VII. A theoretical model of the relation between estrogen/progestin and prostaglandins which also has a relation with pain seen from a technical point of measurement and control (1981).

ABSTRACT
In this article the feature described by Horrobin and Manku about prostaglandins E1 and 6-keto pgF1a: effect reversal at an increasing concentration illustrated in a practical example,
The feature described is especially suitable for linking moments in a biochemically regulated measuring and regulation system.
By this feature the occurrence of cyclic events can be understood better. By this the electronically known "saw tooth curve" has a biochemical analogon.
It is a description of the assumed relationship between hormones and the guiding prostaglandins and the hormone effects based on their well-known concentration course.
The practical consequences of the experimentally found sensitivity of biochemical effectors with respect to the guiding prostaglandins are highlighted.
It shows in what way the coherence between the effects of estrogen and progestagen results in the Basal Temperature Curve.
The modulating and linking prostaglandins play a part in the origination of pain,
The origination of pain reactions at a dysregulation of the estrogen-progestagen system thus may be better understood, just as the possibility to observe these reactions by non contactile infrared thermography on the skin surface.

Principles/hypotheses;
This theoretical model has three basic principles. For the sake of understanding the model they are explained first. The adjustment to the state of science in 2012 follows in the discussion after-wards.

No 1:Horrobin and Manku (1,2,3) wrote:
a. It may be that it is a mistake to look for direct actions of prostaglandins themselves. What one should be looking for is a modulation of the action of another agent known to affect the system concerned.(1).
b. The prostaglandins in the second group (bell shaped) may have powerful potentiating effects on a biological response at one concentration and powerful inhibiting effects at another.(2).

In order to have a functional significance, within a measuring and control system for substances which can only exert effects as a co-factor there must be a relationship between the concentration of PG's and the concentration of their buddy. Here a one to one relationship is assumed.

No.2:An antagonistic effect is assumed between PGF and PGE, although this in fact can only be determined in a pure bell-shaped free PG system.
The literature found in 1981 indicates:
PGF: relationship with: estrogen, proliferation, anti-atherosclerosis.
PGE: relationship with progesterone, edema, anti-proliferative, atherosclerosis, hyperthermia.
The estrogenic hormone variations are brought into relation with PGF concentrations and the progesterone variations with PGE.

No.3: PGE has an influence on the central temperature regulation.
PGE is brought into relation with hyperthermia.

Conversion forms:
in the model the estrogen-progesterone concentration is converted into PGF-PGE concentration.
Graphic: in a time-concentration curve.
Consequently the "concentration in time" is being converted into "effect per time" based on the concentration-effect curve by Horrobin and Manku,(3).
Graphic: time-effect curve.
Finally the values of the PGE effect are reduced by those of PGF: PGE-PGF.

Result: a resultant of the prostaglandin effects in time. This is compared to the body temperature curve in the time, as known in 1981.

Cave: The top of the prostaglandin CONCENTRATION does not equal the top of the maximum prostaglandin EFFECT as indicated in the curve by Horrobin and Manku.
The **maximum prostaglandin effect** is about halfway the ascending and descending limb of the concentration-time curve. At a maximum concentration in time the parabola cuts the concentration-effect curve on the baseline. The effect there is **zero**.
Higher concentration has the effect turn over to the opposite.

Prostaglandins general.
Prostaglandins (PG's) are substances which occur ubiquitously in the body and are synthesized from fatty acids (4,5). They are formed under influence of various biologically active substances.
In the course of time many publications have appeared about prostaglandins:
(January 2012: Google:5.5 *10^6 hits in 2.5 sec; Pubmed: 96797, of which 17787 available as free full text.

From these Pubmed publications 77470 (80%) have appeared after 1982, so after the concept of this article. An evaluation in 2012 should not be missed then.

PG's play a mediating and modulating role in almost every area of the mammalian functioning (3,4) and therefore have a guiding effect. PG's as a cofactor do not have a biological effect themselves.
Only in combination with a biological substance otherwise they exhibit their tricks. This other substance then follows the dose-effect pattern of the PG concerned. In case of pain the PG's have this guiding function but also in the hormonal field (3,6,7,8,9,10,11).
From the feature that the operation of certain types of prostaglandins not only depends on the concentration but can turn from an agonistic to an antagonistic effect, these types of substances have biochemical switching potential. This can be of great importance in an organism containing cyclic processes. The menstruation cycle is such an example in which functionality periodically switches and there is also much pain.
Then the question arises as to how this cycle is switched and if prostaglandins can play a switching role in this.
It is known that the hormonal cycle is controlled by hypothalamic-pituitary systems.
Direct control of the cycle is not likely because PG's have a too short half value time(destruction in one lung passage (12,13).
Moreover in a number of tissues systems occur that may inactivate those PG's (14).
This indicates on an especially local short-lasting control that can cause effects on a distance via CZS.(This plays a part with CRPS)
Already in 1963 this possibility was mentioned (15). The hypothalamic region can be stimulated by hormones in combination with prostaglandins (6,7,8,10,15,16,17).
The PGE that is brought into connection with the prolactin level has exudative properties (6,7,8) and the ability to generate hyperthermia via stimulation of the hypothalamus, although there is no complete consensus about this (23,24).
Both properties can be found in the second part of the menstrual cycle. The hypothesis seems to be justified that the locally released estrogens and progestagens can activate the peripheral nervous system under the influence of PG's.
This activation, on its turn, can release PG's in central areas such as the hypothalamus, PG's that mediate in releasing "releasing factors" which in turn regulate the hypophysis in activity.
Feedback can take place then via the "trope" hormones, the CZS and PG's as a result of which on a local level a feedback level occurs as well.
The question remains why on various points switch moments occur, such that concentrations of hormones are synthesized in a smooth transition and also why this production run has a fixed cycle in time.

An ideal biologically active linking substance would have to meet the following profile:

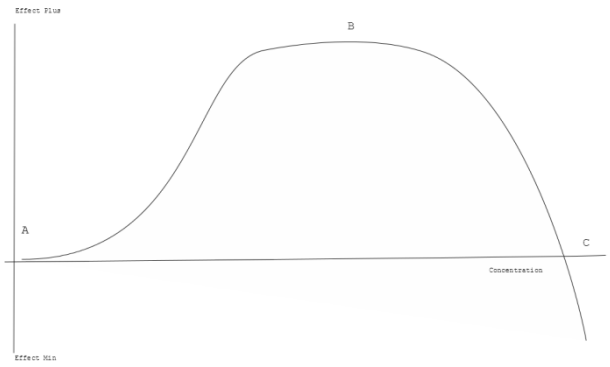


Fig.1.

A long stable phase for homeostatic situations (B), a short steep phase for switch situations (B-C) and a long run and end stage at A.
The latter prevents "accidents" such as dysfunction in scarcity. There is as it were a brake built in at low concentrations.

A long plateau phase at B, at which "B' is the point where the effect of the linking substance decreases in strength at an increasing concentration.

Horrobin and Manku (3) described an intriguing and striking finding concerning the relationship between PG concentration and effect. Particularly the PGE1 bell-shaped curve strikes and the logarithmically going dose-effect curve in PGE2 (linearly dose : plateau phase).

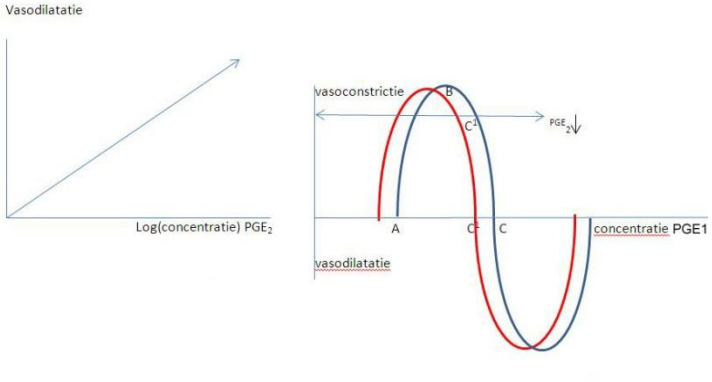


Fig.2.

From PGE2 PGF 2a is enzymatically synthesized with similar properties compared to the dose-effect curve.
From PG1 6-keto PGF 1a is not enzymatically made. PGI is situated in an unstable phase.
From 6-keto PGF1a 6-keto PGE originates enzymatically. From the way of originating we may expect that both 6-keto PGE1 and 6-keto PGF1a have the same dose-effect curve.

From literature a number of estrogen and progesterone effects are known.
PGF has, like estrogen, a proliferative stimulating effect on the endometrium and also an anti-atherosclerotic effect. PGE and progesterone have edema increase, ant proliferation and atherosclerotic effects in common. (The side effects which may develop during the use of oral contraception are not kept as standard for this because they can be attributed to a relative overdose, according to the scheme by Horrobin and Manku).
When the PGF and PGE effects are compared to the estrogen and progestin the resemblance is striking.
When the estrogens and progestagens start operating with PG's as modulator and cofactor, a relationship should exist with both concentrations. The concentration course of estrogens and progestagens in the 28 days cycle is known. Upper two curves Fig.3/1.
A one to one ratio is assumed between the concentration of hormones and cofactors.
Fig 3/II that is why these are identical to the concentration of hormones in time.

Fig 3

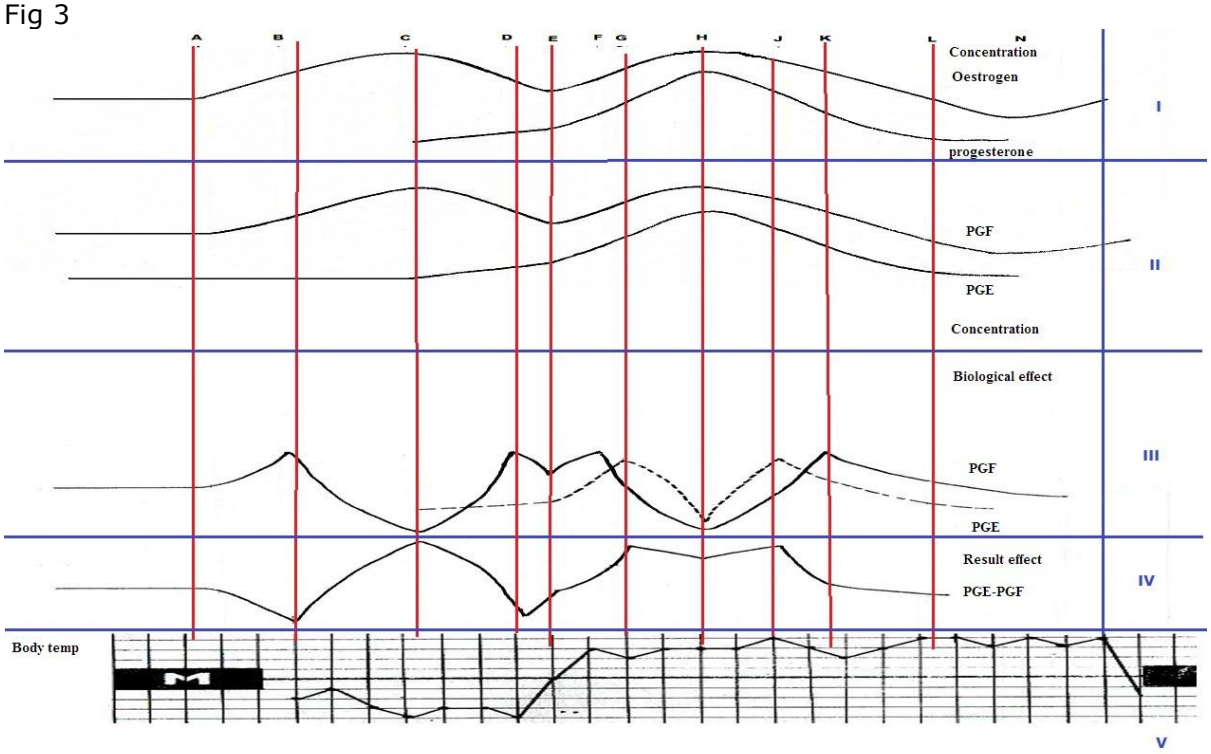
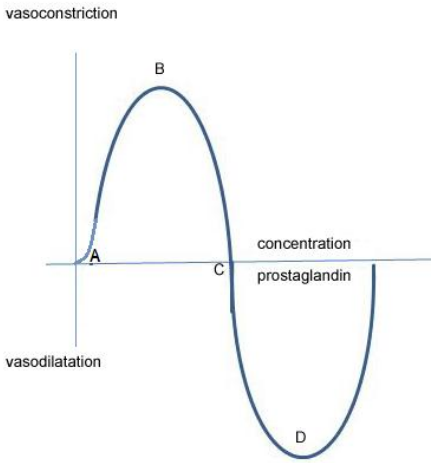


Fig 3/III shows the effect curves of PGE and PGF in this case corresponding to the effect of estrogens and progestagens in the lapse of time.

Fig 4.



This requires explanation: Figure two shows the PG(x-as) concentration against its effect (Y-as).
A,B and C in figure two are similar to A,B and C in figure 4.

In A there is a steady state corresponding to the horizontal line in the PGF graphic (fig.3/III).
B is the point of maximum effect. At an increasing concentration the effect decreases. In the PGF curve (fig.3/III) the effect is zero when the top C has been reached.

(the dip in the curve).
When the concentration decreases, the effect increases till point B is reached again In fig 3/III this is point D now. From point B to point A in fig.2 the effect decreases. A is point E in fig.3/III.

After that the concentration increases again and the described pattern repeats itself.
As PGF and PGE are supposed to have an opposite effect, at subtraction a resultant remains:fig.3/IV.
The resulting prostaglandin resultant effect has an unexpectedly remarkable similarity to the Basal Temperature Curve (26). From literature (25) we know that there is a LH peak around day 11 -day 12. A connection is also supposed between PG's and LH (17, 10) in which both PGF and PGE have a stimulating operation.

Consequence of the originating of this resulting "Relative PGE activity curve".

During the estrogen phase the PGE activity decreases as a result of the decreasing progesterone concentration and as a result of the increasing estrogen concentration the PGF

activity increases to respectively min and max at "B". After that when the estrogen concentration increases the PGF effect turns to the opposite. The level of the PGF activity curve decreases, as if less PGF and/or more of its antagonist PGE is produced. The PGF activity "dip"(at point C) can be considered a "virtual peak" of PGE activity, followed by a PGF activity peak. The latter coincides with the ovulation. (At the same time there is a FSH peak in the serum (11).
After that an increase of PGE activity occurs as a result of the increasing progesterone production and a second period of "virtual PGE" activity as a result of the second peak of estrogen production.
The resulting PGE activity is maintained up till the menstruation.

Functional model:

As a result of the combined activity of the regulating and regulated hormones the following may happen:
From "A" to "B" PGF activity increases (fig.2/III), the FSH stimulation increases. Combined with the present LH the estrogen level increases because of this, (fig.3,1), as a result of which PGF activity further increases and the FSH production increases.
At "B" there is a reversal from PGF activity into PGE activity, (fig 2, III), by which LH stimulation occurs and the estrogen production still increases.
At the same time the FSH production is slowed down by the increased PGE activity and by this also the increase of the estrogen and PGF concentration.
Thus a balance between PGE and PGF activity ("C") gradually arises. The PGE effect stimulates the progesterone production (fig.1,2) which in its turn promotes the PGE production. At an increasing PGF concentration the PGF the PGF effect turns into a PGE effect. (fig.4).
The increase of PGE concentration slows down the PGF and /or estrogen production. The PGF concentration decreases again, and in doing so the PGF effect increases. The FSH production increases. The LH stimulation decreases. In "D" the effect turns over again.(The same concentration as "B") The PGF concentration further decreases as does the effect. The LH concentration has now passed the maximum. The FSH stimulation is at its maximum. The peak of the FSH production coincides with the ovulation. The LH peak is a few days earlier.

At "C" prolactin stimulation LTH arises by maximum PGE effect and LH concentration as a result of which progesterone starts.(17 hydroxyprogesterone peaks at the moment of LH peak(11). (It is not clear why in this table the FSH peak coincides with the LH peak which should not be expected). From "D" a further concentration decrease takes place. The FSH stimulation decreases. The estrogen concentration decreases. The PGE activity increases. The LTH concentration increases. The progesterone production increases. The net PGE effect increases more rapidly by this. The PGE effect also stimulates the LH production as a result of which the estrogen concentration will increase. The FSH decrease at the beginning is stronger than the LH increase in order that the resultant causes a temporary estrogen decrease.
At "E" the PGE and PGF concentrations are in balance, after that the estrogen production increases again as a result of increasing LH stimulation as a result of increased PGE activity as a result of the increasing progesterone level.
That same PGE activity stimulates the LTH production for the purpose of progesterone.
In an identical way as described in the estrogens in the first part of the cycle an effect switch takes place in respectively "F" and "G" for estrogens and progestagens and then in "K" and "J ". In this case both the PGF and PGE effect turn over. The resultant is an increased level of PGE activity with a "dip" at "H". (Because the concentration of progesterone quicker increases or decreases then the estrogen concentration).Then, by the decrease of PGE activity the LTH stimulation disappears as a result of which the progesterone concentration decreases and the difference between PGF and PGE increases in favor of PGF, by this the FSH stimulation increases.
By the PGF increase the contraction of the smooth muscle tissue is stimulated causing the spiral arteries to withdraw and ischemia in the uterus occurs.

According to the same reasoning the estrogen concentration and the PGF concentration increase. The effect turns over again so that at the beginning of the menstruation a "PGE effect" occurs. The arteries widen and the bleeding begins. The PGE effect slows down the FSH

production and thus the estrogen production and hence the PGF production. The PGF concentration decreases again and so the PGE effect decreases to the level of the turn over. After that there is PGF effect and FSH stimulation again. The estrogen concentration increases. The arteries close and the bleeding diminishes, thus ending the cycle.

Evaluation 2012

In the model estrogen is linked to PGF and progesterone to PGE. PGE and PGF in many aspects have opposite effects, also in temperature. Considering linking to hormones this is logic. Also modern literature indicates an opposite effect in the body temperature of estrogen and progesterone although that mechanism is not clear yet to people in the year 2012. (27).

In 2012 much more is known about prostaglandins, how they work as a cofactor and the relationship between prostaglandins and hormones than in 1981, a reason to test this theoretical model based on publications between 1981 and 2012.

Google generates more than 250 figures of hormone concentration courses. Only the Elsevier graphic looks like the scheme used in 1982. All others have the profile as in the three figures below.

In Wikipedia (2012) the following graphic reproduction appeared about the hormone concentration during the menstrual period. (fig 5). The reproduction is very similar to fig. 5 (28) and fig.7 (29).

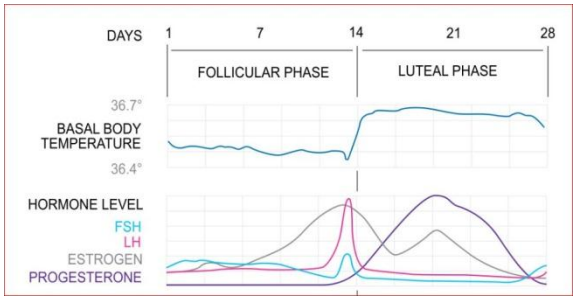


FIG.5.

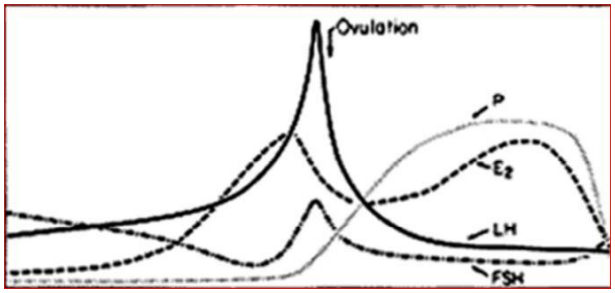


FIG.6.

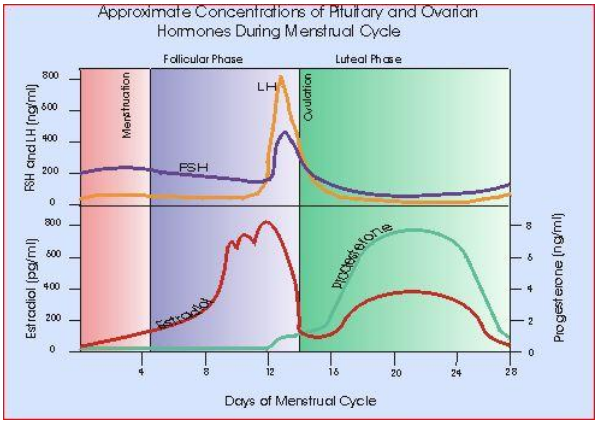


FIg.7.
Common is the correlation between ovulation and LH and FSH peak.
Also common is the biphasic estrogen course with the second peak lower than the first one, a progesterone concentration which has a peak simultaneously with the estrogen after ovulation and a progesterone concentration bigger than the estrogen concentration after the ovulation.
The estrogen peak in Wikipedia is symmetrically bell-shaped and in fig.5 asymmetrical, steeping down. The LH and FSH peaks in fig. 5 are situated at the top in the estrogen concentration curve.

Fig. 7 gives quantitative concentration information.
That raises questions: The progesterone peak lies above the estrogen peak, but the concentration is 3 nanogram/ml=3000 picogram/ml and the estrogen concentration is almost 400pg/ml.
There is a lot of variation in the measured peak values as well. Progesterone between 8000-20000 pg./ml and estrogen between 120 and 800 pg./ml. By that the mutual relationships may differ. Anyway, the average concentrations and concentration courses differ from the model used in 1981
Reason to repeat the procedure based on the average values.

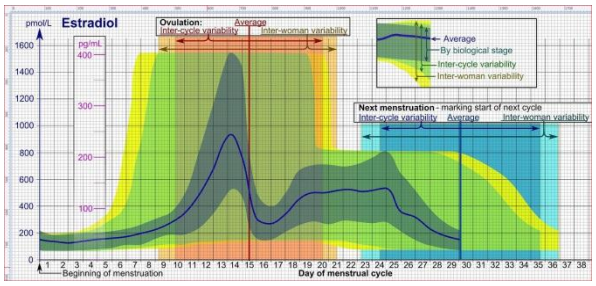


FIG.8.(30)

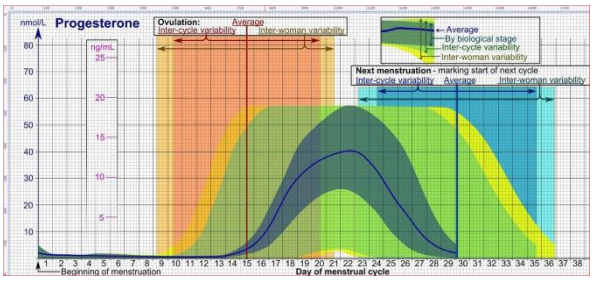


FIG.9.(30)

In order to do this the Wikipedia quantitative information is best to use.
According to the theoretical considerations from 1981 the following curve occurs:

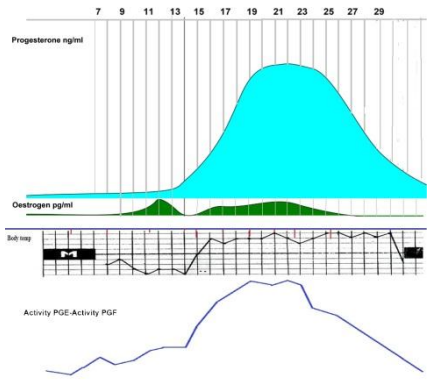
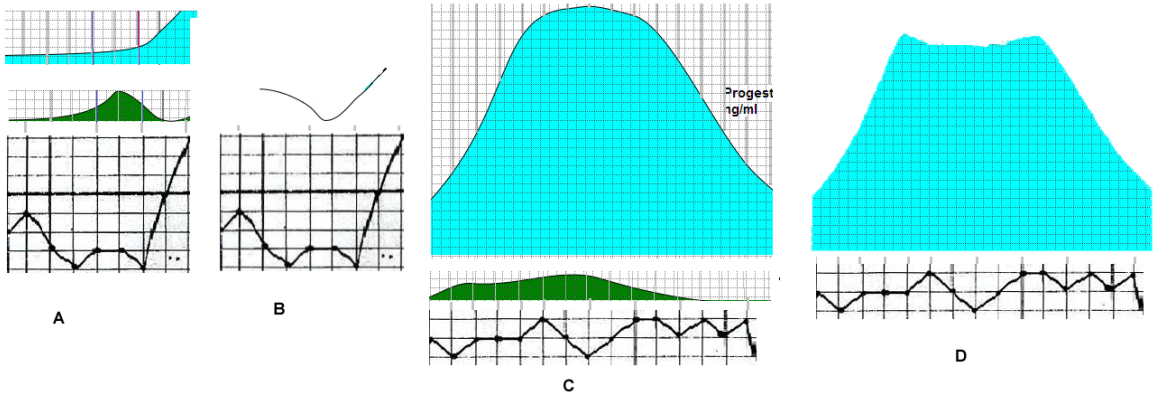


fig. 10

As the concentration course of progestagens is measured in nanogram/ml and the estrogen is measured in picogram/ml both curves are upon each other. The activity curve course is determined to a very large extent by the progesterone concentration and the PGE activity.
The resulting curve has not much in common with the BBT (Basal Body Temperature) curve which may be due to the overruling influence of the progesterone.
In a situation in which prostaglandin effects are proportional to the concentration, the prostaglandin E effect would increase a thousand times to that of the prostaglandin F. Then F no longer has an influence on E.

Considering this, a proportional effect of the concentrations of progesterone and estrogen is assumed. Unexplainable is the consensus about the course of estrogen and progestagen concentrations as we see in fig. 4, 5 and 6. There the estrogen and progesterone curves cut each other and the differences in the concentration are not calculated as in fig.9.
Considering the different parts of the curve only from a point of view of progesterone-estrogen **concentration difference** then the following curves occur:
FIG.11.



"A": Progesterone concentrations, estrogen pre-ovulatory. Below that the BBT curve.
"B": Subtraction curve of progesterone-estrogen concentration pre-ovulatory and the BBT curve.
"C":As in "A" but postovulatory
"D": As in "B" but postovulatory.
The curve at "B" lacks the convex "soul" of the BBT.
The curve at "D" is concave instead of straight and remarkably shorter than the BBT.

Conclusion

So there is no conformity between the BBT curve and the hormone concentrations if the effect of estrogen and progesterone concentrations are opposite to each other and proportional to the concentration.
The BBT curve thus cannot be explained from the subtraction of opposite working progesterone-estrogen levels. Nor can an addition of progesterone-estrogen levels explain the BBT curve. The estrogen effect then completely disappears into the amount of progesterone.
From the thought that the estrogen-progesterone effects can only be achieved by their cofactors: prostaglandin E respectively F this is also impossible when a proportional effect of hormone-prostaglandin is assumed.

That is only possible if the progesterone effect above a certain level is cut off so to speak so that the effect width of the prostaglandin E enters the range of the effect width of prostaglandin F
In this situation we have a change of progesterone effect. Progesterone is accompanied by its cofactor PGE. PGE changes the effect direction at concentration level "B".
Then there is a plateau phase in which the effect on a big concentration course hardly changes (Fig.1) At the end of the plateau phase the effect of the combination progesterone-PGE decreases with increasing concentration to the linking point "C". There the effect reverses again. (Fig1,fig.2,fig.4)

Point "B" is the point of maximum effect. However, this is not the same as maximum concentration. The effect of maximum concentration corresponds to point "C" in fig. 2.
As previous curve shapes already showed it is difficult to determine on theoretical grounds at which moment in time point "B" is reached.
Considering the great concentration differences of estrogen and progesterone it is unlikely that point "B" at both is the same in time. It is more logic if the sensitivity of estrogen versus prostaglandin is at a different level than that of progesterone and prostaglandin.

Something to hold on is a publication from 1980 (31).
In the early luteal phase day 16 and day 19 were measured, in the mid-luteal phase day 20 and day 22 and in the late luteal phase day 23 and day 26.
The phase in which point "B" of the progesterone curve and the reflection of point "B" from the first peak of the second estradiol curve ("BB") are supposed to be is the early luteal phase.
The reflection of point "B" of the progesterone curve should be situated in the late luteal phase.
Also the reflection of point "B" of the second estradiol curve should be situated in this phase.
Considering the symmetric concentration course of progesterone in fig.9 the average concentration of the early and late luteal phase should be equal.
However, in the article concerned the progesterone concentration of the early luteal phase is 16 micrograms/grams tissue and in the luteal phase 7 micrograms/grams tissue. This big difference makes it difficult to draw conclusions. According to fig 9 there is a large "inter woman "variability. That may explain the difference. But the associated prostaglandin level should change by this as well.
For the early luteal phase group the prostaglandin/progesterone ratio is 1/12400. For the late luteal phase this ratio is 1:1727 whereas this should be about the same extent. So there is more to the results of this publication than just a difference in "inter woman" variability. The question is which values are correct or nearly close to the truth.

Considering all measured values and relationships, then the early luteal phase deviates considerably from the mid-late luteal phase, both in concentrations of hormones, prostaglandins and in ratio numbers.
The tissue concentration of the late luteal phase and the mid-luteal phase, respectively 7 micrograms/g and 22 micrograms/g are fairly corresponding to each other despite the big differences in serum concentration of progesterone in this phase, from1.5ng.ml increasing to 13ng/ml (fig.9).
The prostaglandin/hormone relationship is of the same size as well; (progesterone respectively

1:1727 and 1:1083, estradiol 1:18 and 1:14).
The differences measured can be attributed to a combination of sensitivity of hormone to prostaglandin, this recedes at a high hormone concentration (32) and "inter woman" variability.
A ratio of 1:13 for PGF/estrogen results in 10 pg./ml PGF at 130 pg./ml estradiol. That is the described turn over concentration (32) This result seems surprising because it is based on found values in the mid-luteal phase and the turn over points can be expected in the early luteal and the late luteal phase.
However, the estradiol curve in the luteal phase as a whole has a fairly flat course with small concentration differences. Probably there is hardly any sensitivity shift as a result of the concentration difference. This is different from the progesterone. The ratio progesterone/estradiol increases from factor 30 to a factor 70 in luteal tissue and 50-100 in serum. The increase of the found tissue values and the serum values described in literature fairly correspond to each other in magnitude. This probably does produce a sensitivity shift at high progesterone concentrations.
As a result of this the turnover will probably occur in the low progesterone concentrations with a sensitivity more than 1:1000 in the ratio PGE/progesterone.

To the turn over point of progesterone the investigation by Patwardhan and others (31) has but little value because the low concentrations are before the 17^{th} day respectively after the 25^{th} day of the cycle on which these measurements are based and there are no turn over points from early luteal to late luteal:
According to the sensitivity measured in the mid-luteal and late luteal phase the turn over point should be between 10830pg/ml and 17270pg/ml. These values are close to the 20000 pg./ml peak.
According to the starting point (Fig.2), however, there is point "C". In this situation there is no point "B'. So the turn over points should be before the early luteal and after the late luteal phase.
This means before the 16^{th} and after the 26^{th} day. For the effect of this theoretically based hypothesis the found turn over points for estradiol and the supposed progesterone turn over points will be assumed.

The estrogen course during the pre-ovulatory peak has a concentration of 140pg/ml twice: once at the ascending leg and once at the descending leg. The concentration at the ascending leg is reached on day 11. On the descending leg between day 14 and day15 right before the ovulation.(fig 8).

We stick to day 16 for progesterone and symmetrically day 29. In the choice "sensitivity" plays an important role.

Sensitivity

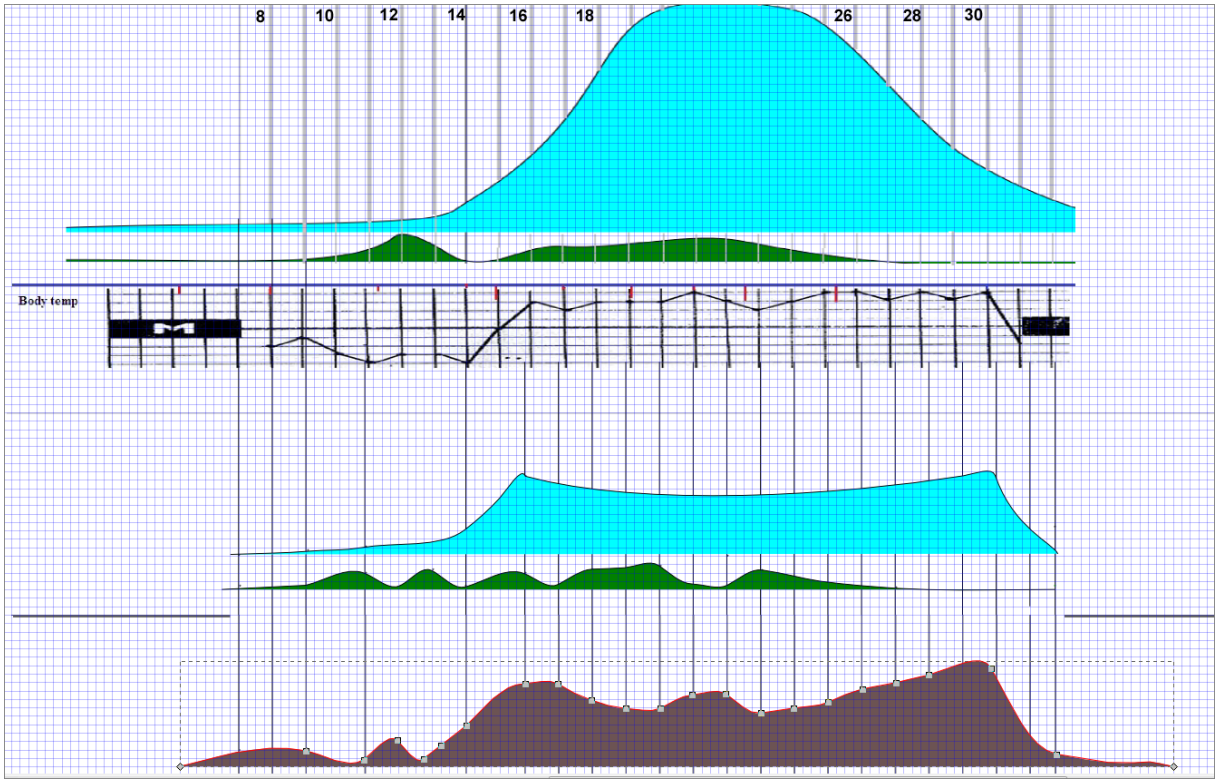
The word "sensitivity" has been mentioned a few times. In their investigation Manku and others described that a high dose of an effector substance can reduce the sensitivity to prostaglandin cofactors. (noradrenaline 10ng/ml with 10pg/ml PGE produces a higher effect than noradrenaline 100ng/ml with 10pg/ml PGE.
The turn over point shifts by a factor 1000)
As the estradiol concentration and the prostaglandin concentration are situated in the order of magnitude of pg./ml, that effect will hardly occur here.
However, progesterone with a concentration of 13 ng/ml is about 50 times as high as the estradiol maximum (250 pg/ml)
From the ratio 1:1038 the PGE concentration can be estimated at 13 pg/ml (31).
10 pg./ml then is about day 18. However, according to the findings of Manku and others(31) the sensitivity at these progesterone concentrations will be lower. And they could easily have a difference of 10^{3}. In other words, at these high concentrations it can be that the turn over point only is reached at 100 picogram /ml or even at 10 nanogram/ml.
The value calculated on day 18 is 10 pg./ml which in that case is too low for a turn over point.
The 10 pg/ml PGE serum value must be reached in a previous stage of the curve.
It is clear that the inherent sensitivity then must be higher than 1/1083.
At a sensitivity of 1/300 the limit of 10 pg/ml is reached at a progesterone concentration of

3000 pg./ml=3 nanogram/ml.
That level is at day 16 of the cycle.

Assuming the same reasoning as followed in 1981 and the concentration curves by Wikipedia (fig.8,9) then the following curve series occurs: fig. 12.

The upper curve is the average progesterone course in time. Each vertical line is a day in the cycle. Under this in green (proportional) is the average estradiol concentration in time.
Under this the ideal BBT(Basal Temperature Curve)
Under this the theoretical PGE effect in time (blue)
Under this the theoretical estradiol effect in time (green).
Last the subtraction graphic "PGE -effect PGF".

FIG.12.



There are obvious similarities to the BBT curve.
1.Preovulatory a dip with a peak in the same period of time
2.A rapid increase of the curve per-ovulatory
3.A peak at day 16 and at day 30
4. A rather equal course between day 16 and day 30
5. 5.A dip around day 23
6. A steep descent after day 30.

The curve obtained is the result of theoretical considerations concerning the pharmacological linking effects of the prostaglandins described. The considerations have been applied as an illustration of the theoretical background of the measuring and regulation technical properties on a naturally regulated cycle with fixed linking moments.
The same measuring and regulation techniques on the same theoretical grounds may cause deregulations on spots of chronic pain having an acute exacerbation such as CRPS as a result. This will be discussed in a separate article.

P.H.E. van der Veen.

Heerhugowaard, 2012-04-15

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