

The Nature of the Problem of Immunity and its Solution

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Abstract

Tens of millions of our own kind are killed by diseases in spite of the laudable effort of our healthcare teams every single year that the problem of immunity remains unsolved. But this problem is not longstanding because of the complexity of the nature of immunity but rather because we have been trying to obtain the knowledge we require to solve problems from theories that are logically deduced from observations when such knowledge can only be obtained from theories that are obtained with a method that requires reality to be illustrated and deductions to be made only for the purpose of knowing whether or not we have obtained the knowledge we seek from the results of our illustrations through the agreement or disagreement between facts and the consequences we have deduced from such results. The most influential among the theories of immunity is that which Ilya Mechnikov logically deduced from inflammatory phenomena in which phagocytosing cells that envelope and store foreign entities are brought to sites of cell death even in the absence of pathogens. This theory of immunity aimed to find proof for the logical deduction in which Pasteur and co-workers proposed the mechanism by which

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Tens of millions of our own kind are killed by diseases in spite of the laudable effort of our healthcare teams every single year that the problem of immunity remains unsolved. But this problem is not longstanding because of the complexity of the nature of immunity but rather because we have been trying to obtain the knowledge we require to solve problems from theories that are logically deduced from observations when such knowledge can only be obtained from theories that are obtained with a method that requires reality to be illustrated and deductions to be made only for the purpose of knowing whether or not we have obtained the knowledge we seek from the results of our illustrations through the agreement or disagreement between facts and the consequences we have deduced from such results. The most influential among the theories of immunity is that which Ilya Mechnikov logically deduced from inflammatory phenomena in which phagocytosing cells that envelope and store foreign entities are brought to sites of cell death even in the absence of pathogens. This theory of immunity aimed to find proof for the logical deduction in which Pasteur and co-workers proposed the mechanism by which

pathogens cause diseases to be one through which they attack their hosts as well as the deduction that emerged as its logical consequence, that the mechanism of immunity must necessarily be those that defend such hosts from attack by destroying pathogens. After all, the repeatedly proven germ theory was assumed by its deniers to be proven false by the prosperity of pathogens in organisms that enjoy complete immunity which should not be observed at all if indeed, the attack mechanism and defence theories have any truth in them. And in the same manner, the prosperity of pathogens in completely immune individuals was seen as disagreeing with the repeatedly proven germ theory by its proponents and therefore as an observation that is not capable of disproving the attack mechanism and defence theories which were logically deduced from this verified theory. But immunity is really the reduction in the severity of diseases which occurs differently in different individuals even when exposure to their causes is similar so that while their manifestations are so severe in those who are not immune that they are killed, severity is reduced through different degrees in those who survive because they are sufficiently immune with the completely immune experiencing no symptoms at all in the phenomenon of asymptomatic infection. An illustration of the reality in which these immunological phenomena occur reveals immune mechanisms to be those which do not reduce disease severity by eliminating causes but rather by attenuating their influence on the mechanisms that bring destructive entities such as the phagocytosing cells of Mechnikov to the tissues, not only in response to pathogens but also to sterile causes in the phenomenon of sterile inflammation. The same illustration reveals that such destructive mechanisms are really pathological mechanisms which, at some point in our natural history, began to control our genetic information for a purpose which is not our own good even though they have appeared to be beneficial mechanisms for as long as the evolutionary law was thought in the manner of Charles Darwin to be that

according to which the species descended by and for their own good from common ancestors. And according to the illustrated reality, destructive entities such as the phagocytosing cells of Mechnikov are present in humans and other animals because the evolutionary law is that according to which the genetic information can be similarly changed by such pathological mechanisms even in organisms of different species. The problem of germ denialism is solved as soon as the deniers see that the prosperity of pathogens in organisms that enjoy complete immunity is a demonstration of the truthfulness of the result that emerged from this illustrated reality, that when conditions permit immune mechanisms to attenuate the influence of the pathogen on such pathological mechanisms so much that they fail to respond to the presence of the pathogen with destruction of the tissues, the host is as asymptomatic as those in whom the pathogen has been eliminated and the pathogen appears to be a harmless entity in the absence of this knowledge of reality when it is observed prospering in such an asymptomatic host. Our topmost research priority now, therefore, ought to be an illustration of reality which enables us to understand so well as to become capable of stabilizing such protective conditions that give rise to immunity and therefore of being protected from diseases even as pathogens prosper and mutate into the variants and sub variants we presently dread.

Keywords: Immunology; inflammation; sterile inflammation; infectious diseases; COVID-19; vaccination; remission; cancer; malignancies; autoimmunity; evolution; neurodegeneration

Why should a paper in which the presentation of a new theory of immunity begins be given a title “The Nature of the Problem of Immunity and its Solution”? My answer will be that the

solution to the problem of immunity must begin with an accurate description of the nature of immunity which the zoologist, Ilya Mechnikov logically deduced to be defence against pathogens when he observed mobile cells that envelope and store foreign entities at sites where transparent animals have been damaged and their cells have died.¹

I believe that the love for Science, which requires all our statements to be in complete agreement with facts, must necessarily lead you to the view that such an accurate description is demanded by the fact that the response in which the phagocytosing cells of Mechnikov and other white blood cells are brought into the tissues from the blood is the very same response that harms the organism² which ought to be protected if indeed white blood cells, which include those that kill cells directly as well as those that destroy them with antibodies, are indeed immune cells. And I also believe that the same love will lead you to the view that observations such as high levels of antibodies to the coronavirus known as SARS-CoV-2 in many patients dying from COVID-19³ require this demand to be urgently met for the goal of preventing such unfortunate losses of our own in this pandemic and others which, if such a requirement is not met before they appear, may even be as deadly as an Ebola pandemic or a pandemic of malignancies such as the one that decimated Tasmanian devil populations.

Yet, you must necessarily find it counterintuitive that a theoretical scientist should see an accurate description of the nature of immunity as the path to the solution to the problem of immunity. After all, Charles Darwin had concluded in 1859, on the basis of the observation that all living things have much in common, that the evolutionary law that governs the appearance of

endless forms from previously existing forms is the biological law according to which species appeared on the planet such that all species must have descended from a single biological entity and the similarities between them, such as the phagocytosing cells of Mechnikov, must have been the consequence of changes which occurred in their common ancestors by and for their own good.⁴ “Analogy would lead me one step further, namely, to the belief that all animals and plants have descended from some one prototype. But analogy may be a deceitful guide. Nevertheless, all living things have much in common...” he wrote.⁴

And it was because Mechnikov viewed the presence of such phagocytosing cells in animals as a consequence of their descent from the same ancestor as those organisms such as amoeba which acquire nutrients by enveloping their food in the same manner as these phagocytosing animal cells that he concluded that such cells were once part of the digestive system of animals.¹ The following is how Mechnikov presented this view in his 1908 Nobel lecture which he titled ‘On the Present State of the Question of Immunity in Infectious Diseases.’

“While studying the origin of the digestive organs in the animal world, we were struck by the fact that certain of the organism’s elements which have no part to play in the digestion of food are nevertheless capable of storing foreign bodies. For us, the reason was that these elements had once been part of the digestive system. This question of pure zoology has no further place here, so we will only stress the general outcome of our research in this field, which was that the elements of the organism of man and the animals, gifted with autonomic movements and capable of enveloping foreign bodies are no more than remains from the digestive system of primitive beings.”¹

But it was clear to me 23 years ago, when I first came across the problem of the mechanism of immunity, which Mechnikov declared unresolved in his 1908 Nobel lecture¹ and which has remained unresolved until now,⁵ that this problem does not have its origin in the complexity of the animal organism as Mechnikov concluded.¹ I was convinced that the origin of the problem is the use of a method of obtaining knowledge which requires logical deductions to be made from observations instead of the use of a method which requires the illustration of the phenomena to be elucidated after empirical mastery has been achieved through immersion in all that is known about such phenomena. And I was convinced that reality could only be known through such a method in which logical deductions are made only for the purpose of obtaining consequences from the results of illustrations that emerge from such empirical mastery so that through their agreement or disagreement with facts, we may know whether or not we have obtained knowledge of reality in the painstaking process of developing theories through this superior method.⁶ And this happened because I knew, even before I began my studies in the basic medical sciences where I was exposed to this great problem of medicine, that the problems of astronomy, which overpowered the practically useful logical deductions that the astronomer, Sir Isaac Newton made from observations, were not solved until a patent clerk named Albert Einstein, who was not even an astronomer at all, investigated gravitational phenomena with this superior method of obtaining knowledge which requires the illustration of reality.

Given that an investigation which will lead us to the solution of the problem of immunity must therefore begin with an accurate description of the phenomena to be illustrated, with which Mechnikov himself furnished us in his 1908 Nobel lecture, we ought to turn to that description of what is known about immunological phenomena through experience which is what a theory of

immunity ought to account for and not what is known about the inflammatory phenomena in which phagocytosing cells are brought to sites of cell death.

“There is no need to be a doctor or a scientist to wonder why the human body is capable of resisting so many harmful agents in the course of everyday life. It is often seen that in households where all members are exposed to the same danger, or again in schools or troops where everyone lives the same life, disease does not strike everyone indifferently. For some individuals who go down at the attack, there are others who have immunity to a greater or lesser extent.

There used to be only a vague answer to the problem of the body's resistance, remarkable as it is. Since the memorable discoveries of Pasteur and his co-workers who found that immunity could be conferred by means of vaccination with microbes, the question has all at once become vastly clarified. The problem has become open to study by experiment. For Pasteur, who was a chemist, the fact that the undamaged organism does not allow certain morbid agents to spread within it, could be explained simply in terms of the chemistry of the environment. In the same way that plants will not grow on soil that lacks some substance indispensable to their growth, so microbes, these microscopic plants which cause infectious disease, are unable to grow in an organism which does not give them all the substances they need.

This theory is completely logical but contradicted a number of factors to be found in the protected organism. Pasteur and his fellow workers realized this themselves when they found that infectious microbes develop very well in the blood of animals that enjoy complete immunity.

The animal organism is very complex and for this reason it is often hard to explain in simple concepts the phenomena to be observed. To achieve the purpose, a different approach has had to be called for. It has been necessary to look from the point of view of biology, and attempt to simplify research conditions without going beyond the scope of the living organism. This is the idea that has been behind our research. Disease is not the prerogative of man and the domestic animals, so it was quite natural to see if the lower

animals, with very simple organizations, showed pathological phenomena, and if so, infection, cure and immunity could be observed among them.”¹

From Mechnikov’s description, we can see that the following are known about immunity from experience.

1. The consequence of immunity, the capacity of the human body to resist so many harmful agents in the course of everyday life, is the reduction of the severity of the pathological manifestations of the pathological effects of such diverse harmful agents.

2. In groups such as households where everyone is likely to become exposed to a spreading harmful agent such as a pathogen and even in groups such as troops where lifestyles and therefore exposure to harmful agents which do not spread must also be similar, the members differ in their immunity or the capacity to resist such harmful agents to which they are similarly exposed and therefore are affected differently by the manifestations of the diseases that such agents cause because such manifestations are reduced by different degrees in such different members. Upon illustrating reality, I found the origin of immunity in conditions that permit immune mechanisms to attenuate the influence of the pathogen on pathological mechanisms so that even when the loads of the pathogen in different individuals are exactly the same, disease severity is reduced by different degrees in such individuals if the pathogen’s influence is unequally reduced in strength in them.⁷

3. Since the manifestations of the disease that a harmful agent causes will not be reduced in severity at all in those who are not immune to the disease and therefore are unable to resist the disease at all, they will go down with the manifestations of the disease while others who are similarly exposed to such a harmful agent survive either because the severity of the disease is completely reduced in them, in which case the disease is asymptomatic, or because severity is so reduced that manifestations become more or less rendered moderate or mild depending on the degree of the immunity in such symptomatic survivors.

4. Pasteur and his co-workers assumed that the mechanism by which complete immunity is obtained by means of vaccination with pathogens is that which eliminates such pathogens completely when upon illustrating the reality in which immune mechanisms bring about such immunity, I found complete immunity to have its origin in conditions that permit the influence of the pathogen on pathological mechanisms to be completely attenuated so that pathological manifestations are not brought about in response to the pathogen at all irrespective of high the load of such a pathogen may become.^{7,8}

5. Instead of evidence of the inability of pathogens to spread in an immune organism which Pasteur and co-workers expected on the basis of the logical deduction that the mechanisms that bring about immunity are those that defend the host by destroying pathogens which followed the logical deduction that the mechanism by which pathogens cause diseases is one in which the host is attacked, what they found was the consequence of the new theory of immunity that has emerged from the reality we have illustrated so far – that pathogens must necessarily develop

very well in animals that enjoy complete immunity because the influence through which such pathogens cause diseases has been completely attenuated in them.

6. The capacity to explain immunological phenomena in simple concepts, which we have been given by the superior method of obtaining knowledge through the illustration of reality, was beyond the reach of the logical deduction of Pasteur and coworkers, that the mechanism through which pathogens cause diseases is one in which the host is attacked as well as the logical deduction that emerged from it as a logical consequence, that the mechanism of immunity must necessarily be those that defend the host from attack by destroying pathogens.

Also, from Mechnikov's description of immunity, we can see that he made the following assumptions in reformulating the defence theory of immunity which predicts the absence of the pathogen in organisms that are completely immune to the disease it causes via a mechanism of attack after it was demonstrated false by the prosperity of pathogens in completely immune individuals and germ theory deniers interpreted this observation to be a proof of the germ theory's falsehood. It is important to note that in the same manner, the prosperity of pathogens in completely immune individuals was seen as disagreeing with the repeatedly proven germ theory by Mechnikov and other proponents and therefore as an observation that is not capable of disproving the attack mechanism and defence theories or any other theory that is deduced logically from this verified theory.

1. Mechnikov assumed that the goal that Pasteur and co-workers tried to achieve by making logical deductions, to justifiably describe the mechanism by which immunity is brought about, could be achieved by answering the question “How is the pathogen eliminated from the organism?” which is extraneous and not connected with the question that is connected with what is known about immunity from experience which they asked. And that question, “How do immune mechanisms reduce the severity of the manifestations of the diseases that pathogens cause so much in completely immune animals that the symptoms of such diseases fail to appear in them at all even when they are similarly exposed to such pathogens as those that are killed or those that are affected more less by such diseases?”

2. He assumed that he simplified research conditions and avoided going beyond the scope of the living organism when, upon finding it hard to explain in simple concepts the phenomena of immunity as known through experience by Pasteur and his colleagues, he searched for phenomena which would answer the question “How is the pathogen eliminated from the organism?” which is unconnected with such empirical knowledge.

In reality, however, he went beyond the scope of the living organism by answering a question which is unconnected with what is known about immunity from experience in his investigation because the concepts in the theory of immunity which was founded on the logical deductions he made from inflammatory phenomena, concepts such as immune cells, immune system, and immune response, do not represent things that actually exist or occur in the immunological phenomena in which the things we know about immunity from experience actually occur.

The reduction in the severity of the pathological manifestations of the effects of pathogens is not brought about by cells and substances that make up the system that is referred to as immune on the basis of his deductions but rather by tolerance mechanisms which we normally do not think of as “immune” because they bring about immunity without eliminating pathogens.^{7,9} Indeed, in bats which are famous for having high loads of viruses in their sera or tissues without the manifestations of the diseases that such viruses cause in humans and other animals, the studies of Matae Ahn and coworkers revealed a mechanism that dampens the inflammation that occurs in response to infections with three different zoonotic RNA viruses as well as sterile factors without reducing the viral loads in those cells that are referred to as “immune” cells.¹⁰

The consequence of the absence of connection between the question “How is the pathogen eliminated from the organism?” which Mechnikov asked at the beginning of his investigation and the question “How do immune mechanisms reduce the severity of the pathological manifestations of the pathological effects of the pathogen so much in animals that enjoy complete immunity that pathogens are able to develop very well in their blood as observed by Pasteur and co-workers?” must necessarily be the absence of connection between the results of studies of the whole physiological response of a body in which the function of immunity is investigated in parallel to biological mechanisms and the results of studies of such cells which are referred to as immune on the basis of the extraneous question of Mechnikov. And indeed, instead of the significant overlap which Ayres and coworkers expected to find between genes that ensure the survival of the organism in the face of disease which they investigated and those

which were considered to be immunity genes in studies of such cells that are referred to as immune, none was found.¹¹

4. Finally, on the basis of the belief of Charles Darwin that the evolutionary law governs the origin of species,⁴ Mechnikov believed that phagocytosing cells which envelope and store foreign entities are present in humans and animals because they all originated from a common ancestor and that these cells exist by and for the good of this ancestor and its descendants.¹ But the results obtained upon illustrating reality revealed that the evolutionary law is not the biological law by which species appeared on the planet.⁸

In this reality, the evolutionary law is that according to which biological entities of different species become similar through convergent changes within a short period of time if they are exposed to the same conditions within such a period.⁸ And the illustration of the reality in which the inflammatory responses that bring phagocytosing cells to sites of cell death in animals reveal the trigger of evolution to be mechanisms which do not exist for the good of the species but rather mechanisms which took control of the genetic information in their cells for a selfish purpose which may require them to destroy the organism if necessary. However, until the results that emerged from drawing further consequences from this reality revealed the evolutionary law to be the law according to which convergent changes occurred in the species and not the biological law according to which they appeared on the planet as Darwin inferred from analogy, I refrained from presenting this counterintuitive result of the reality in which inflammatory

responses bring the phagocytosing cells of Mechnikov and other white blood cells into our tissues until such consequences were drawn.

In this illustration that emerged from immersion in the observations of our experimental scientists, the dog in the porous house is not aggressive for the purpose of exempting the occupants of the house from the disturbance that our old friends, the aliens, observe from their location outside porous houses which does not permit them to obtain knowledge of the reality in such houses. Rather, the dog is the source of the disturbing rage that the aliens observe from their location even though a billboard footage which shows the aggression of dogs towards cats may lead these visitors from a planet without animals to the false conclusion that the destruction of the cats that entered porous house B by the dog prevented their entry of such cats from being followed by the disturbing rage and ultimately to the false conclusion that it is through the destruction of cats that the occupants of porous houses are made immune to such disturbing rage that followed the entry of a cat into porous house A. In reality, however, dogs are not aggressive for the purpose of defending the occupants of houses from cats and they will attack such occupants even in the absence of cats when conditions that permit them to be aggressive in a manner that appears beneficial to the occupants of houses disappear.

And it follows as a consequence of the reality thus illustrated that phagocytosing cells are not present in animals because all animals originated from a common ancestor but rather because they all became exposed to conditions that enabled pathological mechanisms to change their genetic information in a manner that differentiated their cells into cells of such kind, not to

defend animals against pathogens as Mechnikov assumed but rather for a purpose which may require animals to be destroyed if necessary. If we have indeed obtained knowledge of reality in our illustration, the genome must no longer be a static set of instructions that is passed between generations which it must necessarily have been at the origin of the species when their genomes were controlled exclusively by the beneficial mechanisms.

The consequence is a genome to which pathological mechanisms must make changes in order to differentiate cells into forms such as immune cells which will destroy the organism if necessary to achieve the goal for which they began to control the genome when the different species became exposed to conditions that brought about sudden convergent changes of evolution. Such changes include those which mineralized animal species in a manner that changed them, within a period that is so short, from forms which could not be preserved in rocks which they were at their origin to mineralized forms which can be preserved in such rocks so that their remains appeared suddenly in the lowest known fossiliferous rocks in the phenomenon known as the Cambrian explosion.⁸ The changes of evolution must therefore be observed by our geneticists to be sudden outcomes of the struggle between such pathological mechanisms that control the genome to bring about changes which require the destruction of the organism under certain conditions and beneficial mechanisms which must necessarily repress such control when conditions permit them to make the necessary changes so that such pathological changes lose the beneficial appearance they have had in the absence of our illustration of reality when such conditions that permit repression disappear.

The representation of these consequences in reality is the fact that the expression of transposable elements, those “controlling elements” in the Nobel prize-winning discovery of Barbara McClintock which challenged the concept of the genome as a static set of instructions that are passed between generations,¹² is linked with defects in developmental processes that include aberrant proliferation of male germ cells, oogenesis defects, disruption of homologous chromosome synapsis during meiosis, activation of the unfolded protein response during differentiation of antibody-secreting B lymphocytes and inappropriate activation of what was referred to as innate immune response¹³ on the basis of the assumption that such a response occurred for the good of the organism. And evidence is mounting that transposable elements play a role in the etiopathogenesis of illness-causing manifestations that accompany inflammation and the recruitment of inflammatory cells which are as diverse as cancer, “autoimmunity” and neurodegeneration even though their biological significance was not understood and the pattern of transposable element expression in disease states remained enigmatic.^{14,15}

But it follows from the reality we have illustrated that when conditions do not permit animals to be destroyed by the pathological mechanisms that serve the purpose for which such cells as phagocytosing cells and antibody-secreting B lymphocytes were brought into existence in animals, such pathological mechanisms and the cells they control appear to be beneficial to the organism hence the pattern of transposable element expression in disease states must necessarily be enigmatic in the absence of the knowledge of that the mechanisms that differentiate cells into such destructive cells are pathological or of the conditions that give them a beneficial appearance.

For as long as sterile inflammation (inflammation in the absence of infection) was seen as a beneficial response which facilitates rapid detection of injury and leads to timely healing, researchers have tried to understand why it would become pathological and lead to tissue damage and the plethora of chronic inflammatory diseases.^{16,17} Yet, little is understood about the signals and mechanisms that turn off this powerful response despite the fact that much is known about its initiation.¹⁶ And the exact cause and mechanism of the cell death process in inflammatory diseases has remained unknown.¹⁸

But the reality we have so far illustrated has revealed that the origin of the protection in which this pathological response is turned off to be conditions that permit immune mechanisms to reduce the severity of the pathological manifestations that are brought about through such responses so that upon the disappearance of such conditions, the response appears to be a double-edged sword when it is viewed as beneficial in the absence of knowledge of its pathological origin which we have uncovered by illustrating reality. And it is because sterile factors also exert influences on the source of this pathological response in which phagocytosing cells of Mechnikov are brought to the sites of cell death, those pathological mechanisms which we referred to as the gravity-like unobservable in another paper,⁷ that the phenomenon of sterile inflammation (inflammation in the absence of infection) occurs.

It is presently impossible to predict specific protective antibody levels that prevent breakthrough infections in patients who have been vaccinated and the astute conclusion which has followed such observations that are a consequence of the reality we have illustrated so far is that the

antibody response is a biomarker of either infection or vaccination rather than the biomarker of the protection which was expected to be brought about through the elimination of the pathogen and the prevention of breakthrough infection³ on the basis of the logical deductions that immunity has its origin in this response. In the reality that yielded the observed consequence, the origin of the immunity we obtain by means of vaccination with an entity that is immunologically linked with the pathogen (such as the killed virus in the polio vaccine or the cowpox virus in the smallpox virus) is not the inflammatory response in which such antibodies are produced which we have viewed as an immune response in the absence of knowledge of the reality in which immune mechanisms protect us.⁸ In this reality, the origin of such immunity lies in the conditions that permit immune mechanisms to obstruct the pathway through which such responses occur not only in response to the pathogen (such as the smallpox virus or polio virus) but also in response to etiological factors that are immunologically linked with it (such as the cowpox virus or the killed polio virus) which vaccination presents.⁸ Asymptomatic infection rather than the prevention of infection by white blood cells and antibodies is the consequence of the complete immunity obtained by means of prior infection and vaccination when the protective conditions that permit complete attenuation are present.

These results have pointed us in the direction of what should be our topmost research priority if we will put an end to deaths from COVID-19 which have already surpassed 6 million, deaths from malignancies which, despite constituting most of the nearly 10 million deaths that cancer causes in the absence of treatments that are capable of curing cancer with precision, disappear in the phenomenon of remission along with pathological manifestations that occur in response to pathogens such as COVID-19 pneumonia¹⁹ when conditions permit immune mechanisms to

attenuate the influence of such pathogens.⁷ And this priority is an illustration, in the shortest possible time, of the reality that leads us to a complete understanding of such conditions that give rise to immunity by means of prior infection and vaccination with pathogens or entities that are immunologically linked with them, conditions which permit dampening of the inflammation that occurs in response to pathogens and factors that are immunologically linked with them, such as SARS-CoV-2 and the sterile causes of the malignancies that disappear concomitantly with the manifestations of COVID-19, and asymptomatic hosting of such pathogens in phenomena which have demonstrated since the time of Pasteur that complete immunity is complete reduction of disease severity in spite of the prosperity of pathogens.^{1,10}

Declaration of Competing Interest

I declare that there are no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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