The Action of Aspirin in Preventing the Niacin Flush and its Relevance to the Antischizophrenic Action of Megadose Niacin

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Aspirin has been observed to block or attenuate the flush reaction caused by niacin in 90 percent of a group of schizophrenic and non-schizophrenic outpatients. The patients were not treated with tranquilizers or antiinflammatory agents concurrently.

The basis for this phenomenon, the blocking of the niacin flush by aspirin, is probably due to inhibition of prostaglandin synthesis by aspirin. In addition inhibition of bradykinin by aspirin may also suppress the flush.

The various components of the inflammatory system *are briefly described, and their relationship to the flush response is discussed. It is speculated that continued megadose niacin therapy leads to depletion of bradykinin and histamine and a small increase in prostaglandins, particularly of the E type. These are known to exert an inhibitory effect on noradrenergic pathways and, along with the probability of reduced tissue histamine levels, an overall sedative effect. Thus niacin, at megadose levels, is often observed to act like a tranquilizer. This may account, in part, for the antischizophrenic action of megadose niacin therapy.*

There are five cardinal signs of inflammation: redness, heat, pain, swelling, and loss of function of the affected part. The niacin flush reaction fulfills three of these criteria to suggest that it is certainly related to the inflammatory process. In addition, clinical observations indicate that various anti-inflammatory agents, such as cyproheptadine (Periactin) and especially aspirin, can attenuate or block the niacin flush. Furthermore, continued exposure to niacin at above flush threshold doses usually leads to disappearance of the flush response in a few days or weeks. Thus it seems likely that modulation of the inflammatory mechanisms is a basic part of the pharmacological action of megadose niacin therapy.

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It is well known that at even a slightly increased dose, often as little as 50 mg, a flush reaction is provoked by niacin. The peripheral vasodilatation and erythema occurs within half an hour and persists from 15 minutes to several hours and occasionally over a day. At low doses the flush is incomplete and a transitory prickling or itching sensation may be the only manifestation. At higher doses a definite threshold is reached at which a generalized vasodilatation occurs, covering the entire integument with a hot and prickly rash, like a sunburn.

Niacinamide does not evoke this flush reaction, a fact of considerable practical importance in Orthomolecular psychiatry. It is important because there are some patients who are frightened by the flush reaction and therefore refuse to try megadose therapy. In addition the flush reaction might imply a difference in mode of action between niacin and niacinamide.

In this regard it is known that niacinamide does not share the ability to lower serum cholesterol levels as does niacin, nor does it lower the serum levels of fatty acids. There are some indications that niacinamide is preferred in human physiology. For example, liver slices can methylate niacinamide, but not niacin. More niacin is excreted in the urine. There is very little deamidation of niacinamide into niacin in human red cells, and the serum half-life of the amide is threefold greater (Miller Message, 1971).

Hoffer (p. 9, 1962) described the flush response to intravenous nicotinic acid as follows: "(1) a period of intense vasoconstriction which may produce a cir-cumoral pallor, (2) a vasodilatation which usually begins in the forehead and gradually or rapidly spreads downward. It may cover the entire body but usually reaches the chest, arms and knees. There is great variation from person to person . . . (3) a brief period of chilliness with occasional tremor. This entire cycle may be over within thirty minutes when given by vein but may last up to several hours if given by mouth."

We may conclude from this last observation that there is a mediator of inflammation in the gut that is released by orally administered niacin but bypassed with the intravenous route. The possibility that this may be related to the very high concentration of histamine and serotonin in the intestinal tract is obvious, but has not been verified.

Hoffer also observed that "if one gram of nicotinic acid is given orally after a subject has ceased flushing following 200 mg I.V. there is no further flush." This implies that a stored mediator of inflammation is depleted, rendering the subject unresponsive to further stimulation. A similar reduction or abolition of the flush response occurs with oral niacin megadose therapy.

Hoffer speculated that the flush response might be caused by histamine, but he found no fall in blood pressure as would be expected from histamine research. This could be because histamine-induced hypotension occurs due to large, abrupt, intravenous doses, whereas niacin-induced release of inflammatory mediators is more gradual and less complete. It is also possible that other mediators may accompany the niacin flush and modulate blood pressure effects to the point of negligible change.

Hoffer was unable to prevent the niacin flush by pretreating himself with antihistamines (Periactin or Polaramine) before taking 1,500 mg of niacin. He concluded that serotonin or another histamine-like substance might be implicated.

In 1967 Robie (Robie, 1967) reported the contrary observation that cyprohep-adine (Periactin) was an effective antidote for niacin-induced "hyperthermia." He said that it could be given after the flush has already started and that it is dose-related in effect: a 4 mg dose was effective up to 250 mg of niacin, and 6 mg of Periactin was required above that. He warned that Periactin should be taken only as needed, not regularly, since it can cause weight gain. It is now known that Periactin is both antihistamine and antiserotonin in action.

It is beyond the scope of this paper to review the mechanisms of inflammation in detail, but the following table lists some of the more important factors involved in inflammation and immunity.

We can interpret Table 1 to suggest that there are two major types of inflammatory stimuli: externally applied physical and chemical agents of injury and internally developed antibody responses that develop in response to specific antigens. Both trauma and antigen-antibody responses can trigger off release of all mediators of inflammation and immunity.

Much of our understanding of the relationships of the mediators of inflammation has been provided by studies of substances found in bleb fluid caused by injection of carageenan directly into tissue sites (Zurier, 1974). In this experimental model of inflammation, histamine and serotonin are found in the first minutes after injection. Histamine is a strong vasodilator, and serotonin causes venoconstriction. This combination increases blood flow into the inflamed area, but interferes with its drainage. The result is local swelling that thus serves to dilute noxious substances.

Polymonine is known to deplete tissue stores of histamine and serotonin. In other studies with carageenan blebs after pretreatment with polymonine, swelling and inflammation were delayed for one and a half hours after injection, following which bradykinin appeared in the bleb fluid along with signs of inflammation. Prostaglandins appear in an additional hour and reach peak activity 12 hours after the initial injection of carageenan.

Cellulose sulfate is a known bradykinin antagonist. When both polymonine and cellulose sulfate are administered before the carageenan injection, swelling and inflammation are delayed for two and a half hours until prostaglandins make their appearance in the bleb fluid.

Such experiments suggest that histamine and serotonin mediate the immediate effects of inflammation in tissues, while bradykinin action is delayed for an hour and prostaglandins take over after two to 12 hours.

There is substantial evidence that prostaglandins are important in the delayed component of the inflammatory process. For instance, indomethacin, a potent inhibitor of prostaglandin activity, is known to prevent the delayed erythema, i.e., sunburn, due to exposure to ultraviolet light.

However, I do not believe that bradykinin activity is necessarily delayed for one and a half hours as these bleb experiments suggest. I find it more plausible that kinins, which are normally present within the blood plasma and which are degraded from plasma proteins, are immediately active in and about blood vessels. Since they are quickly inactivated by kininases and have a duration of action less than a minute, it would be surprising if they

TABLE 1

Agents	Cells/Tissues	Mediator /Chemical	Action
Physical or Chemical Trauma	Collagen	Hageman Factor (XII)	Activate bradykinin
	Reticuloendothelial	Bradykinin	Vasodilatation, pain
		Serotonin	Venoconstriction, permeability
	Mast cell	Histamine	Vasodilatation, inflammation
		SRS-A (lung only)	Bronchoconstriction
Antigen-Antibody Reaction	T-lymphocyte	Prostaglandin E1	Increase cAMP
	B-lymphocyte	Prostaglandin E2	Decrease cAMP
	Plasma cell	Prostaglandin F2a	Neurotransmitter modulation
	Leukocyte	Other prostaglandins	Modulation of cell function
	Basophil	Complement (C1-C11)	Cell lysis
		Antibody (IgA. IgM, IgE)	Cell lysis. Immunity. Allergy.
		Epinephrine	Increase cAMP
		Acetylcholine	Increase cGMP, inhibit cAMP

should appear at once by diffusion into bleb fluid. Histamine, on the contrary, is not normally present in blood in quantities significant of activity except packaged in basophils (Code, 1974). Instead it is formed directly by decarboxylation of histidine in tissues throughout the body and stored in mast cells in the interstitial tissues and in circulating basophils. It is likely that bradykinin is the immediate intravascular mediator of inflammation while histamine is the immediate extra-vascular mediator of inflammation. Prostaglandins, formed from fatty acids present in all cell membranes everywhere in the body, act as mediators of delayed inflammation in both intravascular and extravascular locations. They also modulate inflammation by inhibiting further release of histamine and sensitizing the immune mechanism in white blood cells. Hageman Factor, also called Factor XII, is a small plasma protein that is readily activated, by contact with almost any foreign surface, into a proteolytic enzyme of low activity, Factor XIIa. Even a minute trauma, just sufficient to expose the negative charges on the subendothe-lial collagen, will initiate this transformation, along with coagulation, due to the activation of thrombin, fibrinolysis, due to the activation of plasmin, and complement transformation as well.

Plasmin further degrades Factor XIIa into PKA, more active proteolytic fragments that convert gamma-globulin pre-kallikreins into kallikrein, a plasma proteolytic enzyme that acts on alpha-globulin peptides, kininogens. These kininogens are thus degraded into the nonapeptide, bradykinin, which has strong vasodilating action, tenfold more potent than histamine. Bradykinin is quickly inactivated by kininases that split off the terminal arginine and phenylalanine moieties, but bradykinin also self-perpetuates by further activation of Hageman Factor. It is also associated with the release of other mediators of inflammation and immunity: histamine, serotonin, prostaglandins, and SRS-A. The intricacy of this interrelationship of defensive factors is shown in Figure 1 (adapted from Colman, 1974).

It is known that Hageman Factor is activated with particular ease by collagen and substances of negative charge, such as that of the carboxyl radical,

Such a configuration is part of the niacin molecule but not of niacinamide, as a glance at Figure 2 will demonstrate. This might account for the fact that niacin evokes the flush reaction while niacinamide does not.

If niacin evokes the flush reaction in part or all via the Hageman Factor pathway to bradykinin, it is clear that this must also increase the coagulation process by simultaneous increase in thrombin and fibrin. However, coagulation would be counterbalanced by the equally potent activation of the plasmin system, which is fibrinolytic and therefore anticoagulant. In fact, intravenous administration of niacin does produce a fibrinolytic response of half an hour's duration as a result of these mechanisms (p. 1660, Goodman and Gilman, 1966).

In addition, the Hageman Factor activates the complement system and this implies that niacin could theoretically trigger a cascade of complement-

FIGURE 1

Mediators of Inflammation

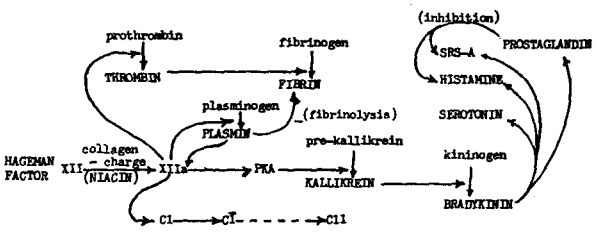
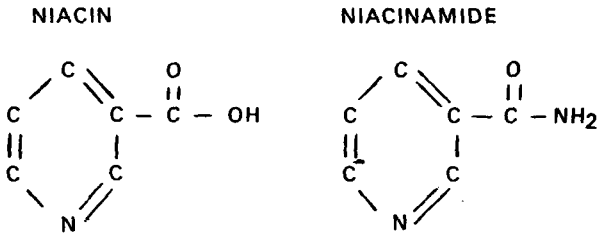


FIGURE 2



mediated allergic manifestations. Perhaps those subjects who develop rhinorrhea or skin blisters after niacin administration might fall into this category. Isolated cases of anaphylactic reactions have been reported after niacin also.

If the degree of inflammation is of sufficient magnitude, other components of the inflammatory system in addition to the kinins are likely to be activated. Hoffer's description of the perioral blanching due to intravenous niacin suggests the likelihood that serotonin, well known for its venoconstrictor action, is also involved. This is well known also for its effect in increasing swelling in tissues so it may have some effect on blistering with niacin. Also serotonin might counterbalance the vasodilatation effect of histamine and thus prevent the lowering of blood pressure that has been found with experimental injection of histamine.

It is already implied that the niacin flush phenomenon is based only in part on the action of histamine. Experiments with carageenan-induced inflammation indicate that in the initial phase of inflammation there is a release of bradykinin, histamine, and serotonin. The action of kinin is of very brief duration, however, averaging only 40 seconds. Prostaglandins, in contrast, are observed at three hours following injection of carageenan and reach maximum activity in 12 to 24 hours. Since the flush response is almost immediate and, when complete, lasts a day or more, it must be that it is mediated by all of these substances: bradykinin, histamine, serotonin, and prostaglandins. Since anaphylaxis has occurred after niacin (p. 1660, Goodman and Gilman, 1966), it implies that SRS-A (slow reacting substance-anaphylaxis) is also released in the lungs, and some subjects should experience a premonition of dyspnea. Rhinorrhea and some wheezing are quite common with the niacin flush reaction in my experience, but they disappear along with habituation of the flush response.

In summary, it appears that bradykinin and other physicochemical factors initiate histamine and serotonin synthesis, perhaps by influencing the pyridoxine-activated decarboxylase enzyme that converts histidine to histamine and also converts 5-hydroxytrypto-phan to serotonin (5-hydroxytryptamine). All of these factors appear to promote prostaglandin activity also, perhaps by increasing the activity of phospholipase-A. Norepinephrine and epinephrine also increase prostaglandin formation this way.

Of great importance is the fact that prostaglandins not only mediate inflammation and immunity but also limit these processes as well; hence the conclusion: prostaglandins are modulators of inflammation and immunity. Although the complexities of this operation are beyond our present comprehension, in general it appears that low concentrations are associated with inflammation and high concentrations with inhibition of inflammatory and immune mechanisms.

For example, both PGE 1 and PGE 2 inhibit histamine release from sensitized mast cells and basophils, prevent histamine release (as well as SRS-A) from basophils and lung fragments, prevent lymphocyte-mediated cytotoxicity, and in rats suppress adjuvant-induced arthritis and cartilage destruction. Although prostaglandins increase the release of pituitary ACTH, treatment with PGE 1 will prevent arthritis even in adrenalectomized animals. It is known that PGE compounds also reduce release of lysosomal enzymes from human leukocytes when these are exposed to immune complexes. The anti-inflammatory action of prostaglandin includes suppression of the numbers of circulating lymphocytes. The exact mechanisms for the specific effects, either inflammatory or anti-inflammatory, are unknown but probably have to do with in situ synthesis of specific prostaglandins in response to the conditions at a given site.

My attention was first drawn to consider the relationship between the niacin flush and the general operations of the inflammatory response quite by

accident. In cleaning out an accumulation of outdated journals in my office I happened upon an article on aspirin in **Scientific American,** November, 1963 (Collier, 1963). The author, J.O.J. Collier, reviewed the pharmacology of aspirin, and in so doing he referred to the work of Truelove and Duthie, who had demonstrated that a single dose of aspirin, 650 mg, abolished the swelling and delayed the flush reaction from thurfyl nicotinate locally applied to the skin.

Collier also reviewed the work of Adams and Cobb, who described inhibition of the skin flush response to thurfyl nicotinate for several days after a single dose of 225 mg of aspirin. Neither sodium salicylate nor phenylbutazone were active at the dosage tested, and it was estimated that acetylsalicylic acid is at least 12 times more potent than sodium salicylate in blocking the flush.

I reasoned in response to the above that if aspirin could prevent the flush reaction due to locally applied thurfyl nicotinate it could also attenuate the flush reaction due to ingested niacin. Therefore I embarked on sufficient clinical experimentation to convince myself that this prediction is correct.

I tested an initial 20 cases by giving niacin at gradually increasing doses from 50 mg to their own flush dose, usually 100 or 200 mg. Then, after administering 625 mg of aspirin, 18 out of 20 (90 percent) experienced reduction or absence of the niacin flush. This compares with a 92.5 percent occurrence of skin flushing in over a thousand subjects taking a gram of niacin, three times daily, in the recent coronary drug project (Coronary Drug Project Research Group, pp. 360-381, p. 376, 1975).

In order to observe the phenomena more carefully I enlisted a volunteer subject in addition to myself. Because the action of aspirin is prolonged, it is necessary to wait a week in between clinical trials in order to avoid over-lapping effects from the previous trial into a current one. In addition to aspirin I also tested acetaminophen (Tylenol), which is known to block the action of prostaglandins in the nervous system but not the periphery, and indomethacin (Indocin), which blocks bradykinin, serotonin, and PGE.

My observations are summarized as follows:

1. Most of my patients developed a flush between 50 mg and 300 mg, usually between 100 and 200 mg. A few did not flush even at higher doses, over 1,000 mg. The nonflush subjects were not necessarily schizophrenic, contrary to Hoffer and Osmond's observation that the appearance of the flush is sometimes a good prognostic factor.
2. The flush reaction is also blocked or attenuated by phenothiazines and tricyclic antidepressants. Since chlorpromazine is known to inhibit bradykinins, histamine, serotonin, prostaglandin, epinephrine, and acetylcholine, it is no wonder that it also blocks the niacin flush. None of my subjects was on phenothiazines while testing their flush reaction.
3. Aspirin at a single dose of 325 mg would prevent the flush in most cases, but only up to 250 mg of niacin.
4. Aspirin at a single dose of 650 mg would prevent or diminish the flush in most cases, even above 500 mg per dose of niacin.
5. To be effective the aspirin must be taken at least a half hour before the niacin. Results are better if aspirin is taken two days in succession, one dose per day.
6. Acetaminophen did block the flush reaction at doses comparable to aspirin in two subjects, but the effect was not as complete.
7. Indomethacin achieved a partial reduction of the flush reaction at a dose of 25 mg. This is in accord with the observation that indomethacin is 20 to 40 times as potent an inhibitor of prostaglandin as is aspirin.
8. In those cases where aspirin was successful in blocking the flush reaction the effect was maintained for several days. Thus after one or two doses of aspirin the niacin dose could be raised without recurrence of flush. If the niacin

is raised to megadose level the inhibition of flush continues due to the effect of niacin itself.

9. A flush threshold dose of niacin can be taken indefinitely without attenuating the flush reaction. To extinguish the flush requires a super-threshold dose, well above the amount necessary to just cause flushing.

10. Periactin and aspirin together offer more complete prevention of the flush response to a 500 mg dose of niacin. This combination appeared to be more complete in its effect than either alone.

11. Periactin, 4 mg, was able to attenuate but not block the flush response to 500 mg of niacin in two subjects. Periactin, 6 mg, was slightly more effective, but still not completely able to block the flush response to 500 mg of niacin.

The fact that the flush reaction occurs at all tells us that it is related to the dynamics of the inflammatory response. That it occurs in different individuals at variable doses may tell something of the relative sensitivity of the mechanisms of inflammation in the individual. Those whose inflammatory response is more easily triggered may perceive and respond differently than those whose response is inert. This is relevant in schizophrenia because, as the work of Carl Pfeiffer shows, about half of the schizophrenic population are histapenic, low-serum histamine, and about a fifth are histadelic, high-serum histamine (Pfeiffer, 1974). Pfeiffer has observed that the high histamine is often associated with depression, while the low histamine is more likely to accompany paranoia (Pfeiffer, 1972). I would think that megadose niacin would be of value in the histadelic patients, but Pfeiffer has concluded that the opposite is true and he recommends niacin for the hist-apenics. I cannot account for this.

When aspirin is used to block the flush response there is a remote possibility that an allergic response might occur. If this were a great danger aspirin would not be the popular nostrum that it is. In those with a known aspirin sensitivity, of course, this treatment is not indicated. It should not be used in asthmatic children, or in patients with known collagen disease, who have a greater risk of anaphylaxis. There are warning signs: the development of asthmatic symptoms after aspirin may herald anaphylaxis in a repeat dose. In fact, Lampe says that the occurrence of profuse rhinorrhea in an asthmatic adult may herald sudden death due to anaphylactic bronchospasm at the next exposure (Lampe, 1974).

The early vasodilatation and flush response to niacin is almost certainly mediated by bradykinin, histamine, and serotonin as discussed above. The delayed and prolonged component of the flush is characteristic of the action of prostaglandins (Wilson, Ed., 1974). These are a family of oxygenated cyclic C-20 fatty acids that are derived from the essential fatty acids. The five types of prostaglandins are based on the structure of the cyclopentane, ring at the bend in the hairpin structure of the molecule. They are readily synthesized and released in most tissues and organs by lipolysis of cell membranes, thus releasing free fatty acids, in particular arachidonic acid. This step is catalyzed by phospholipase-A and is the rate-limiting step in prostaglandin synthesis. It is stimulated by bradykinin, histamine, serotonin, epinephrine, and norepinephrine, which probably increase the activity of phospholipase-A. The liberated fatty acid is then oxidized with the aid of prostaglandin synthetase enzyme, to an endoperoxide intermediate, which is then converted to a specific prostaglandin by an isomerase or a reductase enzyme.

The specific prostaglandins are not interconvertible and once synthesized are then simply degraded in the cytosol and in the extracellular fluid by prostaglandin dehydrogenase and prostaglandin reductase, the two most widely distributed catabolic enzymes in the body. In addition the side chains are degraded by beta-oxidation, just like other long-chain fatty acids. Prostaglandin removal is accomplished within one circuit of the circulation through the

lung for all types but Prostaglandin-A (PGA), which is more persistent and thus influential in regulating kidney activity and blood pressure.

Because of the swiftness of Inactivation of the prostaglandins it is unlikely that they increase in concentration except by continual stimulus to their production. However the aftereffects of a single dose may persist for hours due to the initiation of intracellular increase or decrease of cyclic AMP activity.

On the other hand, because of the ubiquity of substrate fatty acid molecules and the ease of activating phospholipase-A, it is doubtful that prostaglandins can be depleted except by deficiency of essential fatty acids. However synthesis can be blocked by inhibition of prostaglandin synthetase, hence the potent anti-prostaglandin effects of aspirin, in-domethacin, and tetrahydrocannibinol (marijuana). This anti-prostaglandin effect probably also accounts for their anti-inflammatory effect. Prostaglandin release is inhibited by barbiturates and chlorpromazine also.

It is well demonstrated that both niacin and prostaglandins have a marked anti-lipolytic action. In fact it is likely that niacin inhibits prostaglandin activity by inhibiting lipolysis, thus preventing release of arachidonic acid from cell membranes (Skidmore et al., 1971).

Recent studies indicate that niacin's inhibition of lipolysis in fat cells is due to interference with cyclic AMP. This is not caused by interference with adenyl cyclase, or enhancement of phosphodiesterase. The mechanism is unknown, but the outcome is measured as the well-known lowering of serum free fatty acids that occurs after niacin, even in the face of pre-administration of epinephrine or norepinephrine that normally cause lipolysis (Skidmore et al., 1971).

The ultimate action of all mediators of inflammation appears to be to increase cyclic AMP within the cells. In most organs this is associated with increased cell function: contraction, secretion, protein synthesis, etc. In the immune system, however, this is associated with a decrease of the amplification of the immune response. Hence the observation that, as immunity builds up, sensitized lymphocytes and leukocytes develop increasing numbers of histamine receptors on their membranes (Bourne et al., 1974). These receptors bind increasing amounts of histamine at the cell membrane and thus increase cyclic AMP within the cell. The build up of cyclic AMP within the cell is associated with abolition of release of lysosomal enzymes or histamine from the cell. This limits the inflammatory component of the immune response and accounts for the development of host resistance: the body cells no longer are subject to cytolysis themselves, while the pathogen or foreign body is not protected with these receptors and thus is destroyed.

In Hoffer's study (p. 11, 1962) niacin administration was associated with leukocytosis after two to four hours, a sign of inflammation and probably caused by histamine and initial low prostaglandin activity. This disappeared at 24 hours after continued niacin administration and probably reflects suppression of inflammation during the prostaglandin phase of the flush reaction.

The inflammatory mediators that increase cAMP appear to be essential to the development of specific immune reactions, such as the formation of antibody to a specific antigen. For example, Mozes et al. (1974) demonstrated that mouse spleen cells could be exposed in vitro to a multichain synthetic polypeptide antigen, then after washing off the antigen the cells were injected into irradiated syngeneic recipient animals without causing an antibody response. But if the lymphocytes were exposed to PGE1 in vitro during the first contact with antigen, then the antibody response did occur. Repeat experiments showed similar sensitization after exposure to histamine and cyclic AMP.

We can speculate from this that niacin therapy, by depleting tissue stores and inhibiting release of histamine, would

minimize antigen-induced cAMP response, thus reducing development of new hypersensitivity responses and minimizing already established allergy. Perhaps this accounts for the benefits I have observed after niacin therapy in cases of allergic rhinitis and also in asthma.

If niacin does deplete the tissues of stored histamine in mast cells, does niacin also deplete the tissues of prostaglandins or interfere with prostaglandin synthesis? Or, on the contrary, could it possibly increase prostaglandin activity? And if there were an increase in prostaglandin activity induced by continued exposure to niacin, would this affect the flush response? The answer to the latter must be positive. For example, solar erythema, which involves variable degrees of tissue damage due to ultraviolet light penetrating to the dermis, characteristically is at maximum after a delay of about 12 hours. This implies that it is mediated primarily by prostaglandins because kinins and histamine would no longer be operative unless continually regenerated. Furthermore, Snyder has recently used the prostaglandin inhibitor,. indomethacin, both locally applied and systemically administered, to suppress sunburn (Snyder and Eaglstein, 1973).

In the relative absence of histamine, prostaglandins evoke a dose-related flush of the same character as sunburn. It is known that prostaglandins inhibit histamine release from mast cells and basophils and thus prevent amplification of the immune response. This feedback relationship implies the possibility of a situation where prostaglandin activity can be high enough to inhibit histamine, but not so high as to cause a strong flush response. That this may be the case is borne out by the observation that most patients on prolonged megadose niacin therapy do exhibit a slight vasodilatation, enough to impart a pink glow to their complexion.

Thus there is a possibility that continued megadose niacin increases the resting prostaglandin level slightly, interferes with inflammation-induced prostaglandin release, and gradually depletes histamine. These predictions should be checked.

That histamine depletion is possible has been demonstrated by administration of compound 40/80 and also by use of polymonine, which also depletes serotonin and SRS-A. The clinical response to administration of compound 40/80 is like an exaggerated niacin flush: there is a fall in blood pressure, acceleration of the pulse, headache, bronchospasm, nausea, acid stomach, and giant hives. This type of anaphylactoid reaction has been reported, but only rarely, after niacin. As with niacin, this response to compound 40/80 habituates readily on repeated administration (p. 630, Goodman and Gilman, 1970). The many similarities suggest that the depletion of inflammatory mediators is similar in both cases.

When histamine stores are depleted it may take weeks before the tissue levels return to normal. Since the human epidermis and nervous system are devoid of mast cells yet rich in histamine, it is plausible that synthesis of histamine from the amino acid, histidine, is usual there. That this is possible has been dramatically demonstrated by measuring histamine levels after scalding. After two minutes the histamine content is doubled (Dekanski, 1945).

Garbarg et al. (1974) recently demonstrated an histaminergic pathway in the brain. It is known that, in the hypothalamus, histamine is present at double the concentration of serotonin. A 50 percent reduction in histidine decarboxylase in the ipsilateral hypothalamus, midbrain, and hippocampus is observed after lesions to the median forebrain bundle at the lateral hypothalamus. They concluded that histamine is important in the control of cortical cells upon which several kinds of amine-containing fibers from the median forebrain bundle project. Histamine and norepinephrine are synergistic in stimulating cAMP in the cortex, hence they evoke cell activity in the cerebral cortex.

It is common knowledge that most

antihistamines are also sedatives. In light of the foregoing, it appears likely that this may be due to direct antihistamine action within the central nervous system. In support of this is the observation that decreased histamine turnover is observed after treatment with most hypnotics and barbiturates. The H2 histamine receptors that have recently been found in the brain, heart, stomach, and bone marrow and their newly discovered blockers, Metiamide and Buriamide, will probably shed much light on histamine activity in the brain.

Could there be long-range adverse effects due to niacin-induced histamine depletion? The recent five-year evaluation of niacin therapy in coronary heart disease and hyperlipidemia revealed no increase in mortality compared to the double-blind control group in over a thousand patients treated with 3 g of niacin per day (Coronary Drug Project, pp. 360-381, 1975). In fact the overall morbidity from recurrence of myocardial infarction was decreased in the niacin group as was the occurrence of stroke-Slight increase of serum uric acid and of the occurrence of gouty arthritis was observed as was an increased occurrence of blood sugar elevation without actual diabetes. Skin flushing and itching were the most common morbidity associated with niacin, occurring in 92.5 percent and 48 percent, respectively, of this group of 1,119 patients over a five-year period of observation.

If the antihistamine action of niacin is a significant part of its action in treating schizophrenia, it is of interest to find that both niacinamide and ascorbic acid share additional antihistamine activity (Bekier and Maslinski, 1974; Zuskin et al., 1973). Both can inhibit symptoms of experimental asthma, for instance. Both are also reported to be beneficial in some cases of schizophrenia. In short, it seems possible that the therapeutic effects of megadose treatment with niacin, niacinamide, and ascorbic acid may be at least partly due to their antihistaminic activity. In addition, at least where niacin is concerned, there must be some action via alteration in prostaglandin activity as well and this may account for its special value in arthritis, dysmenorrhea, and allergy, in addition to schizophrenia.

A few hours after the beginning of the niacin flush, when prostaglandin activity is beginning to climb, there develops a sedative effect, probably due to the increase in PGE. When the flush is strong enough to persist beyond two hours, the activity of prostaglandin is surely implicated. With continued administration of niacin the sedative action may also be due to the depletion of histamine and inhibition of histamine release, possibly related to increased prostaglandin activity. Most patients report that the niacin response is like a tranquilizer.

Prostaglandin E is known to exert a direct sedative effect in most animal species. Then why does aspirin, a prostaglandin inhibitor, exert a sedative effect also? I doubt that prostaglandin depletion is sedative in this case. However there are some questions here. Nevertheless, I think it is more likely that aspirin sedates by increasing the amount of free tryptophan in the brain. Guerinot et al. (1974) recently demonstrated this fact, with increases being particularly large in the hypothalamus and hippocampus. Since tryptophan is readily hydroxylated and then decarboxylated into serotonin, and since serotonin is an essential neurotransmitter in the regulation of sleep, aspirin would thus enhance sleep.

In summary, niacin is a potent activator of the vasodilatation component of the inflammatory response, an effect mediated by bradykinin, histamine, and prostaglandins. This effect can be blocked by aspirin, due to its potent blocking effect on prostaglandin synthesis as well as its lesser ability to inhibit the action of the kinins. When combined with an antihistamine, the blocking of the niacin flush is quite complete.

Since the continued administration of niacin by itself also attenuates or abolishes flushing, it is possible that

megadose niacin depletes all of these mediators, especially bradykinin and histamine. The anti-lipolytic action of niacin may inhibit prostaglandin synthesis, but prostaglandins are also being generated by continuous exposure to niacin. Thus megadose niacin may have substantial effects on the inflammatory and immune systems and on the central nervous system as well.

Regardless of the many implications that this suggests in the physiology of niacin therapy, one application, the use of aspirin, with or without antihistamine, provides an expedient way to initiate megadose therapy without a disturbing flush reaction.

In clinical practice it is worthwhile to determine the flush dose of niacin and then use aspirin, if necessary, to attenuate the flush while building up rapidly to megadoses. The method I find most convenient is as follows:

1. Dispense the 100 mg size niacin. Break a tablet in half to begin with 50 mg, t.i.d.
2. Next day increase the dose to 100 mg, t.i.d.
3. Then increase the dose by 100 mg each day until the flush occurs. Note the flush threshold dose.
4. Now take 600 mg of aspirin, preferably at bedtime, two consecutive nights. This should prevent the flush.
5. Next day the niacin may be doubled. This is usually sufficient to prevent further flushing, and double the flush dose may be an optimal maintenance dose.
6. If the flush should recur, simply take aspirin again, 600 mg, plus Periactin, 4 to 6 mg, if the initial aspirin was insufficient, and then double the niacin dose once again.
7. The dose may be doubled each day without further flushing until the therapeutic dose is established. I have observed that the lowest dose that will prevent flushing is often the optimum therapeutic dose.

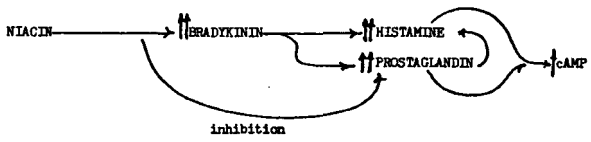
Since a prickling sensation after niacin is commonplace, even after the flush has habituated, I surmise that bradykinin activation goes on, but without the amplification of inflammation beyond the intravascular mechanisms. The failure to ignite the histamine component of the flush in the extravascular field is due to the fact that mast cells are depleted of their histamine granules by continued exposure to niacin. In addition, histidine decarboxylase, the enzyme that catalyzes the conversion of histidine to histamine, is inhibited by prostaglandins and these are probably present at above-normal levels in the flush-habituated, niacin-treated patient because of the continued production of bradykinin which, though depleted below initial levels, is present in above-normal amounts nevertheless, due to the persistent activation of Hageman Factor by niacin.

On the other hand, prostaglandin synthesis is limited by the anti-lipolytic effect of niacin, which inhibits the liberation of arachidonic acid from cell membranes. Thus we are left with the likelihood that the initial flush is primarily due to bradykinin and with histamine and prostaglandin activity secondarily. Figure 3 depicts these relationships.

As the niacin flush becomes habituated I presume that the bradykinin may become depleted due to using up the circulating kallekrein more rapidly than it can be synthesized in the liver. Histamine is also reduced, due to mast cell depletion and inhibition of histidine decarboxylase caused by increased prostaglandin activity secondary to the chronic bradykinin presence that has been induced by niacin. In short, I predict that histamine is reduced while bradykinin and prostaglandins are all increased to a limited extent due to

FIGURE 3

Immediate Effects of Niacin on Inflammation



niacin. This is worth testing. The relationships are charted in Figure 4.

The initial prostaglandin activity is undoubtedly quite high because there is a marked initial inflammatory response to the niacin, before the depletion of bradykinin. So, at the beginning, the sedative effect of niacin is also more noticeable, probably reflecting increased PGE activity, which is known to be sedative. Later this effect is reduced as the presence of PGE, which is associated with inflammation, is very likely reduced.

In addition there are important effects due to the diminished but persistent action of PGE within the central nervous system. In particular it is known to inhibit the release of norepinephrine at presynaptic sites in the adrenergic pathways. This anti-norepinephrine effect could be of utmost significance in schizophrenia. For instance, amphetamine psychosis has won favor as a pharmacologic model of schizophrenia, and the basic action of amphetamine is to increase the synthesis and prevent reuptake at noradrenergic synapses. PGE has on opposite effect and therefore may account for some of the antischizophrenic action of megadose niacin.

Further research into the relationship between niacin and the mediators of inflammation and immunity is indicated. Meantime, the fact that niacin is active in modifying the chemical mediators of inflammation and immunity, and the fact that there are obvious effects on cerebral neurotransmitters as a result, provides another avenue from which to approach an understanding of the antischizophrenic effect of megadose niacin therapy.

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FIGURE 4

Effects of Prolonged Niacin Administration