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Aug. 6, 1986

Mr. Perry Chapdelaine
The Rheumatoid Disease Foundation
Franklin TN.

Dear Perry:

I write to you about a failure of antiamebic treatment in RA. The patient is Mrs. Rosi Miller of 405 Gull Court, North Palm Beach FL 33408. In time we will get the name of her doctor. She has had three courses of metronidazole and allupurinol. The dosage was right. The first two was of six weeks and the last one of twelve weeks. She has been helped but she still has much pain and she has had a great lot of steroids in the past.

She did not get lacto-bacillus and she did not get intraneural injections and it could be that with intraneural injection she would be free from pain. By this letter I am giving her Dr. Gus Prosch's address.

I have some ideas for everyone to consider. I have managed to get an Australian RA patient feeling well. In his country the doctors are in a straight jacket. All the doctors work for the government and a head doctor in the capitol tells them what they can and cannot do. What they cannot do is to give metronidazole and intraneural injections for RA. This fellow spent a fortune calling me by phone. I told him to stop spending money on the phone and to come see Dr. Prosch. He said that first I should guess what he should do.

So I took a big guess and told him to stop eating white potatoes and all wheat products. Things he told me made me suspect gluten intolerance. I told him to avoid meat. I had him take eight evening primrose oil caps a day and I sent to him 1000 of Vitamin Specialties Co. copper aminoacid pills that contain 2 mg. of copper each. He took four a day and that was it. End of problem.

Enclosed is page 323 from Medical Hypothese for Aug 1985. This shows the arachidonic acid cascade. Also enclosed is pages 829 and 830 from The Lancet for Oct. 8, 1985.

The arachidonic acid cascade is very much involved both in pain and in the inflammatory process. The enzyme cyclo-oxygenase converts arachidonic acid, which we get out of meat, to 2 series prostaglandins. Some of these prostaglandins of the F2 series cause pain. Aspirin and the NAIDs inhibit cyclo-oxygenase and they thereby reduce pain by preventing arachidonic acid from being converted to F2 prostaglandins.

The inflammatory process, however is mediated by leukotrienes that are produced from arachidonic acid by the enzyme lipoxygenase. Here we see orthodox treatment of RA working at cross purposes. Give a RA patient aspirin to help the pain and with the cyclo-oxygenase pathway closed down more arachidonic acid goes into the lipoxygenase pathway to make the inflammatory process worse.

Enclosed are copies from The Lancet for July 20, 1985, and July 19, 1986. In the first of these reports we see the

suggestion that aspirin in Reye's Syndrome may cause the fatal inflammatory reaction by inhibiting the cyclo-oxygenase pathway and hence causing lipoxigenase to convert more arachidonic acid into inflammatory leukotrienes. In the second of the above reports, we see the suggestion that inflammatory brain odema can be treated with an inhibitor of lipoxigenase.

Dr. David Horrobin of Efamol Research Institute has reported that a metabolite of gamma linolenic acid in evening primrose oil is an inhibitor of lipoxigenase.

The name nonsteroid anti-inflammatory drugs may be misnomer. They seem to inhibit the pain producing prostaglandins of the F2 series but at the same time by throwing more arachidonic acid into the lipoxigenase pathway, they seem to be pro-inflammatory rather than anti-inflammatory.

What we get from this is that at least much pain is caused by prostaglandins derived from arachidonic acid via cyclo-oxygenase. It follows that people who eat no meat and thus who limit arachidonic acid may suffer less pain. It also follows that the limitation of arachidonic acid by avoiding meat may limit the inflammatory mediators made from arachidonic acid by lipoxigenase. Aside from the limitation of arachidonic acid intake by eating no meat, it would be well to inhibit lipoxigenase by taking evening primrose oil caps.

Also enclosed is copy from The Lancet for Nov. 20 1981. This report from The Royal Hospital for Rheumatic Diseases in Bath England deals with the harm of iron. It is now well established that our immune cells that foster the inflammatory reaction are attracted by iron. Here it is felt that first iron is deposited in synovial tissue. Then inflammatory immunocytes, attracted by iron rush in giving off leukotrienes that damage synovial tissue. They report that as women enter the menopause, existing rheumatoid disease gets worse and that iron deficient natives in third world nations suffer from less rheumatoid disease.

When I suggested to my Australian friend that he avoid both meat and bread he thereby avoided much iron as meat is rich in iron and all bread has iron added.

For the RA patients not cured by anti-amoebic treatment, I suggest that meat, bread, and iron in general be avoided, and that copper pills and evening primrose pills be taken. Also it may be productive that aspirin and NAIDs be avoided.

BEST:

Wayne

THE LANCET

Inflammatory Mediators of Asthma

UNTIL 1970 the only inflammatory mediators thought to play a role in asthma were histamine and slow-reacting substance of anaphylaxis (SRS-A). The identification of reaginic antibody as IgE,¹ and the realisation that in-vitro immunological challenge of lung tissue or purified mast cells released, non-cytotoxically, an array of inflammatory mediators, led to an explosion of interest in the mechanisms of asthma. Since then, in-vitro and in-vivo studies have identified at least fifty potential inflammatory mediators of asthma. Much of our initial understanding of the mechanisms of immunological release of inflammatory mediators has been derived from work on purified rat peritoneal mast cells.² Lately, however, research has concentrated on inflammatory mediators released from human lung cell fragments and purified human lung mast cells, macrophages, monocytes, and circulating basophils.

Inflammatory mediators released by immunological challenge can be classified as preformed (present in cytoplasmic granules ready for release) or newly generated (manufactured secondary to the initial triggering stimulus, after release of preformed mediators). Newly generated mediators may be manufactured within the stimulated cell itself or in an alternative cell source consequent upon primary mediator release. Preformed inflammatory mediators associated with human lung mast cells include amines (histamine), exoglycosidases (arylsulphatase B, β -hexosaminidase, β -glucuronidase, and β -galactosidase), neutral proteases (trypsin, carboxypeptidase B), chemotactic factors for eosinophils and neutrophils, other enzymes such as superoxide dismutase, and the basic proteoglycan, heparin.³ Many newly generated inflammatory mediators are derived from arachidonic acid, either via the cyclo-oxygenase pathway (prostaglandins, PGs; and thromboxanes,

TXs), or via the lipoxygenase pathway (monohydroxyeicosatetraenoic acids, HETEs; and leukotrienes, LTs). In addition there are other newly generated mediators such as prostaglandin-generating factor of anaphylaxis and platelet activating factor, PAF-acether, whose metabolic derivation is not yet known. One of the outstanding achievements of recent research has been the identification of SRS-A as the lipoxygenase products of arachidonic acid metabolism—LTC₄, LTD₄, and LTE₄.⁴

This list of putative mediators of asthma is both daunting and fascinating to the ordinary clinician, who must try to relate the latest biochemistry to the disease as seen in practice. In 1881 Koch formulated his famous postulates to test whether some new microbiological discovery was or was not the cause of a given clinical disease. Perhaps we should apply some modified Koch's postulates for putative asthma mediators.

1. The mediator should reproduce some of the pathophysiological features of asthma when administered to man.
2. The mediator should be identified in body fluids during an episode of clinical asthma.
3. Pharmacological antagonism of the given putative mediator should ameliorate or modify the disease process.

Taking postulate no 1, it has been possible to base the complete pathological picture of asthma as we know it on the current list of putative mediators. The main features of asthma seen clinically are bronchospasm, mucosal oedema, cellular infiltration of the mucosa and desquamation of cells, mucus production, and long-term basement membrane thickening with muscle hypertrophy.^{5,6} All these features can be produced artificially by the mediators named above.³ To take a few examples, histamine, LT C₄, D₄, and E₄, PGD₂, PGF₂ α , and thromboxane A₂ are all capable of contracting bronchial smooth muscle with differential effects on central and peripheral airways. Infiltration by eosinophils and neutrophils can be accounted for by the appropriate chemotactic factors, the HETEs, and another leukotriene, LTB₄. Histamine, PGE₂, LTC₄, LTD₄, and LTE₄ all increase capillary permeability and hence produce mucosal oedema due to leakage of serum proteins. Mucus secretion can be induced readily by LTC₄, D₄, and E₄, PGF₂ α , PGD₂, PGI₂, PGA₂, TXA₂, prostaglandin-generating factor of anaphylaxis, and histamine. Granule-matrix-derived proteolytic enzymes may contribute to the desquamation of the surface epithelium by weakening intracellular bonds. Thus there is no problem in

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demonstrating that the putative mediators may produce the pathophysiological features of asthma.

What about the demonstration of mediators in body fluid? Here there are considerable difficulties, and it is one of the most disappointing features of present research that so few of the mediators have been demonstrated in relation to the disease, either occurring naturally or induced by exercise or inhalation challenge. Changes in plasma histamine have been identified in acute asthma⁷ and in both antigen and exercise induced asthma, although contradictory reports exist.⁸ In the case of antigen-induced asthma this may partly be explained by patient selection with respect to their non-specific airway hyperreactivity.⁹ With antigen inhalation, both mediator release, presumably of mast cell origin, and airway hyperreactivity are important determinants of the airway response.¹⁰ The balance between these two variables may determine whether change in peripheral blood histamine is detectable in association with bronchoconstriction. The inability to find plasma histamine change does not imply absence of mediator release, but serves only to illustrate the difficulties in relating peripheral blood mediator levels to intrapulmonary events. Also compounding the problem with histamine is the finding that a significant component of plasma histamine is basophil-derived, so changes in basophil numbers which occur with exercise challenge make interpretation of changes in plasma histamine difficult.^{11,12} As yet there are no published reports of changes in leukotrienes in the blood during asthma, although degradation products of LTB₄ have been found in the sputum during acute disease.¹³ The 13, 14-dihydro, 15-keto metabolite of PGF₂α has been shown to rise in peripheral blood in association with antigen¹⁴ but not exercise induced asthma.¹⁵ A possible complicating factor in this instance is that platelets are also a source of prostaglandin production. The most promising mediator so far is neutrophil chemotactic factor.¹⁶ This has been demonstrated in exercise-induced asthma, and its levels seem to follow both the immediate and late

increase in airway resistance following antigen inhalation. This neutrophil chemotactic factor is of high molecular weight and is released in parallel with histamine in cold urticaria and antigen-induced asthma, suggesting a mast cell origin. None of the other mediators has been reported in the blood of patients with asthma. It would probably be more fruitful to look for the mediators in the lung substance itself, or in draining pulmonary venous blood, but the technical problems are formidable and there is no good animal model of human asthma.

Regarding the question of specific antagonists for the various putative mediators, the story is similarly disappointing. We have good antihistamines, but their effect in asthma is paltry compared with that of other anti-asthma compounds such as the beta agonists. There are many good antagonists of the cyclo-oxygenase pathway of arachidonic metabolism, which should switch off prostaglandin production, but their effect in asthma has also been disappointing. Preliminary trials with anti SRS-A compounds have been unremarkable,¹⁷ although we are awaiting more precise inhibitors of the lipoxygenase pathway of arachidonic metabolism.

Should the failure of so many putative mediators to fulfil the second and third parts of our modified Koch's postulates mean that such mediators are unimportant? Clearly, since many of the mediators duplicate each others' function, antagonism of one mediator may have little effect on the disease process. Indeed antagonism of the cyclo-oxygenase pathway of arachidonic metabolism (for example by aspirin) may exacerbate asthma.¹⁸ This is thought to be due to increased availability of substrate for lipoxygenase metabolism and hence increased leukotriene production. Since leukotrienes C₄ and D₄ are 500 times more potent than PGF₂α this paradoxical response is understandable. One might compare the production of asthma by the cooperation of perhaps hundreds of pharmacological mediators with the performance of a Brahms symphony by a full symphony orchestra. The removal of the second bassoon makes little difference to the average listener's ears, and even the conductor can be disposed of without noticeable effect (if the orchestra is well trained). According to this analogy it may be inappropriate to apply Koch's postulates strictly to a complex disease such as asthma.

In summary, research on asthma mediation has leapt forward in one particular area—namely, the discovery of mediators either preformed in mast cells or synthesised after the activation of mast cells. Many of these mediators have yet to be proved to play a part in human asthma, and their origin, whether from mast cells or from other cells, is also often obscure.

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Hypothesis

THE IMPORTANCE OF IRON IN RHEUMATOID DISEASE

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Summary The hypothesis is that iron, which accumulates in rheumatoid synovial membrane and fluid contributes to the variable expression of rheumatoid disease in two ways. Firstly, it catalyses oxidative radical reactions which lead to the formation of the hydroxyl radical and subsequent lipid peroxidation. Hydroxyl radicals and lipid peroxidation cause extensive disruption of cellular and organelle membranes and promote inflammatory tissue damage. Secondly, the infiltration of the rheumatoid synovium by chronic inflammatory cells may be due not to an antigenic process but to the tendency for these cells, which have receptors for iron-binding proteins, to migrate towards deposits of iron.

INTRODUCTION

SIGNIFICANT quantities of iron occur in the rheumatoid synovial membrane and fifteen years ago the question was raised as to whether these deposits may influence the course of rheumatoid disease.¹ In this paper we attempt to rekindle this debate by suggesting two potential mechanisms by which iron deposits may do so.

IRON AND RHEUMATOID DISEASE—THE FACTS

The basic disturbances in iron metabolism resulting from the development of rheumatoid disease are well known. The rapid fall in serum iron at the onset of inflammation is followed by a drop in haemoglobin concentration. The haemoglobin concentration in patients with established rheumatoid disease is 9–12 g/l, which indicates a redistribution of 500–850 mg of iron.² This iron can be found not only in the usual storage sites (liver, spleen, bone marrow) but also in the rheumatoid synovial membrane¹ and lymph nodes.³ The drop in serum iron correlates closely with the activity of the inflammatory process⁴ and can be reversed

by corticosteroids—the rise preceding improvement in other indices of disease activity.⁵ Since corticosteroids stimulate erythropoiesis,⁶ the rise in serum iron may be mediated by release of iron from reticuloendothelial cells.

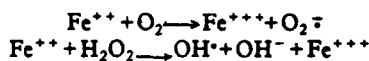
Free iron is extremely toxic to living cells and so cannot be stored as such.⁷ A major intracellular site of storage of iron is the protein apoferritin which, when it stores iron in its hollow centre, becomes ferritin. Each apoferritin molecule can store up to 4500 atoms of iron, but it is normally much undersaturated.⁸ The stimulation of apoferritin production at the onset of inflammation forms part of the acute-phase response.⁹

Iron is present in the rheumatoid synovial membrane mainly in the form of ferritin, which is concentrated within the cytoplasm and lysosomes of the type A reticuloendothelial cells.¹ Both free iron and ferritin also occur in rheumatoid synovial fluid,^{10,11} where the concentration of ferritin correlates closely with levels of other indices of intra-articular disease activity, such as the polymorphonuclear leucocyte count and putative immune complexes.¹¹ Iron levels within the synovial membrane do not correlate closely with the duration of disease, perhaps because the iron there originates at least partly from traumatic microbleeding, but it does correlate with the presence of erosive bone damage.¹² In early rheumatoid disease the presence of ferritin and haemosiderin iron (the degradation product of ferritin) in the synovial membrane implies a poor prognosis.¹³

Despite the striking temporal association between changes in serum iron and the development and remission of rheumatoid inflammation a direct causal relation is difficult to substantiate. However, recent developments in our understanding of free-radical chemistry and lymphocyte migration may provide explanations for a direct relation.

IRON AND THE INFLAMMATORY RESPONSE: SPECULATION CONCERNING RADICALS

Iron is an important redox intermediate with ready access to two oxidation states, the divalent Fe^{++} and the trivalent Fe^{+++} form. The rapid interchange between these two states allows iron to act as an electron donor and acceptor, which gives it important catalytic properties. However, the reduction of oxygen tends to be a univalent process. When oxygen reacts with ferrous iron, a species with an unpaired electron is formed. This is referred to as the superoxide anion radical (O_2^-). The superoxide radical and hydrogen peroxide are released during phagocytosis by polymorphonuclear leucocytes and macrophages.¹⁴ In the presence of traces of free iron salts, superoxide and hydrogen peroxide can react together to produce the hydroxyl radical (OH^\cdot).¹⁵ The reactions concerned are as follows:



The overall reaction is:



The Fe^{++} required for this reaction is thought to be derived from the more stable Fe^{+++} form by a reductive process that requires superoxide.¹⁵ The hydroxyl radical (OH^\cdot) is the most toxic of the univalent reduction products derived from oxygen; it is able to attack or destroy cell membranes, DNA, and most other cell constituents.¹⁶ Since it will react with any molecule in its immediate surroundings, its very reactivity limits its biological lifetime. In-vitro studies have also shown that hydroxyl radical produced in the presence of iron

DR BAKER AND OTHERS: REFERENCES—continued

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degrades the hyaluronic acid that is responsible for the lubricating properties of normal synovial fluid.¹⁷ However, since O_2^- and H_2O_2 do not react with each other except in the presence of free iron, the variability in toxicity of O_2^- and H_2O_2 may depend on the amount of free catalytic iron available.^{10,18}

Free catalytic iron is present in rheumatoid synovial fluid,¹⁰ along with large numbers of active polymorphonuclear leucocytes. Free radical oxidation products (degradation products from lipid) also occur in synovial fluid.^{19,20} However, superoxide dismutase and catalase, enzymes that scavenge the superoxide anion and hydrogen peroxide, respectively, are absent from the synovial fluid cell-free supernatant.²¹

Iron exists in a free state in the reticuloendothelial cell before binding to apoferritin occurs. The incorporation of iron into apoferritin must involve the oxidation of Fe^{++} since ferritin iron is stored in a stable Fe^{+++} form, and it is thought that this iron oxidation and deposition as ferritin involves activation of molecular oxygen.²²

Ferritin is concentrated mainly in the lysosomes of the reticuloendothelial synovial cells.¹ The lysosomal membrane contains large amounts of polyunsaturated fatty acids which can undergo lipid peroxidation. Lipid peroxidation is an autocatalytic degradation process induced by free radicals,²³⁻²⁸ in this process the subsequent generation of organic oxygen radicals is followed by the formation of lipid peroxides,²⁹ which can further fragment to produce gaseous hydrocarbons and reactive aldehydes, which may damage structural membranes and enzymes.^{30,31} Disruption of lysosomal membranes by lipid peroxidation will release hydrolytic enzymes and potentiate inflammation.²⁷ Free iron will invariably stimulate lipid peroxidation,^{7,24,32} though iron complexed to protein has a variable effect.^{33,34} We have found that apoferritin, without iron, does not affect the rate of lipid peroxidation, but saturated ferritin is stimulatory.¹³ A similar response has been observed with another iron-protein complex lactoferrin; apolactoferrin (the protein) will inhibit hydroxyl radical formation and lipid peroxidation, but when saturated it will promote these reactions.³³

SPECULATION CONCERNING LYMPHOCYTES

The rheumatoid synovium is characterised by an infiltrate of inflammatory cells, mainly lymphocytes and macrophages, and a proliferation of lining synovial cells. Muirden has shown that synovial cell proliferation is independent of the lymphocyte infiltrate, and that in patients with established disease (>8 months) a heavy lymphocyte infiltrate is associated with "less" damage to surrounding bone and cartilage.³⁵ The precise mechanism by which these cells migrate to the inflammatory sites is not established, though our basic concept centres around the role of immunological surveillance and elimination of foreign or altered self elements.

An alternative mechanism by which such cells might migrate to the site of inflammation has been proposed, since iron binding proteins have been found either within or on the cell surface of certain lymphocytes and macrophages.³⁶ The latter have receptors for lactoferrin and synthesise ferritin.^{37,38} Activated T and B cells have transferrin receptors,³⁹ whilst T cells contain transferrin,⁴⁰ and in patients with Hodgkin's disease T lymphocytes have been shown to have ferritin on their surface.⁴¹ The significance of these iron binding proteins and iron-protein receptors is not established, but there has been a suggestion that iron may

influence lymphoid cell traffic.³⁶ Certainly, in both rats and man, lymphocyte circulation in the gut runs parallel with iron absorption, being highest in the jejunum and duodenum and lowest in the ileum; in iron deficiency this pattern is lost.³⁶ Our histological studies of the early rheumatoid synovial membrane—the close correlation between the number of lymphocytes and the amount of ferritin plus haemosiderin Fe^{+++} , and the paucity of lymphocytes in the absence of ferric iron—support the hypothesis that lymphoid cells migrate not towards an antigen but towards reticuloendothelial iron deposits.

FACT OR FANTASY

The suggestion that both acute and chronic phases of the inflammatory process are mediated through an element as ubiquitous as iron may seem naive. However, the hypothesis is attractive because it can be tested by observing the effect of iron depletion on animal models of acute and chronic inflammation and can be supported by teleological argument.

The fall in serum iron and the redistribution of iron in stimulated reticuloendothelial cells both deprives potential pathogens of an essential nutrient (iron is essential for many microorganisms) and may stimulate an inflammatory response mediated by hydroxyl radicals. In response to inflammation, the cell produces the protein apoferritin, which stores iron in a stable trivalent form (as ferritin), thus reducing the likelihood of iron-catalysed oxidative free-radical reactions. This protective effect operates as long as the ferritin remains poorly saturated with iron. When fully saturated, ferritin promotes the production of toxic organic oxygen radicals and lipid peroxides. Thus the protective mechanism (low saturation) maintains a balance between two damaging processes—free iron and fully saturated ferritin. The role of apoferritin as an anti-inflammatory protein seems to be greatest in iron-deficient states. Should apoferritin become saturated, cells of the immune system may be attracted to the focus of iron because of their iron-binding receptors.

The variability in the expression of rheumatoid disease may therefore relate to the amount of free and complexed iron within the reticuloendothelial system, a factor which could be influenced by iron chelating drugs. It is already physiologically regulated in both sexes by diet and in women by the menses. Epidemiological data would support our hypothesis, since the incidence of rheumatoid disease in women increases rapidly after the menopause,^{41,42} and rheumatoid factor is more likely to develop in men than in women.⁴³ Severe rheumatoid disease, with systemic complications, is rarely reported in underdeveloped rural populations where malnutrition and parasitic infestation help to maintain low iron levels, but it is quite common in Western Europe and North America.

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Minor injuries may precipitate symptoms, and one of our early cases was a 30-year-old viola player with sympathetic reflex dystrophy following tennis elbow (lateral epicondylitis). This patient had been disabled for 14 months, not responding to several therapies, including eleven sympathetic nerve blocks. Complete recovery followed training with thermal biofeedback: she learned to raise the skin temperature of her fingers from 22.1°C to a physiological 32.1°C. She returned to full professional life and remains well on a 5-year follow-up.

Details of treatment are described in our *Textbook of Biological Feedback*⁴ and in a 1984 report.⁵ Twenty selected patients responded to various modalities of biofeedback. Our patients learn voluntary control of skin temperature and motor self-regulations; they learn to scan the entire body for muscle tone (tension) and to keep muscle tone at appropriate levels. They learn to shift their focus of attention rapidly and comfortably. Conscientious home practice for biofeedback is emphasized. We also record skin conductance, but we are not using this modality for feedback learning. Six patients improved well with median nerve decompression, physical therapy, muscle re-education, and appropriate modification of posture and work habits. Interesting research questions arise, such as the role of the cerebellum in motor learning, in kinaesthetic memory, and in conditioning.⁶

A musician's medical survey is being collected by the International Conference of Symphony and Opera Musicians, and we hope thus to gather further information. Many aspects are being addressed, such as the widespread use of beta blockers by players during performance, the effects of poor lighting and cramped conditions in orchestral pits, and harmful decibel levels of sound for players seated just in front of the brass section.

Prevention of these occupational disorders is obviously the next logical step. With the cooperation of the administration of a major orchestra, we are preparing courses for players, so that musicians may gain more conscious appreciation of the cerebral surveillance that their motor and sensory discipline requires in order to express non-verbal emotions through music.

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MENINGORADICULITIS ASSOCIATED WITH INFECTIONS BY BORRELIA BURGENDORFERI

SIR,—Dr Weill and colleagues (June 15, p 1400) reported two cases of meningoradiculitis due to *Borrelia burgdorferi* in France. We have seen two similar cases, suggesting that the neurological abnormalities of Lyme disease may be a common finding in France if antibody to *B. burgdorferi* is systematically looked for in such patients.

A 61-year-old woman was bitten by an "insect" on the left thigh in a forest near Paris, in July, 1984. 2 weeks later, excruciating backache and a motor and sensory radiculopathy developed in her left leg (femoral nerve). 1 month later, bilateral facial palsy and a right motor and sensory radiculopathy (femoral nerve) developed. Her cerebrospinal fluid contained 476 leucocytes/ μ l (100% lymphocytes) and protein 0.87 g/l. She was treated with intravenous penicillin G (24 million units/day in divided doses) from Sept 14 to Oct 3, 1984, and then with oral penicillin for 5 months. By the second day the severe backache and the pain in the lower limbs were much improved and they disappeared within a week. By the second week, the bilateral facial palsy and lower limb weakness began to subside and had disappeared by the second month, except for the left facial palsy which took 6 months to

resolve. Specific IgG antibody titres against *B. burgdorferi* were 20 (Sept 27, 1984) and 80 (Jan 30, 1985). Antibody titres were assayed in Prof Edlinger's laboratory at l'Institut Pasteur, Paris; the American B31 strain, kindly provided by Dr Taylor, Texas Health Center, was used. IgG titres in normal controls are less than 20.

A 28-year-old man was bitten by an "insect" on the left thigh, in a forest near Paris, in June 1984. Over the next 7 days, erythema chronicum migrans developed near the site of the bite; it resolved over the ensuing 3 weeks. 10 days later neurological abnormalities developed: backache, left lower limb pain, emotional lability, and, finally, bilateral facial palsy. The cerebrospinal fluid contained 110 leucocytes/ μ l (90% lymphocytes) and protein 1.2 g/l. He was treated with intravenous penicillin G (30 million units/day in divided doses) for 1 month. All clinical symptoms progressively disappeared within 4 months. Specific IgG antibody titres against *B. burgdorferi* were 40 (Nov 6, 1984) and 80 (March 20, 1985).

These two patients with lymphocytic meningoradiculitis had raised antibody titres against an American *B. burgdorferi* strain, suggesting that a related or identical organism is the causative agent of neurological abnormalities of the "Lyme complex" in France.¹⁻³ These findings also suggest that in Europe, as in the USA, specific serological studies to *B. burgdorferi* may be especially helpful in the diagnostic laboratory work-up of patients with atypical neurological abnormalities or oligoarthritis of unknown origin.^{1,4,5} In our two patients, high-dose intravenous penicillin⁶ induced a dramatic (case 1) or progressive (case 2) clinical improvement. Because of the low yield of cultures^{1,7} and the delay in the specific antibody response,^{1,4} lymphocytic meningoradiculitis consistent with the diagnosis of Lyme disease should be treated with high-dose intravenous penicillin as early as possible, even before the rise in specific antibody titres.

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CYCLO-OXYGENASE AND LIPO-OXYGENASE INHIBITORS MAY SUBSTITUTE FOR STEROID TREATMENT IN BRAIN OEDEMA

SIR,—Brain oedema is an important complication both of brain tumours and of radiotherapy to the brain. Conservative treatment of brain oedema usually consists of steroid therapy, though barbiturates also alleviate central nervous system oedema. Non-steroidal anti-inflammatory agents have been explored as well, with variable results.¹⁻⁴ Most of these are cyclo-oxygenase inhibitors, which decrease prostaglandin and thromboxane synthesis. However, inhibitors of cyclo-oxygenase may push the process into the lipo-oxygenase pathway, resulting in more leukotriene synthesis.^{5,6} and leukotrienes may contribute to brain oedema as much as some of the prostaglandins do. We have explored an inhibitor of both cyclo-oxygenase and lipo-oxygenase (sodium meclofenamate) in a primate model and found significant reduction in radiation-induced brain oedema.⁷ Patients with brain oedema often respond to steroids but, at the risk of dependency,⁸ which may eventually result in severe steroid toxicity. In a few patients we have

Hypothesis

IS REYE'S SYNDROME CAUSED BY AUGMENTED RELEASE OF TUMOUR NECROSIS FACTOR?

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Summary Reye's syndrome affects children with a history of viral infection treated with aspirin. Its pathogenesis is unclear. Tumour necrosis factor (TNF) is released by macrophages activated by viral infection, endotoxin, and phagocytosis, and it has been shown to be a mediator of the toxic and metabolic effects of endotoxaemia. The metabolic effects of endotoxin and TNF are similar to those found in Reye's syndrome. Raised levels of TNF are released from macrophages treated with non-steroidal anti-inflammatory drugs, and young animals are known to be more sensitive than mature animals to both TNF and endotoxin. These observations lead to the hypothesis that an increased release of TNF in selected young patients treated with aspirin contributes to the development of Reye's syndrome.

INTRODUCTION

Reye's syndrome is an important cause of morbidity and mortality in babies and children. It is characterised by encephalopathy and acute fatty degeneration of the liver.^{1,2} Antecedent viral infections (notably influenza A or B, varicella, and occasionally gastrointestinal infections) are recognised in over 90% of patients. Case-control studies have shown that over 95% of children with the full-blown syndrome have a history of aspirin ingestion.³

We present evidence in support of the hypothesis that increased release of tumour necrosis factor (TNF) in salicylate-treated children contributes to the pathogenesis of Reye's syndrome.

ACTIVATION OF MACROPHAGES BY VIRUSES, ENDOTOXIN, AND PHAGOCYTOSIS AND RELEASE OF TNF

Macrophages release a number of mediators when they are activated by diverse stimuli.^{4,5} These mediators include two forms of interleukin-1 (IL-1),⁶ arachidonate metabolites,^{7,8} various enzymes,^{9,10} complement components,¹¹ interferon,¹² and TNF.¹³ Viruses and bacteria provoke the release of these mediators^{4,13} by means of endotoxin¹⁴ and lymphokines such as gamma interferon¹⁵ and by stimulation of phagocytosis.¹⁶ The acute-phase response,^{17,18} characterised by fever,¹⁸ myolysis,¹⁹ a fall in serum zinc and iron,^{20,21} and de-novo synthesis of various hepatocyte proteins,²² is mediated by IL-1.^{18,23} TNF probably contributes to this host response.¹³ Beutler et al²⁴ provide strong evidence that at least part of the lethal effect of endotoxin is directly mediated by its stimulation of TNF release by macrophages; a rabbit anti-TNF antiserum given to lipopolysaccharide-challenged mice reduced lethality several-fold.²⁵ Furthermore, TNF contributes to inflammation by stimulation of granulocytes (unpublished),²⁶ endothelial cells,²⁷ and fat cells.²⁸

SIMILARITY BETWEEN TOXIC AND METABOLIC EFFECTS OF TNF AND ENDOTOXIN AND THOSE FOUND IN REYE'S SYNDROME

Laboratory rats given sub-lethal doses of *Escherichia coli* endotoxin have shown metabolic changes (increased plasma ammonia, free fatty acids, and serum lactate levels) and histological changes (microvesicular fatty changes in liver and ultrastructural evidence of hepatocyte mitochondrial damage) similar to those found in Reye's syndrome.²⁹ Kim et al³⁰ showed that the function of hepatic Kupffer cells is impaired and endotoxaemia commonly results after infection with a number of viruses. Endotoxin has been found in the plasma of patients with Reye's syndrome,³¹ but how it contributes to the pathogenesis of the syndrome is not known. Concentrations of short-chain and medium-chain fatty acid are raised in the serum of patients with Reye's syndrome.³² When these substances are injected into experimental animals many of the clinical, pathological, and biochemical features of the syndrome are reproduced.³³ Studies of mice infected with influenza B showed them to have a block in mitochondrial β -oxidation of fatty acids with subsequent elevations in serum free-fatty-acid concentrations.³⁴ Released TNF can stimulate a catabolic state characterised by hypertriglyceridaemia.²⁸ Many of the metabolic effects associated with Reye's syndrome may be mediated by monokines such as TNF or IL-1, and/or by endotoxin released by bowel flora.

INCREASED RELEASE OF TNF BY MACROPHAGES TREATED WITH NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

We have shown an augmented release of TNF by macrophages stimulated with lipopolysaccharide in the presence of cyclo-oxygenase inhibitors.¹² The augmentation of TNF release by non-steroidal anti-inflammatory drugs parallels their potency—indomethacin is more potent than aspirin, which is more potent than paracetamol (see table). When a phagocytic stimulus (*Staphylococcus aureus*) was incubated with freshly adherent peripheral blood human monocytes for 14 h, a similar increase in TNF release after non-steroidal anti-inflammatory drugs was seen: cells alone, 0 units TNF;³⁵ phagocytic stimulus alone, 18 units; phagocytic stimulus plus indomethacin 10^{-5} mol/l, 360 units; 10^{-6} mol/l, 250 units; 10^{-7} mol/l, 50 units. Because prostaglandins and the non-steroidal anti-inflammatory inhibitors of their synthesis have been shown to modulate IL-1 release^{7,36-38} it is likely that irregularities in this pathway contribute to the enhanced release of other macrophage products including TNF.

EFFECT OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS ON TNF RELEASE FROM MACROPHAGES*

Drug	Concentration (mol/l)					Control value
	10^{-5}	10^{-6}	10^{-7}	10^{-8}	10^{-9}	
Aspirin	1380†‡	972‡	510‡	486‡	324	380
Indomethacin	..	1458‡	1800‡	750‡	420	380
Paracetamol	524	418	408	338	354	380

*Mouse peritoneal macrophages were harvested 12 days after intraperitoneal injection of 0.5 ml of a 1:1 solution of complete Freund's adjuvant and saline. Cells were stimulated overnight with lipopolysaccharide in the presence of inhibitors.¹²

†Units of TNF are defined as the reciprocal dilution that produces half-maximal cytotoxicity in a standard L929 mouse fibroblast assay.³⁵

‡Values significantly different from control ($p \leq 0.05$).

tried to reduce the steroid dose by giving non-steroidal anti-inflammatory drugs. At first we used ibuprofen, a cyclo-oxygenase inhibitor, but with only limited success. Lately, we have tried sodium meclofenamate.

A 55-year-old woman with biopsy-proven glioblastoma multiforme was treated with 60 Gy to the tumour with no apparent clinical improvement. Due in part to residual marked peritumoral oedema. Dexamethasone 16 mg daily resulted in a good symptomatic improvement but repeated attempts to taper off the steroid dose produced recurrence of neurological symptoms. However, administration of sodium meclofenamate 500 mg daily allowed gradual decrease of the dexamethasone to 0.75 mg daily with no neurological deterioration. The patient is alive 11 months after diagnosis and 9 months after starting sodium meclofenamate therapy. Sodium meclofenamate seems worth investigating clinically for reduction of tumour and irradiation-related brain oedema and, possibly, for central nervous system oedema due to trauma.

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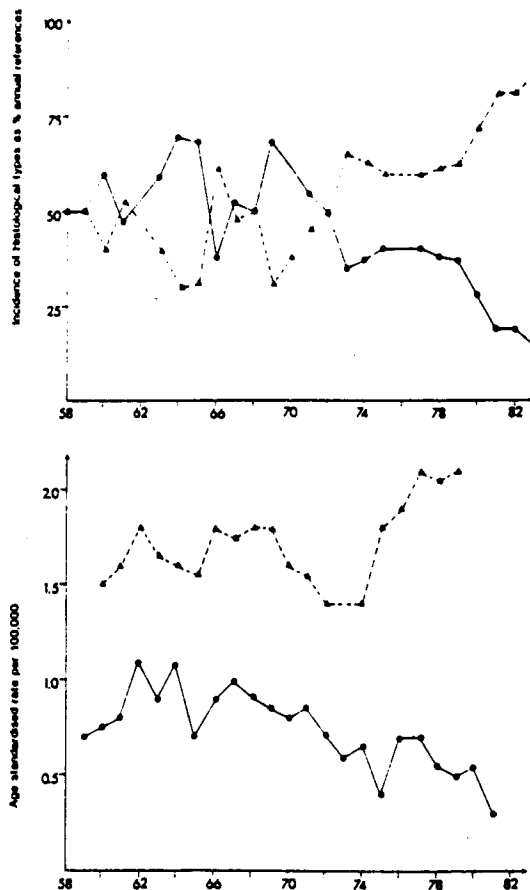
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DIVERGENCE BETWEEN MORTALITY AND INCIDENCE RATES OF THYROID CANCER IN SCOTLAND

SIR,—Data provided by tumour registries in the USA have suggested that the incidence of thyroid cancer is increasing.¹ We have examined Scottish thyroid cancer mortality data (by age and sex) in the annual reports of the Registrar General for Scotland for 1959-82 and incidence data from the Scottish National Cancer Registration Scheme, which incorporates five population-based registries (Inverness, Aberdeen, Dundee, Edinburgh, and Glasgow).

In keeping with previous studies² we have found the disease to be uncommon in males. The incidence and mortality trends did not change significantly during the period studied. However, we have noted a divergent trend of increasing incidence and decreasing mortality in women (figure).

New diagnostic techniques have probably improved the clinical diagnosis of thyroid cancer, but this is unlikely to have accounted for all of the increase in incidence. Nor have there been major advances in therapy over the past decade to account for the improved mortality. There has been a change in the distribution of histological subtypes seen at our clinic. Most cases of thyroid cancer in the West of Scotland are treated at a combined clinic staffed by endocrinologists and radiotherapists. The distribution of histological types in our clinic (upper part of figure), although based on a selected population, does suggest that "poor prognosis tumours" (spindle cell, giant cell, and small cell anaplastic tumours; lymphomas) have declined whereas the "good prognosis tumours" (papillary and follicular) now predominate.



Thyroid cancer in Scotland 1958-82.

Upper graph summarises data on frequency of histological subtypes seen in West of Scotland: ●—● = poor prognosis tumours; ▲····▲ = good prognosis tumours. Lower graph presents age standardised incidence (▲····▲) and mortality (●—●) rates for Scotland as a whole.

Unfortunately cancer registry data do not include information on histological classification, but our data do suggest that there has been an alteration in the natural history of thyroid cancer.

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GOITRE AND IODINE DEFICIENCY IN SPAIN

SIR,—The European Thyroid Association report on goitre and iodine deficiency in Europe (June 8, p 1289) provides some data for Spain but specifically mentions only the 86% goitre prevalence rate in schoolchildren of Las Hurdes.¹ A survey of 3872 schoolchildren from a mountainous region in Galicia in the north-west² has revealed a 79% prevalence of goitre with 85% excreting less than 25 µg iodine/l urine.³ Another survey, among 4949 schoolchildren from the eight provinces of Andalucia in the south, revealed an overall goitre prevalence of 29%, with 40% excreting less than 40 µg iodine/l urine, ranging from a 10% prevalence for Malaga to 45% for Huelva, with a good inverse correlation with urinary iodine excretion.³ In Catalonia, in north-east Spain, an epidemiological survey has been done in 1697 people older than 2 years, chosen at random from 255 rural communities comprising a total population

AGE-RELATED TOXIC EFFECTS OF TNF IN ANIMALS

The median lethal dose for lipopolysaccharide is lower in young than in mature animals. Young animals are also more susceptible to gram-negative bacterial infections¹⁴ (unpublished). Although many host factors contribute to these findings, the greater susceptibility of young mice and rats to the toxic effects of TNF (unpublished) may be important. The fact that Reye's syndrome is seldom found in adults is consistent with increased susceptibility to TNF in children.

HYPOTHESIS

We hypothesise that the metabolic irregularities seen in Reye's syndrome may be caused by salicylate-augmented release of TNF (or a related cytotoxin such as IL-1 or lymphotoxin) in children who are unusually sensitive to the toxic effects of these factors. There is evidence of a link between the hepatic metabolic changes observed in Reye's syndrome and TNF, and other idiopathic syndromes may result from increased levels of TNF or related toxic monokines. The acute fatty liver of pregnancy is one such syndrome.³⁹ The placenta is a rich reservoir of macrophages⁴⁰ that may become activated by a stimulus (as yet unidentified) late in pregnancy. Despite their superficial resemblance, Reye's syndrome and the acute fatty liver of pregnancy can be differentiated by hepatic mitochondrial morphology and clinical course. Clearly, timing of events, hormonal state and age of the patient, as well as other host factors determine the outcome of an inflammatory pathway that has gone awry. The augmented release of inflammatory mediators such as IL-1 and TNF by macrophages treated with inhibitors of prostaglandin biosynthesis, as well as the sensitivity of young animals to these mediators, suggest a novel pathogenic mechanism for Reye's syndrome.

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"Advanced cancer is a problem that requires teamwork. It involves the needs of the patient, the resources of the family, the therapeutic strategies of the doctor, the bedside and management skills of the nurse, the emotional and spiritual support from social worker and chaplain, and most important of all, the interplay and fusion of these elements to produce a strategy agreeable to the patient. The patient needs to feel actively concerned in his management rather than a helpless prisoner.

This cannot be helped by the fact that nearly a third of dying patients have little idea of their real situation. And basic teamwork is greatly prejudiced when a third of doctors are unwilling to entrust to capable and experienced nursing colleagues honest discussions with the patients about the future. Although lies are rare, evasion is common, but it is not enough to tell the patient the truth and let them get on with it. This is a recent and growing tendency that can be as damaging as uncertainty.

Prognosis should remain uncertain within limits, for that is the truth of it. Patients should be encouraged to ask for information they want, but not have it forced upon them. Someone dying may, early in the illness, feel the need for less information than is required later on. The young usually need more information than the old, but generalisations are to be mistrusted. Relatives are to be listened to courteously but the plea 'You won't tell him will you, he couldn't stand it' is often to be translated as 'You won't tell him will you? I don't think I can handle it.'—ERIK WILKES. Terminal care: how can we do better? *J R Coll Physicians Lond* 1986; 20: 216-18.

copy of a newly published handbook: *Essentials of Human Biochemistry*, by Patterson (3):

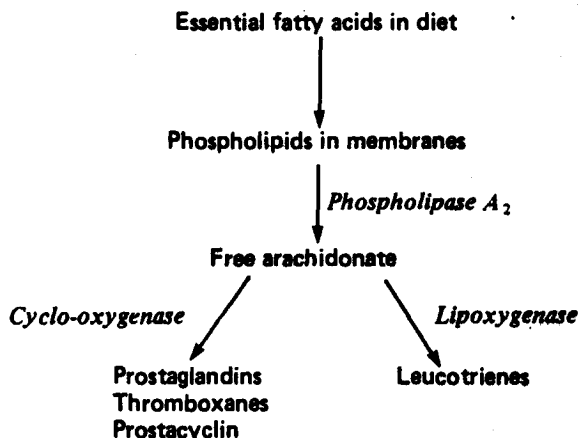


Fig. 4.8 The pathways for the formation of the prostanoids

This schema assumes that both the parent dietary essential fatty acids linoleic acid (LA) and alpha-linolenic acid (ALA) are metabolised to AA which is then incorporated into membrane phospholipids. It is known however that there is no metabolic pathway for the conversion of ALA + LA. In this respect, therefore the schema is incorrect. It is also incorrect in showing PG and LT synthesis from AA with the latter as the only source of PGs and LTs. The schema is followed by a brief description of the biochemistry and pathophysiology of some of the eicosanoids derived from AA. Again no reference is made to the physiological importance of either DGLA or EPA, or of their respective eicosanoid products, in AA metabolism.

A recent reviewer (4) of the formation and actions of leukotrienes states in the introduction that "Because analogous compounds can be derived from 5, 8, 11 eicosatrienoic acid, 5, 8, 11, 14, 17 - eicosapentaenoic acid, and 5, 8, 11, 14 - eicosatetraenoic acid (arachidonic acid), a subscript has been used to describe the total number of double bonds in the molecule". The review then deals exclusively with leukotrienes derived from AA. The concluding chapter commences with the following statement: "Leukotrienes are a novel group of arachidonic acid metabolites"

Similar examples of the singular preoccupation with AA metabolism and eicosanoids in isolation can be cited from the literature *ad nauseum*.