

A MECHANISTIC APPROACH TO TREATMENT OF RHEUMATOID TYPE ARTHRITIS NATURALLY OCCURRING IN A GORILLA

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INTRODUCTION

The concept that hypersensitivity is basic in the pathogenesis of rheumatoid disease has grown in significance during the past few years through increasing interest and knowledge in tissue immunology. The clinical usefulness of this concept would be greatly enhanced by an animal model with tissue reactivity comparable to that of man, allowing a better controlled means to measure and attempt to modify the antigen-antibody reaction and its pathologic resultants. It would appear that the induction of a hyperreactive state in an animal would be a prerequisite for the establishment of the rheumatoid process. The proper conditions for this development would not only include a host response similar to man but a persistent invisible source of antigen needed to sustain the chronicity of the reaction. These precise conditions seem to have been satisfied for the first time in a gorilla found to have a naturally occurring rheumatoid type illness associated with a new strain of antigenically active mycoplasma.

The gorilla is more closely related to man, serologically, than any other primate including the chimpanzee and the monkey.¹ The mycoplasma strain isolated, although having distinctive properties, is related to a human mycoplasma species with serologic responses comparable to those noted in man, providing additional evidence of the close relationship be-

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tween these biologic types. The detection of rheumatoid factor activity and a specific mycoplasma antibody response in serum from the arthritic gorilla, also suggested pathologic as well as biologic association of the species.

Pleuropneumonia bovis, discovered in 1898 by Nocard and Roux,² was the first member of an unusual group of microorganisms now known as mycoplasma. This agent was found to be the cause of a cattle disease characterized by pleurisy, pneumonia and arthritis. As other similar microbial types were discovered in the 1930's, they were termed Pleuropneumonia-like organisms, and described as minute filter passing, tissue invisible agents with many of the features of both viruses and bacteria. In recent years they were reclassified as Mycoplasmataceae. The principal isolates thus far have been from domestic animals including goats, sheep, dogs, mice, rats, chickens, turkeys and swine, and arthritis has been a common pathogenic feature of mycoplasma infection. There have been very few reports of mycoplasma isolation from wild species of animals, especially primates, prior to prolonged captivity.^{3, 4} In 1937, Dienes and Edsall⁵ reported the first isolation of mycoplasma from humans and in 1939 a relationship to human rheumatic diseases was suggested by Swift and Brown.⁶

No other microbial agent is known to possess an arthritogenic potential comparable to the mycoplasma. However, the type of joint involvement induced in the lower animals by these organisms bears little pathologic relationship to rheumatoid arthritis in man. We have suggested previously that the unique immunologic complexity of the human could promote a state of hypersensitivity when exposed to long-standing mycoplasma infection.^{7, 8, 9} This host-parasite interaction would be expected to produce the many constitutional as well as local articular expressions characteristic of the rheumatoid pattern as opposed to the infectious type of mycoplasma arthritis in the lower animals which is highly localized and generally devoid of systemic features.

It is characteristic that the tissue hypersensitivity state in man induced by prolonged exposure to bacterial antigens may obscure detection of the microbial antecedents. This phenomenon is exemplified in the most reactive phases of rheumatic fever, tuberculosis, brucellosis and syphilis where the causative agent is either very difficult to isolate or is unobtainable even when known to be present because of continued progression of the disease state. Parenthetically, the mechanism of hypersensitivity can be considered an important aspect of the defense system. With the human host sensitized to antigen from intracellular mycoplasma even greater difficulty in isolating the offending organism could be expected. It would follow that any major advance in the exploration of the mechanistic

concept of rheumatoid disease would have to await a new approach involving both the host and the parasite such as the animal model which is now at hand.

The immunologic similarity of the gorilla host response to that of man appears to be the primary factor allowing the spontaneous development of rheumatoid type disease in this animal. This example of a disease relationship providing an immunologic bridge between lower animals and man through the gorilla has escaped attention in the past possibly because of circumstances rather than absence or rarity of this phenomenon in nature. It has been customary to view articular derangement in animals as either due to injury or the effects of aging. In humans separation of arthritic types into precise diagnostic categories has been dependent upon detailed physical and laboratory examinations. Veterinary medical progress with new anesthetics and special methods of anesthesia induction in wild animals such as the tranquilizing gun would provide safe and efficient means for extensive case finding studies in gorillas. It is hoped that this report will encourage similar investigations at zoos, primate centers, and in the wild whenever articular and non-articular evidence of the rheumatoid disease pattern becomes apparent. Other examples will no doubt be found when searched for.

The present study represents an extension of the mechanistic approach to the treatment of rheumatoid disease which we have employed for a number of years.^{7, 8, 9} Direction in therapy has been aimed at suppression and ultimate elimination of microbial antigens considered basic in promoting continuous disease activity. Previous investigations have continued to point to mycoplasma or tissue hidden bacterial variants such as L-forms and protoplasts as a likely antigenic source for the rheumatoid reaction. Unlike true viruses, mycoplasma are sensitive to certain chemotherapeutic substances such as gold salts²⁰ and antimalarials²¹ used empirically for years in the treatment of arthritis. The growth inhibition of mycoplasma by certain antibiotics such as tetracyclines and lincomycin and the uniform resistance of these microbes to penicillin, ampicillin and sulfonamides has been a distinctive biologic characteristic.^{9, 14}

We have observed that antibiotics which possess antimycoplasma properties, when used in the proper dosage for the individual patient, may suppress rheumatoid activity without the risk of toxic effects often encountered with other antirheumatic substances. It is of particular interest that in the most severely involved rheumatoid subjects the antimycoplasma medication dosages must be carefully titrated to avoid the Jarisch-Herxheimer effect from the sudden release of antigen in the highly sensitized host.⁹ This common therapeutic and reactive effect resulting from any one of three different classes of drugs which bear no chemical

relationship to each other is consistent with the concept that antigen derived from mycoplasma is primarily responsible for the development of the rheumatoid state.

The information gathered through comparative observations and experiences in the human with various therapeutic probes, has provided support for the basic concept used to guide the treatment in the gorilla. This report covers an eighteen months' study testing a mechanistic approach in the treatment of a gorilla, the initial aspects of which were reported earlier.²³

METHODS AND MATERIALS

Physical examinations were made and throat cultures, urine specimens, and venous blood samples as well as biopsied synovial tissue were obtained while the gorilla was under general anesthesia with Sernylan (1 mg./Kgm., intramuscular).

Antigen and antiserum preparations. Standardized mycoplasma antigens were prepared from 48-hour broth cultures sedimented and washed with saline as previously described by Bailey, et al.¹⁰ with the suspensions adjusted to specific protein concentration. Immune sera were produced in rabbits by intravenous inoculation of mycoplasma suspensions totaling 3.0 mg. protein over a three-week period.

Serodiagnosis. The growth inhibition method used was the tube dilution technique reported previously by Bailey, et al.¹¹ The complement fixation (CF) method used was essentially the 100% lytic unit test previously described by Clark, et al.¹² Briefly this consisted of incubating 1 volume (0.2 ml.) of diluted serum overnight at 4° C, with 10 micrograms of mycoplasma protein antigen and 1 unit of guinea pig complement. One volume of 5% sheep blood cells sensitized with 2 units of hemolysis was then incubated at 37° C for 15 minutes with the reacted complement. Complete fixation of complement with no lysis was considered 4+. The rheumatoid factor level in serum was determined by the bentonite flocculation test (BFT) as reported by Bozichevich, et al.¹³

Antibiotic sensitivities. The minimal inhibitory antibiotic concentration was determined essentially as previously described by Robinson, et al.¹⁴ Twenty-four hour cultures of mycoplasma were diluted to contain about 1×10^4 colony forming units (CFU) per ml. Agar plates of "PPLO" media, prepared to contain the appropriate antibiotic dilutions were inoculated in triplicate with 0.05 ml. of culture. After 48 hours incubation the average number of CFU on the antibiotic agar plates was compared with the control plates and expressed as % inhibition.

Mycoplasma cultures. Swab specimens from the throat and minced synovium tissue were streaked on commercial PPLO agar and fresh media

of pancreatic digest (PD) of beef heart muscle.¹⁰ Both agar and broth media were enriched with 20% horse serum and 10% yeast extract and further supplemented with penicillin (1000 units/ml.) and 1:2000 thallium acetate for primary isolates. Initial cultures were incubated both aerobically and anaerobically at 37° C for periods up to 2 weeks.

Serum protein analysis. Serum gamma globulin levels were determined by the Kunkel ZnSO₄ precipitation method.¹⁵ Specific serum protein fractions were measured by standard paper electrophoresis and immunoelectrophoresis techniques. Protein concentration was determined by the Folin-Ciocalteu method.

Electron microscopic analysis of mycoplasma was made using the diluted broth culture sedimentation technique previously described by Clark.¹⁶

CLINICAL OBSERVATIONS

A 9 year old male gorilla "Tomoka" was born in captivity on September 9, 1961, at the National Zoological Park, Washington, D. C. His early life was uneventful except for an episode of severe gastrointestinal disorder in infancy due to a salmonella infection. Growth was normal and the animal appeared playful and active until October 1965 when lameness in the right foot was first noted. Initially the cause of the lameness was uncertain, but by 1967 it became evident that he had developed a progressive rheumatic disorder characterized by migratory arthritis principally in the small joints and by failure to grow and mature normally. In the several months prior to the onset of this study the arthritis had remained localized in the left foot (metatarsophalangeal area) and in the left hand and wrist. The affected areas were visibly swollen and obviously painful with severe functional impairment. During the three and one half year period from the onset of the illness, twenty-nine therapeutic agents had been employed with only transitory symptomatic effects in the otherwise progressive disease process. By February 1969 his condition seemed so poor and his disability so marked that euthanasia was considered seriously by the Zoo officials.

On February 13, 1969, the colony of seven great apes at the Zoo underwent a series of tests to appraise their state of health and to rule out tuberculosis.¹⁷ The blood examination, which included several tests for arthritic activity, revealed abnormalities in Tomoka warranting further study. The gamma globulin was elevated and the rheumatoid factor test positive in low titer. The alkaline phosphatase and IgM were elevated. The chest was clear and the joints were negative for destructive changes by x-ray examination.

The Arthritis Research Unit was asked to assume the responsibility for

treatment of the gorilla on March 18, 1969, and extensive detailed laboratory and clinical studies were undertaken. The physical examination under anesthesia revealed a number of abnormalities. The coat was thin and lusterless. The weight and size were greatly reduced for his age. The muscle tone was generally very poor. The fingers of the left hand were markedly swollen with increased local heat over the affected area. Even under anesthesia the fingers were stiff and unyielding on passive motion. The left wrist was considerably enlarged with increased local heat over the swollen area. The skin of plantar surface of the left foot was keratotic. The tissues in the metatarsal-phalangeal area were thickened and warm to palpation and the toes were resistive to passive motion. At the time of the examination the right hand and foot revealed no gross abnormalities, but the right calf muscles were atrophic.

The keeper at the Zoo who raised the gorilla from infancy commented on a state of apparent depression associated with the illness.

Figure 1 illustrates the gorilla limping across his cage unable to use his painful left hand and balancing part of his weight on the left heel. The left foot was swollen on the medial aspect and the skin on the sole appeared thickened and keratotic (Fig. 2). The nearly complete disuse of his left hand is evident when the animal attempts to grasp the top bars of the cage (Fig. 3).

Typical colonies of mycoplasma appeared in the cultures from the throat (Fig. 4). This strain was not a penicillin induced bacterial "L" form as similar characteristic mycoplasma colonies were seen also on the penicillin free plates in the presence of bacterial colonies. After two passages on agar, the gorilla strain of mycoplasma isolated from Tomoka (TK) was cultured in broth free of penicillin and after 200 transfers has not changed its characteristic properties. The electron photomicrograph (Fig. 5) of the gorilla mycoplasma revealed the various morphological stages of growth including the classical "doughnut" shaped bodies also observed in cultures of human strains.¹⁶

The cultures of wrist synovial tissue yielded several atypical colonies resembling mycoplasma which could not be transferred beyond the second passage. These findings are similar to those often obtained with cultures from arthritic tissues homogenates. It is known that extracts from inflamed tissues inhibit the growth of viable mycoplasma and thus limit the likelihood of isolation of the organisms. However, when the minced synovium tissue was administered to rabbits, it did evoke the development of antibodies specific for the TK strain as shown in Table I. These results suggested that the TK mycoplasma antigen was also present in the affected tissue area. Subsequent studies with human synovium homogenates were found to contain antigenic material also reactive to specific myco-



FIG. 1. An underdeveloped young male gorilla, Tomoka, with severely crippled left hand and foot prior to I.V. therapy.

plasma antisera. Whether this antigen is of tissue or mycoplasma origin remains to be demonstrated.

The pathologic findings in synovium from the left wrist revealed occasional rheumatoid type nodular aggregates of mononuclear inflammatory cells, primarily lymphocytes, but with rare plasma cells (Fig. 6). Hypertrophy of synovial villi was not a prominent feature, although lymphocytes and plasma cells were scattered diffusely through the connective tissue underlying the synovial membrane. A peculiar myxoid appearance of the fibrous tissue beneath the synovial membrane was also noted. These areas stained intensely with alcian blue but did not take the PAS stain. Uric acid (alcohol fixation) stain was negative and H&E sections of the

tendon sheath appeared normal. A solitary microfocus of neutrophilic exudate was present, with hyperemia and margination of leukocytes in adjacent vessels. Several small vessels showed "cuffing" by lymphocytes but there was no vasculitis.



FIG. 2. Swollen left foot of gorilla with dry, rough skin prior to treatment.

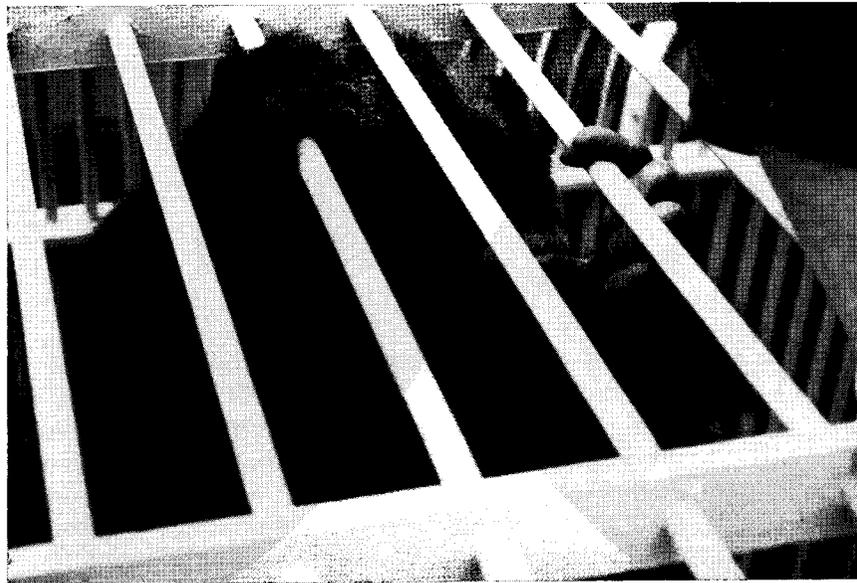


FIG. 3. Extensive disuse of gorilla's crippled left hand grasping the top bars of his cage.

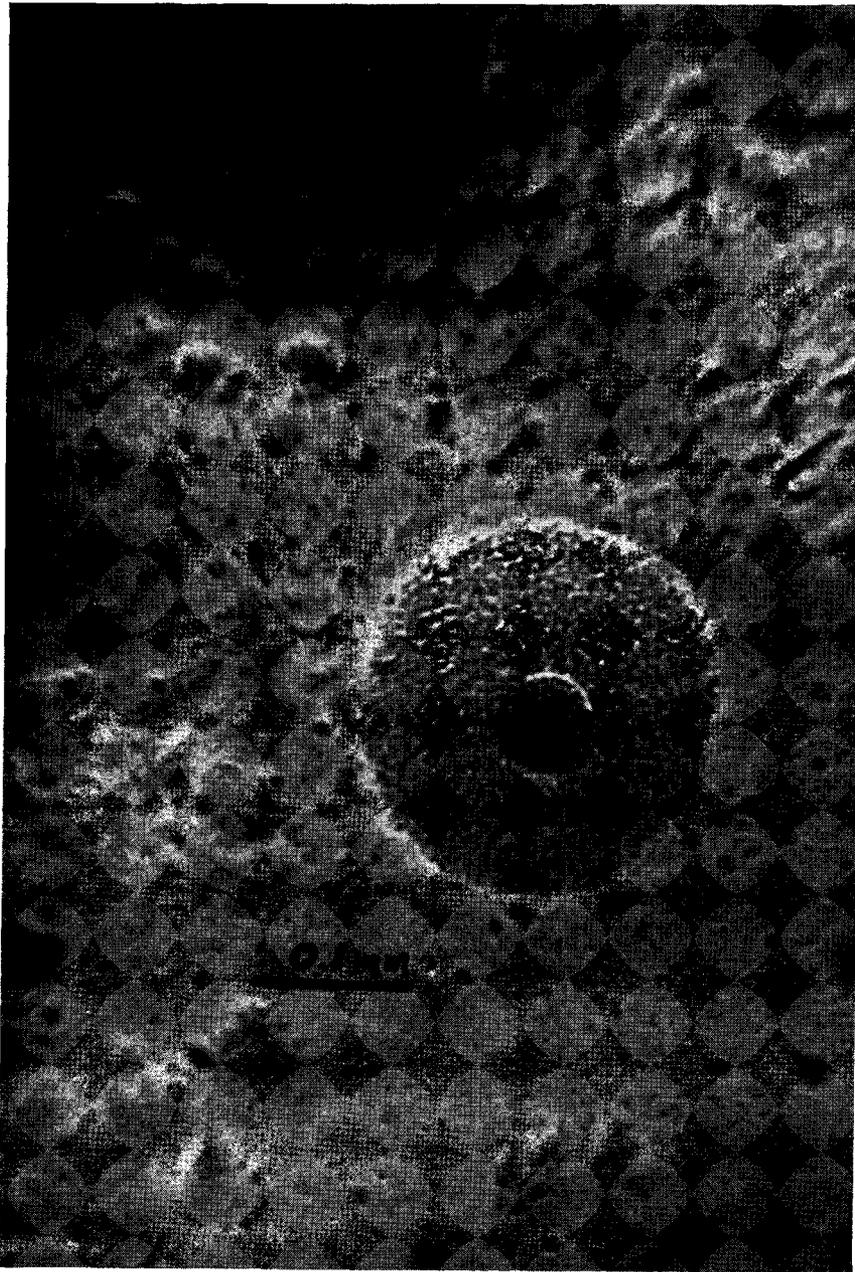


FIG. 4. Typical mycoplasma colony on agar culture surface isolated from gorilla throat (200 \times).

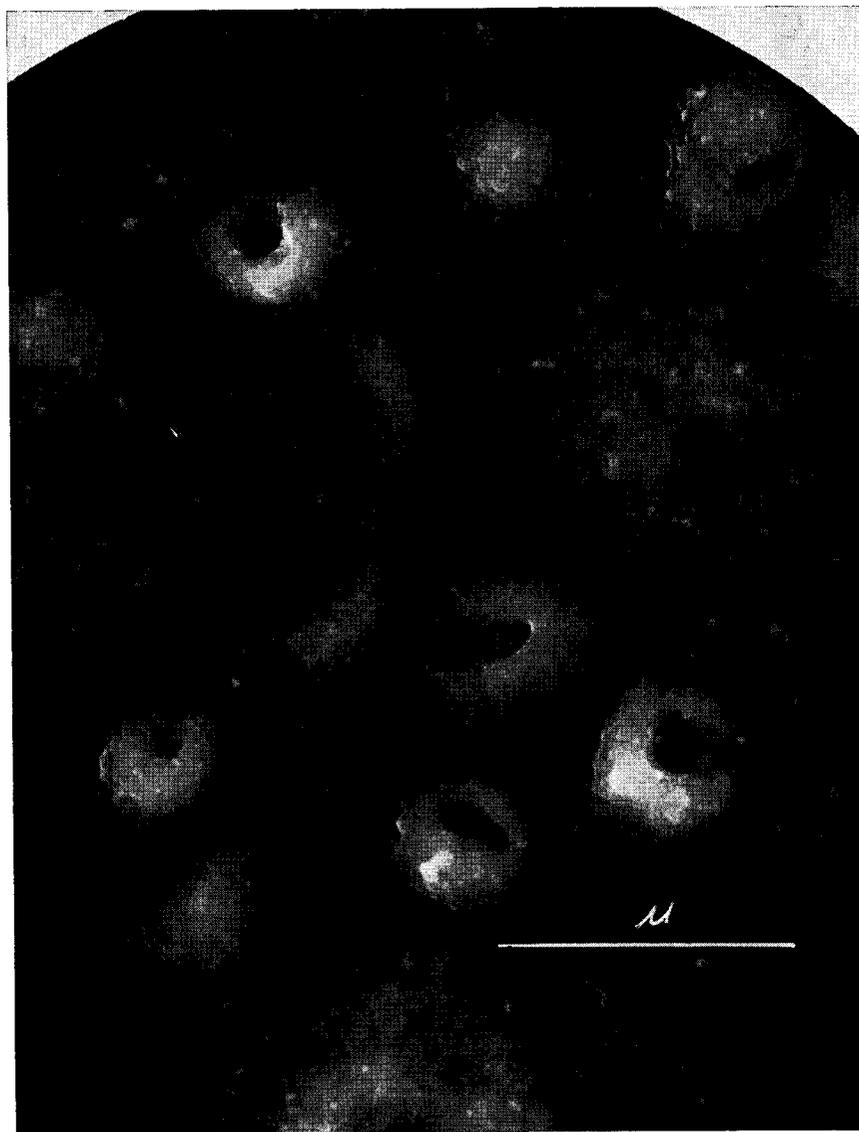


FIG. 5. Electron photomicrograph of the gorilla mycoplasma, sedimented from broth culture, fixed with osmic acid and shadowed at 30° showing the unique doughnut shaped particles and other stages of development (20,000 \times).

TABLE I
Inhibition of Mycoplasma Growth by TK Synovium and TK Mycoplasma Immune Sera*

Immune Sera	Levels of Mycoplasma Growth Inhibition			
	TK	M. salvarium (PG-20)	M. orale I (Patt)	M. arthritidis (Campo)
Synovial tissue.....	75	25	0	0
TK mycoplasma.....	100	75	0	0
Normal rabbit.....	0	0	0	0

* Percent inhibition when compared with colony growth in control.

The tissue findings were interpreted by several pathologists to be those of an inflammatory reaction, consistent with either rheumatoid or arthritis of traumatic origin. The changes were unlike those seen in the usual mycoplasma arthritis of lower animals or other types of infectious arthritis.

APPROACH TO TREATMENT AND RESULTS

The established connection between arthritis and mycoplasma infection in lower animals has suggested the probability that a similar but more complex relationship might exist in the gorilla, a higher animal, in which the conditions for the development of tissue reactivity are comparable to those of man. The concept that hypersensitivity to mycoplasma antigen may be basic in the pathogenesis of the gorilla arthritis provided direction in the treatment plan, with the additional guidance of regular serologic and physical measurements. The decision regarding which medication to employ was reached by several factors including comparative *in vitro* antimycoplasma effect particularly in relation to the isolated gorilla mycoplasma strain TK, Table II, and also the acceptability of the drug for intravenous use in order to achieve high tissue concentrations to attempt to rid the host of the parasite.

Mycoplasma in parasitized cells can remain isolated from the body defenses and from antimicrobial drugs in a manner quite unlike usual bacteria in their extracellular location normally encountered in infections. If gold salts or antimalarials were to be used to attack mycoplasma, limitation of dosages would be necessary because of the hazard of toxicity. Low medication levels could be expected to suppress mycoplasma antigen formation and promote temporary improvement, but the likelihood of producing a sustained or permanent remission could not be visualized.

Tetracycline for intravenous use was therefore selected at the outset as the principal therapeutic agent to be employed with the plan to substitute other antimycoplasma substances such as lincomycin for a comparison of

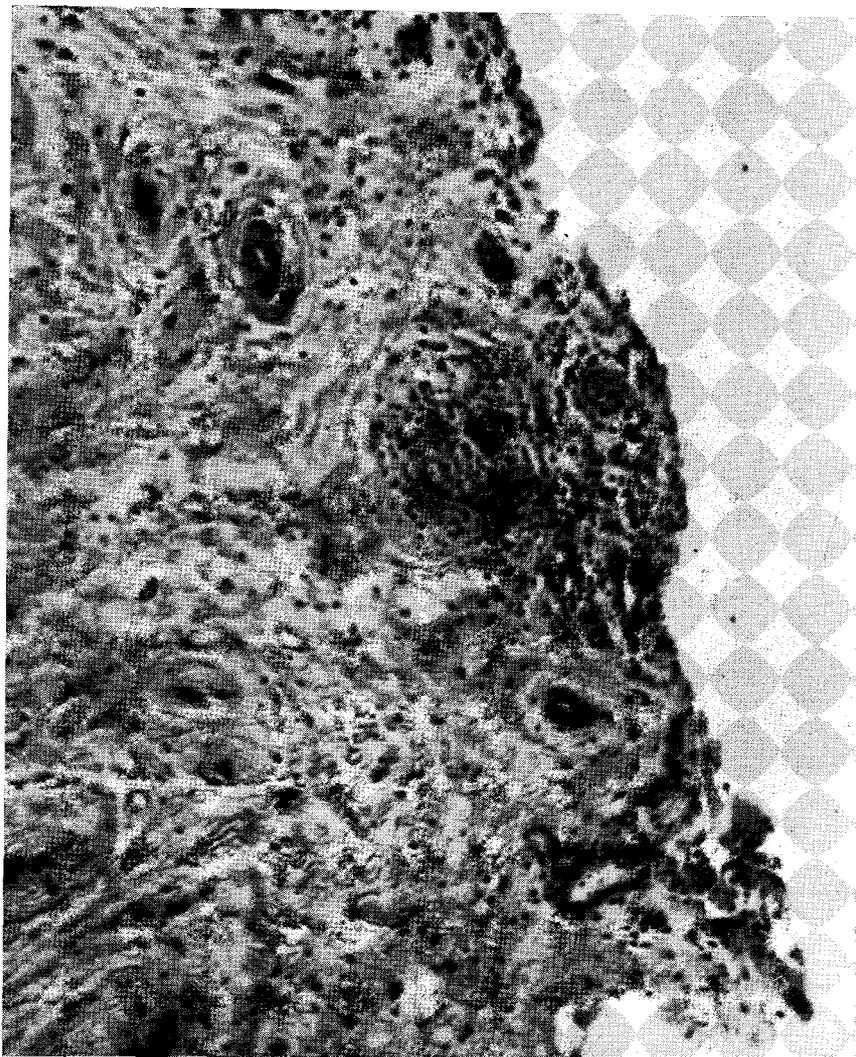


FIG. 6. Section of wrist synovium tissue showing rheumatoid-like arthritis "nodule" composed of lymphocytes and plasma cells, some showing tendency for arrangement around vessels. Note loose, myxoid appearance of soft tissues beneath synovium, H&E, $\times 119$.

in vitro and in vivo effectiveness at comparable dosage levels. The first intravenous treatment was given on March 18, 1969, following anesthesia with Sernylan (frequently employed in veterinary medicine). Administration of the medication was by drip in a fluid volume of 500 ml of 5%

dextrose solution. The dosage of tetracycline during the period of treatment ranged from 250 to 1500 milligrams.

Prior to the initiation of treatment, the Zoo staff was informed of the likelihood of a marked exacerbation of symptoms from antigen release through destruction of mycoplasma by the medication. As anticipated following the first intravenous treatment there was a marked exacerbation of symptoms which persisted for seven to ten days. The arthritis became so severe that the animal remained in the corner of his cage and moved infrequently except to rub his obviously painful joints. Listlessness and depression were more marked than usual. The reaction was clinically typical of a Jarisch-Herxheimer type effect and was supported by laboratory evidence of antigen release with the sharp rise in gamma globulin and rheumatoid factor and the subsequent appearance of specific mycoplasma antibody. The predictable aspect of this response provided additional scientific support of the disease concept used for guidance, and the observed therapeutic paradox also indicated that continuation of this approach in management would be ultimately rewarding.

Following the initial exacerbation improvement was rapid and progressive. In addition to the increase in weight and growth (Fig. 7), the gorilla began showing a pronounced change in behavior and his former playfully active state returned. The reappearance of natural coloring and texture of his hair and skin as well as the increased muscle tone and greater body mass definitely indicated a profound systemic improvement. Thus the response to therapy was a total constitutional gain and not just localized improvement of peripheral joint inflammation. In contrast with initial disability (Fig. 1), marked joint improvement after 9 months of therapy

TABLE II
Antibiotic Sensitivity of TK Mycoplasma*

Antibiotic	Micrograms/ml Agar Media							
	50	25	12.50	6.25	3.12	1.56	0.78	0.39
Ampicillin.....	0	0	0	0	0	0	0	0
Erythromycin.....	100	90	90	80	50	30	30	20
Penicillin.....	0	0	0	0	0	0	0	0
Tetracycline.....	100	100	100	100	100	100	75	70
Lincomycin.....	100	100	100	100	100	100	100	100†
Kanamycin.....	100	100	100	100	100	100	90	70
Oxytetracycline.....	100	100	90	90	85	70	50	30

* Percent inhibition when compared with colony growth in control.

† 100% inhibition continued through the 0.095 μ g level.

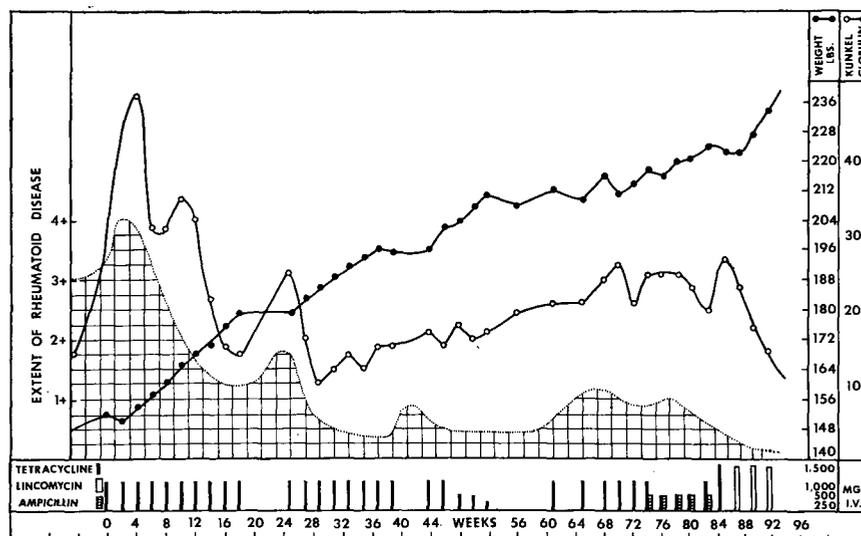


FIG. 7. The response of rheumatoid disease, growth and gamma globulin to I.V. antibiotic therapy in the gorilla.

was observed with his ability to perform a standing high jump to grasp the top bar of the cage (Fig. 8).

A comparison of data (Fig. 7 and Fig. 9) indicates a correlation between reduced serologic activity and constitutional improvement. The measure of gamma globulin level by the Kunkel turbidometric technique closely paralleled the apparent initial release of antigen and the subsequent increase of mycoplasma antibody levels. This type of exacerbation following antibiotic therapy has been observed in humans.⁹ Perhaps the most significant laboratory finding was the inverse correlation of the rheumatoid factor activity with the mycoplasma antibody. This observation appears to be of sufficient significance to suggest that the rheumatoid factor may have an anti-antibody effect on the complex mycoplasma antibody (Fig. 9). This relationship was suggested when a rise in mycoplasma antibody preceded the reappearance of the rheumatoid factor by 2 to 3 weeks. These findings would be compatible with the postulated destruction of cell bound mycoplasma and the release of their antigen quantitatively sufficient to evoke a specific antibody response, which may further stimulate anti-antibody production in the presence of released antigen.

There were three occasions during the eighteen month period of intermittent treatment when either the frequency of administration or the



FIG. 8. Tomoka the gorilla able to make a standing jump to the top of his cage 9 months after therapy.

dosage of the medication were altered to test the cause and effect relationship. In all instances there was a clinical relapse as well as a change in the laboratory findings indicating worsening of the disease state. Following reinstatement of treatment, improvement was rapid in the first instance when the dosage of tetracycline was high. In the second instance the improvement was not evident in association with the lower dosages (250 mgm. of tetracycline) but definite when the dosage was increased to 1000 mgm. It would appear that the 1000 mgm. of tetracycline I.V. may represent a level where tissue penetration is sufficient to suppress viable antigen and elicit progressive clinical improvement. The addition of ampicillin

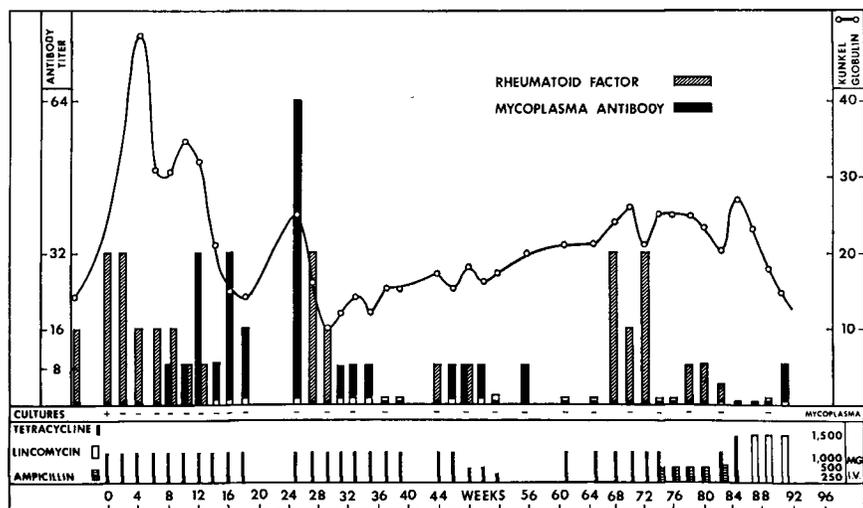


FIG. 9. Serologic responses in the gorilla to I.V. antibiotic therapy.

which has no effect on mycoplasma provided no apparent benefit nor indicated other bacterial involvement.

One of the most revealing aspects of the therapeutic program became evident in the latter phase of observation (Fig. 7). During this period the arthritis had greatly improved but was still smoldering in the right foot where increased heat was noted intermittently on palpation of the area surrounding the proximal first toe joint. At this time the left hand and foot were completely asymptomatic and normal on palpation. The calf muscles of the right leg were atrophic and the tone remained poor, attesting to the long standing involvement of the right foot area, the site of onset of the arthritis.

In order to reach this oldest and most resistant area of involvement and to test further the principles used for guidance, the tetracycline dosage was increased to 1500 mgm. This was immediately followed by clearing of the right foot which has remained normal since. From this point on lincomycin in the same dosage has been substituted to test its comparative *in vivo* action. During the course of the study lincomycin was found to possess the most marked inhibitory effect of any of the antibiotics tested on the TK strain of mycoplasma and also several human strains.

With the high antibiotic dosage, presumed to allow greater tissue penetration, there was a rapid drop in gamma globulin and increase in weight and the reappearance of a positive mycoplasma complement fixing antibody level specific to the TK strain. This last finding supported the view

that a previously unreached area had been penetrated and mycoplasma had been destroyed as indicated by the rise of specific antibody through further antigen release.

DISCUSSION

In the long and complex history related to the study of rheumatoid disease, a major missing component has always been a true animal model which possessed two essential elements; an invisible source of persistent antigen and a host with a reactive potential very close to that of man. Lower animals apparently do not satisfy the specific tissue reactive aspect of these criteria despite the presence of arthritogen mycoplasma.

A young male gorilla at the National Zoological Park, with naturally occurring, progressive, disabling arthritis of 3½ years' duration has been found to represent the first complete counterpart of rheumatoid disease in man.

In the past there has been minimal evidence of arthritis in any of the higher mammals such as monkeys and great apes. One report which is of particular interest in light of the present findings was published in 1939 by Fox¹⁸ who found evidence of arthritic conditions predominating in gorilla skeletons which resembled the changes seen in human rheumatoid arthritis.

An epidemiologic survey of the large primates at the National Zoo and also the staff members who handle them is being undertaken. Preliminary findings have revealed type specific antibodies to the TK strain in the serum of Tomoka's three year old sister (now at Yorke's Primate Center in Atlanta, Ga.) as well as the young female gorilla with whom he was in contact and the zoo keeper's wife who cared for Tomoka in infancy.

The isolation of a new mycoplasma strain with both tissue and serologic reflections suggests a potential etiologic relationship. Therapy directed specifically toward suppressing cellular mycoplasma antigen formation has been highly effective. Other symptomatic antirheumatic medications previously administered had not provided sustained effect. Suggestive pathogenic relationship of the isolated mycoplasma to the arthritis in this animal species was indicated by the emergence, the rise, and the fall of a specific antibody to the gorilla strain during the course of treatment. The present study of an animal model has also demonstrated a highly significant inverse correlation between serum mycoplasma antibody and the rheumatoid factor, thus providing evidence for the occurrence and support for the anti-antibody concept. This same inverse correlation in human rheumatoid arthritis has been observed and recently reported by Brown, et al.²²

From these results it would appear that a consideration of the patho-

genesis of rheumatoid disease must include not only an understanding of the antigens but also equal consideration of the host with emphasis on ever improving measurement and study of the host-parasite relationship. In a recent editorial on Prevention of Disease due to *Mycoplasma Pneumoniae*, Clyde¹⁹ also emphasized that "Greater attention should be focused upon these basic aspects of host-parasite interaction."

Perhaps this is the time for an official drafting of a corollary to Koch's postulates which would provide recognition of the host as well as the parasite in the production of certain disease processes where the specificity of the tissue reactive state plays an essential role in pathogenesis.

SUMMARY

A young male gorilla, the animal most closely related to man serologically, was found to have developed spontaneously systemic and articular manifestations of a severe progressive illness which satisfied the ARA diagnostic criteria of definite rheumatoid arthritis. The observed expressions similar to the human counterpart were: general retardation in growth, localized muscle atrophy associated with joint inflammation, altered behavior, small joint involvement—at first migratory and later localizing in the left hand and foot, weakened muscles, changes in skin and hair, synovium tissue biopsy findings of inflammatory changes consistent with rheumatoid arthritis, elevated gamma globulin and the presence of a rheumatoid factor. A new mycoplasma strain that cross-reacted with a human strain was isolated from the throat and its antigen detected in the synovial tissue.

A mechanistic approach to therapy using intermittent intravenous tetracycline for mycoplasma antigen suppression, has been highly effective following failure of other types of treatment. The antibiotic apparently reached the tissue bound mycoplasma and released antigen as demonstrated by the subsequent increased gamma globulin and the appearance of mycoplasma antibody with correlated constitutional and articular improvement. The mycoplasma antibody produced by the host, following therapy initiation, was specifically related to the gorilla strain of mycoplasma. This first natural expression of rheumatoid factor in the animal model is of particular importance because of the inverse correlation between mycoplasma antibody and the rheumatoid factor in the serum. The finding is consistent with the anti-antibody concept of the rheumatoid factor activity.

The most significant conclusion of this investigation would be the revelation that the gorilla is an accurate test model for studies of rheumatoid disease. Future studies should include attempts to reproduce the disease in the gorilla and test therapeutic mechanisms. An important result of the

present finding is the further justification for the inclusion of mycoplasma in the consideration of the complex etiology, medical management, and prevention of rheumatoid disease in man.

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DISCUSSION

DR. LEWIS DEXTER (Boston): Would you extend your observations to man and suggest that a man with rheumatoid arthritis should be treated with ampicillin?

DR. BROWN: I would not use ampicillin because of the lack of effect on mycoplasma.

DR. DEXTER: I'm sorry. What did you give? Tetracycline?

DR. BROWN: We used tetracycline and lincomycin both effective against mycoplasma.

Actually the plan of treatment of the gorilla was the result of using the antibiotics which possess antimycoplasma activity in the management of rheumatoid arthritis, a method which we have been employing for many years. This idea came first from laboratory studies when we were searching for substitutes for gold salts which concerned us because of unpredictable serious toxicity as well as their tendency to sensitize the host and lose effectiveness with continued use. The substrates used for testing were human mycoplasma strains and we soon found that tetracyclines were even more effective than gold salts. From this beginning came the hypersensitivity concept when the same Jarisch-Herxheimer type effect appeared in clinical trials with antibiotics as with gold. Later on we reported the inhibitory effect of antimalarials²¹ on mycoplasma which explained the similar effect of all these drugs. The Jarisch-Herxheimer type effect has also been noted from antimalarials.

We have not discussed details of treatment results with antibiotics except in general terms. It can be stated that we believe the antibiotics with antimycoplasma properties are entirely safe in long-term use and are effective as long as one continues to individualize, and uses the mechanistic concept of the host parasite interaction for guidance. Also treatment success is dependent upon frequent readjustment of dosage in relation to indications provided by clinical patterns and laboratory tests.

Before more can be said of results, a far better means of measurement must be available which would encompass the patient as a whole. At present we have nearly completed a computer study dealing with more than eight thousand variables which we have found are involved in the programming of the various types of arthritic and rheumatic diseases. These variables can no doubt be reduced to a few hundred of the most significant factors needed for measurement which will make this method generally available. When this is complete, we believe an accurate appraisal of the value of any form of management including antibiotics can be made. It can be stated that

the information gained through these studies in the gorilla have paralleled and reinforced our findings in the human.

It would appear that treatment of the human rheumatoid arthritic with the enormous number of variables to contend with from unlimited environmental influences reacting upon the delicate disease balance, is like viewing a scene through mist and fog. The experience with the gorilla provides a view of the same scene after the fog has lifted. The most interesting aspect of all is that those landmarks which we believed to be there through the fog have been found to be precisely as we had pictured them when the fog finally lifted.