

REVIEW

A two-phase network theory of atopy and asthma causation: a possible solution to the impact of genes, hygiene and air quality

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Introduction

Although the proximal cause of asthma is well understood, the mechanism by which predisposing and protective risk factors interact to create the distal cause remains unclear. The 'hygiene hypothesis' suggests that early exposure to microbes and allergens can be protective [1]: a clean western lifestyle causes the immune system to mature in a way that predisposes to asthma in genetically asthma prone individuals. Apparent inconsistencies in data suggest that multiple processes may be operating [2]. For example, some studies show that exposure to microbes and allergens are associated with increased risk [3–9]; others with decreased asthma risk [10–13]. More consistently, several different genes [14] and types of air pollution including smoking [15,16], are associated with increased asthma risk. There is some evidence that different types of psychological [17,18], and dietary [19,20] factors also contribute to asthma through unknown mechanisms

Networks are a special type of complex system [21], and some properties of asthma are consistent with the distal cause being a network, rather than a backward sequential continuation of known inflammatory mediators (Fig. 1) [22]. This review uses network theory to suggest that asthma onset within the network involves two phases. In Phase 1, a combination of genetic factors and lack of exposure to microbes and allergens throughout the body creates an inadequately trained or atopic immune system. In Phase 2, a combination of immune challenge and immune suppression in the lung creates the self-regulatory error of asthma, a process potentiated by other genes and an atopic immune system. Microbes and allergens protect against atopy at Phase 1 but contribute to asthma at Phase 2. This theory provides a way of integrating different types of causal factor, as well as providing an explanation for apparent inconsistencies in findings.

Background to network and control system theories

The two-phase network theory of asthma is based on two types of mechanism: network systems and control systems. A network is a set of units with massive parallel causal interconnections, and this complex structure confers unique emergent properties collectively known as 'intelligence' [23]. Two of these intelligent properties are pattern recognition ability and the ability to learn from experience. Figure 2 shows the structure of a pattern recognizer that is capable of learning. Control systems are simpler mechanisms: the simple feedback loop is an example that creates homeostasis [24,25]. The two types of mechanism can be combined in the form of a network-controlled control system, when a control system is embedded in a network (Fig. 3).

Current medical theory assumes that many of the body's control systems are independent or at most coincidentally connected. The intelligent body hypothesis suggests that all the body's control systems are embedded in a single extended network system that integrates their functioning in an intelligent manner [26]. When a control system is embedded in a network, then the parameters of the control system (normally seen as fixed) are nodes in the network, and so can be controlled by the network. That is, control system parameters, such as the reference criterion (the set point or goal) or the gain (the amplification of response to detected error), are determined by the network. When a control system is embedded in a network, then the control system acquires the emergent properties of the network, namely pattern recognition and learning.

Networks are an efficient mechanism for recognizing patterns that are infinitely variable. If a control system acquires pattern recognition capability, then the reference criterion need no longer be a single set point but can be a complex pattern, a pattern that may, for example, be temporally sensitive. Network-embedded control systems can therefore control more complex outcomes than simple

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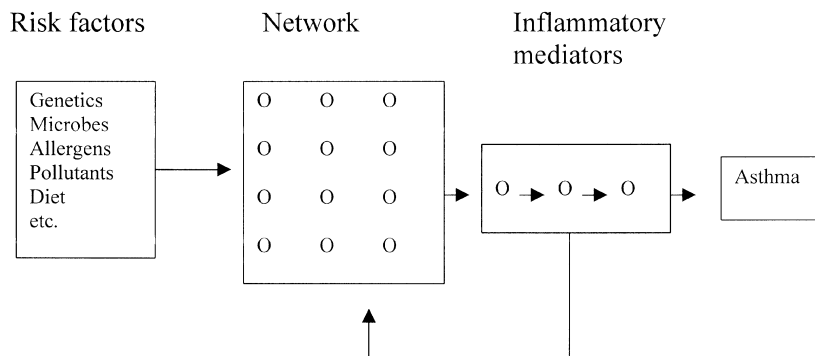


Fig. 1. A network system (parallel causality) may precede the sequential causality of the known inflammatory mediators of asthma.

control systems. For example a network-embedded control system can achieve homeodynamic control in contrast to the simpler homeostatic control of the stand-alone negative feedback loop. Many physiological parameters are homeodynamic rather than homeostatic (e.g. diurnal rhythms).

Complex networks are also capable of learning or self-organizing. A pattern recognizer can learn to recognize patterns if a supervisor provides the correct answers. Equally, a control system that is embedded in a network can become more efficient at self-regulation, if a supervisor provides information about successful and unsuccessful self-regulation. Such a control system, called a self-organizing self-regulating system, has the advantage that it can modify itself in response to the particular conditions it operates within – it can become a more efficient self-regulator through experience.

A self-organizing intelligent body would need a supervisor. If some genes specify patterns rather than structures, they could act as supervisors in an intelligent self-organizing

self-regulating network. Pattern-specifying genes would work in the following way. First, the gene detects if a particular pattern occurs in the network. If the pattern specified by the gene occurs, then the gene would be inactive. However, if the pattern does not occur, then the gene activates self-organizational change until the network creates a pattern similar to that specified by the gene. The network evolves until it gets it right, where 'right' is genetically specified.

If genes act as pattern specifiers, then some body structures are not genetically specified but are created when the network evolves during the early development of the individual, guided by the pattern specified by the genome. Consequently, the way the network self-organizes depends not only on the genetically specified pattern but also on the environment in which the network is growing. The eventual network structure also depends on the environment.

It seems likely that patterns of immune response are genetically specified – e.g. there is genetic specification that a particular pathogen should lead to a particular type and level of immune response. This 'correct' immune response should therefore evolve in the network as the organism grows, and even when adult, a self-organizing system should check that it is producing an appropriate immune response – and if it is not, evolve again until it gets it right. An intelligent immune network should be able to produce the correct genetically specified immune responses.

Network theory of asthma

The network theory of asthma is that the distal cause of asthma is an error in the intelligent network that controls the body's control systems. The output from the network initiates the sequence of inflammatory mediators that are known in asthma (Fig. 1). The network output that initiates the inflammatory sequence involves two phases.

Phase 1: the development of atopy

Let us suppose that there are pattern-specifying genes for

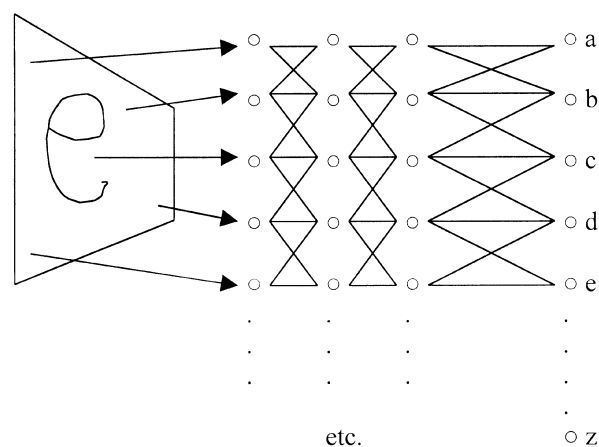


Fig. 2. A simple network pattern recognition device, showing a sample pattern (a handwritten letter 'e') on the left, then the 'input' layer of the network, then two 'hidden layers' and on the right the 'output layer' of the network. Activity in the output layers indicates the classification of the pattern.

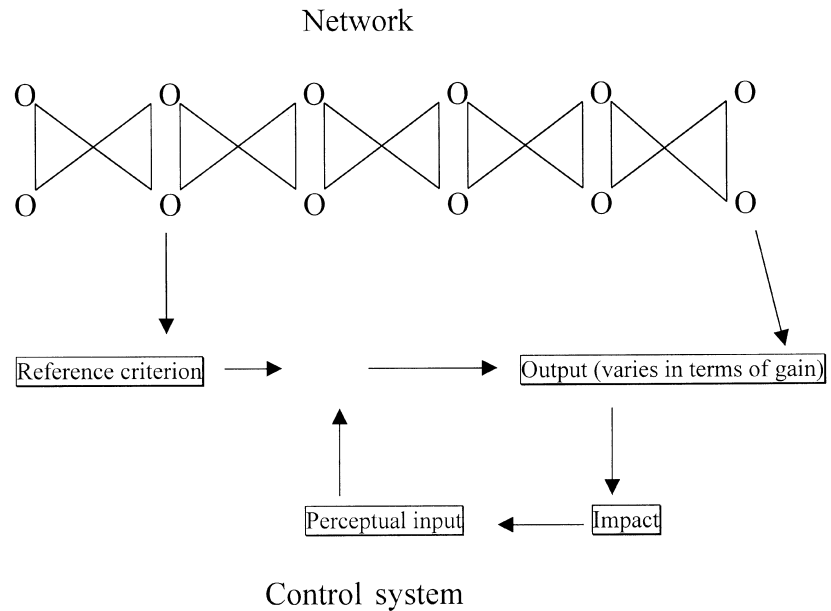


Fig. 3. A single negative feedback loop where two parameters, reference criterion and gain, are controlled by outputs from a network.

the function of the immune system, but that while the network is self-organizing to achieve that specification, insufficient training material is provided. Network theory predicts that the immune system will, under these circumstances, self-organize in a way that is suboptimal: Consider what might happen in the analogous case of a pattern recognition device designed to recognize handwriting (Fig. 2). The supervisor specifies that there are 26 letters in the alphabet, but some letters are always missing in the examples presented during the training phase. Suppose that the 'e' is always missing. The network will learn to recognize most letters, but it will not learn to recognize an 'e'. Instead, when tested, it will tend to confuse an 'e' with other letters, and this confusion will also extend, because pattern recognition is distributed over the entire network, to other letters as well. In terms of the immune system, inadequate training of the network means that the network has insufficient exposure to the variety of different pathogens. Insufficient exposure leads to inappropriate network outputs. One way of representing atopy is that it is an inappropriate pattern of immune responses to allergens. In atopy the weak T helper (Th)2 immunity with which most children are born does not deviate to the Th1 cytokine profile, suggesting that there is a failure in a maturational process [27]. It would be consistent with network theory that the immune system matures into an uneducated form, due to poor training opportunity.

As supervisors, genes play a role during immune training. Some genetically specified patterns may be more sensitive than others for producing a suboptimal network under circumstances of inadequate training. It is therefore likely that there are several different atopy genes that

facilitate suboptimal network learning when the network is taught in an inadequate learning environment. The atopy genes do not create atopy directly: they merely facilitate suboptimal learning when the immune system is presented with inadequate training material, and so atopy genes are neither necessary nor sufficient for atopy.

In addition to the quality of training material and genes, immune education may depend on other contextual factors, just as psychological education depends on context. However, what these other contextual factors are remain uncertain.

Phase 2: the development of asthma

Not all atopics have asthma. Nor is atopy a necessary condition of asthma [28]. Atopy merely contributes to a second phase of asthma development within the network. From the perspective of a network-embedded control system, asthma involves two kinds of self-regulatory error. First, the immune response is set too high, suggesting that the network has altered a control system reference criterion. Second, asthma is an intrinsically variable or oscillating disease. Oscillation is a feature of control systems where the gain is set too high in relation to the lag (lag is the time taken for information to flow round the loop). (A common sense illustration of such oscillation is what happens when someone alters the temperature control in a shower too fast. Knowledgeable shower takers move the control knob slowly!) Both these features suggest that the self-organizational change in Phase 2 is a response of a network that has detected that self-regulation is inadequate. Asthma develops

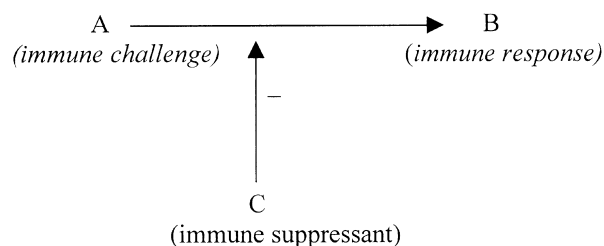


Fig. 4. The compensation rule: if the signal from A to B is interrupted by C, then the activity in the pathway increases. Either A's output increases or B becomes more sensitive to A.

because the intelligent network 'thinks' that it has been getting the immune response wrong.

Self-organizing networks correct persistent self-regulatory error by using the compensation rule [22]. Suppose that there is a genetically-specified pattern that activation of one unit in the network, node A, always leads to the activation of node B (see Fig. 4). If this pattern is interrupted by the inhibiting effect of C, then a self-organizing network should compensate, either by increasing the output from A or by increasing the responsiveness of B to A – in other words, the system learns to compensate for the interruption one way or another. A common sense example illustrates how this works. Suppose that there is a thermostatically controlled room where the temperature is generally too low. If the parameters of the control system are controlled intelligently by the room's owner, then the owner can either install a more powerful boiler (i.e. increase the gain) or the owner can raise the thermostat (i.e. change the reference criterion).

Phase 2 of asthma development uses the compensation rule in the following way. Immune challenges normally produce a level and type of immune response that is genetically specified. However, when immune challenge is coupled with an immune suppressant, the level of immune response will be less than the genetically-specified pattern. Although a few such combinations will simply register as self-regulatory failure, repeated combinations of immune challenge and suppression will lead the intelligent self-organizing network to alter some control system parameters. The alteration compensates for the effect of immune suppression. Initially, gain is increased (the system 'tries harder' [29]) leading to an oscillatory pattern created by excessive gain, and then the reference criterion is changed (the system 'does something else' [29]). The change in reference criterion involves an increase in immune response, particularly to the immune challenge. The overall result is a hyperactive immune system that is also sensitized to the particular antigens that contributed to the self-organizational change. The system becomes sensitized to particular microbes and allergens through associative learning.

A number of additional factors contribute to the proposed Phase 2 network changes. First, an immune system with suboptimal pattern recognition capability (i.e. atopy) will increase the likelihood of the Phase 2 error. In the non-atopic individual, the immune system is better educated and so is less prone to detect the combination of immune challenge and suppression as an error; consequently less compensation takes place. Second, the detection that immune self-regulation in the lung is inadequate will have some genetic basis. Genes that confer propensity to detect error will increase the likelihood of the Phase 2 changes. Thus, there should be asthma genes in addition to atopy genes, though again, asthma genes do not create asthma but only facilitate the asthma-creating network learning environment. Finally, because the immune system is part of a wider network, other factors, such as general immunocompetence, may also affect the way the immune system learns to self-regulate in the asthma format – a format that the intelligent network 'thinks' is the correct format.

Discussion and empirical evaluation

The two-phase network theory of asthma suggests that atopy results from a combination of genetic predisposition and inadequate exposure to microbes and allergens in early life. Then, atopy and other genetic factors predispose to asthma when immune challenge is repeatedly combined with immune suppression (Fig. 5). The term 'phase' rather than 'stage' is used because although Phase 1 is a contributor to Phase 2, both phases may develop simultaneously in the young child.

A central feature of this theory is that atopy and asthma causation involve different processes, and that genetic and environmental risk factors operate differently at either phase. Familial patterns of asthma suggest that atopy and airway hyper-responsiveness are inherited independently [30]. Several different types of candidate asthma-related genes have been identified, but no clear relationship with the asthma phenotype has been established [14]. This is consistent with the prediction that genes contribute to a network environment in which either the Phase 1 or Phase 2 learning takes place, rather than genes directly manufacturing structures for atopy or asthma. Further support for the independence of atopy and asthma causation comes from research on environmental allergens suggesting that the induction of immunoglobulin (Ig)E and the development of childhood asthma are determined by independent factors [31].

A second feature of the theory is that it predicts that exposure to microbes and allergens have a protective effect at Phase 1 but a detrimental effect at Phase 2. Phase 1

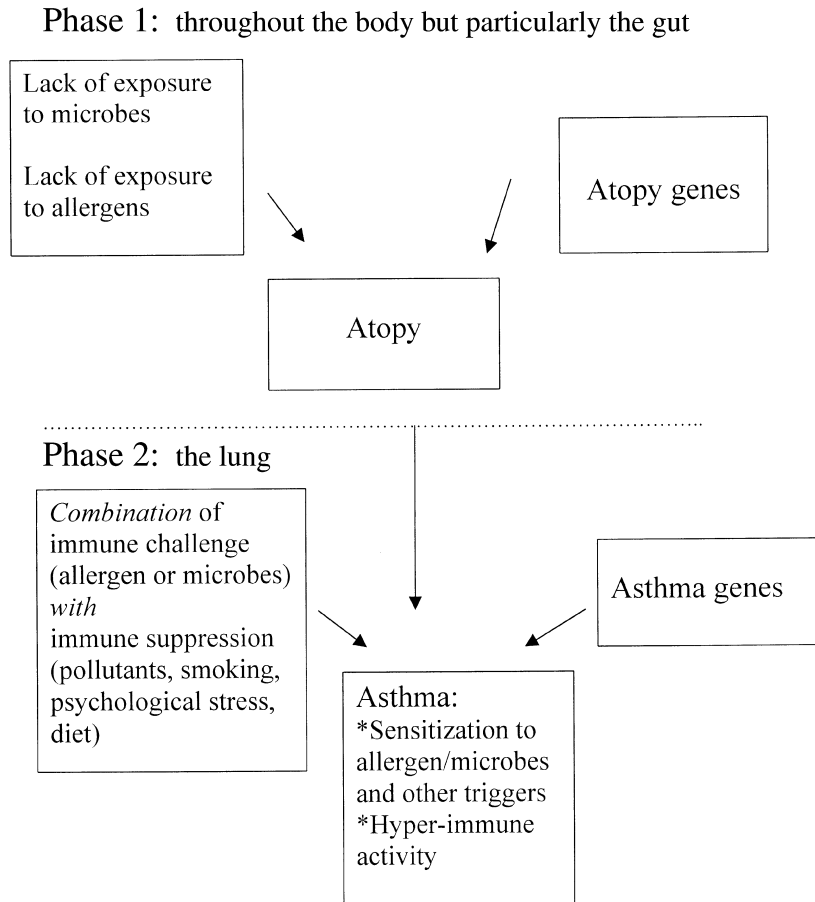


Fig. 5. Two-phase network theory of asthma.

effects occur throughout the body: Phase 2 effects occur only in the lung.

Several studies show the protective effect of early infection, particularly in the gut [32,33]. The network theory is supported by recent suggestions that it is high turnover of different bacteria genera, species and strains rather than any particular type of bacterium that protects against atopy [2,34]. High turnover provides a network with the ideal learning environment, as training in pattern recognition occurs most rapidly when there is repeated exposure to a variety of different patterns. Factors such as sibship size and birth order would affect microbial turnover [2]: younger children in larger families have the advantage of more immune education.

However, viral respiratory tract infections [3,4,9] but not bacterial infections [35] are associated with increased asthma risk. Other airborne viruses do not appear to have any consistent effect [33]. These findings are generally consistent with the theoretical prediction that infections in the lung tend to contribute to the development of asthma at Phase 2, but may also have a protective effect against atopy at Phase 1. Whether infection contributes to or protects

against asthma depends on its nature and timing. One large cohort study [35] identified a subgroup of asthmatic children who had experienced repeated fever infection but were less related to the atopy syndrome and who had a better prognosis. This finding is consistent with fever (frequently viral respiratory tract infections) contributing to Phase 2 but not Phase 1. That is, there are some children with frequent infections whose asthma has developed as part of Phase 2 changes, but without the poor immune self-regulatory capability created in Phase 1.

Exposure to allergens is also predicted to protect at Phase 1 but have a detrimental effect at Phase 2, and these two roles may explain conflicting results. For example, although pets are often associated with increased asthma risk [9,36], findings that exposure to pets below one year of age has a later protective effect [11] may be because, in the latter case, the protective effect of pets on atopy at Phase 1 outweighed the asthma promoting effects at Phase 2. However, once the allergen has become associated with immune suppression in Phase 2 then the system is sensitized to the allergen and further exposure leads to increased inflammation [36].

The phenomenon of neural sensitization may provide a parallel with immune sensitization, and thereby explain the circumstances under which sensitization occurs. The response to repeated weak neural stimuli normal habituates over time, i.e. there is a decreased response over time. However, if a weak neural stimulus is combined with a strong stimulus elsewhere in the body, then the response to the weak stimulus increases over time – i.e. there is sensitization [37]. Sensitization to allergens may occur because of the association of the allergen with other events that have a more disturbing effect on the immune system than the allergen itself.

A third feature of the theory is that it predicts that atopy genes create atopy only when the immune system develops in a poor training environment. Several studies support this. For example, antibiotics create a poor training environment, but increased risk of asthma, hay fever and eczema was found only in those high antibiotic using children with parental hay fever, but not those without parental hay fever [38]. This finding is consistent with theoretical prediction that genes create a network environment where poor immune maturation results from inadequate microbial turnover, caused in this instance, by the action of antibiotics.

Fourth, although the theory is not specific with regard to the effects of immunosuppressants (such as pollutants) at Phase 1, there is a clear prediction that they have a deleterious effect at Phase 2. That immunosuppressants are more important at Phase 2 is confirmed by the finding that exposure to traffic-related air pollution was associated with increased prevalence of cough and bronchitis, but not atopic sensitization [15]. That it is the combination of immune challenge and suppression that is important is consistent with two studies showing that the combination of urban air pollution and respiratory allergens is particularly harmful for asthma [39,40]. However, the possibility of immune suppression having a negative impact at Phase 1 cannot be ruled out, as contextual factors (they may include immune suppression) also affect the development of atopy.

The prediction that Phase 2 involves a combination of immune challenge and suppression may explain the mechanism underlying psychological and dietary influences on asthma onset [17–20]. Poor diet and psychological stress suppress immune activity [41]. Both these factors may contribute to asthma by creating a network environment in which reduced response occurs in response to inevitable exposure to allergens and microbes.

Finally, the theory explains why persistent exposure to triggers creates a destabilizing effect leading to more variable respiratory function. Triggers act in the same way as the initial Phase 2 determinants, and the intelligent body responds by increasing the control system gain – which leads to oscillation. The finding that stress produces no

increase in the risk of asthma attacks in the first two weeks after a severe event, but that risk then increases in the subsequent four weeks [42], suggests that stress creates self-organizational change in the network, but this change is slow. Slow change is a necessary feature of learning in networks [23].

Therapeutic implications: network-orientated therapy

Current treatments for asthma treat only the proximal part of the disease process, but it may be possible to treat the distal, network, part. Such network-orientated therapy will have a long-term effect of stabilizing the underlying asthma generating process, and possibly even create a cure. The two-phase network theory does not provide an optimistic view of gene therapy. If genes promote network learning, then changing the gene will not necessarily undo that learning. Changing the gene would be like closing the door after the horse has bolted. The theory does, however, support the recent suggestion in this journal of immuno-education in early life [2]. Safe immuno-education may achieve the benefits of microbes and allergens in Phase 1 without the disadvantages of Phase 2. Gradual exposure to allergens so that they do not become associated with other immune disturbing events may lead to the desirable outcome of an educated immune system without sensitization. Two questions need answering. The first is whether immuno-education is something that occurs during a critical phase of maturation (e.g. up to one year of age) and then remains fixed, or whether it is something that can be modified throughout an individual's life. The behaviour of other network systems in the body suggests that later network modification is possible but it is easier during early maturation (e.g. it is easier to learn a language when young but possible into old age). If immuno-education occurs throughout life, then this leads to the possibility that immuno-education may be of benefit in those who have already developed asthma, but only those with atopic asthma. Immuno-education would differ from current probiotic perspectives [43], in that what is important is not 'good bacteria' but an appropriate turnover of different bacteria. A second question is how best to achieve that immuno education – the gut may be an important site [2] but our knowledge remains limited.

At Phase 2, the theory suggests that combinations of risk factors are important in the causation of asthma. These causative immune challenges or immune suppressants then act as exacerbating triggers once asthma has developed, triggers which tend to maintain the network pathology of Phase 2. Consequently, trigger avoidance is highly recommended as a network stabilizing factor at Phase 2. While it may not be possible to avoid triggers all the time, it may be helpful to avoid airborne immuno-suppressants

(e.g. smoke, industrial or vehicle emissions) when respiratory infections occur, as the combination of the two is predicted to be particularly harmful. Other factors that improve immuno-competence such as moderate but not excessive exercise [44] and a healthy diet may also help at Phase 2, by reducing the body's immunosuppressant burden when exposed to allergens and microbes. Trigger avoidance, diet and exercise are common non-pharmaceutical advice given to patients [45].

Finally, conventional treatment of the sequential, inflammatory mediators remains important to network-orientated therapy, as inflammation itself may signal immune challenge within the network and therefore act as an internal trigger contributing to the Phase 2 change. Some studies suggest that early intervention with inhaled steroids appears to improve prognosis in early asthma [46], and this would be consistent with the control of inflammation being an element of network-orientated therapy. Clinical observation that the stability achieved by steroids can last for some time after withdrawal is also consistent with inflammation acting as an internal trigger for the network. Theoretically, steroids might be expected to have two different effects on the network: a beneficial anti-inflammatory effect and a harmful immunosuppressive effect. The positive effects appear to outweigh the negative effects, but the theoretical implication is that there is an optimum level of inhaled steroid treatment for the network. Too little treatment creates inflammation, and this would act as a signal of immune challenge within the network; excessive treatment would create unnecessary immune suppression. Network-orientated therapies may therefore be most successful if conventional therapy is optimized.

New types of network-orientated asthma therapy may yet be discovered. If asthma is the result of an interaction between genes and patterns of environmental impacts, then a cure may also need to be some kind of interaction. Gene therapy may be useful but only in the context of other forms of therapy, perhaps including, but not limited to, conventional therapy.

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