Hypothosis

Effect of pregnancy and obstructive jaundice on inflammatory diseases: the work of P S Hench revisited

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Hench considered that cortisone improved inflammatory joint symptoms during pregnancy and obstructive jaundice. However, the improved symptoms are probably due to changes in the proportions of fatty acids in plasma and inflammatory cell phospholipids. These changes decrease the superoxide anions and eicosanoids produced and also reduce tumour necrosis factor α production.

OBSERVATIONS OF P S HENCH

In 1950 the Nobel Prize in physiology or medicine was awarded to Kendall, Hench, and Reichstein. Kendall and Hench were colleagues from the Mayo clinic in Rochester, USA, and Reichstein was from Basle, Switzerland. The award was for the introduction of corticosteroids in the treatment of rheumatoid arthritis. Kendall and Reichstein were chemists and their contribution was the isolation of corticosteroids, elucidation of their chemical structure and, finally, the development of semisynthetic methods for the production of isomers capable of prolonging the life of adrenalectomised animals. Hench was responsible for the use of cortisone, then known as compound E, for the treatment of chronic rheumatoid arthritis. The reason why Hench decided to try cortisone is not entirely clear but depended upon his interpretation of his previous observations of the circumstances in which rheumatoid arthritis improves.²

In his Heberden Oration of 1948, Hench described how impressed he was by the dramatic improvement in inflammatory joint symptoms that occurs in the majority of patients, although not all, during pregnancy or jaundice. He had come to the conclusion that the mechanism must be due to “a biologic compound specific in nature and function, a compound, which was normal to the human organism” and this he called “substance X”. In retrospect it is difficult to know why the improvement of rheumatoid arthritis during pregnancy and jaundice suggested to him that substance X might be a corticosteroid. He knew, of course, that bile acids, which are retained in obstructive jaundice, could be used as the starting material for synthesis of corticosteroids, but he had already tried the effect of bile salts on patients without success.³ He also knew, from Reichstein’s work, that a corticosteroid could be converted into a substance with the biological effect of the male sex hormone because the chemical structures of testosterone and corticosteroids are similar.² During pregnancy there is an enormous increase in circulating sex hormones and an increase in the size of the adrenal glands. He also knew that minor temporary remissions in rheumatoid arthritis could be induced by procedures capable of stimulating the adrenal glands, such as general anaesthesia or surgical operation. He recognised that rheumatoid arthritis is not the only condition improved by pregnancy and jaundice, he cites fibrositis, psoriasis, and asthma, and therefore might have postulated a connection between the adrenal function and inflammation.

“The result of steroid treatment in RA was dramatic”

Whatever the reason, the result of steroid treatment was dramatic and showed that rheumatoid arthritis is not the chronic untreatable condition it was thought to be until that time, but that at least the inflammatory component could be reversed. However it is now clear that corticosteroids are not the explanation for the effect of pregnancy and jaundice and cannot be substance X. During obstructive jaundice corticosteroids are not significantly increased. During pregnancy cortisol certainly increases progressively, but the concentrations achieved do not affect inflammatory cell function in vitro in the way that cell function is affected by pregnancy serum. Furthermore, blood levels fall rapidly after delivery returning to normal in two to three days, which does not coincide with the pattern of rheumatoid arthritis relapse.³

If factor X is not cortisone then what is it? There are some clues from the observations of Hench and others. It was in 1938 that Hench published his classic account of the amelioration of rheumatoid arthritis during pregnancy.³ This was not a new observation as there had been individual case reports since the end of the previous century but Hench was the first to publish a series, 37 pregnancies in 22 patients, and he made a number of important clinical observations. The improvement starts towards the end of the first or beginning of the second trimester and progresses until term before relapse within a few weeks of delivery. Approximately 70% of patients have a clear response, which is usually greater than can be achieved with (even modern) drug treatment and if the patient responds during her first pregnancy she is likely to respond again during subsequent pregnancies. Others have since repeatedly confirmed all of these observations.³ During the 1930s and 40s Hench also reported observations on the improvement of rheumatoid arthritis during jaundice.⁶ Like pregnancy the effect is temporary and disappears as the jaundice
clears. It requires quite intense jaundice either due to hepati-
tis or biliary obstruction but not haemolysis. Hench consid-
ered that jaundice and pregnancy shared a common mech-
anism, substance X, because the same women responded to
both pregnancy and jaundice. However, the effect of jaundice
was not confined to women and therefore it is unlikely to be
due to female sex hormones. Unfortunately, the observations
of Hench and others on the effect of jaundice have largely been
forgotten so that recent work has tended to concentrate on
pregnancy-specific factors. It is clearly necessary to look for a
factor which is common to both pregnancy and jaundice and
which is potent enough to produce dramatic improvement in
inflamed joints.

**LIPID CHANGES**

One thing that pregnancy and jaundice have in common is
their effect upon lipids. Both are associated with hyper-
cholesterolaemia and yet the arterial lesions associated with
raised cholesterol do not happen except in patients with very
chronic biliary obstruction. The reason may be a change in the
proportions of fatty acids in plasma phospholipids, with an
increase in monounsaturated oleic acid and a decrease in
polyunsaturated fatty acids, particularly arachidonic acid,
thus reducing the tendency of circulating lipids to oxidise. Because fatty acids exchange with phospholipids at two
dimensional surfaces it is their proportions in plasma which
matter and not absolute concentrations. This is also true for the
function of fatty acids in membranes as the total fatty acid
composition is generally unaltered and compositional changes
occur without changing total lipid pool. Some types of
inflammatory cells such as neutrophils and macrophages lack
the desaturase enzyme necessary for creating further double
bonds and the conversion of essential fatty acids such as lin-
oleic acid, into less saturated fatty acids such as arachidonic
acid. It is therefore not surprising that the proportions of fatty acids in the membranes of these inflammatory cells
closely reflect the proportions of fatty acids in plasma
phospholipids, although the exchange is probably through the
small free fatty acid plasma pool. This exchange is rapid so
that changes in plasma fatty acids are quickly reflected in
membrane phospholipids, certainly within a matter of hours. In both jaundice and pregnancy, particularly in the
third trimester, there are large changes in the proportions of
fatty acids in plasma, neutrophil, and mononuclear phospholi-
pids. These changes are much larger than can be achieved by
dietary manipulation. For example, during the third trimester
of pregnancy the proportion of arachidonic acid in both
plasma and neutrophil phospholipids is 30% less than in non-
pregnant women. Obstructive jaundice the changes are
even greater with a reduction of between 40% and 50%. There
is no doubt that such changes will have a profound effect upon cell function in a number of different ways.

**FATTY ACIDS AND INFLAMMATION**

Arachidonic acid is the precursor of inflammatory eicos-
oids, including prostaglandins and leucotrienes. The rate
limiting step in the cascade that produces these eicosanoids
is the release of arachidonic acid from the syn 2 position
of phospholipids by phospholipase A1. A reduction in the
proportion of phospholipid arachidonic acid means a reduc-
tion in substrate and should predict less free arachidonic acid
when inflammatory cells are activated, with consequently less
eicosanoid production. This prediction has been confirmed for
neutrophils from patients both during jaundice and during
the third trimester of pregnancy. Women who are pregnant,
compared with those who are not, show a significant
reduction in arachidonic acid release from pregnancy neu-
trophils after stimulation with a physiological agonist (formyl
peptide, fMLP) whether or not the cells were first primed by
incubation with the cytokines, tumour necrosis factor α or
interleukin 8. Similarly, there is a reduction in release of
leucotriene B4, the major eicosanoid produced by neutrophils.
Leucotriene B4 is an extremely potent chemotactic factor
important in inflammation. Exactly the same results were
obtained with neutrophils from jaundiced patients compared
with cells obtained after correction of their jaundice.

One of the major functions of neutrophils is the production
of superoxide radicals which are then converted into other
oxygen species and play a part not only in killing of micro-
organisms but also in damage of surrounding tissues during
uncontrolled inflammation. There is certainly an enormous
traffic of neutrophils through rheumatoid joints, and in
the synovial fluid the cells are activated to release oxygen radicals
so there is little doubt that they contribute to the
inflammation. Again during both pregnancy and jaundice the
generation of superoxide radicals from activated neu-

*During both pregnancy and jaundice the generation of superoxide radicals from activated neutrophils is significantly depressed*

There is another and perhaps more important way in which
a shift in fatty acids can affect not only enzymes such as
NADPH oxidase, which is assembled within the cell mem-
brane, but also signalling mechanisms which control cell
function. This is the inevitable change in membrane fluidity
that accompanies changes in the length and degree of satu-
ration of phospholipid fatty acids. A reduction in the propor-
tion of polyunsaturated and an increase in monoun-
saturated fatty acids will reduce cell membrane fluidity and
have potentially profound effects on cell function. It should be
noted that the increase in plasma cholesterol during
pregnancy is not accompanied by an increase in neutrophil
membrane cholesterol, which would also affect membrane
fluidity (unpublished observations).

Longitudinal studies throughout pregnancy and the puer-
perium have shown that a reduction in the release of arachi-
donic acid and eicosanoids and reduced generation of
superoxide anions are all detectable towards the end of the
first trimester, then increase progressively during the remain-
der of pregnancy, and are largely reversed within six weeks of
delivery. In other words the time course of these changes is
the same as the pattern of improvement and relapse of rheu-
matoid arthritis during pregnancy.

It has been known for many years that plasma from women
in the last trimester of pregnancy can affect inflammatory cell
function and, indeed, this is one of the observations that argue
against cortisone being responsible for the suppression of joint
inflammation during pregnancy. For example, after only four
hours’ incubation of normal neutrophils in pregnancy plasma,
arachidonic acid, leucotriene B4, and superoxide anion release
are all reduced to the levels expected from pregnancy
neutrophils. At the same time the proportions of fatty acids
in cell membrane phospholipids shift dramatically so that
they mimic the fatty acid content of pregnancy neutrophils.

Exactly the same results are obtained when normal neu-
trophils are incubated in plasma from jaundiced patients.
Furthermore, similar changes in cell function can be produced
when normal neutrophil cell membrane fatty acids are
exchanged by incubation in solutions of pure fatty acids as
long as the fatty acids are presented in conditions which allow
exchange with membrane lipid fatty acids—that is, linked to
albumin, as otherwise some fatty acids such as arachidonic
acid will directly stimulate neutrophils. These are powerful
arguments linking changes in phospholipid fatty acids with changes in inflammatory cell function that may well underlie the improvement in joint inflammation during both pregnancy and jaundice.

"Powerful arguments link changes in phospholipid fatty acids with changes in inflammation"

Possibly, when patients with rheumatoid arthritis become pregnant their cells do not respond in the same way as those from patients without an inflammatory condition. In fact, although the circulating population of neutrophils in patients with rheumatoid arthritis differs from normal, the effect of pregnancy is quantitatively the same as in normal pregnant controls so that the arguments, which can be applied to normal pregnancy, certainly apply when patients with rheumatoid arthritis are pregnant.34

THE TH1/TH2 PARADIGM

While neutrophils are important in contributing to the joint inflammation and damage of rheumatoid arthritis, present thinking about rheumatoid arthritis is that it is a Th1 driven disease connected to the production of Th1 associated cytokines, including tumour necrosis factor α and interferon γ.35 Indeed immunotherapy with humanised tumour necrosis factor antibodies has been successfully used to produce temporary remissions reminiscent of those which occur in jaundice and pregnancy.28 A reduction in the proportions of polyunsaturated fatty acids affecting the availability of arachidonic acid, membrane fluidity, or both, will not only affect neutrophils but also other cells involved in inflammation—certainly macrophages and, possibly, lymphocytes.36 There is evidence that macrophage function is altered, at least during pregnancy, as when mixed mononuclear cells from the third trimester are stimulated with lipopolysaccharide, tumour necrosis factor α production is significantly reduced.49 This observation is in keeping with the already reported influence on cytokine production when macrophage cell membrane fatty acids are manipulated in vitro.28 It is also in keeping with the known reduction in circulating tumour necrosis factor α during pregnancy.37

To return to the work of Hench, reported more than 50 years ago, it is now possible to explain the striking similarity between the effects of pregnancy and jaundice on rheumatoid arthritis.3 Both cause changes in the proportions of fatty acids in plasma and inflammatory cell membrane phospholipids associated with a reduction in inflammatory cell responses to activation. It is this change, particularly the shift away from polyunsaturated fatty acids, which is "factor X" and not the single "biologic compound, specific in nature and function" as originally envisaged, and certainly not cortisone. Figure 1 summarises this. In his Heberden Oration in 1948, Hench listed a number of conditions that he suggested may improve during pregnancy or jaundice.3 One of these is psoriasis with or without arthritis, a disease in which activated neutrophils are now known to play an important part and therefore might be expected to respond.30 Others such as asthma, hay fever, and migraine are more contentious. Pregnancy is now thought to cause a shift away from a Th1 towards a Th2-type of immune response that may well be important in allowing tolerance of the antigenically foreign fetus, at least during the second and third trimesters.31 Of course the mechanism underlying the shift from Th1 to Th2 is not understood. Certainly Th1 driven diseases improve during pregnancy, particularly rheumatoid arthritis but also Crohn’s disease and multiple sclerosis.32 33 All these conditions are associated with higher than normal levels of circulating tumour necrosis factor α which is known to be reduced during pregnancy and may be explained by changes in membrane phospholipid fatty acid saturation. Whether Crohn’s disease and multiple sclerosis also improve during jaundice is not known.

FATTY ACID METABOLISM

The partial success of γ-linolenic acid supplements (evening primrose oil) for the treatment of rheumatoid arthritis appears to confirm the importance of arachidonic acid metabolism. The mechanism involves elongation of γ-linolenic acid to dihomo-γ-linolenic acid by neutrophils, but then dihomo-γ-linolenic acid cannot be converted to arachidonic acid because the cells lack the 5-desaturase enzyme. As a result dihomo-γ-linolenic acid accumulates in the cell membrane where it competes for phospholipase A₂, so reducing available arachidonic acid and leucotriene B₄.36

The changes in membrane fatty acids in pregnancy and jaundice are much larger than can be produced by diet, but the modest changes resulting from increased intake of fish oils containing n-3 fatty acids aimed at reducing arachidonic acid and eicosanoid production do improve joint symptoms.33 The other situation in which fish oils or olive oil may be beneficial is in the prevention of ischaemic vascular disease. Atherosclerosis is an inflammatory disease caused by uptake of oxidised low density lipoprotein cholesterol by macrophages in vessel walls.37 A reduction in polyunsaturated fatty acids and substitution by monounsaturated acids would reduce the susceptibility of low density lipoprotein cholesterol to oxidative stress and at the same time reduce the production of inflammatory mediators by macrophages. All this emphasises the need to understand the mechanisms and manipulate them.

The first rate-limiting step in production of arachidonic acid (20:4, n-6) is the desaturation of linoleic acid (18:2, n-6) by a δ-6 desaturase.28 This enzyme is missing from neutrophils and monocytes so that arachidonic acid in their lipid membranes depends upon uptake from plasma of arachidonic acid synthesised in the liver.39 The implication is that the

![Figure 1](http://www.annrheumdis.com) Fatty acid hypothesis.
proportions of polyunsaturated fatty acids in plasma and inflammatory cell membranes depend upon hepatic desaturases. Both δ-6 and δ-5 desaturases have been cloned, their manipulation may become made to develop drug treatment to inhibit the hepatic desaturase, responsible for conversion of stearic (18:0, n-9) to oleic acid (18:1, n-9) is stimulated. Consequently, it seems likely that the changes in fatty acids during pregnancy relate to the enormous hormonal changes taking place. The mechanism in jaundice is uncertain but bile salts are the most likely candidates as, despite Hench's failure to show an effect when these were given either orally or intravenously, chenodeoxycholic acid has been shown to improve joint symptoms in rheumatoid arthritis. Whether bile salts affect desaturation activity is not known. Attempts have already been made to develop drug treatment to inhibit the hepatic δ-6 desaturase, and now that both the human δ-6 and δ-5 desaturases have been cloned, their manipulation may become possible.

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