

# What is the Relationship between Asthma and Worms?

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"Common to both bronchial asthma and *Ascaris* infestation is an increase of the eosinophils of the blood. One may well ask the significance of the eosinophilia in this association".

W. W. Herrick, 1913.

Herrick (31) may have been the first person to recognise the association between asthma and helminthiasis, to question the significance of the relationship, and to attempt to investigate it. Nearly seventy years have passed since his paper appeared, but many of the problems that he raised still defy solution.

Eosinophils have provided the longest historical link between atopy and worm infection. Twelve years after Erlich described the specific staining properties of these cells in 1879, Muller & Rieder (52) recorded an eosinophilia in hookworm infection. This was confirmed two years later (82), then eosinophilia was found in rapid succession in a variety of infections with metazoan parasites including ascariasis, taeniasis (12), trichinosis (9), filariasis (30), and schistosomiasis (18). Meanwhile, eosinophils were being found in asthmatics. According to Herrick (31), Muller in 1889 observed many eosinophils in the sputum of patients with asthma. In the following year, Fink (20) described increased numbers of eosinophils in the blood of asthmatics and this was soon confirmed (21, 75).

Despite these early observations, little attention was paid to the relationship between atopy and helminthiasis for many years. A new impetus was provided by the discovery of Johansson in 1967 that asthmatic individuals had raised levels in the serum of a new class of immunoglobulin, IgND, later renamed IgE (34). In the following year, elevations in the serum levels of this same immunoglobulin were also reported in children with helminth infections (35). These discoveries provided a further nexus between helminthiasis and atopy and stimulated a number of investigations over the next decade. Since asthma is a significant and common atopic disorder, these studies have been largely confined to an examination of the interaction between asthma and worm infections. Unfortunately, the data are sometimes conflicting, interpretations have differed and many of the issues have remained unresolved.

This review attempts to analyse the information which has been reported from human studies. Limitations of space and uncertainties of significance have precluded any attempt to relate these findings to evidence obtained from experimental studies in animals. Three different strands of thought are discussed: 1) worms cause asthma, 2) worms ameliorate

asthma, 3) asthmatics inhibit worms. The evidence for and against these views is marshalled, conclusions are drawn and areas for further research are suggested.

#### *Worms cause asthma*

In 1910, Goldschmidt observed that laboratory workers who dissected *Ascaris* developed asthmatic attacks which became increasingly severe with repeated handling of material (25). It was then suggested that both asthma and many of the symptoms seen in ascariasis could be classified as anaphylactic phenomena (48, 51). Although the ability of *Ascaris* to induce the formation of reagins was realised (58), little further attention appears to have been paid to the idea that helminth infection may cause asthma until Tullis (67) reported that almost 99% of a group of Canadian asthmatics living in a non-endemic area were infected with intestinal nematodes. Most of these patients were infected with *Ascaris lumbricoides*, although a few were said to be infected with *Strongyloides stercoralis* or *Necator americanus*; none of these parasites were found in a group of allergy-free controls. In an accompanying editorial (5), the New England Journal of Medicine observed that despite its apparent outlandishness, the question that this report raised was so important that it required confirmation or denial. This was soon forthcoming. Despite some anecdotal support for the concept that worms cause asthma (8, 15), Tullis's study was strongly criticised by a number of commentators on a variety of grounds (19, 32, 42, 60, 66). These included criticism of the small size of the control group and the fewer number of times that faeces from control persons were examined. Furthermore, eradication of ascariasis with anthelmintics failed to relieve asthma. More important, however, was the failure to explain why and how asthmatics in a non-endemic area were infected with these worms. Finally, ignorance of the nature of infection in ascariasis was emphasised; each fertile female *A. lumbricoides* adult worm releases many thousands of ova per day and eggs are found relatively easily in a single direct smear. Thus, it should not take examinations of multiple speci-

mens of faeces for a single egg to be found. These considerations lead several commentators to conclude that inexperienced technicians may have misdiagnosed artefacts or vegetable particles as *Ascaris* ova (19, 42).

Not surprisingly, it did not take long for another study from a similar geographical area to appear. 123 patients with asthma in Minnesota were investigated: *A. lumbricoides*, *S. stercoralis* and *N. americanus* were not found in any patient (74). In addition, a number of reports indicated that asthmatics who lived in areas of the world endemic for a variety of intestinal nematodes were no more likely to have such parasites than non-asthmatic control subjects (2, 16, 41, 60).

Despite these findings a further paper claiming that asthma is associated with intestinal parasitism has appeared recently from Turkey (39). This report must be discounted as the asthmatics and control subjects were not age-matched. Furthermore, their environments and life styles were not comparable as asthmatics were culled from the general population while control persons were students at a nursing college. Moreover, no mention is made of the sex of either groups. Similarly, it has been suggested recently that patients who responded immunogenically to parasite infections may be predisposed to asthma (36). This view appears to have been based on the finding that subjects with skin reactivity to *Ascaris* had a higher prevalence of asthma than did subjects with negative reactivity. An alternative interpretation of these results is simply that asthmatics exposed to *Ascaris* are more likely to mount a reaginic response to parasite antigens than are non-asthmatic people.

There seems little reason to doubt that people exposed to helminths or their products in unusual ways such as laboratory or abattoir workers may develop allergic reactions including asthma. Pulmonary infiltrates with eosinophilia, sometimes associated with wheezing, may occur during the migratory phase of infection with certain worms, especially *A. lumbricoides* and *S. stercoralis* (45), and as a response to microfilariae in tropical pulmonary eosinophilia (78). Nevertheless, even though there is limited evi-

dence to suggest that human helminth infections may potentiate the production of high levels of IgE-antibodies that are not specific for worms and could cause asthma (70), the weight of epidemiological data indicates clearly that naturally-occurring infections with intestinal helminths do not cause or predispose to asthma.

#### *Worms ameliorate asthma*

The increased production of IgE in helminth infections and in atopic disorders led to the suggestion that these parasitic infections might mitigate against the development of atopic disease (57). One possible mechanism for such an hypothesis was provided by the demonstration that saturation of mast cells by myeloma IgE inhibited the Prausnitz-Kustner reaction (64). Similarly, if helminth infections stimulated excessive production of IgE, then occupation of all the binding sites on mast cells and basophils by this anti-helminth antibody would reduce the likelihood of developing reactions to environmental allergens likely to cause asthma. An anecdotal example of such an effect has been provided by Turton (73) who recounted how his longstanding hay fever did not recur after he infected himself experimentally with hookworm. *In vitro* studies have also provided some experimental evidence in favour of this suggestion. When human lung fragments were exposed to IgE-rich serum from West African subjects, they became resistant to subsequent passive sensitisation with serum containing grass pollen-specific IgE (23). An alternative suggestion was that a vigorous IgE antibody response to parasitic antigens might inhibit, by antigenic competition, the capacity of individuals to mount an effective IgE antibody response to inhaled allergens; this possibility could not be verified (37, 71).

The relevance of these ideas however, can only be indicated by epidemiological investigations of the prevalence of asthma in areas similar in all respects except for the presence or absence of endemic helminth infections. Unfortunately, this ideal is almost impossible to achieve.

Several studies have reported that asthma is uncommon in parts of the tropics including Papua New Guinea (3), the Gambia (22) and Rhodesia (49). In the Gambia, Godfrey (22) investigated the prevalence of asthma in a population said to be heavily infected with helminths. He failed to find any cases of asthma amongst 131 rural schoolchildren and 100 rural villagers of various ages, or in 60 urban schoolchildren, although a number of asthmatics were seen in an urban hospital. He concluded cautiously that these observations were consistent with the hypothesis that high IgE levels due to parasitic infections helped prevent the development of atopic illness. Further support for this view was given by the failure to find any asthmatics in 100 subjects attending a rural clinic in Rhodesia, although asthma was common in the capital city (49).

The belief that asthma is rare in the tropics, particularly in rural areas, where helminths are endemic has been enthusiastically endorsed (6, 68). But is it true? It is very difficult to define the prevalence of asthma in developing countries where health and medical services are frequently grossly inadequate. Asthma is an intermittent disorder and if the diagnosis is made on the basis of the demonstration of reversible airways obstruction (22, 76), then the chances of finding such patients during a transient visit to a rural area must be very small. Indeed, when provocation tests such as exercise-induced bronchospasm were used to identify asthmatics, then affected persons were easily found in rural regions (13, 14). Nor is it reasonable to claim that there are differences in the prevalence of asthma between urban and rural areas in the tropics on the basis of finding asthmatics in the large towns or cities. It is well known that the usage of hospital facilities in developing countries varies inversely with the distance the patient lives from the health centre (40). This effect must surely be exaggerated when asthma is considered; not only is the rural asthmatic too dyspnoeic to walk to hospital for treatment, but experience has taught him that attacks frequently subside spontaneously. Finally, even if there were a reduction in the prevalence of asthma in rural as opposed to urban

areas, no satisfactory explanation of why this should be so had been advanced. Godfrey (22) surmised that the prevalence of parasitic infections may have been reduced in the urban population but provided no data to substantiate this hypothesis. Although patterns of infection undoubtedly vary, helminth infections may be very prevalent in many tropical urban areas. Among the many examples which could be cited are filariasis in Calcutta (29), schistosomiasis in Belo Horizonte (7) and intestinal helminths in Nairobi (79) or in the major towns of south western Iran (47). All of these helminths are capable of stimulating high levels of IgE production and might be expected to interfere with atopy in urban areas if the hypothesis is correct.

In contradiction of the claims that asthma is rare in the tropics are a multitude of reports from many different countries emphasising the prevalence and importance of asthma in the tropics or in other areas where helminths are endemic. Some of these reports are derived from clinical impression and hospital data in Barbados (55), Ghana (4), India (61), Israel (44), Kenya (77), Nigeria (1, 46, 63, 76), Malaysia (43), Maldives (80), Singapore (65), Sri Lanka (53) and Zambia (11), while others are based on community studies of lesser or greater degrees of sophistication and comprehensiveness in rural and urban areas of Cuba (59), Dominica (26), Micronesia (10) and Tanzania (13, 14). While many of these studies were simply concerned with describing the patterns of asthma in these various locations, several studies specifically addressed the question of the interaction of helminthiasis and atopy. None of these studies could support the theory that helminth infections, high levels of IgE or rural living prevented the development of asthma (13, 14, 46, 80).

As an extension to the hypothesis that helminths prevent asthma, it has been suggested that there should be a lower prevalence of immediate skin reactivity in people in helminth-endemic areas (14). When patterns of skin reactivity between different countries are compared, interpretation may be made difficult by uncertainty as to whether allergens in one country are significantly allergenic in an-

other. Nevertheless, no differences were found between Papua New Guineans (in an helminth-endemic area) and Australians (where helminths are non-endemic) (81). Similarly, if asthma is less prevalent in rural areas compared with urban areas of the tropics, then there should be less skin reactivity in populations inhabiting rural areas. This could not be shown in two studies (22, 46). Finally, skin reactivity was observed to be greater in African than in Caucasian blood donors in Capetown, despite the fact that the former group had a much higher prevalence of intestinal ascariasis (54). Thus, it appears that there is little evidence that helminths reduce skin immediate hypersensitivity reactions.

Similarly, it has been suggested that if asthma is less prevalent in rural than urban areas as a result of greater helminth infection, then total serum IgE levels ought to be higher in people living in such areas (14). Conflicting results have been found when these populations have been compared. Several investigators found higher levels in rural normal subjects (22, 49) but this could not be confirmed (46). In any case the significance of this observation is doubtful since IgE levels in both urban and rural tropical areas are much higher than are seen in countries where helminths are not endemic.

In conclusion, it can be seen that support can be gathered for and against the hypothesis that worms ameliorate asthma. Indeed, some authors have sat on the fence with a foot in each camp (14, 49). The weight of evidence favours the view that asthma is common in both rural and urban areas of the tropics and that helminths do not inhibit the development of asthma. Nevertheless, the question still remains open. There is a need for more long term studies of defined populations in various rural and urban areas of the tropics with particular reference to the prevalence and nature of helminthiasis and the prevalence of atopic disorders. Valuable evidence might be obtained if Turton's (73) experience could be verified. Although it has been suggested that a group of asthmatics might be deliberately infected with worms (6), most would agree that such a course

would not be ethical. It might be possible, however, to analyse in retrospect or in prospect, the effects of naturally acquired helminth infections on asthma in a group of people, for example, servicemen or migrants from temperate zones, who moved to helminth-endemic areas in the tropics.

#### *Asthmatics inhibit worms*

The fundamental question of why humans should possess the ability to make IgE needs to be answered. It is well understood that antibodies of other immunoglobulin classes have protective actions against other micro-organisms. On the other hand, the well-recognised effects of IgE are generally deleterious and result in the various atopic disorders. Not only are these conditions extremely frequent in the community, but they produce considerable morbidity and occasional mortality. Furthermore, the tendency to atopy is inherited (17, 62). This seems paradoxical unless there is some counterbalancing advantage in being able to mount efficient reaginic responses.

Eosinophilia and an elevated serum IgE level are characteristic features of the atopic state. The occurrence of these same two phenomena in the helminthiasis makes worms obvious candidates as targets for IgE antibodies. Since helminth infections have long been important causes of morbidity and mortality, they could provide a continuous pressure on the gene pool. According to this hypothesis, then, the genetically-controlled capacity to manufacture IgE antibodies efficiently confers a survival advantage by increasing resistance to worms. By the same token, however, IgE antibodies may also be made more easily against a wide variety of ubiquitous but non-helminthic allergens. Thus, the price of a greater ability to deal with helminth infections may be a legacy of atopic disease.

If this hypothesis is correct, then atopic individuals living in areas endemic for helminths ought to have less worms than their non-atopic counterparts. Before considering relevant evidence, however, it is necessary to review briefly a number of aspects of helminth infections.

Firstly, it must be remembered that with one or two exceptions, worms do not have the capacity to replicate within the human host. This means that the worm burden is directly related to the intensity and duration of exposure to infective forms and is inversely proportional to any resistance that may have developed. Secondly, in many helminth infections, the presence or absence of disease is not dependent upon the presence or absence of worms, but upon the number of worms. Thirdly, the ease with which the presence of helminth infection is diagnosed depends upon the morphology and reproductive characteristics of the worm under consideration. For example, the large adult female *A. lumbricoides* produces some 200,000 eggs per day and it is easy to detect light infections on a single smear of faeces. On the other hand the much smaller adult female hookworm produces only 5–10,000 eggs per day and ova may be harder to find in the stools. Similarly, larvae of *S. stercoralis* may only be found if an assiduous search is made for the parasite. Fourthly, an immune response, whether involving eosinophils, IgE or other arms of the immunological defences, is only likely to develop if worms have a phase of tissue migration at some stage during their life cycle. Consequently, worms such as *Enterobius vermicularis* which develop and dwell within the lumen of the gut do not stimulate IgE production (33). Fifthly, when an effective immune response is mounted, there is frequently not an elimination of all the worms but a reduction in the worm burden. For example, in dogs immunised against the dog hookworm, *Ancylostoma caninum*, hookworm infection may still develop but the worm burden may be reduced by up to 90% (50). This is usually sufficient to prevent disease and thus confer a clinical advantage.

It follows from these observations that when testing the hypothesis that asthmatics inhibit worms, it is more relevant to consider worm burdens than the simple prevalence of infection. As far as I am aware, only one study has taken these factors into account. In that investigation, a rural population in the highlands of Papua New Guinea was surveyed (28). Not only was hookworm infection universal, but interpreta-

tion was simplified by the absence of concurrent infections with other intestinal helminths. Five hundred villagers were tested for immediate hypersensitivity skin reactions to a variety of allergen preparations; 10% of the population were identified as being atopic on the basis of skin reactivity. When hookworm worm burdens were quantified by faecal egg counting, a significant reduction was found when atopic persons were compared with non-atopic villagers. This was confirmed when egg counts in control subjects were compared with those in a group of asthmatics seen in the local hospital who had come from a similar but more dispersed area. Thus, it was concluded that the atopic state conferred increased resistance to infection with this worm.

Despite what has been said about the importance of quantifying the intensity of infection, some useful information may still be gleaned from the simple prevalence figures of certain helminth infections reported in some studies. Since light infections with *A. lumbricoides* are so easy to detect, any differences between atopic and non-atopic populations are unlikely to be discerned when this infection is considered. Infections which are harder to diagnose, such as hookworm infection and strongyloidiasis are more likely to be missed if the worm burden is light. Thus, an apparently reduced prevalence in a particular population may reflect lighter worm burdens in that population.

Person & Su (56) compared the prevalence of infection with *E. vermicularis* in atopics and non-atopics in Minnesota. They found no differences between the two groups but realised that it would have been better to perform a similar study in a region where tissue-migrating nematodes were endemic. Salako & Sofowara (60) had, in fact, already reported the prevalences of *Necator americanus* and *S. stercoralis* infections in African asthmatics and control subjects. They were simply concerned to refute the observations of Tullis (67) and show that people with helminthiasis need not have asthma. Consequently, they paid no attention to the reduced prevalence rates that they described in their asthmatic patients. They reported that

14% of 250 asthmatics and 44% of 182 control subjects were infected with *N. americanus* and 4% of asthmatics and 12% of control persons had strongyloidiasis. Analysis of these figures by the Chi-square test reveals that there is a significant reduction in the prevalence of hookworm infection ( $P < 0.001$ ) and *Strongyloides* infection ( $P < 0.01$ ) in the asthmatic population.

Although some authors did not observe any appreciable differences in prevalence rates of helminth infections between asthmatics and non-asthmatics (14), suggestive information is sometimes given by others but in insufficient detail to analyse it properly. For example, Warrell et al. (76) found that 22% of 36 asthmatics had *Necator*, *Taenia* or *Strongyloides* infections, compared with 37% of 415 unselected outpatients. These same authors noted that 9% of Kenyan asthmatics had stool parasites compared with 26% of the general ward population, but gave no details or references.

It can be seen that there are a number of observations that are consistent with the idea that asthmatics are more resistant to helminths. Since a proposed mechanism is that as asthmatics are able to mount an eosinophilic and IgE response more easily, the eosinophilia and the elevation of serum IgE levels might be expected to be greater in such persons. If such responses do occur they would be consistent with this hypothesis but not prove it, since each effect could be triggered in different ways in each condition and may simply be additive in asthmatics who happened also to have a worm infection.

In the Papua New Guinean subjects mentioned earlier, both eosinophil and IgE levels were significantly greater in asthmatics and non-asthmatic atopics, the same groups that had lower hookworm egg counts (27). Nevertheless, subsequent studies have given conflicting results. Serum IgE levels were also noted to be significantly greater in asthmatics than in control subjects in two investigations (46, 69) and in rural but not in urban asthmatics in another study (46). On the other hand, no significant differences were found between asthmatics and non-asthmatics in other investigations (14, 22,

71). Finally, asthmatics had lower serum levels than did control subjects in one study (76).

It may be that serum titres of specific anti-worm antibodies are more important than are total IgE levels. Again, the available data are confusing. The prevalences of IgE antibodies against *A. lumbricoides* were not different between Papua New Guinean asthmatics and control subjects, but were increased in patients with chronic obstructive lung disease (69). On the other hand, IgE antibodies to *A. lumbricoides* were common in Indonesian atopic children but were not present in a small number of control subjects (72). Finally, no differences were found between Papua New Guinean asthmatics and non-asthmatics with respect to IgE antibodies against *A. lumbricoides*, but antibodies against hookworm were higher in asthmatics (71).

It seems a pity that so much effort has been paid to measuring total and specific IgE levels in asthmatic and non-asthmatic individuals living in tropical countries. These are certainly valid objectives when mechanisms are being investigated, but the crucial question is whether or not helminthiasis, and in particular, the intensity of infection, is reduced in atopic persons living in areas with endemic worm infections. The evidence so far garnered is tantalising but not yet conclusive. Further studies are needed to confirm that intestinal worm burdens are reduced in atopic populations. Furthermore, similar studies of the effects of atopy on worm burdens in tissue nematode infections such as onchocerciasis and in trematode infections such as intestinal and urinary schistosomiasis may be worthwhile.

#### *The fourth possibility*

It may be of course, that atopy and helminthiasis may have no direct causal relationship with each other at all. Common hallmarks such as eosinophilia and increased IgE production might be mere epiphenomena with these effects occurring as a result of quite independent mechanisms in the two groups of conditions. Whether or not this is the case can be shown only by the demonstration that all other hypotheses are incorrect.

#### *Conclusions*

On the basis of the data that have been published, it seems most unlikely that helminths have a causal role in the development of asthma when infections are acquired naturally. More evidence is available to support the notion that infection with worms ameliorates asthma. Nevertheless, there are serious grounds for doubting the validity of one of the major prerequisites for this hypothesis, namely that asthma is uncommon in the tropics, particularly in rural areas. Although the majority of studies are unable to support this theory, the question is still undecided and further investigations are required. Such studies should attempt to identify asthmatics in the population by examining the effects of exercise, inhaled histamine or allergen provocation on airways obstruction. Pioneering studies have suggested that atopic individuals may be more resistant to helminth infections. This view is not yet proven and further well-designed studies are needed to assess the effects of the atopic state on worm burdens in a variety of helminth infections.

There is no reason to suppose, however, that these latter two theories are mutually exclusive. It is possible that an asthmatic is more resistant to worms, but that should he become infected, than the severity of his asthma may be decreased. It seems to me that epidemiological investigations must be the final arbiter in establishing a relationship between atopy and helminthiasis. If such a relationship is eventually defined, then the mechanisms of this interaction will need to be elucidated. What is the role of the IgE and how does it act? What are the functions of the eosinophils and how do they perform? Ideas are abounding. For example, a dual role for eosinophils with destruction of worms and containment of the immediate hypersensitivity reaction invoked by released parasite antigens has been suggested (24). Similarly, an ingenious hypothesis linking IgE, mast cells and eosinophils has been proposed by Kay (38). He has postulated that helminths activate complement which coats the worm tegument. This, in turn, allows adherence to the worm of mast cells via their membrane receptors for comple-

ment. Interaction of helminth antigens and IgE then releases pharmacological mediators which recruit and arm the eosinophils that finally destroy the worms.

Investigation of these growing edges may provide new insights into basic biological processes and may lead ultimately to the development of novel ways of treating and controlling both the allergic disorders and the helminthiasis.

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