the evidence is in favour of a virus disease. The cutaneous reaction is greater and deeper than in herpes simplex. Haemorrhagic, purulent, or necrotic vesicles may occur and leave severe scarring. Many cases have been described as

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