An aetiological model of chronic pain and CRPS
Phases of the same inflammatory condition

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Abstract
Hypothesis: **Chronic pain without a detectable substrate and CRPS are part of the same inflammatory disease process and differ only in its process phase.**

The background of the thought process was published earlier as: *CRPS: A contingent hypothesis with prostaglandins as crucial conversion factor* Med. Hypoth., Elsevier, 2015.
The present article is a practical elaboration of the former publication which integrates chronic pain without a detectable substrate and CRPS in the same pathogenic process.

The process can be observed with infrared imaging and can be biochemically analysed. Treatment has already been available for 30 years and its progress can be followed and measured. This article addresses the disease process and its phases in a process-oriented medical way.

The hypothesis is supported by much evidence, the collection of which is still incomplete. This article provides an applicable model suitable for further pure scientific research as well as a practical pursuit of therapeutic initiatives. It is also an ode to the impressive and significantly underestimated research conducted by Horrobin and Manku in 1977.

Conclusion: Chronic pain and CRPS overlap each other and both develop from an inflammatory accident resulting from trauma, fracture or haematoma.
Chronic pain (the kick off) comes first and CRPS (the knockdown) follows. It explains why CRPS occurs after relatively small injuries.

Introduction

Chronic pain without a detectable aetiology (further referred to as "chronic pain") is a major worldwide problem which has psychosocial, societal and financial consequences (1,2,3,4). Complex Regional Pain Syndrome (CRPS) formally known as Südeckse dystrophy and Autonomic reflex dystrophy is also a major problem (5). The latter has much less of an incidence than does chronic pain, but it has a more severe prognosis usually resulting in severe disability. Chronic pain without a known substrate usually presents itself as fairly stationary, whereas CRPS in its acute phase is a clearly inflammatory condition. When in remission it presents as a neuropathic-like condition.

The aetiology of chronic pain as well as CRPS is unknown. CRPS is referred to as a "syndrome", and chronic pain is not. In order to have a model there must have been a cause at one time, but that pain had since lost its function as an alarm signal, which is also stated in the official publications of the Dutch government (6). MRI scans, however, reveal structure changes in the brain that recover when the pain disappears. That can be explained by the plasticity of the central nervous system (3). The treatment is symptom-oriented.

Despite the fact that CRPS has no theoretical model, and that chronic pain has a psychogenic processing disorder as its model, there are diverse aspects that correspond with each other. It is remarkable that they are mainly reported from sources of non-traditional medicine. The emphasis here is "medical science" and not "the art of healing". The reports are dated from the same timeframe as the reports that include current medical concepts in the most current medical treatments. The nature of the reports and the studies that have led to the current scientific concepts are not structurally different than those which are no longer used. There is a reason for that, but that falls out of the scope of this article.

What is important for the concept of chronic pain and CRPS are the things that correspond between the two of them and the things that differ between them. They have all been reported before 1980 and in the context of recent science are considered "obsolete", or as a contemporary professor recently expressed: "The bar is currently a bit higher". But a modern puzzle cannot be solved without the historical pieces fitted into place.

The thesis that CRPS is a more severe phase of chronic pain in the same clinical course is based on an impressive publication by Horrobin and Manku (H&M) in 1977, which has never received the interest that it still deserves (7). That would not have been possible without the scientific findings dating from the period of 1870 to 1970; on the one hand because the findings have opened the line to an objective research method, and on the other hand because the practical significance of H&M are evident in earlier studies.

This hypothesis is an elaboration of the earlier published article: *CRPS: A contingent hypothesis with prostaglandins as crucial conversion factor*.

Historical conceptual developments of chronic pain

There have been six essential developments for the concept of chronic pain and CRPS.

* The first development was the discovery around 1850 of the anaesthetic effect of cocaine on the eye.
* The second one was the development of a local anaesthetic in 1905, and the development of analgesic medications from the manufacture of aniline.
* The third development was the 1898 discovery of pain sites on the skin which were named after their discoverer called *Head's areas*. Although three years earlier the German homeopath Weihe found 195 continuously recurring pain sites in the skin by different diseases (8).
* The forth was the discovery by Baumann and Ueckert in 1954 that 65% of the pain sites

in the skin are cold in comparison with their surroundings and 11% of them are warm (9).
* The fifth development was infrared thermography for medical purposes in the 1960s which allowed for temperature measurements of the skin without contact.
* The final development was the discovery by Horrobin and Manku in 1977 of a bell-shaped doses-effect curve of certain prostaglandins (7). This discovery is the keystone of all mentioned findings and explains why the findings have been such as they are.

All of the studies mentioned over a period of more than 100 years are about pain without clearly defining how the pain process functions. The explanation is only retrospective. It has been evident for a long time that the skin and the sense of pain have a close relationship (10). That element now seems to be completely forgot.

Cocaine and local anaesthetics are prostaglandin agonists and antagonists (7). The first analgesics are the forerunners of the contemporary ones. Almost all of them have a mechanism of action that inhibits prostaglandin synthesis.

Prostaglandins

Prostaglandins were discovered in 1935 and were synthesized for the first time in 1969. They are hormone-like substances, a subgroup of the eicosanoids and are in fact different than hormones in that they develop locally throughout the body, distributing their effectiveness locally or in their immediate surroundings. They have a directive and modulating role in practically all biochemical processes.

Prostaglandins are related to temperature regulation, vasodilation/vasoconstriction, inflammatory processes regarding pain, and activation/inhibition of stimulus transmission via the central nervous system. They also have a mutual a role in reflector processes such as viscerocutaneous reflexes, which in turn effects prostaglandins. Changes in blood circulation of the skin influenced by prostaglandins make it possible to trace physiological processes with infrared thermography, which makes it an important measurement instrument for chronic pain and CRPS because the pain process also expresses itself in the segment of the skin (10), which is very accessible for examination.

Prostaglandins interact with calcium, cyclic AMP (7,11, PubMed “PGE and cyclic AMP: 938 hits) and nucleotides (7, PubMed “prostaglandins and cyclic nucleotides”: 7712 hits). The focal point of a biological measurement and regulation system is that the impact of their effect is much greater than is generally assumed. Horrobin and Manku (H&M) discovered that that effect has to extend much farther than a local hormonal effect: “*However we do not feel that a locale hormone role is sufficient to account for the ubiquitous distribution of the prostaglandins*”. Nevertheless, they did not realize that the meaning could lie in a conversion function of an autonomously regulated biochemical organism. Switches are the essential core structures of each measurement and regulation system. All processes in a body are converted many millions of times per nanosecond and there is no known regulation system.

There are two general characteristics of each biological measurement and regulation system: feedback and a feedback loop. The feedback or negative feedback is for achieving homeostasis and the feedback loop functions when the feedback systems fail. A situation develops that “seems to continue out of control”. That is the situation with CRPS (5).

H&M describe the following dose-effect curves for the prostaglandins E1, E2 and a combination of E2 with E1. (7, 12)
See Figure 1. These findings were further worked out in Figure 2.
Figure 1.
Adapted from Horrobin & Manku

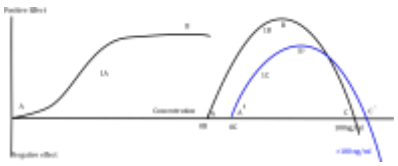
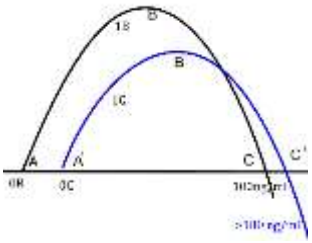


Fig.2.

Adapted from Horrobin and Manku



Excitation converts to inhibition with a certain concentration prostaglandins. A switch takes place in the form of negative feedback. Apparently the accompanying concentration determines “enough is enough”. When these properties are adapted to an excellent example of a regulation process such as the menstruation cycle, the result of two undulating hormone curves of oestrogen and progestagen is a basal temperature curve (13).

This simple system explains negative feedback, but not the failure in a feedback loop which indicate that it “seems to continue out of control”. In an efficient measurement and regulation system two systems are actively opposing each other simultaneously. This allows for timely and immediate responses to changes. This ought to be possible with a biochemically regulated system as well.

There is a mutual counterpart to the examined prostaglandins. While PGE has a demonstrably intrinsic vasoconstrictive promoting mechanism of action, PGF-2 alpha has an intrinsic vasodilative mechanism of action (14). PGF (Figure 3) and PGE (Figure 4) differ only in the presence or absence of one hydrogen ion at position nine.

Figure 3. 6 keto PGF 1 alpha

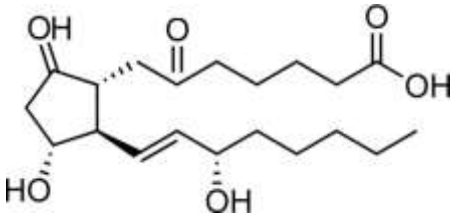
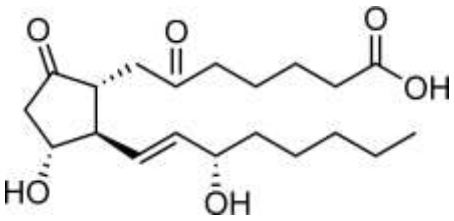


Figure 4. 6 keto PGE1



Even though it is plausible that 6-keto-PGF1 as a stable metabolite of prostacyclin is also vasodilative, that has never been formally demonstrated. What has been demonstrated is that PGF2 alpha (Figure 5) is vasodilative and that PGE2 (Figure 6) is vasoconstrictive (14).

Figure 5. PGF2 alpha

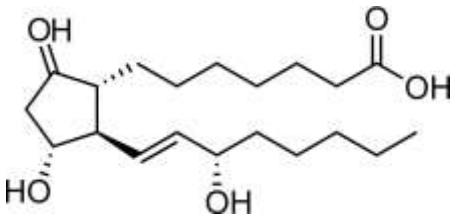
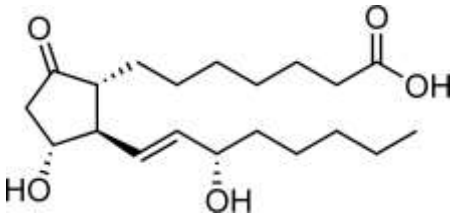


Figure 6 PGE2



The similarity between both vasoconstrictive prostaglandins is the presence of the ketone group at position nine. Both of the Prostaglandins F have a hydroxyl group there. Both prostaglandins without a ketone group

on position six have a dose-effect curve with a plateau phase: a dosage higher than the maximum causes the same effect. Both with a ketone group on position six have a demonstrable bell curve, which suggests that position six ketone group is responsible for the "bell phase" and the hydroxyl group on position nine is responsible for the vasodilation.

Together with the information that 6-keto PGF1 is a stable metabolite of prostacyclin, of which the vessel dilating effect stagnates, it does not seem improbable that 6-keto PGF1 alpha along with a "bell shape" would also be vasodilative and would therefore be a complete counterpart to PGE1.

A problem is the amount of literature claiming that prostaglandin E is not only for vasodilatation, but also for inflammation, exudation and pain. The release of administered prostaglandin concentrations has rarely been clearly defined (15).

Horrobin and Manku already pointed out this problem in publications in 1977: "***If we are correct, the great majority of the studies on the biological actions of PG synthetase inhibitors require reinterpretation. Rarely if ever have amounts of inhibitor sufficient to reduce intracellular PG synthesis to critical levels*".**

Many studies do not achieve the minimum inhibition concentration of indomethazine (64 microgram/ml) or use agonistic pharmaceuticals with a concentration far above 100 ng/ml. That has not improved much in 2017. For PGE1 or PGE1-agonists, this means that an effect reversal will then always be measured, namely: inflammatory effects. In normal physiological situations that is therefore not the case. PGE1 then has a vasoconstrictive effect.

This thesis assumes the vasoconstrictive properties of PGE in a concentration of PGE less than 100 ng/ml, such as reported by H&M. In addition, it assumes the vasodilatative properties of PGF in a concentration PGF less than 100 ng/ml as well. This makes it possible to have the necessary regulation options at a very stable level. It has been demonstrated that the rising leg of the dose-effect curve begins at a few femtograms per millilitre and increases to 1 nanogram at the apex of the curve. The physiological concentration is between picograms and nanograms per millilitre with the regulation of the female hormonal cycle (13).

The disadvantage of this regulation system is that it not only gives effective negative feedback, but also a feedback loop (Figure 7).

Thesis

Figure 7. Bell shaped Dose-Effect curve.
(A modified dose-effect curve by H&M.)

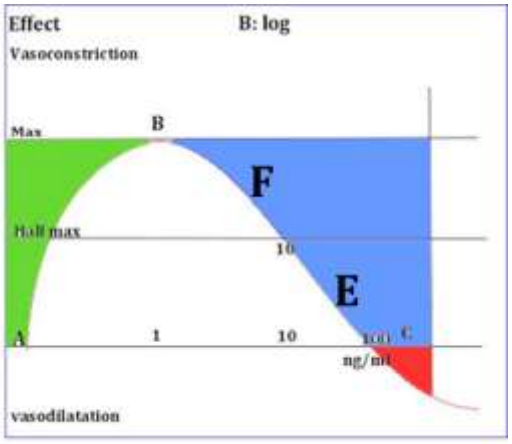


Figure 7 is an enhanced version of the original bell curve of H&M. On the X-axis is the concentration represented in ng/ml on a logarithmic scale. A is the starting point. B is the maximum effect and C is the conversation to the opposite effect. Point B is the first transition point and C is the second transition point. The green area is physiologically active. The blue area can play a role in conversion processes when there is inflammation, haematomas and fractures, and may also play a role in regulating hormones. A powerful opposition is possible from Point C onwards. Moreover, the regulation can become "out of control" from this point on also.

Imagine a situation in which the concentration of PGF exceeds the maximum effect point B

(10 ng/ml> F> 1ng/ml and point E, which represents the concentration of PGE, lies between 10 and 100 ng/ml. The result is then the effect of F minus the effect of E. F_E>0 and therefore vasodilative. Feedback is possible when the concentration of F is increased and the concentration of E is reduced. Increasing concentration of F reduces the effect of F and decreasing concentration of E increases the effect of E. This could explain various symptom profiles. For example: a simple cold or other viral infection is often accompanied by a feeling of being cold, bodily temperature decrease and increased muscle activity: trembling. An increasing concentration of PGE could explain that. PGE2 increases the concentration of cAMP (16). A decrease of the calcium (CA2+) also increases the cAMP (17). The consequence is that PGE2 reduces calcium (Ca2+). This is also found elsewhere (18).

Histamine increases the CA2+ depending on its dosage (19), but preparatory treatment of the cells with PGE2 reduces the threshold for histamine. That could indicate that PGE2 increased the CA2+, which seems contradictory to the previous findings. However, PGE2 does increase the cAMP resulting in an extracellular toward intracellular influx of Ca2+ (19). Ca2+ binds to calmodulin and activates the Myosin Light Chain Kinase (MLCK) which causes muscle contraction (20). This process also takes place intracellularly by binding intracellular Ca2+ to calmodulin.

> "*Due to the versatile nature of a Ca24-signal, modulation of intracellular signalling is an ideal mechanism for viruses to create a cellular environment that is permissive to viral replication*" (20).

The conclusion can therefore be that PGE2 can cause smooth muscle tissue to contract in vivo which is necessary for a virus to be able to enter into a target cell. (H&M already demonstrated contraction for PGE2 and PGE1 in vitro).

In a few days or hours after the infection, the sense of cold and the temperature decrease which then reverses into an inflammatory condition with an increase in temperature. A plausible explanation would be that an increasing concentration of PGE and a decreasing vasoconstriction that just barely exceeds Point C of the dose-effect curve is where PGE suddenly has an inflammatory mechanism of action.

We also see this type of intense temperature change physiologically in the menstrual cycle. They are accompanied by other sudden changes, for example, ovulation (13). Exceeding beyond Point C is a very abrupt process. Haematomas and fractures also evoke an intense inflammatory process with pain (21). Prostaglandin E is intensely involved in that (22,23,24). The concentration of PGE in these situations easily exceed 100ng/ml.

Figure 8. Feedback loop.

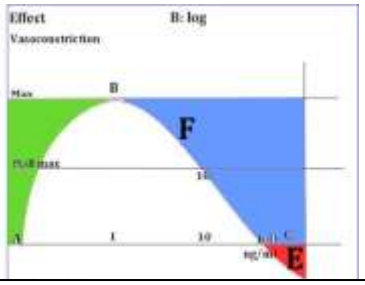


Fig.8. Concentration PGF<concentration PGE. Result: Effect PGF>Effect PGE. PGF and PGE both vasodilatative. Resulting in: vasodilation +++.

The effect of PGF intensifies every time Point C is exceeded, a feedback loop exists because of intensified vasodilatation. Attempts to suppress this process with vasoconstriction fail because the PGE it generates suddenly has a vasodilative effect. Only increased concentration of PGF will work provided the concentration of PGF is greater than 1 ng/ml. If the concentration of PGF is less than 1 ng/ml, then the vasodilatation increases through vasoconstrictive as well as vasodilatative influence. The process is "continuing out or control", which is the situation that seems to occur with CRPS. This does not occur with inflammation that accompanies haematomas, fractures and

infections. If the concentration of PGE is less than 100 ng/ml, the inflammatory effect has to be caused by PGF. Nevertheless, PGF is usually not related to inflammatory processes. However, it is theoretically possible if the concentration of PGF is much smaller than that of PGE. More probable is, however, that this concentration of PGE is greater than 100 ng/ml and the concentration of PGF lies somewhere between 10 and 100 ng/ml. PGE does cause vasodilatation, but it merely intensifies PGF mildly because that only has a slight effect. Presumably, spontaneous recovery usually takes place in these cases. The inflammatory symptoms often disappear without leaving a detectable trace behind. Nevertheless, abnormalities including pain, cold spots (found with infrared thermography), allodynia, cutaneous resistance changes and geloses can be found. Baumann and Ueckert found 65% cold spots and 11% warm spots with pain (9). Apparently this is a rather fixed relation and was later confirmed with infrared thermography (25, 26).

Recovery after PGE exceeds Point C

If the concentration of PGE decreases again after some time, then Point C will be exceeded once again. The presence of PGE then becomes vasoconstrictive (See Figure 9).

Figure 9. Warm chronic pain

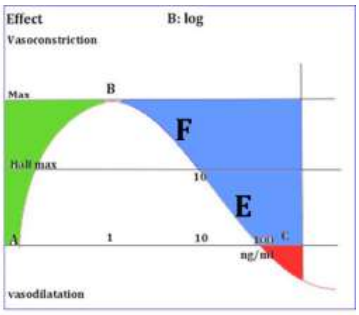


Fig.9. Concentration PGF<concentration PGE. Result: Effect PGF>Effect PGE. PGF :vasodilatative and PGE vasoconstrictive. Resulting in: vasodilation ++.

The result is then continuously vasodilative, but also actively inflammatory. In the case of CRPS the same pro-inflammatory cytokines are still found as in the most active phase.
If with CRPS Point F is ever exceeded by Point E, that would then result in a vasoconstrictive situation. After that result vasoconstriction would then regress into active inflammation (Figure 10).

Figure 10. Cold chronic pain

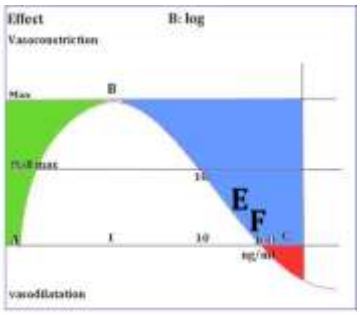


Fig.10. Concentration PGF>concentration PGE. Result: Effect PGF<Effect PGE. PGF :vasodilatative and PGE vasoconstrictive. Resulting in: vasoconstriction ++.

That is easily verifiable by testing the continued presence of pro-inflammatory cytokines: TNF-alpha, IL 1β, IL- 6. In addition, the area is vasoconstrictive. Infrared thermography reveals a cold area; in other words, colder than the immediate surrounding area or the other extremity. Clinically there is one situation demonstrated by CRPS (27,28) but ….. this situation has an analogon. The same cytokines are released by inflammation resulting from an infection, haematoma or fracture as by CRPS (5). Upon recovery, the concentration of prostaglandins shift from a concentration of PGE (cPGE) greater than the concentration of PGF (cPGF) to one of cPGE less than cPGF. This initially results in a vasodilatation with inflammation factors (hot spot) that converts to vasoconstriction (cold spot). There is absolutely no reason to assume that in the same situation with CRPS cytokines would remain, but in these hot and cold spots no cytokines would remain. Chronic pain could develop later if this situation remained unchanged. Chronic warm pain and chronic cold pain as was already measured in 1954 (9).

Intervention

Administration of a methylxanthine (PTX) reduces pain and converts the

vasoconstrictive area into a vasodilatative area as seen with infrared thermography (25). PTX, marketed as TRENTAL®, has a phosphodiesterase inhibiting action and it also blocks pro-inflammatory cytokines TNF-alpha IL-1β and IL-6, which also seem to occur in the cold spot with CRPS (29, 30). It is a prostaglandin agonist/antagonist. There are no known cytokine measurements of a chronic pain site.
As expected, the cold spots of chronic pain sites, just as a cold spot after acute CRPS, contain pro-inflammatory cytokines and TNF-alpha, IL-1β and IL-6.

Infrared thermography
Infrared thermography has proven to be a method that can detect cold and warm pain spots by chronic pain and CRPS in the acute and resting phase. The technique is used for specific tests for chronic pain, threatening CRPS and active CRPS. These tests are based on the fact that stimulation of the orthosympathetic component of the autonomic nervous system causes vasoconstriction in the skin. In a healthy situation it becomes colder. In principle the test is simple: when there is pain in the lower extremities the sympathetic nervous system gets stimulated by cooling off the upper extremity and vice versa.
A cold pain site becomes colder to varying degrees and a warm spot becomes less warm. When CRPS threatens to arise it is initially cold but becomes warm. An active CRPS gets warmer. Everything is compared with the healthy contralateral side. This can also explain the curve of H&M.

Cold Stress results.

Figure 11. Chronic cold pain becomes colder.

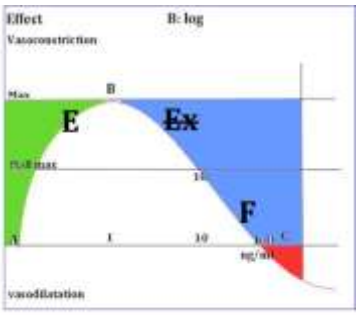


Fig.11. Concentration PGF>concentration PGE. Result: Effect PGF<Effect PGE. PGF :vasodilatative and PGE vasoconstrictive. Upregulation of PGE is leading to upregulation PGE-effect. Resulting in: vasoconstriction ++.

A cold scar remains after an inflammatory reaction. Vasoconstriction is possible, but inflammation factors are still present. Orthosympathetic stimulation causes more temperature reduction and hence vasoconstriction. Vasoconstriction is induced by prostaglandin E. There are two places (E and Ex) where PGE give the same effect. On the left leg and the right leg of the curve. The concentration of PGE has to be on the ascending leg because an increase of the concentration on the right leg induces a decrease of the vasoconstrictive effect, which in turn results in a temperature increase because of that reduced vasoconstriction. Ex is therefore not an option. F in the green area is not an option because that area has a very low concentration of PGs that chronic pain is not realistic. (In the cold phase, the IL-6 concentration lies on the diseased side between 10 and 800 pg/ml and on the healthy side at approximately 8 pg/ml (27). That corresponds fairly well with the estimate in Figure 11). It seems that chronic pain, which becomes colder with “cold stress”, can only exist in this situation.

The same situation as in Figure 11 occurs in Figure 12, but orthosympathetic stimulation causes temperature increase, hence less vasoconstriction.

Figure 12. Chronic cold pain becomes warmer.

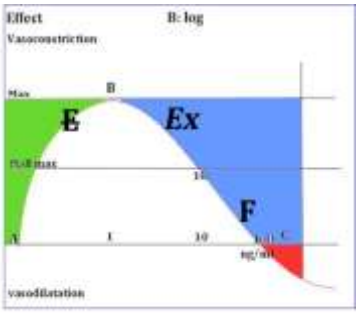
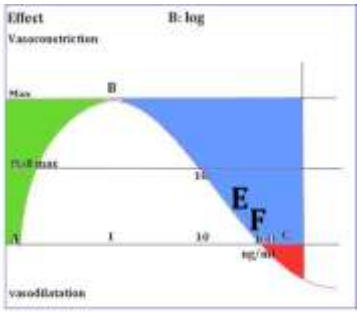


Fig.12. Concentration PGF>concentration PGE/PGEx. Result: Effect PGF<Effect PGE/PGEx. PGF :vasodilatative and PGE vasoconstrictive. Upgregulation PGE is leading to downregulation PGE-effect. Resulting in: upregulation PGF-effect and upregulation vasodilation.

Point E should lie on the right leg here: Point Ex. An increase of the concentration of prostaglandin E caused by sympathetic stimuli results in an effect reduction of the PGE and therefore a relative vasodilation and temperature increase. F cannot lie higher on the decreasing leg because there has to be a warm pain site already at the start.

Figure 13. Threatening CRPS



In the situation in Figure 13, cold stress has so much effect that the concentration of PGE exceeds Point C (fig.8). There is then an active vasodilatative situation with inflammation. E lies lower on the descending leg than in Figure 12. This situation is unstable, but it is still not CRPS. It can be considered to be threatening CRPS.

Figure 14. Chronic warm pain that becomes warmer.

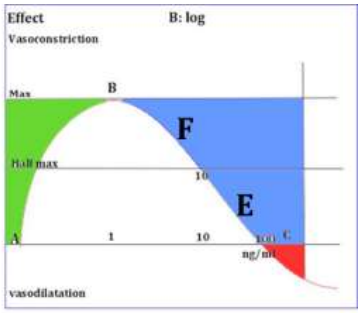


Figure 14 shows that orthosympathetic stimulation causes temperature increase. The concentration of PGF here has to be lower than that of PGE. Increasing vasoconstriction causes less effect of PGE, thus less vasoconstriction and more vasodilatation. In this situation the concentration of PGE does not exceed Point C. Therefore, it is thermographically warmer.

Figure 13 is a representation of threatening CRPS. Figure 14 is a representation of a very unstable situation which can be called CRPS.

Discussion

Origin of CRPS

Even though the aetiology of CRPS use to be considered a reflector condition caused by activity of the orthosympathetic nervous system (Autonomic reflex dystrophy), currently there is a different trend, namely, that CRPS falls under two immunological-oriented categories (5). CRPS-1 involves tissue damage and is therefore secondary to neural injury. CRPS-2 involves primary neural injury whereby tissue damage and inflammation are secondary. The consequence of the reported thesis is that these differences fall away.

Everything starts with tissue damage which does not have to be problematic and may be undetected for a long time. References about neural therapy address the Z*weitschlag* phenomenon (31). There has to have been an earlier injury either directly or reflectory in the segmental skin area. A

second injury reinforces the scar that is visible with infrared but not with the naked eye. An interference field develops. That can be a place with chronic pain or even with CRPS.

Neural therapy is a non-regulated treatment method with local anaesthesia, originating from around 1925, over which much was published in Germany mainly before the Second World War. This method does not contradict this thesis. Local anaesthetics are namely prostaglandin agonists and antagonists (7).
Autonomous sympathetic activity can also induce CRPS, as described in this thesis.

Methods of testing

H&M write at the end of their article: "*Popper has convincingly demonstrated that even a wrong idea leads inevitably to scientific advance if it stimulates people to look at old problems in a new way. Our ideas may well be wrong, certainly in detail, and probably even in broad outline. Nevertheless, we hope that they will stimulate new approaches*."
And that is exactly what this article wants to be and wants to endorse. However, a good thesis is no fantasy ride. In addition to a reliable foundation there have to be testing options – in accordance with Poppers.

Even though prostaglandins are difficult to test because each attempt changes the concentration, there are possibilities: results on their mechanism of action which are measurable with infrared thermography, for example (25). In addition, prostaglandins function as "buddies" together with effectors, which have a longer lifecycle and are easier to test.

Findings from the past can also help here. Prostaglandins are vasoactive substances. Each activity is accompanied by vasodilatation or vasoconstriction. Regardless of the processes taking place that lead to those in the skin, muscles, skeleton or viscera, the reflection of it can be found in its segmental zone up to the physiological level (32). That activity changes skin temperature and can be measured with infrared thermography with accuracy up to 0.1 °C. Niehoff wrote his doctoral thesis on this (33).

There are also contemporary publications that support this. They show that visceral processes can be followed via skin temperature. They show that pain roused in the viscera can be found not only through temperature change in in the segmental part of the skin, but that the pain in that segment is also generated, reflectory (34).

Cytokines such as Il-6 and TNF-α are found in significantly higher dosages in skin blister liquid in the acute phase of CRPS and in the "Thermographic Cold" resting situation. Groeneweg earned a doctoral degree investigating this (28). The technique for these skin blisters has been around a long time and is frequently used. (PubMed: "blister liquid" 1069 hits). The first publication in PubMed dates back to 1915 (35). Suction blister technique was found in 1967 in PubMed (36). Huygen et al. used a modern technique to test cytokines (37).

Therapy methods

One patient was successfully treated at Erasmus University in Rotterdam with a TNF-alpha inhibitor because of the presence of cytokines and special TNF-alpha (38). The cost of it makes further investigation with it difficult. Another, cheaper TNF-alpha inhibitor has been around since 1986: TRENTAL®, generic: Pentoxifylline. A successful study with chronic pain patients was conducted with it in 1989 (25).

Final conclusion

H&M were the first in history to describe the human measurement and regulation system. Only an automatic regulation system with feedback and a feedback loop can have the property of "out of control". CRPS looks to be the feedback phase of the regulation system that has become "out or control". Chronic pain is a precursor to that and is the one "in control".

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