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Rheumatoid arthritis is caused by *Proteus* : the molecular mimicry theory and Karl Popper

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TABLE OF CONTENTS

1. ABSTRACT

Rheumatoid arthritis is a crippling and disabling joint disease affecting over 20 million people. It occurs predominantly in women and smokers, and affects the HLA-DR1/4 individuals who carry the "shared epitope" of amino acids EQRRAA. The cause of this disease was investigated by the methods of the philosopher of science Karl Popper who suggested that scientific research should be based on bold conjectures and critical refutations. The "Popper sequences" generate new facts which then change or alter the original problem. The new facts must then be explained by any new theory. Using the "molecular mimicry" model, it was found that *Proteus* bacteria possess an amino acid sequence ESRRAL in haemolysin which resembles the "shared epitope" and another sequence in urease which resembles type XI collagen. Antibodies to *Proteus* bacteria have been found in 14 different countries. It would appear that rheumatoid arthritis is caused by an upper urinary tract infection by *Proteus* bacteria. Anti-*Proteus* therapy should be assessed in the management of this disease separately or in conjunction with existing modalities of therapy.

2. INTRODUCTION

The Austrian-British philosopher of science, Sir Karl Popper (1902-1994), was born in Vienna and became Professor at the London School of Economics. Popper proposed that a scientific theory could not be proved but could be disproved or falsified. "It must be possible for a scientific system to be refuted by experience"(1). The theory that "All tigers are carnivorous" is refuted or falsified by the observation of one vegetarian tiger.

An interesting problem in science and medicine is the cause or origin of the disabling and crippling disease "rheumatoid arthritis" (RA). RA is a disease of the musculo-skeletal system, predominantly of the small joints of the hands and feet, affecting women 3-4 times more frequently than men. There are conservatively over 20 million individuals in the world affected by RA or its early stages when a precise diagnosis is not possible.

It is proposed to apply Popper's method to find a solution to the scientific problem as to what is the cause of RA. Molecular mimicry has been suggested as a possible

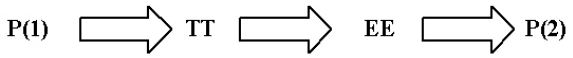

Figure 1. Schematic representation of a "Popper sequence".

model and it will be examined using Popper's ideas and the principle of parsimony enshrined in Ockham's razor (2).

3. THE SEARCH FOR THE CAUSE OF RA

3.1. Popper's method of scientific investigation

The logical basis of scientific research is the method of bold conjectures and of attempted refutations. The process can be described by the following oversimplified schema (Figure 1). We start from some "problem" (P1) proceed to a tentative solution or "tentative theory" (TT) which may be partly or wholly mistaken. The theory will be subject to "error elimination" (EE) which may consist of critical discussion or experimental tests. At any rate new problems will arise (P2) which may require further solutions. At every step, new unintended facts, new unexpected problems will occur which will increase our knowledge of the subject.

The second problem (P2) is in general different from the first, it is the result of the new situation which has arisen, in part, because of the tentative theories (TT) or tentative solutions which had been tried out and the error elimination (EE) which controls them. One could label this schema a "Popper sequence". As new problems arise, new "Popper sequences" can be generated which require further experimental verification.

The task of science is to explain as many facts as possible, in other words to get at the truth. However we are not simply looking for any truth, we are looking for interesting and enlightening truth. We are after theories which offer solutions to interesting problems. If at all possible we are after "deep" theories. We are after theories which have an extensive explanatory power that may lead to even useful applications.

If the cause of RA could be found, then it would have immense repercussions, since this information could be incorporated in the therapy of this crippling disease. A cursory examination of rheumatology books will show that the cause of RA is unknown.

In a famous passage Karl Popper offers a way as how to handle this situation:

> "Assume a young scientist meets a problem which he does not understand. What can he do? I suggest that even though he does not understand the problem, he can try to solve it and criticise his solution. Since he does not understand the problem, his solution will be a failure, a fact which will be brought out by criticism. In this way, a first step will be made towards pinpointing where the difficulty lies. This means precisely, that a first step will be made towards understanding the problem, for a problem is a difficulty and understanding a problem consists in finding out where the difficulty lies. And this can only be done by finding out why certain solutions do not work. So we learn to understand a problem by trying to solve it and by failing. When we have failed a hundred times, we may become even experts with respect to this particular problem. That is, if anybody proposes a solution we may see at once, whether there is any prospect of success for this proposal or the proposal will fail because of the difficulties which we know only too well from our own past failures" (3).

The question "What kind of explanation may be satisfactory ?" leads to the reply, an explanation in terms of testable theories and falsifiable universal laws and critical conditions. An explanation of this kind will be the more satisfactory, the more highly testable these laws are thereby proceeding to better theories.

Each new theory (T2) will contain the previous theory (T1) as an approximation. For instance Newton's theory of planetary motion was a better approximation to Galileo's theories, which in turn were a better approximation of the theories of Copernicus. Thus a theory which leads to the discovery of new facts has changed the debate about the original problem.

3.2. Properties of the RA problem

Some of the attributes or properties of the scientific problem of RA can be summarised as follows:

3.2.1. RA and women

The disease occurs 3-4 times more frequently in women compared to men. Any theory or solution must explain this sex difference. Almost 20% of women aged 20-60 years suffer at least one episode of urinary tract infection per year, which is quite in excess to the experience found in men. Could this explain the increased frequency of this disease in women.

3.2.2. RA and onset in post-partum period

The disease onset of RA is usually in middle-aged women, especially in the post-partum period, following a pregnancy. Often RA starts or flares up 4-6 weeks after delivery. Hence any theory must explain why the disease onset occurs on the completion of pregnancy. It raises the question of what occurs during pregnancy which might facilitate the onset of RA. Could the increased incidence of urinary tract infections during pregnancy play a role or could it be due to hormonal causes.

3.2.3. RA and smoking

There is an increased susceptibility of developing RA in individuals who are smokers (4). This initial report was confirmed by studies from Sweden (5). The smoking frequency and duration were directly linked to the susceptibility to develop RA and this relation continued after cessation of smoking.

However, there is also an association between smoking and urinary tract infections. In a Danish study, the frequency of urinary tract infections was found to be significantly higher in smokers than non-smokers (6).

There would appear to be a common link between susceptibility to RA, urinary tract infections and smoking (7).

Using the principle of parsimony or Ockham's razor, causes should not be multiplied indefinitely but a common denominator looked for, which could link or explain the presence of these attributes in RA.

3.2.4. RA in identical twins

The test of genetic relevance in the study of disease causation is to examine identical twins and measure the concordance index. If 100% of the first identical twins have developed RA, what percentage of the second twins develop RA?

There have been published 3 different studies which give more or less the same results: 12% in Finland (8), 15% for the U.K (9) and 10% in Denmark (10).

Clearly these studies indicate that an environmental factor is involved in the causation of RA, independent of any genetic susceptibility. These results taken together with the increased prevalence of RA in women, could point to an environmental factor, probably involving some infections. However, there is also a genetic factor involved in RA.

3.2.5. The genetic factor in RA

The link between RA and human histocompatibility antigens (ags), particularly HLA-DW4 was discovered by Stastny, in 1976, using leucocyte cultures on cells obtained from American patients (11). Subsequently this link between class II MHC ags was confirmed when HLA-DR4 was identified in English RA patients (12).

The identity of the molecular sequence responsible for an increased susceptibility to RA was found using the polymerase chain reaction. A particular sequence from positions 70 to 74, encoding amino acids Gln-Arg-Arg-Ala-Ala (QRRAA) specific for HLA-DR1, HLA-DR4(DW14 and DW15) was found to occur in RA patients (13). The sequence of this region closely resembles the one in HLA-DR4(DW4) there being only amino acid substitution at position 71 from arginine to lysine (QKRAA). However, this is a conservative substitution since both arginine and lysine are positively charged amino acids. Glutamic acid (E), a negatively charged amino acid, occupying position 69, is common to all DR-beta-1 molecules.

The hexameric sequence EQR(K)RAA between amino acids 69 and 74, forms a powerful antigenic determinant in having a negatively charged glutamic acid (E) at position 69 and two positively charged amino acids, arginine (R) or lysine (K) at position 71 and arginine at position 72. This hexameric sequence forms the basis of the "shared epitope" (SE) hypothesis (14).

There are two possible ways of trying to explain the presence of the SE as a susceptibility sequence in RA patients:

a The receptor hypothesis which states that the SE sequence forms part of a specific HLA cavity that presents some unknown ags to immune cells.

b. The molecular mimicry hypothesis which states that the SE sequence resembles or shows immunological cross-reactivity to some unknown external ag, probably located in a bacterium or other infectious agent.

Which of these 2 models provides a better explanation for the SE will be examined using Popper's methods.

3.3. Molecular mimicry as a model

3.3.1. Rheumatic fever

The best example of an autoimmune disease evoked by an infection, acting through the mechanism of "molecular mimicry" is rheumatic fever. It usually occurs some 3 to 4 weeks after an upper respiratory tract infection by the microbe *Streptococcus*. Some cardiac ags resemble or cross-react with *Streptococcus* microbes and the serum of rheumatic fever patients contain antibodies (abs) which bind and react with cardiac myosin (15).

3.3.2. Ankylosing spondylitis

Ankylosing spondylitis is a chronic inflammatory, autoimmune disease, characteristically affecting the lumbar spine and sacro-iliac joints. HLA-B27 is present in 96% of ankylosing spondylitis patients but in only 8% of healthy controls. *Klebsiella* microbes possess molecules such as nitrogenase (16) and pullulanase (17) which cross-react or show molecular mimicry with HLA-B27. Abs to *Klebsiella* microbes have been found in 1330 ankylosing spondylitis patients when compared to 1191 healthy controls coming from 15 different countries (18). It would appear the model of molecular mimicry has identified the microbe which causes ankylosing spondylitis and this suggests that the same approach could be used with other diseases (19).

3.3.3. Immune response genes and TGAL

It was proposed by Damian in 1964 that parasites can evade the immunological defences of the host by producing substances which show molecular similarity or "molecular mimicry" (20).

Inbred strains of animals show high and low immune responses against defined ags. For instance, C57Black mice give a high response to the chemically defined ag TGAL whilst CBA mice give a low response. Molecular mimicry was demonstrated between Major Histocompatibility ags in the low responder mice and the synthetic ag TGAL, thereby suggesting that this mechanism

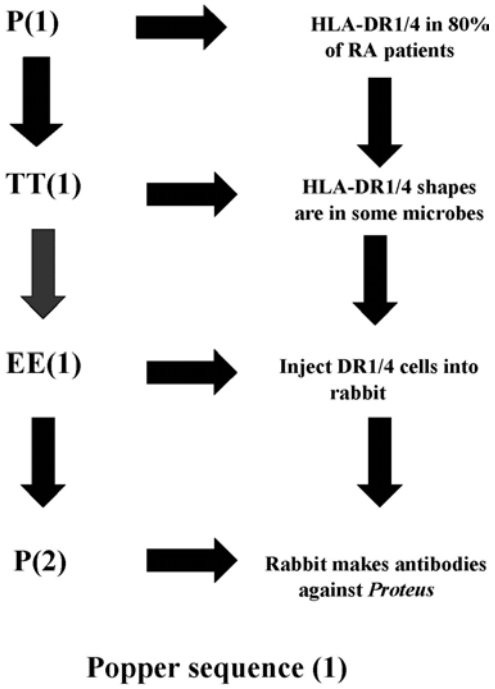

Figure 2. Popper sequence 1.

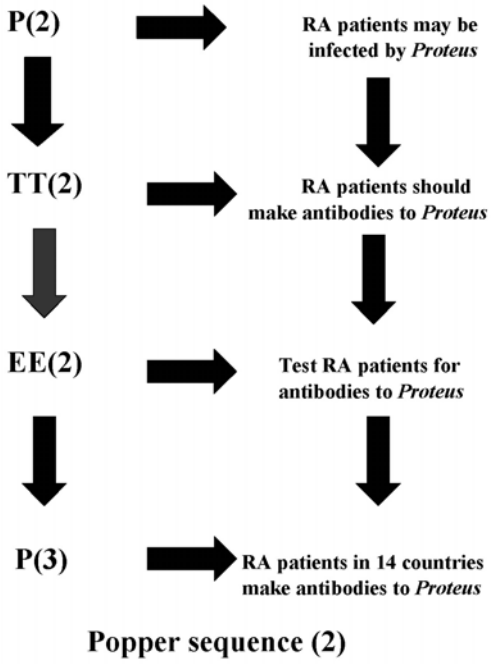

Figure 3. Popper sequence 2.

provides an explanation for the genetically modulated immune response (21).

RA is also linked to transplantation ags or HLA and a similar approach is indicated, to see if it can provide a possible solution to the problem of the cause of this disease (22).

3.4. Molecular mimicry and *Proteus*

3.4.1. HLA-DR4 in rabbits

The demonstration that RA is predominantly confined to individuals that possess the SE (EQR(K)AA) raises the question as to what role such a sequence plays in the onset of this disease. Both the receptor hypothesis and the molecular mimicry models have been proposed as possible explanations to this question.

The Popper criteria can be used to determine which models might provide a useful solution to this scientific problem.

Lymphocytes were obtained from an RA patient who was also HLA-DR4 positive and injected into a rabbit. The resultant antiserum was tested against a panel of 18 different micro organisms. Only 2 bacteria *Proteus mirabilis* and *Proteus vulgaris* reacted with the rabbit antiserum when compared to the serum obtained from the same rabbit before it had been immunised with HLA-DR4 positive lymphocytes (23).

This observation can be summarized in terms of the "Popper sequence (1)" (Figure 2).

The problem (P1) is why 80% of RA patients carry HLA-DR1/4. The molecular mimicry model proposes the conjecture or "tentative theory" (TT1) that HLA-DR1/4 molecules share some similarity with some unknown bacteria or other agents. Therefore, HLA-DR1/4 cells should be injected into an experimental animal like a rabbit and the resultant antiserum tested against a panel of bacteria. This is an attempt at "error elimination" (EE1) to see if any bacteria will react with the rabbit antiserum. If any bacteria react against this antiserum this will present us with a new "problem" (P2), whether such bacteria are involved in RA. The rabbit polyclonal anti-HLA-DR1/4 antiserum reacted with *Proteus* bacteria. Although this observation was to some extent unexpected, it became immediately apparent, that if *Proteus* infection was the trigger factor for the onset of RA, it would explain why this disease was commoner in women.

The two main microbes causing urinary tract infections is the urease-negative *E.coli*, which causes mainly cystitis in the bladder, whilst the urease-positive *Proteus* causes upper urinary tract infections, especially affecting the ureters and the pelvis of the kidneys. The urease molecule of *Proteus* is responsible for the formation of struvite and apatite crystals which leads to the formation of kidney stones. Urinary tract infections are also common during pregnancy and in the post-puerperium period and this could explain the increased incidence in the onset of RA during this period.

3.4.2. Abs to *Proteus* in RA

The second scientific problem (P2) arises whether RA patients have actually been exposed and infected by *Proteus* bacteria. The examination of this question can be summarized in the terms of a new "Popper sequence (2)" (Figure 3). If patients have been exposed to

Table 1 Countries and year of report showing elevated levels of *Proteus* antibodies in RA patients

Country	Year of Report
England	1985
Ireland	1988
France	1994
Scotland	1995
Norway	1995
Bermuda	1995
Japan	1997
India	1997
Netherlands	1998
Spain	1999
Russia	2000
Finland	2004
United States	2005
Canada	2005

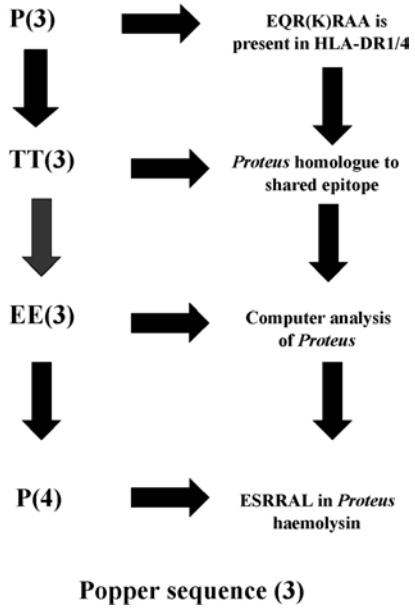

Figure 4. Popper sequence 3.

Proteus bacteria, this raises the "tentative theory (2)" (TT2) that RA patients should make abs to this microbe. The "error elimination (2)" (EE2) consists of testing RA patients for abs against *Proteus* microbes.

Initially abs to *Proteus* in RA patients have been found in England (23) and subsequently in many different countries like France (24), the Netherlands (25) and Japan (26). A study by the National Institutes of Health in Washington confirmed that *Proteus* abs were also found in American and Canadian RA patients (27). RA patients have been tested in 14 different countries and found to have abs against *Proteus* and this presents us with a new "problem" (P3) (28) (Table 1). Furthermore, the isolation of *Proteus* bacteria from the urines of RA patients correlates with the presence of anti-*Proteus* abs, especially during active phases of the disease (29). This method of conjectures and refutations has produced two "Popper sequences" which have altered the original problem. The disease RA occurs not only preferentially in women or smokers but is also found in individuals who possess HLA-DR1/4 and have been infected by *Proteus* bacteria.

3.4.3. Molecular link between HLA-DR1/4 and *Proteus* haemolysin

The studies performed so far, have shown that *Proteus* bacteria have some molecular similarity or molecular mimicry to some component of the HLA-DR1/4 molecule. Genetic analysis of the different subtypes of HLA-DR1/4 have identified that all these molecules share a common hexameric sequence EQR(K)RAA, also called the SE.

This can again be examined using a "Popper sequence" (P3). The problem "P3" states that the SE requires an explanation which will link it to *Proteus* bacteria. The "tentative theory" (TT3) is that some molecule in *Proteus* bacteria has molecular similarity or shows molecular mimicry to some component of these microbes. The "error elimination" (EE3) consist of carrying a computer analysis of the components of *Proteus* bacteria to see if they resemble the EQR(K)RAA sequence (Figure 4).

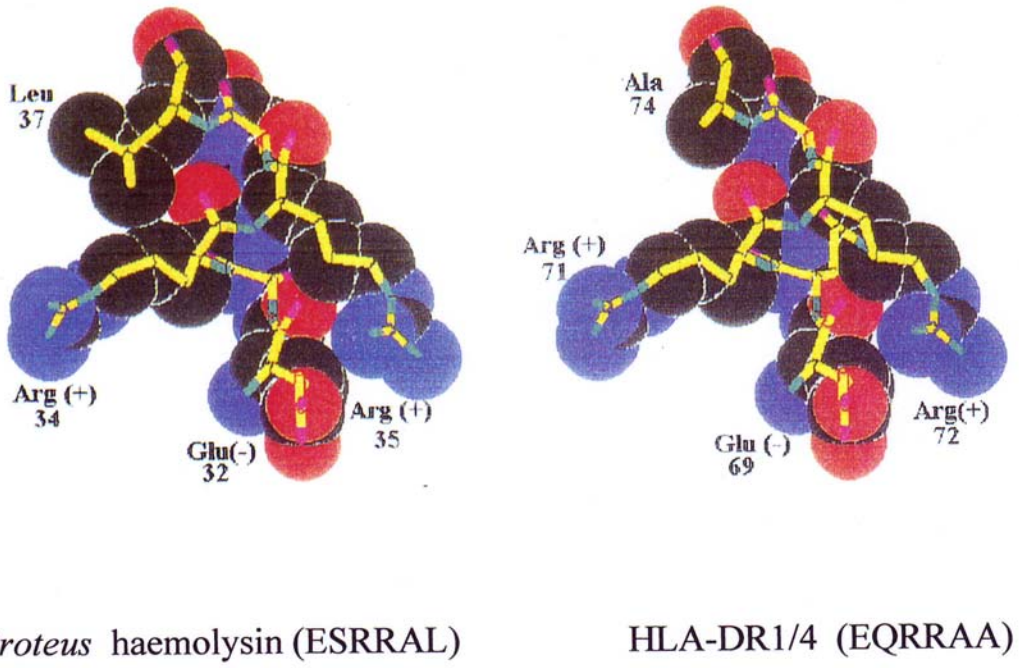

Figure 5. Comparison of space filling model of *Proteus* haemolysin sequence ESRRAL, with the "shared epitope" EQR(K)RAA found in HLA-DR1/4 molecules. Molecular modelling by Dr. C. Ettelaie. Reproduced with permission from (30).

Computer analysis shows that there is a sequence in *Proteus* haemolysin ESRRAL, from amino acid positions 32-36 which is also identical in shape to the SE EQR(K)RAA. (Figure 5). Thus, infection by *Proteus* bacteria in RA patients will evoke abs to *Proteus* haemolysin which will bind to the EQR(K)RAA sequence of HLA-DR1/4 molecules (30).

Clearly molecular mimicry provides a possible answer as to why the RA disease occurs more frequently in individuals carrying the SE found in HLA-DR1/4 molecules.

3.4.4. Molecular link between *Proteus* urease and type XI collagen

The results obtained suggest that molecular mimicry occurs between HLA-DR1/4 and *Proteus* bacteria. However, a chief feature of RA is that it affects especially the small joints of the upper and lower limbs.

The majority of urinary tract infections are caused by *E.coli* but abs to this microbe were not elevated in RA patients (31). The second commonest microbe causing urinary tract infections is *Proteus*. The Popperian question arises (P4) is there something in *Proteus* urease which could resemble collagens, tissues found in joints (Figure 6).

Computer analysis shows that *Proteus* urease contains a sequence IRRET from amino acids positions 337-341 which is almost identical in shape to an alpha-2(XI) collagen sequence, LRREI from amino acid residues 421-425 (Figure 7).

Type XI collagen is a component of hyaline cartilage, found in small joints and therefore provides an antigenic target for anti-urease abs produced during a *Proteus* urinary tract infection. Furthermore RA patients have abs to *Proteus* urease (30) and also to sequences not known to cross-react with self ags thereby indicating that a *Proteus* infection has occurred (32).

Thus four Popperian sequences have been developed which have produced four new facts about the possible cause of RA. Clearly RA patients can make abs to *Proteus* haemolysin and *Proteus* urease and this leads to the next Popperian question: Do such abs have cytotoxic activity against ags found in joint tissues?

3.4.5. Cytotoxic activity of RA sera

The presence of abs to *Proteus* in RA patients raises the scientific question of whether they can have pathological or cytopathic effects which can damage cells of joint tissues (P5). The Popperian proposal or "tentative theory" (TT5) is that anti-*Proteus* abs from RA patients should have cytopathic properties (Figure 8). Sera from active RA patients were tested by a complement mediated cytotoxicity assay with sheep red blood cells coated with EQRRAA (HLA-DR1/4) and LRREI (Type XI collagen) peptides and compared to sera from another disease, ankylosing spondylitis and to sera from healthy controls. This forms the "error elimination" (EE5) section of "Popper sequence 5". The results show that the RA sera had haemolytic activity against both HLA-DR1/4 and collagen peptides coated sheep red blood cells (33). Thus, the presence of elevated levels of abs to *Proteus* bacteria is sufficient to produce cytotoxic activity on synoviocytes

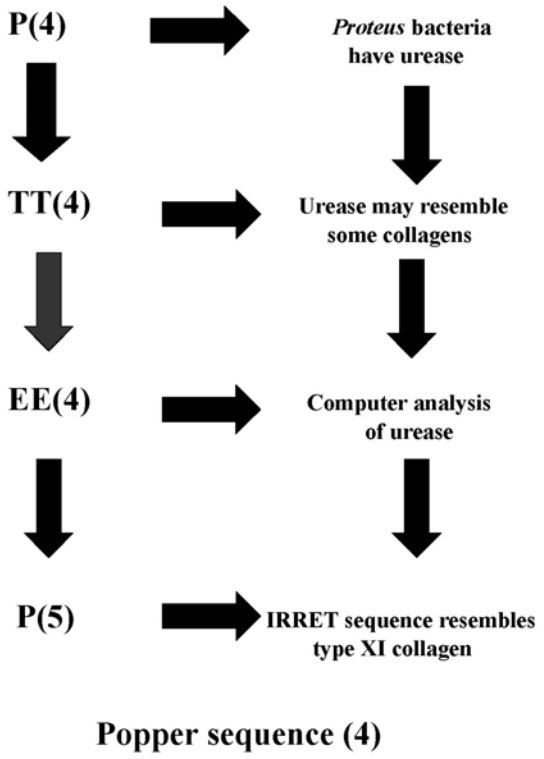

Figure 6. Popper sequence 4.

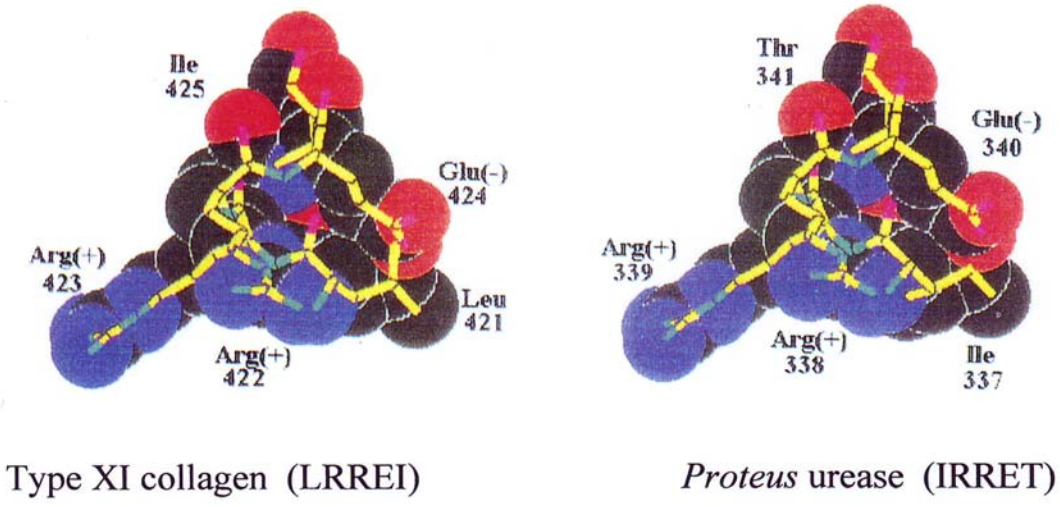

Figure 7. Comparison of space filling model of *Proteus* urease sequence IRRET with the alpha-2 chain type XI collagen LRREI. Molecular modelling by Dr. C. Ettelaie. Reproduced with permission from (30).

carrying HLA-DR1/4 ags and hyaline cartilage present in the joints of the hands and feet.

These extensive results strongly suggest that *Proteus* infection of the urinary tract produces abs which cause RA.

This leads to a new "Popper sequence" (P6) which suggests that anti-*Proteus* therapy might be beneficial in the treatment of RA patients (Figure 9). Whether such therapy is useful in the treatment of RA is at the moment unknown.

3.4.6. Comparison of molecular mimicry and receptor hypothesis models

The molecular mimicry model using Popper's

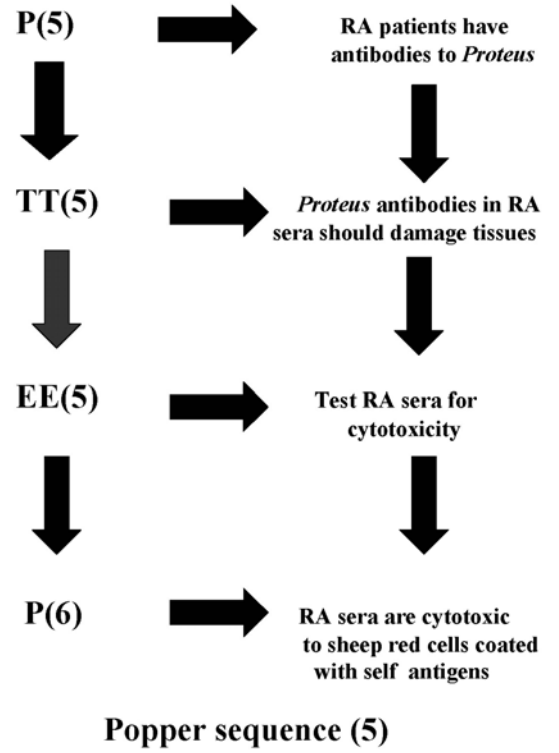

Figure 8. Popper sequence 5.

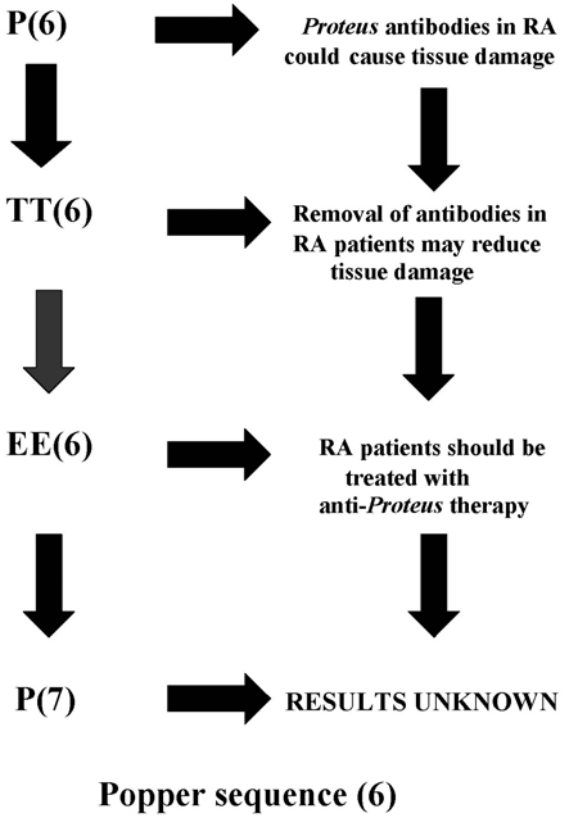

Figure 9. Popper sequence 6.

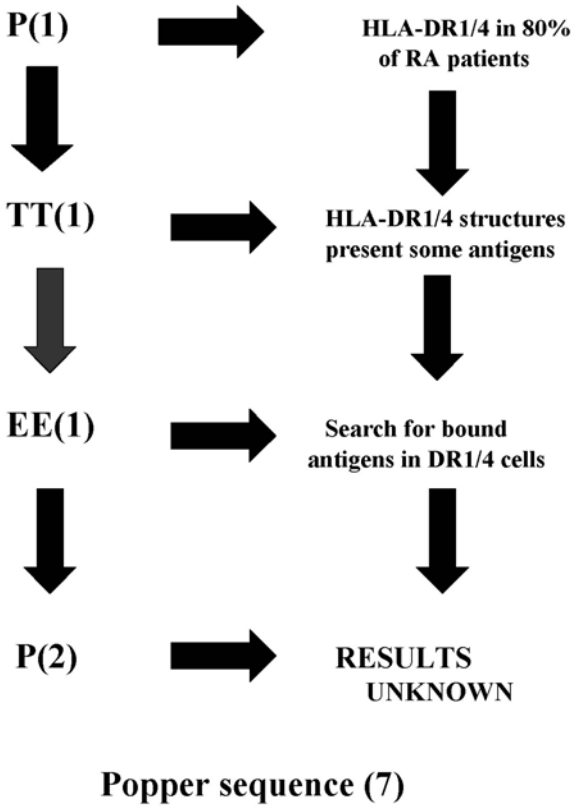

Figure 10. Popper sequence 7.

methods of scientific research has uncovered 5 new facts which alter the nature of the original problem of the causation of RA.

The identification of *Proteus* as the cause of RA, clearly explains why this disease occurs more frequently in women, since they suffer from an increased incidence of urinary tract infections. It also accounts, using Ockham's razor, why this disease is more frequently encountered among smokers, since they also suffer from such urinary tract infections.

The crucial clue which led to the discovery of the cause of RA was the identification that this disease occurred more frequently in HLA-DR1/4 individuals, carrying the SE. We have used the molecular mimicry model and applied Popperian methods of scientific investigations. An alternative explanation for the SE has been suggested that it acts as a receptor for some, as yet unknown ag. If we set up a Popperian sequence (Figure 10) it is clear that the "receptor hypothesis" so far has failed to provide a satisfactory answer to the problem. However, there is an even more serious problem with the "receptor hypothesis". It must account not only why the disease is commoner in women and smokers but it must also explain the "new facts" uncovered by the "molecular mimicry" model, especially that RA patients have abs to *Proteus* microbes. As described by Popper, the nature of the scientific problem has been altered by the discovery of new facts.

4. CONCLUSION

In science, we are trying to get closer to the truth but in medicine, the results of our investigations should help the patient.

It would appear that RA is triggered or caused by *Proteus* urinary tract infections, especially in women and in genetically predisposed individuals. Therefore, patients with RA should be investigated for the presence of urinary tract infections during active phases of the disease.

Sufficient evidence has been uncovered using Popperian methods of scientific research for anti-*Proteus* therapy to be assessed in the management of RA.

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Abbreviations: abs: antibodies, ag: antigen, RA: rheumatoid arthritis, SE: shared epitope

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