THE CAUSATION OF RHEUMATOID DISEASE AND MANY HUMAN CANCERS

by

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--A New Concept in Medicine --

A Précis and Addenda, Including the Nature of Multiple Sclerosis

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Preface

The author's monograph *The Causation* of *Rheumatoid Disease and Many Human Cancers. A New Concept in Medicine* was published in March 1978, but it was, in fact, written during the second half of 1976 and the first half of 1977. In this it was shown that rheumatoid disease is due to infection with a pathogenic free-living amoeba in a sensitive subject and this can be killed by numerous anti-freeliving amoebic substances. Any body tissue may be infected, producing general, local or autoimmune lesions in every combination. Since writing the monograph considerable laboratory work on the free-living amoebae, the substances which kill them in vitro, the effect of these substances on cases of active rheumatoid disease and related conditions and on carcinomatous and lymphomatous states and the significance of antifree-living amoebic substances on cases of multiple sclerosis has been investigated further and the findings confirm and extend the conclusions reached about rheumatoid diseases, malignant disease and multiple sclerosis in the monograph. Any infected part may become malignant in sensitive subjects and treatment of the premalignant condition may prevent the development of cancer.

Rather than rewrite the whole monograph the author decided to publish further findings as an addendum to the original with a Précis of the contents of the latter and proof of the autoimmune nature of multiple sclerosis.

Roger Wyburn-Mason Richmond, Surrey, England

Note:

Roger Wyburn-Mason, M.D., Ph.D. waa convinced that he and protozoologist Vice-Admiral Stamm had proved the amoebic basis to rheumatoid disease and some forms of cancer. To display the tremendous amount of clinical evidenced he'd amassed to substantiate their apparent discovery, he published *The Causation of Rheumatoid Disease and Many Human Cancers* in Japan (IJI Publishing Co., *Ltd.)* , March 1978. This extremely well-done, illustrated, slick-paper, hardbound book consisted of 479 pages (7"X10.25") and might have been described as a *tour de force*, clinical cases, well-reasoned scientific evaluations and comparisons, and volumes of literature research all underpinning a plausible hypothesis.

Jack M. Blount, M.D. purchased a large number of these books which he distributed to medical libraries and other physicians, but, at $125 per book a cheaper version was needed. That's how this prècis came about, being prepared by Prof. Roger Wyburn-Mason just before his death.

Whether or not the Wyburn-Mason/Stamm amoebic hypothesis is verified, a most positive outcome has been the fact that treatments based upon it have obtained wellness on a world-wide basis, covering patients on every continent, and involving a multitude of clinics, over many years.

Thomas McPherson Brown, M.D. (now also deceased) determined that mycoplasm was probably the source-cause of rheumatoid diseases, a hypothesis also still undergoing evaluation. However, like Wyburn-Mason's treatment, the treatment derived by Dr. Brown and his co-workers also resulted in spectacular cures.

Although it would be educational and even entertaining to learn which of many hypotheses are correct, involving "the" cause of rheumatoid disease, this foundation now accepts the idea as fact that "many" causes are involved, and that both Wyburn-Mason and Brown have found regions of truth.

Why?

Because, according to the scientific method, whether or not a hypothesis is correct can only be measured by how well it describes and predicts and otherwise produces results, i.e., wellness. When a

more efficient hypothesis comes along, it is right and proper to discard the more inefficient.

On that reasoning, then, we accept Wyburn-Mason, Brown and also the multiple-causation hypothesis!

Anthony di Fabio

INTRODUCTION: RHEUMATOID A GENERALIZED DISEASE

The following is to a large extent a Prècis of the author's 1978 479 page monograph (Wyburn-Mason 1978). Any obscurities in this may be elucidated by reference to the original. Rheumatoid disease (RD) is not simply a disease of joints, but a generalized condition and every tissue in the body has been reported at some time as being affected. The same histological changes as are found in the joint tissues can be seen in the extra-articular lesions and consist of inflammatory lymphocytic infiltration, formation of germinal follicles and often plasmocytosis, accompanied by arteritis, arteriolitis or endarteritis. Many of the extra-articular lesions constitute so-called autoimmune (AI) diseases, but also include Sjogren's syndrome, bone marrow infiltration and thymic lesions with or without myasthenia, fever up to 40° C, sweating and raised ESR, typical of an infection. Any of the extra-articular or AI lesions may occur in any combination with or without arthropathy. The serum usually contains rheumatoid factor (RF), often auto-antibodies to various tissues and antinuclear factor (ANF). Furthermore, every combination and gradation into one another of the so-called collagen diseases [RD, systemic lupus erythematosus (SLE), derm- or poly-myositis, scleroderma or systemic sclerosis and polyarteritis nodosa] may co-exist or overlap, so-called mixed connective tissue disease and the administration of numerous drugs, for example gold salts, penicillamine (Grennan 1980) and camoquin (Wyburn-Mason 1978) may change RD into SLE. This suggests that these diseases are due to a single fundamental disturbance which may present in various ways. Some regard the disease as due to AI cellular and humoral changes without explanation as to their cause. Most believe they are an infection.

The significance of Rheumatoid Factor (RF) in the serum.

RF so frequently found in the serum of RD patients is a macro-globulin and an

antibody. It occurs in the IgM fraction of the serum and may be found albeit in low concentration in many infections, including subacute bacterial endocarditis, infective hepatitis, pulmonary tuberculosis, syphilis, etc. accompanied by autoantibodies to various tissues (Wyburn-Mason 1978). In these diseases arthritis is not a feature and successful treatment of the underlying disease causes the RFand auto-antibodies to disappear from the blood. Not only RF, but also ANF, a positive Wassermann reaction, thyroid auto-antibodies and lupus erythymatosus cells may also be present in the sera of a high proportion of cases of leprosy as a response to the infection. RF with autoantibodies occurs, however, in *high* concentration comparable to that in RA in chronic infections with many protozoa, including malaria, trypanosomiasis, kalazar visceral leishmaniasis, amoebiasis and giardiasis, as an antibody response to the antigens in the infecting organisms. In the immigrant and indigenous population of Uganda there are found a high titre of malarial antibodies and high levels of IgM, RF and circulating autoantibodies to heart, thyroid and gastric parietal cells. The levels of the latter and of RF are related to that of the malarial antibody titre. The blood changes gradually disappear on treatment with antimalarial (antiprotozoal) drugs. Such observations make it difficult to believe that such serum changes in RD and AI diseases are anything other than due to an infection, probably protozoal, and the lymphocytic and serum changes are reactions to the infection. They are certainly not due to bacterial or mycoplasmal infection, since antibiotics have no effect on RD and there is no evidence of a viral aetiology of this condition. Moreover, the failure of lymphophoresis or lymphoplasmophoresis to produce benefit or nothing more than temporary improvement in cases of RD or SLE (Denman 1981) and of cytotoxic or immunosuppressive drugs to cure the condition points to the fact that the cellular and humoral reactions are not the cause of the disease, but result from some other phenomenon, which could well be a chronic infection. Glynn (1968) postulated an unknown chronic antigenic stimulation as the cause of RD and this theory dominates present thinking, though the antigens concerned are unidentified.

The effect of certain antiprotozoal drugs on active rheumatoid disease and related conditions.

The author and his colleagues in USA, South Africa, New Zealand and Holland have shown in over 16,000 cases that, if the 5-nitroimidazole drugs, metronidazole and its analogues, tinidazole, ornidazole or nimorazole in 2 gram doses on two successive days weekly for 6 weeks, furazolidone (100 mgms. four times daily for a week), allopurinol (300 mgms. three times daily for 10 days), POTABA (postassium p-aminobenzoate) (2 grams six times daily for 30 days) or rifampicin (600 mgms. daily for two months) or isoniazide (300 mgms. daily for six weeks) or rifampicin and isoniazid together (as in treatment of tuberculosis) are administered to cases of active, classical, definite or probable RD or its extra-articular manifestations, they always induce an Herxheimer reaction, that is a transitory, sometimes severe, exaggeration of the inflammatory changes around the joints and elsewhere, and often in the appearance of rheumatoid inflammatory lesions in any part of the body not previously affected. This may be accompanied by influenza-like symptoms, sweating, shivering, pyrexia, headache, lymphadenopathy, rise in ESR and blood eosinophilia. These reactions gradually die down, when all evidence of disease activity usually disappears. Such a reaction, first described by Herxheimer and Krause (1902) when cases of syphilis were treated with mercury or salvarsan, also occurs in cases of syphilis treated with penicillin and in other diseases *due to organisms more complex than bacteria* when drugs which kill the causative organism in the tissues are administered, such as diethylcarbamazine in filariasis cases or oxamiquine in schistosomatosis It is due to the liberation into the tissues of irritant and antigenic substances from the dying causative organisms. This reaction in cases of active RD treated with the above substances has been confirmed in various countries, notably USA, S. Africa, Holland, France, Germany, Australia and New Zealand. It is not observed in healthy persons or cases of viral disease so treated or in RD cases given antibiotics. Rifampicin and isoniazid together produce an Herxheimer reaction more quickly and markedly than either drug alone as they do in giving a positive response to treatment in tuberculosis.

Moreover, in 20 early cases of active RA accompanied by knee effusions the author showed that draining off some of the intra-articular fluid from one knee and replacing it with 100 mls. of a solution of metronidazole in the strength of 500 mgms. to 100 mls. of saline on two or three occasions at weekly intervals usually causes a mild local reaction followed by a rapid easing of pain, absorption of the pre-existing effusion and disappearance of signs of inflammation lasting usually five years or more. The untreated knee remained unchanged. If saline was used instead of metronidazole, no improvement in the knee condition occurred. Similar results were obtained by weekly intra-articular injection into the knee of 500 mgms. of rifampicin SV, closely related to rifampicin (Carusa, Montrone, Fumagalli et al. 1982). In 30 cases with persistent knee effusions a local inflam-

matory reaction followed by complete absorption of fluid and disappearance of inflammation of the knee and an impressive general clinical improvement lasting over five years was found to occur. Saline injections had no such effect. Such observations show that organisms within the tissues of the knee sensitive to metronidazole and rifampicin SV are certainly responsible for the lesions in RD.

The occurrence of the Herxheimer reaction in RD, including its extra-articular and AI lesions, with the above drugs is highly significant. Below it will be shown that all of these have antiprotozoal properties and the inducement of this inflammatory reaction in the above conditions followed by disappearance of evidence of inflammation when given orally or by intra-articular injection must indicate the presence in the affected tissues of a *causative organism* more complex than a bacterium, possibly a protozoon. This is the source of the postulated causative chronic antigenic stimulation in these diseases. Rifampicin and isoniazid separately or together in vitro kill myco-bacteria and are used in the treatment of active tuberculosis but they are also effective in killing free-living amoebae both in vitro together and separately, thus proving the organismal causation of RD. Such an Herxheimer reaction in any disease causes *difficulties in the application* of *a double blind trial* when substances which produce it are investigated. Since the above drugs increase rheumatoid inflammation *none of them can have anti-inflammatory properties* in vivo. By administration of these drugs sometimes in repeated courses to cases of RD after the Herxheimer reaction dies down evidence of disease activity usually completely disappears in both joints and extraarticular tissues and after a variable interval of 4-6 months immunoglobulins and ESR gradually return to normal. RF becomes negative and autoantibodies disappear. This contrasts with the effect of repeated lymphophoresis of lymphoplasmophoresis, which may or may not cause some temporary improvement in cases of RD (Denman 1980) and of the failure of cytotoxic or immunosuppressive drugs to cure RD. Such procedures do not remove the causative agent of the disease. If the joint cartilage or bones are affected, the above drugs naturally produce no improvement in the deformity or pain caused by movement, though the joints are no longer inflamed. Cases of fasciitis, which is a feature of many cases of RD, showed dramatic improvement after oral administration of cimetidine, which consists of an imidazole ring with a cyanoguanidine side chain (Solomon, Barland, Rifkin, 1982). **The response of cases to these drugs is often inhibited by long continued previous treatment with gold injections, penicillamine or corticosteroids. Since antiprotozoal drugs completely inactivate and abolish the rheumatoid process and, in fact, cure the disease or prevent its further progress, it is both pointless and impossible to use a double blind trial with a placebo to evaluate their activity. Double blind trials were never used to evaluate the curative properties of sulphonamides and penicillin in infections nor diethylcarbamazine in filariasis. When many drugs curative to any disease are given to patients with this particular disease, their curative effect becomes so obvious that no double blind trial is required and it is surely unethical to deny a cure from a patient suffering from this particular disease when its cure is available. This is on all fours with the present furious debate on the ethics of carrying out double blind trials with vitamin A given to pregnant mothers at high risk for neural tube defects in which many doctors maintain that substances of proven benefit being withheld from patients at risk amounts to medical negligence. This applies to RD when the agony can be rapidly brought to a halt with the giving of antiprotozoal drugs. In the programme "Doctors Dilemmas" featured on British Broadcasting Company Television on February 8th, 1983, it was stated by distinguished physicians that once one drug treatment has been shown to be superior in any disease, the others should be abandoned. The antiprotozoal drugs mentioned above fall into the former category and only this group of drugs should be continued to be used in the treatment of RD. Double blind trials are useful in comparing non-curative drugs in certain diseases, such as anti-inflammatory drugs in RD, but not in comparing curative and non-curative.**

Reference has been made above to the overlap and gradation of RD with SLE, scleroderma, dermatomyositis and polyarteritis nodosa and the conclusion that they all appear to have the same causation. If this is so, then it would be expected that the above drugs would have a similar effect on these associated conditions to that on RD. It was found that administration of the 5-nitroimidazole drugs in the same dosage as for RD to cases of SLE resulted in exaggeration of the arthropathic effect, an increase in the ESR, ANF and RF titre in the blood and transient increase in the immunoglobulins followed by improvement in the arthropathy and fall in the ESR and other parameters of the blood after a period of 6-8 weeks in-all of the 12 cases in which the antiamoebic treatment was used. In cases of dermatomyositis or polymyositis the above treatment resulted in a complete cure of the disease in the 8 cases in which it was used. This corresponds with the records of the National Academy of Sciences, National Research Council *(Physician Desk Reference* 36 Ed., 1982, Oradell, N.J.) who found that POTABA was curative for both dermatomyositis and scleroderma.

Free-living as distinct from parasitic amoebae.

Numerous species of free-living amoebae are known in all parts of the world (Wyburn-Mason 1978). Most fall into two genera, Acanthamoebae and Naegleria, and some are pathogenic to man and animals. They are found on the surface soil preferring warm, moist conditions and proliferate in warm stagnant pools and the bottom of rivers and lakes, particularly around the entry sites of warm effluents. They have been found in the domestic water supply, in human and other animal faeces and in unpasteurized milk. Pathogenic free-living amoebae are readily isolated from chlorinated swimming pools, potable water, river mud, sewage, lifeless desert sand, marine mud and human nasal and throat cavities. They may contain acid-fast structures (Jadin 1978, Lastovica 1980). They have been recovered from the faeces of the black duck, the alimentary tract of the clawed toad in South Africa (Lastovica 1980), in marine fishes in the Mexican Gulf where they occur in the gut, branchial mucus and skin and may be implicated in mortalities (Overstreet, 1978). They often contaminate tissue cultures. In inimical conditions they form hollow spherical cysts, which are present in the air in most parts of the world and can easily be found on agar plates exposed to air. Such cysts do not occur in animal lesions due to Naegleria, but only in those due to Acanthamoebae. The cysts have fenestrations in their walls through which small amounts of the amoebic cytoplasm can escape and form tiny amoebae which can grow to full size in appropriate conditions. Many pathogenic free-living amoebae prefer warm surroundings and they tend to migrate from cool environments to body temperature or up to 43° C (Lastovica 1980), a property known as thermotropism (Wyburn-Mason 1978).

All terrestrial animals and plants and those inhabiting fresh water and the sea live in a world surrounded by many species of free-living amoebae, which certainly pass into the mammalian respiratory passages as cysts or trophozoites and must also present as trophozoites in the gastrointestinal tract of many animals, including man, since they are found in their faeces. As the organisms are motile, it would be unreasonable to suppose that, once they had entered the orifices of man or other warm-blooded animals, they

would not migrate under thermotropic influences into the warmer body tissues. Since amoebae may prove to be either nonpathogenic or pathogenic to animals, the same must also apply should the organisms reach human tissues. "The discovery that free-living protozoa are not purely nonpathogenic, but are able to infect man and animals has revolutionized the very concept of parasitology" *(Lancet* Editorial 1977).

Human free-living amoebic infection.

Recently it has been shown (Cursons, Brown and Peys 1977) that the sera of all humans, including that of the cord blood, contain antibodies to Acanthamoebae or Naegleria, indicating *UNIVERSAL* present or past infection of man and possibly the foetal tissues with these organisms, the last being via the placenta. The organisms are not necessarily pathogenic. Textbooks on protozoology state that "unspecific types of amoebae have been isolated from every tissue in the body" (Craig and Faust 1970) or "there is hardly an organ in the body from which somebody has not obtained amoebae" (Dobell 1919). A few cases of lesions due to pathogenic species of such organisms have been described in plants, lower organisms and man, in particular amoebic meningoencephalitis (Carter 1972) and infection of the eye and ear (Nagington, Watson and Playfair 1974, Lastovica 1980).

In 1922 the eminent protozoologists, Kofoid and Swezy (1922a, b) reported the presence in the bone marrow in cases of RD without dysentery of an amoeba originally thought to be E. *histolytica*, but later a free-living amoeba, distinguished from human cells by its mitotic processes and which contained only 6 chromosomes as compared with the normal 46 of human cells. It showed a single blunted pseudopodium and numerous vacuoles. They suggested an aetiological relationship between the infection and the arthritic process. In numerous recent publications -- the author (Wyburn-Mason 1964, 1978, 1979a, b, c) has shown that, using the property of thermotropism, free-living amoebae, pathogenic or non-pathogenic, can be made to migrate in varying numbers out of human tissues, including those of the newborn and foetus. They are found especially in all the affected tissues of patients with RD, in extra-articular tissue: affected by AI disease, in all malignant tumours, in the CNS of normal patients and those suffering from multiple sclerosis (MS) in normal mammalian and human faeces, in uncooked butcher's meat and in surface soil. They may be recovered in small number; from some tissues of apparently health humans, when they are presumably of non-pathogenic nature. They appear identical with those found by Kofoid and Swezy except that they are medium to dark brown in colour. These findings have been confirmed in laboratories in various parts of the world, including Vanderbilt University, USA (J. W. Overstreet 111, now Associate Professor of Anatomy, Obstetrics and Gynaecology, University of California), the Oncological Research Institute, Bratislava Czechoslovakia (M. Uhrinova and A. Kwasnicka) and in this country (U.K.). The first named worker has reported that they may contain acid-fast organisms or particles as described by Jadin (1979)*. That these organisms are, in fact, free-living amoebae is shown by the observation referred to in the author's original monograph (1978) that, if metallic copper is present in the apparatus (Fig. 4 found in the full-textd book) used for retrieving them from tissues. the organisms fail to migrate out into the amoeba saline, whereas substitution of the copper gauze by zinc gauze allows organismal migration to occur normally. This sensitivity of the organism to copper and its salts is typical of both amoebae and algae. Furthermore reference will be made later to the fact that the organisms are uniquely sensitive to bile salts, a property of all amoebae and the reason for the fact that in amoebic colitis the pathological changes do not extend from the large to the small intestine, where bile salts are present and kill the organisms. These two facts indicate the amoebic nature of the organisms obtained from RA tissue.

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* Dr. P. K. Pybus and his co-workers of Pietermaritzberg- Republic of South Africa, have recently informed me of a very simple method of isolating the organism and the cysts from the effusion fluids of actively inflamed rheumatoid knee joints. Using a sterile needle and syringe they withdrew all the fluid from inflamed knees and put this into a sterile screwtop bottle. They allowed this to stand and cool for a few hours and then examined the deposit. In all cases the deposits contained groups of typical free-living amoebic cysts identical in appearance with those in Fig. 1 of the article by Jager and Stamm *(Lancet 1972, ii, 1943)* featuring the cysts of an organism of the Naeglerial genus. The size, the fenestrated holes allowing the cytoplasm of the cysts to escape and the varying colouration of the cysts from dark brown to light brown, dark blue to light blue, are typical of the same cysts photographed by the present author as being found with their trophozoites in rheumatoid disease and cancers and photographed at Fig. 7, page 123 in the original monograph. The variation in colour found by Pybus and the author caused the latter to christen the organism, amoeba chromatosa (coloured amoeba). In addition Pybus sometimes found the motile amoebae apparently attempting ingestion of red blood cells and sometimes in the process of encystment. These workers remarked that these objects one would normally dismiss as cell debris or "gubbins," but in view of their features they are undoubtedly small amoebae. (Pybus/Jeon later reported these to be macrophages.)

The organisms can be recovered from tissues in spite of the fact that they are not observed in affected tissues stained by ordinary methods, since they are not numerous and look like macrophages or lymphocytes. This is a feature repeatedly observed in experimental infections with free-living amoebae in laboratory animals. This situation in RD recalls that in symphilitic lesions until stains for the *Treponema pallidum* were discovered. The organisms in RD can, however, be demonstrated in tissue sections by immunofluourescent-staining using sera containing appropriate antibodies to the organisms and by studying their mitosis and chromosome content in marrow biopsy material.

The discovery of the universal presence of free-living amoebae in all human and mammalian, including foetal tissues, coupled with the universal presence of antibodies to these organisms in the blood, represents the basis of an entirely new concept in medicine, and in human and animal disease.

The effect of drugs on the organisms in vitro.

The organisms can be cultured in "amoeba saline", into which a culture of *E. coli* has been introduced. The effect of various antiamoebic substances in killing the organism can then be studied by adding them to a culture in the well of a microscope slide or by the method of Fulton (1970). Those which kill include one per cent solutions of bile salts, 4-aminoquinolines, very dilute solutions of copper sulphate, metallic copper, gold salts, emetine, dehydroemetine, pentamidine, clotrimazole (Anderson and Jamieson 1974) and levamisole (both of which contain an imidazole group), and in particular the 5-nitroimidazole group of drugs, including metronidazole, tinidazole, ornidazole and nimorazole, active against a wide variety of protozoa, including amoebae; furazolidone, which contains a nitrofuran 5-atom oxazole ring related to nitroimidazoles and which also kills amoebae, giardia and other protozoa; allopurinal, likewise containing a 5-atom ring with two nitrogen atoms and thus related to imidazole and which is active against leishmaniasis and other protozoal diseases; and rifampicin active against free-living amoebae as an amoebiastatic or amoebicide (Cursons 1978), mycobacteria, many gram positive and negative bacteria and atypical mycobacteria and many protozoa (Binder, Domenichini, Gothardi et al. 1971). The closely related rifampicin SV is active against gram-positive bacteria, *M. tuberculosis*, atypical mycobacteria and numerous protozoa. Isoniazid is active against mycobacteria and free-living amoebae. As in

cases of tuberculosis rifampicin and isoniazid may be given together. POTABA is an antiamoebic drug (Dwork 1948) and is also effective in curing dermatomyositis and scleroderma (Review of National Academy of Sciences National Research Council, *Physicians Desk Reference*, 36th Ed., 1982, Oradell, N.J.). These diseases show every gradation to RD as indicated previously. Many of these antiamoebic substances induce a Herxheimer reaction in active RD cases as do gold salts (Williams, Lockwood and Russell 1979) and levamisole (Multicentre Study Group 1978), while a rise in the blood level of bile salts in obstructive jaundice lessens the activity of RD (Hench 1949). *The effects of these antiamoebic drugs on RD already described point to the fact that pathogenic amoebae are its cause.*

The other drugs which kill free-living amoebae in vitro described above do not cause an Herxheimer reaction in vivo, but nevertheless are effective in inactivating or lessening the activity of RD when given by mouth, as shown in the author's earlier monograph. These include copper sulphate 10-25 mgms. daily; bile salts given as dehydrocholine (the development of obstructive jaundice in a case of active RD usually results in lessening of RD activity (Hench 1949)); 4-aminoquinolines, such as chloroquine, dehydrochloroquine or amodioquin well known for years as lessening or abolishing the activity of RD; and emetine, dehydroemetine or pentamidine, all of which inactivate RD without causing an Herxheimer reaction (see Wyburn-Mason 1978).

Quinoline derivatives of various kinds are commonly found to be antiamoebic or antifungal agents. These include the 4- and 8-aminoquinolines and the iodohydroxyquin- derivatives. Recently a quinoline derivative known as nitroxoline (8-hydroxy 5-nitroquinoline) has been found to be a potent antiamoebic substance. The writer found that this compound given in doses of 300 mgms. twice daily for three weeks induced a rapid and remarkable disappearance of the evidence of activity in five cases of RA without or with causing an Herxheimer reaction. The treatment can be repeated at four weekly intervals. Care must be taken not to give too large a total dose of the oxyquinoline drug for fear of inducing neurological, in particular ophthalmological, disturbances (SMON).

Whether an antiamoebic drug causes an Herxheimer reaction in cases of active RD appears to depend on the dose of the drug. 1t was found that the above drugs which may cure the disease without causing the reaction will all do so if given in large enough doses, as seen with 5-nitroimidazoles, bile salt derivatives or quinoline compounds. Larger doses producing the reaction may be necessary to cure the disease which they do more certainly and rapidly than smaller ones.

Three almost identical cases of RD in the author's experience throw light on its causation. All were healthy farmers, aged 45-50 years, one in Rhodesia, one in Ontario, Canada, and one in the Middle West of USA. Each was sitting on an open tractor pulling a plough on a dry, windy day and clouds of dry surface soil flew into their mouths and noses. That night each slept restlessly and sweated profusely and on waking found all their joints were hot, swollen and intensely painful. Movements were almost impossible.

Their temperatures reached 40° C. Their condition improved only very slowly over the course of the next three months when the diagnosis of RD was made and in one case the signs of scleroderma in addition to RD appeared. The history is consistent with an infection from something in the surface soil where .free-living amoebae are found.

A recent paper by Harkness, Richler and Payani et al. (1982) has drawn attention to the 24 hour circadian rhythm of symptoms and signs in RD being maximal between 0200-0400 hours and minimal in the afternoon. This was attributed by the authors to alternations in immune and inflammatory responses in the body dependent on alternations in circulating concentrations of steroids. There is, however, a much simpler explanation. Dr. Martin Moore-Ede of Harvard University Medical School, has shown that sleep or periods of lessened metabolic activity alternating with periods of increased activity, that is circadian rhythm, occurs in unicellular animals and insects at 24 hour intervals and the above findings could more readily be explained if RD was due to an infection with a protozoon exhibiting such a rhythm.

Discussion as to the cause of rheumatoid and related diseases.

AI lymphocytic and humoral reactions are thus not the primary disturbance in RD and AI diseases, but are the response to the infection and its antigens and contribute to the tissue damage. The whole syndrome resembles syphilis. Waldenstrom (1963) and others state that "if the spirocheate had not been discovered, syphilis could be taken to be the ideal model of an AI disease. The variety of tissue reaction antibodies, the widespread lymphocytic tissue damage and the vasculitis are characteristic features." RD closely resembles the rheumatic manifestations in leprosy *(Lancet* Editorial 1981), which may present with an acute arthritis affecting one or a number of joints, polymyositis, skin lesions, fever, raised ESR, etc. with increase in circulating gammaglobulins and positive serological tests for autoantibodies, RF and ANF, as in RD. This is an immune complex syndrome with antigen provided by disintegrating *M. leprae.*

The reaction may be .precipitated by anti-leprosy drugs, a reaction known as Lucio's phenomenon, which is identical with the Herxheimer reaction. The syndrome confirms the deductions made regarding RD. Had the free-living amoebae not been isolated as described ,above, the author's observations prove that every tissue in the body, even in the newborn; may contain unsuspected free-living amoebae, which if pathogenic, may cause tissue infiltration by lymphocytes with germinal centres and often plasma cells. They are the source of Glynn's (1968) previously postulated unknown chronic antigenic stimulation as the cause of RD. Since everyone is or has been infected with free-living amoebae, often pathogenic, why does not everyone suffer from RD? Since RD is often familial, it seems that the pathological response to the presence of the amoebae in the tissues is genetically controlled, perhaps as evidenced by their tissue antigens.

Structures which may be affected by RD.

From a study of the world literature on RD and Sjögren's syndrome in the original monograph the author (Wyburn-Mason 1978) showed that the extra-articular lesions may involve:

1) Any **exocrine gland** (exocrinopathy) often producing enlargement and dilatation of the acini and ducts. It may involve the lacrimal and salivary glands . (Sjögren's syndrome, RA in miniature), breast (cystic mastitis), pancreas (lymphocytic pancreatitis, which may exhibit calcification), liver. (active chronic hepatitis, primary biliary cirrhosis), gall-bladder and bile ducts (chronic cholecystitis and stenosing cholangitis) and kidneys (chronic nephritis, pyelitis).

2) **Endocrine glands,** including the thyroid (lymphocytic or Hashimoto's thyroiditis), adrenals, parathyroids, thymus (with or without myasthenia) and pituitary.

3) **Polymyositis,** bursitis, tenosynovitis or rheumatoid nodules in any tissue, including meninges and cerebral choroid plexus; myasthenia.

4) Mucosal inflammation followed by atrophy, which may involve the gastrointestinal tract producing atrophic stomatitis, pharyngitis, oesophagitis, AI or atrophic gastritis or AI coeliac disease (present in a quarter of cases of RA) and ulcerative colitis (often

considered to be AI) or the respiratory tract leading to atrophic rhinitis. Eustachian salpingitis, largynitis or bronchitis.

5) **Fibrosing aleveolitis**, pulmonary nodules, lung fibrosis or pleuritis.

6) **Peri-, myo- or endo-carditis.**

7) **Bone marrow infiltration** with various disturbances of blood formation.

8) **Spondylitis** in any part, including lumbar and cervical.

9) **Paget's disease** of bone.

10) **Lymphadenopathy or splenomegaly** with reactive lymphoid hyperplasia.

11) **Gall-bladder, extra- and intra-hepatic bile ducts.**

12) **Choroiditis, uveitis, retinitis, scleritis.**

13) **Various skin lesions,** including icthyosis, dermatitis, leukoderma and melandoerma, psoriasis.

14) **Fibrositis,** fasciitis (Binder, da Silva, Hazleman 1983).

15) **Myelomata, carcinomata, leukaemias** (ibid).

16) **Parkinson's disease** (ibid).

Cervical spondylitis, lumbago and sciatica in relation to RD.

Rheumatoid infection has been seen to involve all body tissues, including the whole of the spine. It may show itself as neckache, stiffness, sharp pains in the spine and occiptal headache. When the lumbar spine is affected it may appear as lumbago and/or sciatica forming part of the general disease. Radiologically the manifestations in the cervical regions are those of loss of lordosis and intervertebral spaces and degrees of spondylitis varying from minimal to severe. In the lumbar region radiographs may show no abnormality. Treatment of the disease by antiprotozoal drugs may cause an Herxheimer reaction with marked increase in the cervical pain, which extends down one or both arms with paraesthesiae in the peripheries and restriction of movement of the cervical spine. In the case of the lumbar spine even in the absence of radiological changes such treatment may cause lumbago and/or sciatica of varying severity. In either case the symptoms are transient and disappear after a week or more as do the other manifestations of RD.

Patients of any age may develop lumbago and/or sciatica in the absence of generalized evidence of RD and this commonly follows bending or twisting of the lumbar spine or lifting a weight. In such cases it is not uncommon for x-rays of the lumbar spine to show no evidence of disease or simply of lumbar lordosis associated with muscle spasm. Such cases are attributed without foundation to temporary herniation of the lumbar intervertebral discs, which are thought in some miraculous way to go into their correct place spontaneously when the symptoms disappear. There is no sound foundation for such a theory. The lumbago and sciatica differ in no way from that which may form part of RD.

Forty cases of lumbago and sciatica without evidence of RD or bony radiological change in the lumbar spine in whom bed rest and treatment with analgesics had failed to relieve the condition were divided into two groups and 20 were treated in a double blind trial either with 2 gram doses of metronidazole on two successive evenings or with a placebo in the same manner, the patients remaining in bed. In all the cases treated with the 5-nitroimidazole drug there occurred severe sweating and influenza-like symptoms within a few hours followed by a transient increase in the lumbar or sciatic pains lasting for 2-3 days and then rapid and complete disappearance of all symptoms. This was often accompanied by a short lived arthropathy of some joint or tensynovitis typical of rheumatoid infection. In the 20 control cases treated with a placebo no change in symptoms occurred during the first week. In cases of lumbago and sciatica with radiological changes of disc degeneration, whether accompanied by manifestations of RD or not, a similar increase in the lumbar and sciatic pain occurs usually followed by considerable improvement in the lumbar aching and often in the sciatic pain, but without complete clearance of symptoms.

In cases of pain and stiffness in the neck with or without involvement of the brachial and cervical nerve roots giving rise to headache, neck stiffness and pains in the upper limbs and, whether x-rays reveal mild or severe changes, treatment as for lumbago or sciatica usually results in a similar generalized reaction with sweating and general malaise and increase in symptoms for 2-3 days usually followed by dramatic disappearance of all manifestations of disease, including neck stiffness, headache and pains and paresthesiae in the upper limbs. This treatment has been adopted as routine for cases of cervical and lumbar spondylitis.

Frozen shoulder.

This condition has been variously attributed to capsulitis of the shoulder joint, to acromial bursitis or tendinitis of the rotator muscles in contact with the joint capsule. No definite causation has, however, been decided on. The condition begins with pain and limitation of movement of the joint which eventually progresses to complete ankylosis. While this condition can occur alone, it not infrequently forms part of generalized RD and presumably arises from a similar aetiology. This being so, the author has treated all of the last 45 successive cases of the disease as for RD, usually with metronidazole 2 grams on two successive evenings. This results in an Herxheimer reaction with acute sweating coming on within a few hours of the first dose of tablets followed by increased shoulder pain and occasionally by transient arthropathy in one or more other joints. The pain lasts for 3-5 days and then completely disappears and the movements of the joints rapidly become normal in extent. Within two weeks no signs ,of the shoulder disease remain.

Ankylosing spondylitis (AS).

AS is an inflammatory arthritis of the spine, almost always involving the sacroiliac joints and less commonly the peripheral joints effecting predominently young men in the third decade. It is often self limiting. Its cause is unknown. It may proceed to rigid arthritis of the whole spine or be accompanied by iritis, ulcerative colitis, regional ileitis and by endocarditis or rheumatoid nodules. It may present in childhood as juvenile RD. Occasionally. iritis may be the presenting symptom. It causes pain and rigidity of the spine and sacroiliac joints. In some cases there is a family history of RD or it may occur in siblings. As with RD, psoriasis may be a feature of the disease. The costovertebral joints are generally affected and the hip joint frequently. Aortitis and myocarditis, atlanto-axial subluxation and amyloid disease may occur as in RD. The ESR is usually raised. There may be a mild hypochromic anaemia, but the serum RF is consistently negative, while the HLA B27 tissue antigens are almost always positive. Pathologically the changes in the spine are very similar to those in RD, but bony ankylosis is much more frequent than in RD and involvement of the discs is an important feature. Parts of the vertebral bodies are replaced by vascular fibrous tissue accompanied by ossification which appears to affect in particular the outer fibres of the annulus fibrosus. Bilateral sacroiliitis is mandatory for the diagnosis (Mason 1969).

The aetiology is unknown, though genital infection was once considered important. It is uncertain whether the condition is related to Reiter's disease. The author has observed the case of a girl of 21 years who had Still's disease at the age of 10 years clearing up spontaneously after 1-1 / 2 years to be followed by Raynaud's disease and. continued pain between the shoulder blades, especially on jolting, and the development of ulcerative colitis and AS. Her sister suffered from RD and ulcerative colitis as did her mother and grandfather. Such cases and the prevalence of the tissue antigen HLA B27

gene in most cases, the association with colitis, iritis, carditis and psoriasis closely resemble the same associations which occur in RD. In some cases the joints of the arms and legs may be as severely affected as in the latter disease: The only factors clearly distinguishing the disease from RD are negative serum RF and the presence of the specific tissue antibody. No treatment has any appreciable effect in the disease, either in the symptoms or progress.

The author found that free-living amoebae indistinguishable from those in RD and other diseases were present in the tissues of cases of this disease. In the treatment of 10 cases with anti-free-living amoebic drugs very satisfactory relief of pain and increase in the mobility of the spine occurred in those areas where x-rays did not show fusion of the vertebrae. This was most marked in the cervical region where movement returned to normal and pain disappeared in all of the 10 cases. Flexion of the spine improved in the less advanced cases and the patient was able to touch his toes again in 4 of the 10 cases. Chest and back pain on breathing disappeared. When colonic symptoms were present these cleared up on the course of 6 weeks treatment with metronidazole or tinidazole and the ESR fell to normal. Treatment was continued by two successive daily doses of a 5-nitroimidazole every six months and in no case was further progress of the disease noted over 5 years observation. Such results suggest that AS is due to a protozoal infection resembling but differing from that causing RD or the same organism in a genetically different individual.

The effect of anti-free-living amoebic drugs on certain skin lesionsassociated with RD.

Apart from psoriatic arthropathy psoriasis appears to be more frequently associated with RD than non-arthritic subjects. It may also accompany AS. In the course of treatment of either RD or AS accompanied by psoriasis with antiamoebic drugs it was regularly found that with the successful inactivation of the infection the psoriatic lesions disappeared leaving no trace of their previous presence. In a case of RD with severe psoriasis involving the nails present for more than 20 years treated by a colleague with a single weekly dose of metronidazole, 2 grams over 6 months, even the psoriasis of the nails disappeared in company with that of the rest of the skin.

Acquired ichthyosis of the skin is a common manifestation of RD and it was regularly found that successful treatment of the latter with antiamoebic drugs resulted in a disappearance of the skin lesions. Ichthyosis is not infrequently observed in infancy, so-called congenital ichthyosis, in the absence of other manifestations of rheumatoid infection. The condition may. persist into adulthood. In 5 cases in which this condition was present in otherwise healthy subjects they were treated with metronidazole or tinidazole, 2 grams on two successive evenings each week. This produced a mild Herxheimer reaction with sweating and general malaise and mild joint pains. In the next few days these symptoms disappeared and at the end of 2-3 months the skin lesions were no longer present, indicating the congenital form of the skin disease is identical in nature with that associated with RD and results from transplacental infection of the foetus and embryo.

Subcutaneous nodules.

Subcutaneous rheumatoid nodules occur in some 20 per cent of RD patients and sometimes with AS. They occur especially at points of pressure, but also in the viscera, such as the pericardium, at the base of the heart valves, pleura, meninges, lung tissue and even in the choroid plexus of the brain. They may be up to 3 cms. in diameter, single or multiple. The centres are formed of necrotic and disorganized connective tissue, among which are intact fragments of collagen, fibrin and cell debris. Around this zone histiocytes are arranged in a radial pallisade. Giant cells are rare. The granulomatous nodules resemble granuloma annulare microscopically and are superficially like tuberculous or microcytic granulomata, sarcoid and parasitic infestations. Their structure points strongly to the infective nature of RD by some organisms more complex than a bacterium. Treatment with anti-free-living amoebic drugs for a sufficiently long period was found eventually to cause their disappearance without trace, again indicating the infective nature of RD.

Coeliac Disease

In the author's original monograph it was shown that coeliac disease appears to be AI in nature and related to RD, in which it occurs in about 25 per cent of cases. Coeliac disease may occur in siblings and -- be associated with various other manifestations of AI disease, including ulcerative colitis. It is typified by subtotal villus atrophy of the mucosa of the small intestine beginning at the jejunum and extending distally. Symptomatically it is manifested by a failure of absorption of the products of the food stuffs in the small intestine, by weight loss and fatty vertebrae. This was most marked in the cervical region where movement returned to normal and pain disappeared in all of the 10 cases. Flexion of the spine improved in the less advanced cases and the patient was able to touch his toes again in 4 of the 10 cases. Chest and back pain on breathing disappeared. When colonic symptoms were present these cleared up on the course of 6 weeks treatment with metronidazole or tinidazole and the ESR fell to normal. Treatment was continued by two successive daily doses of a 5-nitroimidazole every six months and in no case was further progress of the disease noted over 5 years observation. Such results suggest that AS is due to a protozoal infection resembling but differing from that causing RD or the same organism in a genetically different individual.

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In ten cases with onset at varying periods and varying severity, which had responded to a gluten-free diet and were symptomless, jejunal mucosal biopsy showed an incomplete return to normal of the

mucosa. In all cases the patients were treated with a weekly dose of 2 grams of either metronidazole or tinidazole for two months. This was followed by short-lived central abdominal aching and sometimes by a transient arthropathy of the shoulders or knees with the first 2-3 drug doses. The biopsy was repeated at the end of the course. In all cases it was found that the mucosa had returned to complete normality. The patient was able to give up the dietary treatment. It appears that the small intestinal changes are part of those of RD. After six months without diet or drug treatment, though symptoms had not returned, repeat biopsy showed a partial return of small intestinal villus atrophy.

Ulcerative colitis.

Ulcerative colitis is commonly regarded as an AI disease and is not infrequently associated with RD or can occur in families exhibiting a number of members with ulcerative colitis, RD or AS. The symptoms of ulcerative colitis may be preceded by an arthropathy of the distal interphalangeal joints of the fingers and toes and sometimes shows a positive RF in the serum. In other cases the interphalangeal arthropathy may not appear until an appreciable period after the gut damage. The colonic mucosa shows evidence of inflammation with collections of lymphocytes, plasma cells and haemorrhages with loss of the mucosal epithelium. The cause of the disease has been unknown, but evidence adduced in the author's preceding monograph indicates the AI nature of the condition and that it tends to occur in subjects exhibiting certain tissue antigens. The author treated 15 cases of ulcerative colitis with arthropathy whose symptoms were partially controlled with prednisolone and salazopyrin in spite of which they were subject to frequent bloody stools, abdominal pain and weight loss. The ages varied from 20-42 years and diagnosis was accomplished by sigmoidoscopy, biopsy and barium enema. The distal arthropathy has been present for from 3-5 years.

The patients were treated with weekly doses on two successive days of 2 grams of a 5-nitroimidazole drug for 8 weeks. After each of the doses there occurred central lower abdominal aching pain lasting for 2-5 days. After the first week diarrhoea and bleeding ceased and the arthropathic pain and the signs of inflammation of the interphalangeal joints died down completely, the joints becoming cool with full movements. At the end of 8 weeks the intestinal symptoms had disappeared, normal weight was regained, the colon was no longer tender on pressure and the patient could now take a normal diet and was able to give up the prednisolone and salazopyrin. Depending on the period for which the arthropathy had been present, so the deformity remaining at the distal interphalangeal joints persisted. The patients were watched for 2-3 years without a return of symptoms and **a**t the end of this time sigmoidoscopy showed a normal appearance and a repeat barium enema was normal. These considerations and the associations of the disease with other manifestations of RD show its nature to be the same as that of RD.

Chronic Cholecystitis and Proegressive Sclerosing Cholangitis.

In Chapter 11 (xiv page 41) in the author's original monograph it was pointed out that in cholecystitis uncomplicated by bacterial infection and gall-stones the wall of the gallbladder shows the typical changes of AI disease and RD. Attention was called to the observation that cholecystitis was frequently associated with other manifestations, such as rheumatoid and AI diseases, including ulcerative colitis, coeliac disease, chronic active hepatitis and biliary cirrhosis, all AI diseases. The changes in the walls of the gallbladder may extend into the bile ducts, both extrahepatic and intrahepatic, producing the changes of sclerosing cholangitis and cholangiocarcinoma. Descramps, Gillian, Van Heuverswyn et al. (1977) described such a case showing ulcerative colitis, cholecystitis and progressive sclerosing cholangitis. This patient, a male aged 35 years, underwent a cholecystectomy, but after a period developed obstructive jaundice an operation was undertaken for dilatation of the sclerosed bile ducts with disappearance of the jaundice which, however, recurred after an interval of two years, with pyrexia an operation was again undertaken with relief of the pyrexia and obstructive jaundice. After this he came under the author's care and he developed a third attack of pyrexial obstructive jaundice. On the basis that the changes in the bile ducts were similar in nature to those in the well of the gall-bladder and AI in nature the patient was treated with metronidazole 2 grams on two successive evenings weekly for 6 weeks. This resulted in epigastric pain, severe sweating, a further rise in temperature to 101° F and then after the third dose of metronidazole the pain, pyrexia and jaundice slowly disappeared and did not recur during the rest of the course of treatment. He was a Belgian who migrated to New England, USA, and when last heard of three years after the course of treatment he remained quite symptomless. His symptoms of ulcerative colitis had also completley cleared with the antiamoebic drugs. He gained 10.9 kilograms in weight. This case is of considerable importance in that it proves that the mucosa of the gall-bladder and bile ducts may be infected with free-living amoebae and appropriate drugs will cure the disease.

The Effect of Anti-Free-Living Amoebic Drugs on Iritis, Uveitis and Choroiditis.

Iritis, uveitis and choroiditis are common features of RD. They may be bilateral, recurrent and often precede other symptoms of RD and AS by many years, or they may recur at any time during the course of the generalized disease. Not infrequently they may occur in the absence of symptoms of rheumatoid or AI diseases which never appear throughout life.

In treatment of cases of RD without involvement of the eye with anti-free-living amoebic drugs it was occasionally found that the Herxheimer reaction was complicated by the development of transient iritis, uveitis or choroidits which healed as the Herxheimer reaction died down, indicating that the inflammatory changes in the eye are due to the presence there of causative free-living amoebae. This led the author to consider the possibility of treating these affections of the eye occurring in the absence of any other evidence of RD with anti-free-living amoebic drugs. In 11 such cases the patients in the active stage of inflammation were treated with metronidazole in the same dosage and manner as for generalized RD. In all cases this resulted in an exaggeration of the inflammation of the eye over the course of 2-3 weeks and this was treated by the administration of cortisone drops two hourly. The treated cases were compared with a similar number given only cortisone drops. It was found that the inflammatory changes in the cases treated by the antiamoebic drugs died down completely and during follow up of 5 years there was no recurrence, whereas in the control cases all showed recurrence in from six months onwards indicating that these inflammatory lesions of the eye occurring in the absence of symptoms and signs of RD are, in fact, local manifestations of free-living amoebic infections. Primary malignant disease of the eye is frequently preceded by recurrent attacks of iritis, uveitis or choroiditis.

The Effect of Anti-Free-Living Amoebic Drugs on the Parotid Gland In Sjögren's Syndrome

In cases of RD not infrequently there occurs a painless swelling of one or both parotid glands without any change in the amount of salivary secretion , but eventually this diminishes or disappears. On the other hand in RD the salivary secretion may lessen or disappear without previous swelling of the parotid gland. This may, of course, be accompanied by diminution or disappearance of lacrimal secretion. The author found that in the former case a swollen parotid gland

would disappear within one or two days if an antiamoebic drug, such as chloroquine 250 mgms. daily was administered for 1-2 weeks and did not recur. When Sjögren's syndrome is present as part of RD and anti-free-living amoebic drugs are administered it was found in some early cases that the parotid gland became painful and tender as part of the Herxheimer reaction and that within a period of 3-4 weeks the salivary and lacrimal secretions returned and any swelling of the parotid gland induced by treatment disappeared.

The Effect of Anti-Free-Living Amoebic Drugs on Hashimoto's Thyroiditis.

In the author's monograph of 1978 it was shown that if a patient with thyroid swelling due to proven Hashimoto's thyroiditis with hyperthyroidism and a high titre of serum thyroid autoantibodies is treated with an anti-free-living amoebic drug the swelling usually disappears, the patient becomes euthyroid and the serum autoantibodies decrease in titre and eventually disappear. A repeat needle-biopsy of the gland shows that the structure of the gland has often returned to normal.

Trigeminal Neuralgia.

It was observed that in a small minority of 6000 rheumatoid patients, who had never suffered from trigeminal neuralgia previously, at the height of the Herxheimer reaction they developed typical trigeminal neuralgia, usually unilaterally and affecting one or all three branches of the trigeminal nerve, lasting over a week or more and disappearing as the general reaction died down. This suggests that trigeminal neuralgia is a manifestation of RD involving the trigeminal root ganglion.

The obvious next step was to treat cases of longstanding trigeminal neuralgia not responding to carbamazine, phenytoin, gelsemium or analgesics with anti-free-living amoebic drugs. Metronidazole or tinidazole in doses of 2 grams on two successive days weekly for 6 weeks, furazolidone 100 mgms. four times a day for 7 days, or allopurinol 300 mgms. three times daily for two weeks were administered to cases of long-standing trigeminal neuralgia in a double blind trial. The previous antineuralgic drugs were discontinued. Six cases were treated with each of the three anti-free-living amoebic drugs and six matching cases with a placebo. The age of the patients treated with antiamoebic drugs varied from 45-66 years, 9 being male and 9 female. There was nothing of significance in the past history and no correlation with multiple sclerosis. It was found that similar results occurred with all three anti-free-living amoebic drugs. On the second day of administration of metronidazole, tinidazole or furazolidone in most cases there was an exacerbation of trigeminal pain both in severity and frequency lasting up to several hours followed the next day by almost complete disappearance of pain except for occasional spasms which within the next few days also disappeared completely. Other treatment was discontinued. In the case of allopurinol the onset of exaggeration of symptoms did not occur until the third or fourth day and then rapidly disappeared almost completely eventually clearing within two weeks. In none of the control cases treated with a placebo did any appreciable change in the severity of symptoms occur. The cases were followed for periods of two years and during this time none had any recurrence of trigeminal pain.

From the above arguments and the results of treatment with anti-free-living amoebic drugs it seems that trigeminal neuralgia must be a result of free-living amoebic infection of the trigeminal ganglion by these organisms and is one manifestation of RD. Effective curative treatment rests in the administration of anti-free-living amoebic drugs.

Cystic Fibrosis of the Breast.

Cystic fibrosis of the breast in women is a common condition occurring between the ages of 15 and 55 years. The original lesion is a painful swelling which can affect most of both breasts coming and going in relation to the menstrual periods. Eventually one or more of the swellings may persist in the intermenstrual periods and they may become larger, harder and cystic. Histologically the lesions consist of an area of mammary glandular tissue surrounded by lymphocytes and often plasma cells and some degree of fibrosis which obstructs the ducts of the gland leading to cystic dilatation of the acini. The lesions are commonly found in association with active RD or with other manifestations of infection with free-living amoebae and their size and tenderness may increase with exacerbations of rheumatoid symptoms. Morever, a middle-aged patient developing subacute or acute RD commonly shows evidence of cystic fibrosis of the breast or gives a history of surgical removal of such. Treatment of RD by antiamoebic drugs leading to an Herxheimer reaction in younger patients may induce a severe painful generalized swelling of the breasts lasting the length of the reaction while treatment of an older patient with cystic mammary swellings will cause a further painful swelling of the mass, which usually lessens and/or disappears with the Herxheimer reaction. This phenomenon and the typical histology indicate that cystic mastitis is a rheumatoid lesion of the breast tissue comparable to that of the parotid in Sjögren's syndrome and can usually be cured by antiamoebic drugs.

Rheumatoid Disease and Allergy.

Allergic manifestations, such as angioneurotic oedema, hay-fever, asthma and dermatitis, may be associated with rheumatoid disease. In some cases treatment with anti-free-living amoebic drugs was found to cure both the manifestations of RD and allergy. In other cases the allergic phenomena were unaffected. In the former cases the allergies appear to exist in relation to the amoebae themselves. In the latter the allergens appear to be separate from the amoebic infection. Reference has been made to the observation that subtotal or total villous atrophy of the small intestine occurs in about 25 per cent of cases of RD often without evidence of coeliac disease and this defect is accompanied by increased intestinal mucosal permeability, which may or may not be present after return to normal of the mucosa following the taking of a gluten-free diet (Cobden, Hamilton, Axon 1983). Such observations could explain the occurrence of allergic symptoms in patients with RD by allowing the allergens to enter the body through the small intestinal mucosa and the findings by both the author and various correspondents that successful treatment of rheumatoid and coeliac disease in association sometimes causes the allergic manifestations to disappear, while in others it has no effect.

Observations on the Ineffectiveness of Physiotherapy as Generally Practiced on Cases of Rheumatoid Disease.

Most rehumatologists advise massage, exercise and heat treatment to the affected joints in active RD. These are the worst possible practices. Any inflamed tissue exhibits vasodilatation leading to heat and increased permeability and passage of serum and inflammatory cells through the walls of the capillaries in the inflamed area. Massage, heat and exercise in the cases of joints dilate the capillaries and arterioles in the affected part and will thus increase the inflammation and spread the causative organisms of the disease to areas around. These practices should be avoided. If a joint is sprained the recognized treatment of the resultant inflammation is cooling and rest. Why then is rheumatoid inflammation treated by exactly the opposite methods guaranteed to spread the amoeba and increase the inflammation? The part should be cooled by cold compresses (not ice).

KNOWN CAUSES OF HUMAN CANCER

Genetic factors play a part in about ten percent of cases of

human cancer (Lynch 1950). In only about 10 per cent of other cases is the causative factor known. About 80-90 per cent of cases are thought to be due to an unknown "environmental factor". Recently Doll and Peto (1982) published a book reviewing from the epidemiological aspect the causes of human cancer. In this way they assign only 2 per cent of cases to pollution and 4 per cent to occupational hazards, including asbestos. However, they attribute an astonishing 30 per cent (25-40 per cent) of U.S. cancer deaths to tobacco and 35 per cent (10-70 per cent) to diet! Are we to accept such figures as reasonable? Walker (1981) remarks that controversy exists as to the aetiology of cancer and coronary heart disease and the role of dietary fibre and sugar in health and disease. The same body of evidence may be analyzed by different researchers with different conclusions by each. As an example out of all deaths from lung cancer in the U.S. 20 per cent occur in non-smokers. A large proportion of cancer deaths must occur independent of smoking and life style. Such observations throw doubt on the findings of Doll and Peto.

Certain human lesions are well recognized as premalignant and, if their cause could be elucidated and removed, the possibility of finding the aetiology and of prevention of some forms of cancer arises.

Many premalignant conditions and AI diseases are, in fact, extra-articular manifestations of RD. Almost any form of cancer may arise from such premalignant lesions and collagen diseases are especially prone to develop lymphomata and myelomatosis. A list of some of the extra-articular tissues which may be involved in RD has been given above on page 6. From personal experience and a study of the world literature on the pathology of RD and Sjögren's syndrome (Wyburn-Mason 1978, Agudela et. al. 1981, Black, et. al. 1982, Binder, De Silva Hazleman 1983) it appears that the generalized infection or many of the extra-articular lesions cited show a special liability to malignancy. Here are the more obvious:

Exocrine glands. *Involvement often causes fibrosis in the gland and results in cystic dilatation of the ducts and acini.*

a) **Salivary and lacrimal glands** (Sjögren's syndrome)

The former are liable to leukaemia, local lymphomatous or carcinomatous change or to generalized malignant lymphoma. Waldenstrom's macroglobulinaemia or myelomatosis with or without carcinoma of any organ.

b) Breast (cystic mastitis)

This is well recognized as being premalignant.

c) **Pancreas (chronic lympocytic pancreatitis)**

The gland so affected frequently exhibits radiologically visibile calcification, which is generally regarded as pathognomonic of cancer of the organ.

d) **Liver**

The development of chronic active hepatitis or primary biliary cirrhosis together often precede the development of benign or malignant hepatoma.

Endocrine Glands

a) **Thyroid (lymphocytic or Hashimoto's thyroiditis)**

This predisposes to malignant lymphoma and/or carcinoma of the gland or Hurthle cell tumour. The lymphoma may become generalized or be associated with any form of leukaemia.

b) **Adrenal**

Malignant lymphoma has been reported as beginning in this organ in RD.

c) **Parathyroid**

This is liable to adenomatous or carcinomatous change in RD.

d) **Thymus**

This often exhibits hypertrophy and/or benign or malignant tumour formation and leukaemia. The tumour may be a lymphoma, sarcoma, carcinoma or teratoma.

e) **Ovary**

This is liable to benign or malignant cystic change.

The ***mucosa*** **of the respiratory or gastro intestinal tract** from the mouth to the ileocaecal valve producing atrophic stomatitis, pharyngitis, oesophagitis, gastritis or coeliac disease. All are well recognized premalignant lesions especially atrophic gastritis and coeliac disease, which predisposes to abdominal small intestinal malignant lymphoma or carcinoma or tumours of other parts of the gastrointestinal tract or of other tissues. The field changes in the affected organs predispose to multiple tumours in the affected area.

The colon. This results in the development of ulcerative colitis, markedly predisposing to carcinoma, carcinoid or lymphoma of the mucosa, eventually becoming generalized.

The lungs. Thisxesults in the development of cryptogenic fibrosing alveolitis or of pulmonary rheumatoid nodules or fibrosis. The first preceeds bronchial carcinoma or lymphoma beginning locally, while lung fibrosis from any cause, including RD, is often premalignant.

The gall-bladder. This leads to the development of chronic cholecystitis and possible later formation of stones and often stenosing cholangitis. Histologically there is marked proliferation of the mucosa leading to the formation of deep clefts which penetrate down to or even through the muscularis, like carcinoma (Rokitansky Aschoff sinuses), and polypoid, adenomatous or malignant change may occur.

Bone marrow. This shows the presence of areas of lymphocytic infiltration with germinal follicles and plasmocytosis. There are many reports of the development of these changes into those of multiple myelomatosis or of the appearance of Waldenstrom's macroglobulinaemia with the formation of malignant lymphoma in RD. Both myelomatosis and Waldenstrom's macroglobulinaemia may be accompanied by multiple carcinomata in other organs or any form of leukaemia.

Bones. Paget's disease not infrequently develops in RD and is the most important factor preceding bone sarcoma of any type in later life and may also be associated with myelomatosis.

Lymph nodes. This leads to lymphadenopathy and/or splenomegaly in some cases of RD, the lymphoid tissue exhibiting chronic inflammatory changes. Not infrequently these may eventually develop into any form of malignant lymphoma with or without leukaemia.

Macroglobulinaemia. This has frequently been described as developing in RD or Sjögren's syndrome and eventually in the appearance of malignant lymphoma.

Eyes. Recurrent uveitis or choroiditis frequently result in malignant melanoma.

In cases of generalized RD the involved bone marrow has frequently been reported as developing within 8-15 years multiple myelomatosis or macroglobulinaemia with the formation of malignant lymphoma and these conditions may be accompanied by multiple carcinomata in other organs or any form of leukaemia. The changes in the lympoid tissue of RD have repeatedly been reported as developing into any type of lymphoma with or without leukaemia. Of the affected exocrine glands the parotid is liable to local lymphomatous or carcinomatous change within the gland or elsewhere there develops generalized malignant lymphoma, macroglobulinaemia or myelomatosis with or without carcinoma of the organ. Cystic mastitis, chronic lymphocytic pancreatitis with its calcification, chronic active

hepatitis or primary biliary cirrhosis frequently precede the development of benign or malignant tumours in the lesions, lymphocytic thyroiditis predisposes to malignant lymphoma and/or carcinoma of the gland and the lymphoma may become generalized or associated with any form of leukaemia. The hypertrophed thymus may exhibt benign or any form of malignant tumour sometimes associated with leukaemia. Atrophic stomatitis, pharyngitis, oesophagitis or gastritis are well recognized premalignant conditions and predispose to multiple tumours of the affected mucosa while coeliac disease often precedes small intestinal lymphoma or carcinoma or similar growths elsewhere in the gut or growths of other tissues in as many as 20 per cent of cases. Ulcerative colitis is well recognized as frequently developing into carcinoma, lymphoma or carcinoid of the mucosa. Fibrosing alveolitis or rheumatoid nodules in the lungs have been reported to be followed by a bronchial carcinoma or lymphoma beginning locally. Paget's disease is the most important factor preceding any form of bone cancer in later life or it may be associated with myelomatosis.Dermatomyositis, frequently part of RD, often precedes by 2-19 years any lymphomatous or cancerous lesions (Wyburn-Mason 1978).

To summarize, free-living amoebic infection as RD in any form appears to be an important environmental factor in carcinogenesis. It may give rise to cancers of single or multiple affected organs exhibiting lymphocytes and their derivative plasma cells in their stroma, to any form of leukaemia or to multiple cancers in an affected mucosal field. The chronic amoebic antigenic stimulation must induce antibody formation by lymphocytes and derived plasma cells and this may precede the appearance of any form of lymphocytic or plasma cell proliferation and mutation leading to lymphoma, myelomatosis or macroglobulinaemia. It has been shown experimentally in animals (Damshek and Schwarz 1959) by organ transplants and in human organ transplants that chronic antigenic stimulation is an highly significant factor in the causation of leukaemia, malignant lymphoma and myelomatosis. In so far as all humans, even foetuses, exhibit such amoebic infection, this may be a factor in carcinogenesis in subjects not showing clinical evidence of RD and even before birth. Since freeliving amoebic infection of a tissue in some subjects seems to predispose to malignant change, it seems possible that the presence of the organism in a tissue which alters the enviroment of the tissue cells, may, if the genetic state of the tissue cells is unstable, result in gradual mutation of their genes or their chromosomes *(Nature* 1982, 200, 539) to adapt to their new environment, that is malignancy - a Darwinian concept - or on the other hand the amoebic genes may be taken into the tissue cells and alter their metabolism.

The effect of anti-free-living amoebic drugs in cases of myelomatosis, lymphomatosis and carcinomatosis

As pointed out by Pasteur, Koch and more recently Burrows (1932) and others any organism introduced into the body becomes localized in cancers and this applies to freeliving amoebae, which, as stated, are regularly found in human tumours, possibly causing the lymphocytes and plasma cells in the stroma. In 30 cases the administration of the above antiamoebic drugs, metronidazole, tinidazole, allopurinal or furazolidone to cases of myelomatosis, lymphomatosis and extensive malignancies was found to produce the same very severe Herxheimer reaction as in RD with high pyrexia, drenching sweats and pains in the bones. The cancerous masses swelled and became tender. After 6-7 days the tenderness disappeared and the mass size lessened, the sweating and pyrexia ceased, pain including that in bone lessened or disappeared, the appetite improved and the ESR fell. Provided the treatment was repeated within 3 weeks or so progress of the disease seemed to be halted, especially in cases of glioma. The Herxheimer reaction following later drug courses was far less severe. The reaction is evidently due to the effect of the drug on the amoebae in the tumour.

MODE OF PREVENTION AND POSSIBLE CURE OF SOME HUMAN CANCERS

In order to prevent certain malignant changes it would seem that the premalignant lesions described above must be prevented. This can be accomplished in some cases by the administration of antiamoebic substances to all subjects at regular intervals as every person becomes reinfected with amoebae in the course of his life and these may be pathogenic or the subject sensitive to them. In this way Sjögren's syndrome lymphocytic thyroiditis, iritis, uveitis, choroiditis, coeliac disease, cystic mastitis, ulcerative colitis etc. can be prevented.

In addition in cases of lymphoma, myelomatosis or carcinoma, repeated administration of anti-free-living amoebic drugs may slow the progress of the disease and abolish the toxic symptoms by destroying the disease-producing antigens.

Since all human cancers contain free-living amoebae, and, if these are pathogenic, they produce inflammatory change in and around the cancerous cells. This increased vascularity of the tumour has a tendency to increase the rate of growth of its component cells. It would seem probable that killing the free-living amoebae in the tumour would lessen vascularity, size and the rate of growth of malignant tumours. Such expectations were, in fact, realized and these are referred to in the original monograph on pages 270-279. The cases included one of chronic lymphatic leukaemia in a female aged 60 years who had suffered from late onset diabetes for 10 years and was treated with diet and tolbutamide. She then developed severe ulceration of the gums, fauces and in the inside of the cheeks, pyrexia of 105° F, sweating, dysphagia and general malaise and enlargement and tenderness of the submaxillary and cervical lymph nodes. The blood count showed 14.0 G. per cent and WBC 30,000 per cu. mm., 100 per cent being lymphocytes. The urine contained trace of sugar and the sternal marrow was heavily infiltrated with fully formed lymphocytes consistent with the diagnosis of chronic lymphatic leukaemia. Tetracycline and later ampicillin had no beneficial effect on her condition, but metronidazole 800 mgms. three times daily caused a rapid disappearance of all her symptoms and return to normal of the blood glucose and the WBC count fell to 15,000 per cu. mm. 70 per cent as lymphocytes. Three weeks after beginning treatment with metronidazole she was symptomless and evidence of her diabetes disappeared.

Three cases of cerebral glioma as verified by craniotomy, who were in a comatose state, were treated with injections of chloroquine 250 mgms. daily for two months. One showed no response. In the other two the most surprising improvement in the patient's condition was observed. The coma and papilloedema disappeared and the physical signs in the CNS decreased. After some months, however, the symptoms returned in spite of recommencing the injections.

The administration of copper sulphate to cases of cerebral glioma may likewise produce extraordinary improvement as in a man of 60 years admitted for terminal care, after craniotomy and biopsy, which revealed a Grade III astrocytoma of the left parietal lobe. On admission he was in extremis, only just rousable and able to swallow. He was doubly incontinent and showed bilateral papilloedema and complete inability to move all four limbs. He was given copper sulphate 25 mgms. three times daily. Within 48 hours he began to respond to stimuli and within a week was able to sit up in bed. In two weeks he could use his left limbs and began to talk and feed himself. The dose of copper sulphate was increased to 25 mgms. six times a day. This was surprisingly well tolerated and a previously present bedsore had

now healed. He was then able to sit in a chair. After six weeks movement returned to his right arm and leg and the papilloedema gradually receded. He returned home after two months on the same medication and was still being followed up six years later.

Reference is also made to a patient with proven cerebral Grade 11 astrocytoma of the left frontal lobe, stuporose, incontinent, with a complete right hemiplegia and papilloedema, who was treated with clotrimazole 2 grams daily through a stomach tube at first and later by mouth for 5 months. His symptoms and papillodema all disappeared within the next six months. His right hemiplegia resulting from the surgical intervention remained, but he was able to answer questions normally. He remained under treatment for 9 months and his condition showed no evidence of change.

Reference was also made to Japanese cases of human carcinomatosis who received 250 mgms. of chloroquine intravenously twice weekly. This had no effect in the last stages of the disease and failed to produce improvement in 11 of 40 cases, but in 28 cases resulted in subjective and generalized improvement, relief of pain, regression in tumour size and a tendency for tumour necrosis. When continued for two months up to 1-1/2 years "they never resulted in therapeutic failure". The effects were most pronounced in lung and bladder cancer. The author reported on the effect of the drug on 45 cases of advanced human carcinomatosis, often with enormous masses of malignant tissue, effusions or jaundice. Of the 20 cases with very large tumour masses only 3 showed an obvious repsonse to treatment, two of these being cases of carcinoma of the ovary and another primary carcinoma of the liver without jaundice. None of the cases with jaundice showed any improvement, though of the other 25 cases with smaller tumour masses 18 showed a response to treatment evidenced by absorption of serous effusions, decrease in tumour size, fading or decrease in size of skin metastases, fall in ESR and temperature, decrease in anaemia or a temporary cessation of tumour growth.

Two dramatic cases of regression of carcinomatosis of the lung with diabetes and paraneoplastic neurological manifestations as a result of taking copper sulphate were described, in both of which the patient became symptomless, the lung x-rays cleared, the paraneoplastic lesions and the diabetes disappeared.

Two remarkable cases of carcinoma of the lung which were treated with copper sulphate, one with 50 mgms. daily and the other 25 mgms. three times daily are now described.

Case 1. Male, aged 65 years, Italian, inhabitant of Brooklyn, New York, USA. He presented at Coney Island Hospital, New York, with a history of tiredness, anorexia, cough, sputum, haemoptysis, shortness of breath and the loss of 20 pounds of weight over six weeks. An x-ray of the chest showed a right supra-hilar mass measuring 2 cms. in diameter without significant calcification. Bronchial biopsy yielded an histological diagnosis of poorly differentiated small cell carcinoma of the right main bronchus composed of nests of small ovoid cells with hyperchromatic nuclei, some of which were elongated, while others were irregular. Tumour cells invaded the mucous stroma and there was inflammatory reaction of plasma cells and lymphocytes around. No evidence of metastases was found. The ESR was 60 mms. per hour with some degree of hypochromic anaemia. He was given a course of radiation treatment to the mass without response and one dose of cyclophosphamide, methotrexate, adriomycin and CCNU and scheduled for further treatment. The patient, however, became so ill that he was nauseated, continually vomited, had complete anorexia and continued loss of weight totalling 40 pounds in all, that he was temporarily discharged from hospital. On his return to the hospital he was told of the diagnosis and prognosis and sent home to die. A repeated chest x-ray under the author's care showed increase in size of the suprahilar shadow had occurred. There was no evidence of metastases. Some 6 weeks after his last hospital treatment he began treatment with copper sulphate tablets 50 mgms. daily with the most dramatic improvement in his condition. Within a few days the nausea ceased and after two weeks his appetite began to recover. Gradually his condition returned to normal with a gain in weight of 20 pounds over the next 4 months. At the end of this time he was symptomless. At 6 months a chest x-ray and sedimentation rate had returned to normal. His treatment lasted for six months and at the end of this time he was leading a perfectly normal existence. He retired from his work and went to live in Florida, where he remains well four years later.

Case 2. Male, aged 72 years, physician. He had a long history of heavy cigarette smoking. Four years previously he had sustained a coronary thrombosis following which he suffered from shortness of breath, angina on slight exertion and swelling of the feet. He was treated with digoxin 0.25 mgms. twice daily, frusemide 80 mgms. daily and slow K tablets daily. Fifteen months prior to being seen he noticed clubbing of the fingers and he began to lose considerable amounts of weight with anorexia. He had a slight productive cough and became increasingly dyspnoeic. Three months before consultation a blood count revealed anaemia and an ESR of 51 mms. per hour. A chest x-ray then showed a right-sided Pancoast's tumour with bilateral pleural effusions: He was treated for the next two months with pure copper sulphate 25 mgms. dissolved in aqua chloroformi three times daily and from this time, his symptoms gradually improved. He stopped losing weight and coughing and the dyspnoea lessened. Friends remarked on the improvement in his appearance and he stated that he felt much better. After two months treatment a chest x-ray report stated that the congestive changes had subsided and the basal effusions had absorbed with lessening of the shadow at the right apex. It appeared that it had been replaced by a large. paratracheal gland. He continued to work in his general practice.

It seems, therefore, that treatment with anti-free-living amoebic drugs may cure premalignant rheumatoid lesions and prevent cancer or on the other hand cause regression of some tumours over a long period, especially gliomata or bronchial carcinoma. Doses of such drugs at six monthly intervals may abolish amoebic reinfection.

Carcinoma polyarthritis and dermatomyositis.

Malignant lesions have been shown to contain the same organisms as produce RD. In some cases a cancer may be present as a polyarthritis indistinguishable from RD, so-called carcinoma polyarthritis (Lansbury 1953, Mackenzie and Scherbal 1963). Successful removal of the tumour often lessens or cures the arthritis, a finding explicable on the above contusions. This likewise applies to dermatomyositis, scleroderma, polyarteritis, and SLE occurring as the first manifestation of malignancy (Wyburn-Mason 1978).

The origin of the amoebic infection and antigenic stimulation in cases of human lung cancer, lymphoma and myelomatosis.

Reference has been made to the three cases of healthy farmers who became infected with amoebae from the surface soil while ploughing on a tractor on a dry windy day, when the surface soil, which contains free-living amoebae, blew into their mouths and noses and was followed by acute febrile RD. Agu, Christensen and Baffler (1981) studied geographical patterns of multiple myeloma and industrial correlations and obtained data which supported previous findings of another investigator of a strong association between farming occupations and death from multiple myeloma. An extraordinary consistence in reports of high death rates from cancer of the lung in male butchers and slaughter house workers has been reported in England, Wales, Denmark, Sweden and West Germany (Fox, Lynge, Walker 1982, Wynne-Griffiths 1982, Doerken and Rehenning 1982,

Johnson and Fischman 1982). The last named found excess also in cancer of the traches, bronchus and lung, lymphoma, myeloma and leukaernia. Heller and Roubenoff (1961) reported three simultaneous cases of Jews working in an East African slaughterhouse and meat packing factory employed as religious meat cleaners in stripping certain parts of the slaughtered animals of their blood vessels. The men suffered frequent minor cuts of their fingers and hands. One case developed a mediastinal tumour extending to both lungs with splenomegaly, acute lympatic leukaemia and bone marrow infiltration. The second suffered fever and delusions with acute stem cell leukaemia affecting all organs at autopsy and the third reticulum cell sarcoma and acute stem cell leukaemia. These observations suggest that infection leading to multiple myeloma may originate either from the soil or the faeces of farm animals or lymphoma, myeloma, bronchial and other tumours from meat. In these situations free-living amoebae have been shown to exist in large numbers.

THE CAUSATION OF MULTIPLE SCLEROSIS

The causation of multiple sclerosis (MS) has remained a mystery, though suggestions of infection with slow viruses or spirochaetes and allergic manifestations have been put forward and discarded. McAlpine et al. (1955, 1965) in reviews of demyelinating conditions of the CNS conclude that the classical form of Schilder's disease, Balo's concentric sclerosis and neuromyelitis optica are only variations of MS and are due to the same cause. Others have reached similar conclusions. The massive demeylination processes constituting the condition of progressive multifocal leukoencephalopathy appear to be identical with acute severe Schilder's disease. Mackay and Burnet (1963) concluded that MS is an AI disease of the CNS and comparison with collagen disease has been made. The peculiar course of remission and relapse in the disease points to the presence of some persisting and living organism, the activity of which is in turn excited and controlled by unkown factors, recalling the latent periods of neurosyphilis. For these authors "multiple sclerosis is the rheumatoid arthritis of nervous disease". They point out that histologically there may be collections of lympohoid cells in the Virchow-Robin spaces in demyelinating diseases. Ferraro (1958) postulates two factors, an infection and an allergic reaction to it. If these factors are indeed concerned, then the infection must be chronic and one in which periodic allergic responses and a chronic antigenic stimulation occurs, such as in RD.

It will be recalled that free-living amoebae may be recovered from the CNS in normal subjects, in cases of malignant disease and in MS. MS may sometimes be associated with arthropathy and RD. Cases of this kind were reported by Wernicke (1921), Durr (1936), Schaltenbrand (1943), Keschner (1950), Cossa (1955), McAlpine, Compston and Lumsden (1955), Abb and Schaltenbrand (1955-6). Marteschek, Schaltenbrand and Serbert (1954) found 38 of 947 cases (4.0 per cent) of MS associated with "rheumatism". MS was related to "rheumatism" by Askarov (1965). In Cossa's case there occurred three attacks of acute arthritis in the knees and feet with fever followed by the appearance of the symptoms and signs of MS after each attack. Bing (1939) mentions that in cases of MS joint effusions may be found and "arthralgias are not at all rare in early MS and they may be easily confused with articular rheumatism". Abb and Schaltenbrand (1955-6) talk of a pseudo-rheumatic stage of MS in 7.9 per cent of cases at the onset. Pette (1947) discussed the relationship of rheumatism with MS, especially the acute form of the latter, and suggested that MS is an analogous reaction in the brain to that in the joints. McAlpine, Lumsden and Achisen (1965) comment on the pseudo-rheumatic onset with muscle and joint pains, neuralgia or weight loss which may usher in the symptoms of MS.

Fulford, Catterall, Delhanty et al. (1972) described the condition of "lupoid sclerosis" in six young female patients showing clinical evidence of both SLE and MS and suggested a possible aetiological relationship between the two AI diseases. This was also indicated by the report of Holmes, Stubbs and Larsen (1967) who described monozygotic twins of which one developed MS at 15 years of age and the other SLE at 19 years. Fantelli, Mitsumoto and Sebak (1978) report a case of coeliac disease with MS and quote Langer and Shiner (1976) who record 12 cases of MS with small intestinal mucosal atrophic changes of coeliac disease at biopsy. Two had partial or subtotal villus atrophy and five mucosal inflammatory infiltrates. The changes of coeliac disease are generally regarded as of AI nature and occur in about a quarter of cases of active RA (Leading Article, Brit. *med.* j., 1972), again liking MS to other AI diseases.

Ulcerative colitis, an AI disease, may likewise be associated with MS (Rang, Brooke and Taylor 1982) or MS may be accompanied by AS (Mathews, 1968, Thomas, Kendall and Whitfield 1974, Kahn and Kushner, 1978). This is a variant of RD and is affected in a similar fashion by anti-free-living amoebic drugs. Thus, MS is not infrequently associated with collagen or other AI diseases. It is well known for its association with trigeminal neuralgia, some times bilaterally. According to McAlpine, Lumsden and Achisen (1965) trigeminal neuralgia is associated with MS in 1-2 per cent of cases of the latter, whereas the incidence of MS in patients with trigeminal neuralgia is about 3 per cent. It is not rare to meet with families in which one member has MS and another trigeminal neuralgia or one member has one of these conditions and another both. Occasionally trigeminal neuralgia occurs as the first manifestation of MS. Such observations tend to relate the aetiology of MS to that of trigeminal neuralgia and with collagen and AI diseases, that is to free-living amoebic infection. The sudden appearance of symptoms in this disease may correspond with the appearance of allergic manifestations elsewhere in the body, such as urticaria. This occurred in a number of the cases in the author's series and is considered by McAlpine, Compston and Lumsden (1955). It suggests that some kind of allergic response also occurs within the CNS at the time of development of the lesions.

Progressive multifocal leuko-encephalopathy and malignant disease.

Progressive multifocal leuko-encephalopathy appears to be identical with acute Schilder's disease. It consists of a massive demyelinating process in the CNS. It has been reported as developing especially in cases of malignant lymphoma, leukaemia and multiple myelematosis, but also with carcinomata, in cases of sarcoidosis and in polycythaemia (D'Agnostino, Pease and Kernohan, 1963). These associations have been described by Bateman, Squire and Tannhauser (1945), Christensen and Fog (1955), Cavanagh, Greenbaum, Marshall et al. (1959), Lloyd and Urich (1959), Dolman and Cairns (1961), Richardson (1961), Brain (1963) and Arseni, Danells, Carp et al. (1970). Schapiro (1930) recorded Hodgkin's disease in which demyelination of the cord was present. Cases have also been described in subjects under immuno-suppressive drugs following renal transplantation and also in otherwise normal subjects. Claims have been made that the condition is due to a virus, possibly the polyoma virus (Silverman and Rubinstein 1965), but three different viruses have been isolated in this condition and may well be due to contamination. Castaigue, Buge, Escarolle et al. (1965) regarded the nuclear inclusions reported as probably metabolic or toxic rather than viral. It has been shown above that in cases of sarcoidosis and immunosupression following organ transplantation that the manifestations of RD may appear. A similar depression of immune processes, including those concerned with resistance to free-living amoebae exists in cases of lymphoma, leukaemia and carcinomatosis which

suggests that the demyelination results from the same cause as the tumour or as a paraneoplastic manifestation associated with the free-living amoebae in the tumour.

The association of multiple sclerosis with malignant lymphoma.

Greil (1939) remarked on the association of MS and Hodgkin's disease. Newell (1970, 1971) points out that Hodgkin's disease and MS may be related aetiologically. In both diseases the aetiological event took place years before the clinical onset followed by a relatively long "incubation" period. Rewcastle and Tom (1962) described a case of granulomatous angeitis of the CNS preceding the appearance of Hodgkin's disease. The CSF contained 30 WBC per cu. mm., chiefly lymphocytes. At autopsy the changes of Hodgkin's disease were found in the brain and elsewhere in relation to the affected vessels with aggregations of eosinophils in the tissues. In many parts of the CNS the predominant finding was demyelination with sparing of the axons. The microscopical picture of the white matter of the hemispheres was that of primary demyelinating disease developing in relation to the changes of Hodgkin's disease. This suggests that the association of Hodgkin's disease and MS was not fortuitous, but aetiologically related. Papp and Kiraly (1962) record the case of a male of 61 years with a twenty year history of MS, who eight months before death developed generalized reticulosarcoma with a similar aetiology indication. Below are reported four cases in which a lymphoma developed in long-standing cases of MS. Three of these occurred in a series of over 2000 cases of lymphoma collected by the author and referred to in the author's previous publication (Wyburn-Mason 1964)

Case 3. Male, aged 23 years at onset of illness when he began to suffer from intermittent diplopia followed by slight unsteadiness in walking and urgency of micturition. When examined three months later, speech was slurred, there was nystagmus to both sides, incoordination of the left arm and leg and exaggeration of the tendon reflexes. His condition gradually became worse and by eleven months after the onset he was unable to stand except with a stick and there was very gross ataxia, which prevented walking. Bilateral optic atrophy, nystagmus to right and left, slurred speech and gross intention tremor of the hands were present. The right plantar response was extensor, the left flexor. Urgency of micturition persisted. Twenty-one months after the onset his legs had become spastic, the CSF was normal and WR negative in the blood and CSF. Twenty-three months after the onset an enlarged lymph node appeared beneath the right jaw. This persisted more or less unchanged for some years during which time he became completely bedridden. Four years after the onset he complained of nausea with occasional vomiting and became constipated. He had been sweating profusely for the last three weeks and his friends noticed increased pallor over the last year. Examination at this time showed a pale thin and markedly anaemic patient with marked greying of the hair. A large swelling was present below the left jaw with a smaller mass nearby. Numerous enlarged nodes were present in the left supraclavicular region and in both axillae. The liver was enlarged by three fingers breadth and the spleen by a hands breadth. Nystagmus was present in all directions, both discs showed temporal pallor, there was a general muscular wasting in the arms and a spastic paraplegia. Slight intention tremor was present in the left hand. All the tendon reflexes were brisk in the lower limbs, those in the upper being within normal limits. The plantar repsonses were extensor. The WR was negative; the CSF normal; a blood count showed haemoglobin 60 per cent; the plasma proteins were within normal limits and the bone marrow showed excess of neutrophil polymorphs. Within the next month he developed oedema of the lower limbs. Biopsy of an enlarged lymph node showed complete disorganizaiton of the architecture with reticulum cell overgrowth and many giant and eosinophil cells. He became jaundiced and died four years after the onset of his illness. **Autopsy:** positive findings -- poor nutrition with well-marked oedema of the skin and subcutaneous tissue and slight icteric tinge of the skin. Enlarged lymph nodes were present in the axillae and neck. Both lungs showed marked basal congestion and oedema. The mediastinal lymph nodes were enlarged, the hilar glands slightly enlarged and one very large node was present in the superior mediastinum. The abdomen showed copious free fluid in the peritoneal cavity. The liver was enlarged and showed some cloudy swelling. Several enlarged nodes causing partial obstruction of the bile ducts were present in the portal fissure. The spleen weighed 3 pounds (1.25 kilos), was firm and contained many areas of suet-like infiltration, both on the surface and on section. The appearances were typical of those of Hodgkin's disease. Many enlarged lymph nodes were present in the lesser omentum and along the abdominal aorta in firm loosely adherent discrete masses showing a grey translucent surface with occasional yellow flecks. The CNS showed wide areas of whitish plaques scattered through the radiations, basal ganglia, cerebellum and cord. Histologically sections of the liver showed focal necrosis and areas of reticulum cell proliferation typical of reticulo-sarcoma. Sections of the spleen showed wide areas of necrosis and polymorphous reticulum cell sarcoma. The lymph nodes showed complete loss of normal architecture due to reticulum cell overgrowth, the cells showing great variety of size and shape. Many multinucleated giant cells and occasional mitotic figures were present and also some hyalinized collagenous tissue and scattered areas of necrosis. There were many features of Hodgkin's disease, but the condition appeared to be more malignant, a reticulum cell sarcoma. Sections of the cerebrum, cerebellum, brain stem and spinal cord showed very many translucent plaques consisting of demyelination and replacement by loose oedematous microglial and astroglial tissue. There were areas of perivascular collections of lymphocytes, plasma and microglial cells. The leptomeninges were adherent in parts and showed similar cellular infiltration and small cystic collections of fluid.

Case 4. Male, aged 36 years, when he suffered a sudden onset of "myelitis", that is a spastic paraplegia, for which no cause could be found and which gradually cleared up. Many years later seborrhoeic dermatitis suddenly appeared and persisted for the rest of his life. After a further two years he noticed a painless enlargement of the right axillary lymph nodes. Biopsy showed the presence of *a* reticulosarcoma. A year later there was a sudden onset of diplopia which disappeared and recurred from time to time and three months later his legs suddenly became weak again and he developed a right retrobulbar neuritis. Examination at this time showed nystagmus to both sides, a paracentral scotoma in the right eye, some weakness and intention tremor of the left arm, exaggerated tendon reflexes in the right arm, absent abdominal reflexes and a moderate spastic paraplegia with bilateral extensor plantar responses. Vibration was not appreciated in the lower limbs. The spleen and liver were both enlarged by three fingers breadth and enlarged nodes were present in all superficial areas. He died nine years after the first symptoms of disease and autopsy showed a generalized lymphadenopathy, enlargement of the liver which contained numerous white nodules, "hard bake" spleen and bloody effusions in the pleural and abdominal cavities. On section of the brain and cord there were numerous white plaques scattered throughout the nervous system. The leptomeninges were adherent in parts. Histologically the lesions in the lymph nodes, liver and spleen showed varying appearances, some being those of reticulosarcoma, while others were those of Hodgkin's disease or a reactive hyperplasia. The plaques in the CNS were clear cut

areas of demyelination with astroglial reaction and scattered perivascular cuffing with lymphocytes and plasma cells was present. A diagnosis of MS and malignant lymphomatosis was made.

Case 5. Female, aged 21 years, suffered from right-sided retrobulbar neuritis, but until the age of 40 years apart from mild polyarthritis she remained well. At this age she had a recurrence of the retrobulbar neuritis and a year later transient bouts of weakness of the legs and paraesthesiae. Six months afterwards there was a sudden onset of diplopia which lasted for about three months. At this time examination stowed rightsided optic atrophy, nystagmus to both sides, a spastic paraplegia and cerebellar disturbance in all four limbs. The CSF showed 80 mgms. per cent of protein. While in hospital she developed right-sided D7-8 zoster and from that time began to run an irregular temperature. Eight months later enlarged nodes appeared on both sides of the neck and biopsy of one of these showed the changes of Hodgkin's disease.

Case 6. Female, aged 52 years, admitted to the Royal Marsden Hospital, London, May 13, 1958. One brother was a mild diabetic and the patient was one of uniovular twins, the other of whom died of MS nine years before. At the age of 27 years the patient had suddenly become unsteady on her feet and later had an attack of retrobulbar neuritis in the left eye. She had gradually developed a spastic paraplegia and for the last 10 years had been unable to walk. At the age of 35 years she underwent hysterectomy for fibroids. Some two years after taking to her bed she developed bilateral trigeminal neuralgia, which was treated at the age of 43 years by alcohol injection on the left side with relief of pain on both sides by Dr. J. Penman. A month prior to her last admission to hospital she began to complain of severe backache associated with lower abdominal pain and increasing swelling of the abdomen. Examination showed left trigeminal anaesthesia, gross nystagmus to both sides, leftsided optic atrophy, slurring dysarthria, gross intention tremor in both hands, absent abdominal reflexes and a severe spastic paraplegia. All the tendon reflexes were exaggerated and the plantar responses were extensor. There was a large mass 6 inches in diameter palpable on the right side of the abdomen and another large mass on the left side which on vaginal examination was hard and rising out of the pelvis. X-ray of the chest was normal. A blood count showed a haemoglobulin of 95 per cent., WBC 6200 per cu. mm. with a normal differentiated count. Total serum protein 7.2 grams per cent. Laparotomy showed large retroperitoneal masses and biopsy of these a moderately differentiated lymphosarcoma. She was treated with HVT, but this caused exhaustion and vomiting. The masses subsided considerably. The treatment had to be abandoned because of the appearance of psychotic disturbances. She curled up in bed, spoke sullenly and complainingly to her family and the Nursing Staff. She became incontinent with severe spasms in the legs. Bilateral oedema of the legs appeared and she rapidly deteriorated and died eleven weeks after admission to hospital. **Autopsy** -- Professor N.C. Gowing -- positive findings only. Thin with pitting oedema of the lower limbs. Both pleural cavities contained 11.5 litres of turbid brownish fluid. Some pleural adhesions were present over the collapsed lower lobes of the lungs. The abdomen contained 1.5 litres of turbid fluid. Tumour infiltration of the mesenteries of the small intestine and sigmoid was present. The liver was slightly enlarged and showed several irregular plaques of grey tumour tissue in its capsule, but none in its substance. The spleen was moderately enlarged. The cut surface showed numerous discrete tumour masses up to 0.4 cms. in diameter. The following groups of lymph nodes were involved by tumour: the right and left deep cervical, anterior and posterior mediastinal, tracheobronchial, coeliac, paraortic and pelvic. The nodes in the thorax and abdomen were most markedly enlarged and measured up to 4 cms. in diameter. They were very soft and almost diffluent. They tended to be matted together and tumour extended into the surrounding connective tissue, especially in the paraaortic group, the psoas muscles and retroperitoneal connective tissue being involved. The para-aortic nodes were adherent to the aorta and inferior vena cava, which was compressed and in this region almost occluded by thrombus below the level of the renal veins. The CNS showed numerous translucent greyish patches in the cerebrum, cerebellum, brain stem and cord. These were irregular, but sharply defined and mainly affecting the white matter. In the cerebral hemispheres they were most numerous in the neighbourhood of the ventricles. The largest plaques were 1.2 cms. across. The basal ganglia showed no macroscopic changes.

Histology -- The normal architecture of the nodes was completely replaced by a diffuse mass of lymphocytes which were larger than normal mature lymphocytes. There was a marked tendency to penetrate the capsule and invade surrounding tissues. The picture was that of moderately differentiated lymphosarcoma. In the spleen numerous deposits of lymphosarcoma showed a distribution suggesting replacement of malphighian bodies. The liver showed deposits of lymphosarcoma near the capsule with only a few small tumour foci within the liver. In the lungs small tumour foci were present on the pleura. In the CNS the translucent parts consisted of areas of demyelination with replacement by loose, oedematous, astroglial tissue. The largest lesions were situated in the occipital lobes. A few lesions were present in the cerebellar hemispheres. A patch of demyelination involved the left trigeminal nucleus. Irregularly distributed patches of demyelination were present in the posterior and lateral columns of the cord.

The first of these cases occurred in a series of all the cases of lymphoma and leukaemia in the records of the British Forces in World War II (198 in number) kindly made available by the Chief Medical Officer of the former Ministry of Pensions for the United Kingdom. The last case was kindly put at the disposal of the author by Dr. J. Penman and Professor N. Gowing of the Royal Marsden Hospital, London. It is of considerable interest in that one brother had AI manifestations in the form of diabetes and the patient was one of uniovular twins, the other one of which also died of MS and the patient herself exhibited bilateral trigeminal neuralgia, which appears to be the result of infection with a free-living ameoba.

Thus, it seems that cases of MS may subsequently develop malignant lymphoma of various types, while cases of lymphoma, myeloma, leukaemia and carcinoma may later develop leukoencephalopathy and since the tumours often appear to be associated with free-living amoebic infection the demyelination may be similarly aetiologically related.

The association of multiple sclerosis with primary tumours of the CNS.

MS may be associated with primary malignant tumours of the CNS which develop after the onset of MS. Bosch (1912) described a case of MS which developed a primary melanoma of the cerebellum and Hallevorden (quoted by Peters 1958) one in which a melanoma of the frontal lobe appeared. Ho and Wolfe (1981) state that there are 20 cases in the literature in which gliomata have developed in cases of MS often directly out of the MS plaques and are often multicentric. Zimmerman and Netsky (1950) found that in 41 autopsies of cases of MS 10 developed malignant neoplasms and 2 of these were primary tumours of the brain, one a cerebral glioblastoma multiforme and the other a cerebral haemangioblastoma. Scherer (1938) described another patient with MS which developed glioblastoma and Aubert et al. (1968) the case of a woman of 50 years who suffered from MS for 15 years when a cerebral glioblastoma appeared. Munch-Petersen (1949) recorded a case of MS which devel-

oped an ependymal glioma of the external capsule. Russell and Rubinstein (1959) reported 2 similar cases, one with 2 tumours, a calcified fibrillary astrocytoma and a glioblastoma and the other case also with two separate gliomas. Brihaye et al. (1963) record a case of MS with an astrocytoma of the temporal lobe, and Woltman (1951) a case of MS with spinal astrocytoma. Barnard and Jellinek (1967) describe the case of a woman who developed herpes zoster twice at the ages of 20 and 39 years. At the age of 28 years the first symptoms of MS appeared. She died at the age of 51 years and was found at autopsy to have two oligodendrogliomata, one in the right temporal lobe and one in the cerebellum and a large neurofibroma on the fifth dorsal nerve extending into the thorax. In the brain active perivascular lymphocytic cuffing of the blood vessels of the cerebrum was seen. Currie and Urich (1974) (3 cases), Spaar and Wikstroen (1978) (3 cases), Kalimo, Frey, Raine et al. (1979), Anderson, Hughes, Jefferson et al. (1980) (3 cases), Lahl (1980) also record such cases. In one of the author's series of cases of MS, a female who had suffered from the disease for 8 years developed a Grade III astrocytoma of the internal capsule in which the tumour arose in relation to a large area of demyelination. In the South West Metropolitan Cancer Registry series a man of 43 years who had suffered from MS for many years developed a fibroblastic meningioma in the cerebellopontine angle and a woman aged 45 years suffering from MS an haemangioblastoma of the left side of the cerebellum. In the cases of Scherer, the first of. Russell and Rubinstein and the author's case *the boundries between the neoplastic tissue and the demyelinating lesions were not well defined.* Both Scherer and Russell and Rubinstein suggest an *interaction between the neoplasm and the demyelinating process and a malignant evolution of the sclerotic changes.* Scherer thought it possible that the reactive macroglial cells in the sclerotic plaques underwent neoplastic transformation. Such cases as the above suggest that the demyelination process and the development of glioma may well have the same causation.

The effect of drugs causing an Herxheimer reaction in cases of rheumatoid arthritis on cases of multiple sclerosis.

Since MS appears to be an AI disease, it would be expected that a similar Herxheimer reaction to that with RD and other AI diseases would occur if anti-free-living amoebic drugs were administered to cases of MS. The makers of all 5-nitroimidazole drugs warn against administration to patients suffering from neurological disease, but none of them on close enquiry can give the reason for this warning. The author has now seen three cases of MS in women who developed trichomonas vaginalis infection and to whom metronidazole 200 mgms. three times daily was administered by their G.P.'s. In all three cases the patients had been in a completely stable neurological state for long periods before metronidazole was administered and in which within 24 hours led to severe permanent exacerbation of symptoms. The following are the details of these cases.

Case 7. Female, aged 55 years. At the age of 35 years she suddenly developed weakness of the left leg which began to drag when walking. This was followed soon afterwards by weakness and ataxia of the left upper limb, which disappeared spontaneously within the next two months. There was a mild ataxia of the left leg. Examination showed nystagmus on looking to the left, slight ataxia of the left hand in the finger-nose test, slight spasticity of the left leg with an extensor plantor response on that side. She was unable to walk on her heels. All the tendon reflexes were brisk. The plantar reflexes were flexor and vibration could not be appreciated at the right ankle. A lumbar puncture showed a paretic Lange curve. The CSF contained 50 mgms. of protein per cu. mm. and the WR was negative in blood and CSF. She remained in this condition working at an open air market stall and was completely stable for 20 years taking chloroquine 250 mgms. daily. On stopping this she developed weakness, pain, tenderness and swelling of the calf, quadriceps, bicep and forearm muscles. A muscle biopsy showed the changes of polymyositis. At the same time she developed a foul smelling vaginal discharge and her GP diagnosed trichomonas vaginitis infection and prescribed metronidazole 200 mgms. three times daily. The next morning after taking three tablets there was a rapid exacerbation of the manifestations of MS with confusion, slurred speech, incontinence of urine and faeces, marked increase in the weakness of the lower limbs, generalized increase in tendon reflexes, flaccid paraplegia, bilateral extensor responses and a pyrexia of 100° F. The metronidazole was stopped after the fourth tablet and, though the temperature fell to normal within 3 days and the confusion disappeared, the slurring of speech, incontinence and flaccid paraplegia persisted permanently. She has lived in a wheel-chair for the last three years.

Case 8. Female, aged 18 years. In 1962 sudden onset of "deadness" of the left hand followed two weeks later by numbness of the left side of the lips, tongue and palate and loss of the ability to taste. These symptoms lasted three months and then cleared spontaneously, but while they were present the right hand also felt "numb" for two weeks. At the end of this period she was then symptomless for two weeks when she fainted twice for no apparent cause and developed severe pain in the left eye lasting for four days, but less severe for two weeks. The day after the onset of the fainting she was found on the floor delirious for 10 minutes and remembered nothing of this. One week later she was unable to stand up unless helped and was unsteady on her feet. She was found to have lost the vision in the left eye in part and also had diplopia. Three weeks later she remained markedly ataxic when walking. At this time she was found to have a paracentral scotoma in the left visual field, partial left sixth nerve paresis and impairment of all sensation in the distribution of the left trigeminal nerve. She was treated with daily injections of 100 units of pituitary hormone gradually tapering off over one month. At the end of nine months her symptoms had largely disappeared except for paraesthesiae in the left side of the face. She remained unchanged for two years when the left foot suddenly went numb and the right leg was numb to the mid thigh. She was found to have a left sixth nerve paresis and impairment of sensation to pain and touch in the right leg up to the mid thigh. There was pallor of the left optic disc, but no field defects were found. All tendon reflexes were exaggerated, but the plantar reflexes were flexor. Examination one year later showed some intention tremor in the left hand. The legs were slightly spastic and ataxic, the plantar reflexes extensor. She could not dorsiflex the ankles fully. Tendon reflexes in the lower limbs were exaggerated and Romberg's test was present. She remained unchanged over the next 15 years taking chloroquine 250 mgms., daily, running her home and looking after her child, when she developed trichomonas vaginalis infection, for which her doctor prescribed metronidazole 200 mgms. three times daily. After the fourth tablet the whole of the left side of the face, palate, tongue and cheek become numb. A haze appeared in the upper half of both visual fields. She became intensely unsteady with urgency of micturition. Both legs were weak and flaccid. The right palm felt dead, both arms became extremely weak so that she was unable to feed herself. The feet felt cold, but, in fact, were not. She could walk about in her flat only holding on to furniture and not stand unless supported. Examination showed the lower limbs were flaccid, especially on the right side, tendon reflexes were diminished with extensor plantar responses. Heel-knee test was impossible on the right side and normal on the left. Both upper limbs were markedly weak with depressed tendon reflexes and ataxia. There was impairment of all sensation over the distribution of maxillary and mandibular portions of the left trigeminal nerve. The fundi were normal, CSF

protein 40 mgms. per 100 mls., WR negative in CSF and blood.

She was treated wtih 40 units of pituitary hormone daily for three weeks gradually tapering off over the fourth and during this time the numbness of the face lessened and the haze in the upper visual fields disappeared. Otherwise she has remained in the same state over four years as she was after administration of the metronidazole and is confined to a wheel-chair with crutches.

Case 9. Female, aged 37 years. Ten years previously onset of dizziness, visual blurring, unsteadiness on feet and later weakness of the left arm. Objects kept dropping from her hands and there was a loss of feeling on the left side from the middle of the abdomen downwards. From that time she had periods of vomiting, imparied vision and balance lasting only two days. Four years previous to being seen both legs became weak, especially on walking, and her balance was poor. She had diplopia on looking to the left and continued leaking of urine. Examination showed restricted conjugate movement of the eyes in all directions with nystagmus; both legs were ataxic, but not spastic. The tendon reflexes were all brisk and the plantar reflexes were extensor. Romberg's test was positive, WR negative in CSF and blood, CSF protein 55 mgms. per 100 mls. Lange curve tabetic type. She was observed over the next 12 years during which time she took chloroquine 250 mgms. daily and she remained completely unchanged. She was able to undertake office work and to go on continental holidays and to the USA and the physical signs in the CNS remained as before. The drug was stopped by her doctor and she then developed trichomonas vaginalis infection for which she was treated by her G. P. with metronidazole 200 mgms. three times daily. On the second day her legs became stiff and more unsteady and it became almost impossible to walk and stand. The tablets were stopped. She developed periods of intestinal blockage due to gut paralysis. She was only able to move about holding on to the walls and furniture in her home. She continually caught her toes in rugs. She was unable to write a letter or feed herself. Within a few days control of urination was lost and she remained bedbound. Examination showed nystagmus in all directions, loss of conjugate upward movement of the eyes and impaired movement of the right eye to the left. Finger-nose test was impossible on both sides. The legs showed spastic paraplegia, brisk tendon reflexes, extensor plantar responses and the heel-knee test was impossible. She had to give up work and has remained chair-bound over the last three years.

One of these cases was associated with polymyositis, a manifestation of the collagen or rheumatoid diseases. In all three of these cases metronidazole induced within 24 hours a severe exacerbation of the symptoms of MS in stabilized cases, just as it does in RD. This suggests that the drug induced death of amoebae within the CNS, just as it does in extraneural tissues, with the liberation of toxic and antigenic substances from their bodies leading to plaque formation and that MS results from intraneural infection with pathogenic strains of such organisms. Amoebae are universal infections of humans. Why then are all humans not victims of MS? Firstly not all species of free-living amoebae are pathogenic and secondly not all humans show inflammatory tissue reactions to different infections these being genetically controlled. It seems that whether they do or not depends on their tissue antigens. Shepherd and Downie (1978) point out remarkably similar geographical distributions of MS and HLA antigens, A3 and B7 in the north-east of Scotland, where there is a remarkably high incidence of the disease, suggesting that the appearance of MS in the patient is related to the existence of specific HLA antigens controlling reaction to the intraneural infection.

It is to be concluded that MS is due to the presence in the CNS of pathogenic free-living amoebae in a sensitive subject as evidenced by the tissue antigens and that sudden destruction of the organisms by anti-free living amoebic substances can cause a sudden and violent exaggeration of symptoms due to the action of drugs on the organisms within the CNS. Can such drugs be used in the treatment of MS without running the risk of exaggeration of symptoms? Chloroquine is an anti-free-living amoebic drug often used like its analogues in the treatment of RD, but which does not produce an Herxheimer reaction in these cases. It seems that this substance or other antiamoebic drugs not producing an Herxheimer reaction might possibly be used to prevent the progress of MS by killing the causative agent and preventing the formation of new plaques. Chloroquine has been used in the treatment of the disease by Miller and Schapira (1967) and has been found to be the most promising substance among those tried. The author used chloroquine 250 mgms., camoquin or dehydrochloroquine in the same dose daily in cases of MS over long periods prior to Miller's paper with close attention to the eye condition in some 25 cases of varying severity. Among these were the three cases just described. In all these cases there occurred some degree of improvement in the original symptoms. but after this the condition remained unchanged for up to 20 years. Possible drugs to prevent progression of MS or to lessen the activity in the plaques in the CNS would appear to be any free-living antiamoebic substance that does not cause an Herxheimer reaction in infected patients. These may exist among those found by the author to possess such properties, but a trial would take many years to complete.

References

Abb L. and Schaltenbrand G. *Dtsch. Z. Nervenheilk.* 1955-6; 174; 199.

Agu V.U., Christensen B.L. and Baffler P.A. *Nat. Cancer Inst.* 1981; 735-38.

Agudela C.A., Schumacher E., Glick J.H.. Molina *I.J.Rheumatol. 1981;* 69; 78.

Anderson M., Hughes B., Jefferson M. *Brain* 1980; 103; 603-622.

Arseni C., Danella L., Carp N., Decu P. *Neurolgia* (Buc.) 1970; 15; 513-528.

Askarov S.A., Zbl. *Neuropat. Psychiat.* Korsakov, 1965; 65; 1653-5.

Aubert I., Arroyo H., Daumas B., and Tripier M.C. *Rev. Neurol.* 1968; 119; 37-46.

Barnard R.O. and Jellinek E.H. J. *Neurol. Sci.* 1967; 44; 455-68.

Bateman O.J., Squire G. and Tannhauser S.J. *Ann. int. Med.* 1945; 22; 426-436.

Binder M., De Silva M., Hazleman B.L. *Hospital Update.* 1983; 9; 341-49.

Binder, Domenichino, Gottardi, Orlandi, Ortelli, Pacini, Fowst et al. *ArnzeimForsch* (Drug Res.) 1971, 12th, Year, No. 12A "Antimicrobial activity of Rifampicin in vitro," Chapter 2.

Bing R. *Textbook of Nervous Diseases* 1939, London, Kimpton.

Black K.A., Zilko P.J., Dawkins, R.L. et al. *Arth. Rheum.* 1982; 25; 1130.

Bosch, G.Zbl. *inner. Med.* 1912; 37; 917-926.

Brain W.R. *Lancet* 1963; 1; 179-182.

Brihaye J., Peuer O., and Stennit J. J. *Neuropath. exp. Neurol.* 1963; 22; 128-133.

Burrows H. *The localization of Disease* 1932, Bailliere, Tindall and Cox, London.

Carter R.F., 1972, *Amoebic meningo encephalitis. Transactions Roy. Soc. Trop. Med. Hyg.* 66; 195-6.

Carusa I., Montrona F., Fumagalli M.,
Patrono C., Santandrea S., Grandini M.C., *Ann. Rheum. Dis.* 1982; 41; 231-6. Castaigue P., Buge A., Escarolle R. and Berger B. *Rev. Neurol.* 1965; 112-143.
Cavanagh J.B., Greenbaum D., Marshall A.H.E. and Rubinstein L.J. *Lancet* 1959; ii; 52-13.
Christensen E. and Fog M. *Acta. Psychiat. KBL* 1955; 30; 141-3.
Cobden I, Hamilton J, Axon ATR *Lancet* 1983; 1; 829.
Cossa P. Rev. *neurol.* 1955; 63; 66:
Craig and Faust; 1970 *Clinical Parasitology* Edit. by Faust EC, Russell P.T. and Jung R.C.; 8th Edit.; Philadelphia, Lea and Fibiger.
Currie S. and Urich H.J. *J. Neurol. Neurosurg. psychiat.* 1974; 37; 598-601.
Cursons R.J.M., Brown T.J. and Peys E.A. *Lancet* 1977; ii; 875-6.
D'Agnostino AN, Pease G.L., Kernohan J.W. *J. Neuropath. exp. Neurol.* 1963; 22; 138-142.
Damashek W. and Schwarz R.S. *Blood* 1959; 14; 1151-5.
Denman M. *Brit. med. J.* 1981; 283; 1492-3.
Descamps C., Gillain P., van Heuverzwyn P. et al. *Acta. gastro-ent. Belg* 1977, 40; 55-8.
Dobell C. 1919 *The amoebae living in man.* John Bale, Sons and Danielson, London.
Doerken H. and Rehpenning W. *Lancet* 1982; i; 561.
Doll R. and Peto R. *The Causes of Cancer* 1982; London, Oxford University Press.
Dolman C.L. and Cairns A.R.M. *Neurology* 1961; 11; 349.
Durr W. *Kaugural Diss. Erlangen 1936.*
Dwork H.G. *PABA Bull.* New York Acad. Med. 1948; 24; 391-2.
Editorial *Lancet* 1981; 1; 648.
Fantelli F.J., Mitsumoto H. and Sebak B. A. *Lancet* 1981; 1; 648.
Ferraro J. *J. Neuropath. exp. Neurol.* 1958; 17; 278-280.
Fox, A.J., Lynge E. and Malker H. *Lancet* 1982; i; 165-6.
Fulford K.W.M., Catterall R.D., Delhanty J.J., Doniach D. and Kremer M. *Brain* 1972; 95; 37-38.
Fulton C. *Methods in cell biology* Edit. C.M. Prescott, P. 341, New York, 1970.
Glynn L.E. *Ann Rheum. Dis.* 1968; 27; 105-120.
Harkness J.A.L., Richler M.R., Payani. C.S., et al., *Brit. med.* J. 1982; 281; 551.
Heller H. and Roubenoff A, *Lancet* 1961; ii; 314-5.
Hench P.S. *Ann. Rheum. Dis.* 1949; 8; 90.
Ho K.I. and Wolfe D. K. *Cancer* (Philadelphia) 1981; 47; 293-9.
Holmes F., Stubbs D.W. and Larsen W.R. *Arch. int. Med.* Chicago, 1967.
Jadin J.B., Acanthamoeba Conference, Columbus, Ohio, 1978.
Johnson E.S. and Fischman H.R. *Lancet* 1982; i; 1913-14.
Kahn M.A. and Kushner 1. *Arch. Rheum.* 1978; 22; 74-6.
Kalimott H., Frey H., Raine C.S., et al. *Acta Neuropath.* 1979; 46; 231-4.
Keschner M. Proc. Res. Nerve. Ment. Dis. 1950; 28; 533.
Kofoid, C.A. and Swezy O. (a) Univ. Calif. Publ. *Zool.* 1922; 20; 301.
_____ (b) *Calif. State J. Med.* 1922; 20; 59.
Lahi R. *Eur. Neurol.* 1980; 1973; 192-7.
Langer R. and Shiner M. *Lancet* 1976; ii; 1319.
Landsbury *J. Ann. Rheum.* 1953; 12; 381.
Lastovica A.J. *Trans. Roy Soc. S. Africa* 1980; 44; 269-79.
Leading Article *Lancet* 1972; i; 826.
Lloyd O.C. and Urich H. *Lancet* 1959; ii; 529.
Lynch H. *Prev. Med.* 1950; 9; 231-237.
Mackay I.R. and Burnet F.M. *Autoimmune Diseases* 1963, C.C. Thomas, Springfield, Illinois.
Mackenzie A.H. and Scherbel A.L. *Geriatrics* 1963; 18; 745.
Maretschek M., Schaltenbrand G. and Serbert P. *Dtsch. Z. Nervenheilk* 1954; 172; 287.
Mason R.W., Chapter XIV in *Textbook of the rheumatic diseases,* Edit. by W.S.C. Copeman, 4th Edit. 1969, Livingstone, London.
Mathews W.B. *J. Neurol. Sci.* 1968; 6; 56-173.
McAlpine D.. Compston N.D. and Lumsden C.E. 1955 *Multiple sclerosis* London, Livingston.
_____ Lumsden C.E. and Achisen E.D. *Multiple sclerosis,* A reappraisal, 1965, London, Livingstone.
Miller H. and Schipira K. *Brit. med. J.* 1959; i; 737, 811.
Multicentre Study Group *Lancet* 1978; ii; 1007-12.
Munch-Petersen C.J. *Acta. Pstch. Neurol. Scand.* 1949; 24; 599.
Nagington J., Watson P.G., Playfair S.T. *Lancet* 1974; ii; 1537.
Pette K. *Klin. Wschr.* 1947; 25; 897.
Rang E.E., Brooke B.N. and Taylor J.H. *Lancet* 1982; ii; 555.
Review on PABA by National Academy of Sciences, National Research Concil, USA *Physician's Desk reference,* 36th Ed. 1982, Oradell, N.J.
Rewcastle N.B. and Tom I.J. *Neurol. Neurosurg. Psychiat.* 1962; 25; 51.
Richardson E.P. Jr. *New Engl. J. Med,* 1961; 365; 815.
Russell D.S. and Rubinstein L.J. *The pathology* of *the nervous system* 1959, London, Arnold.
Schaltenbrand G. 1943, *Die Multiple sklerose des Menschen* Leipzig, Thieme.
Schapiro P.F. *Arch. Neurol. Psyshiat.* Chicago, 1930; 24; 509.
Scherer H.G. *Belge. Neurrol. Psychiat.* 1938; 38; 1.
Shepherd D.I. and Downie A.E. *Brit. med. J.* 1978; 2; 314.
Silverman L. and Rubinstein J. L. *Acta Neuropathologica* (Berlin) 1965; 55; 215-225.
Solomon F. W. and Wikstroen J. *J. Neurol.* 1978; 218; 23.
Spaar F.W. and Wikstroen J. *J. Neurol.* 1978; 218; 23.
Thomas D.J., Kendall M.J. and Whitfield A.T.W. *Brit. med. J.* 1974; i; 148-50.
Naldenstrom, Quoted by Doniach D., Roitt I.M., Taylor K.B. *Brit. med J.* 1963; i; 1374.
Walker A.R. S. *Afr. J. Sci.* 1981; 77; 534-37.
Wernicke O. *Semana med. Espan.* 1921; 281, 455.
Williams H.D., Lockwood C.M:, Russell B.A. *Brit. med. J.* 1979, 2, 235.
Woltman H. W. *Arch. Neurol. Psychiat.* Chicago 1951; 66; 71-80.
Wyburn-Mason R. 1964 *A new protozoon, its relation to malignant and other diseases,* London, Kimpton.
_____ 1978 *The causation of rheumatoid disease and many human cancers. A new concept in medicine* Tokyo, Iji Publishing Co., Japan.
_____ 1979 (a) *International Medicine* 1979; i; 20.
_____ 1979 (b) *British Medicine* 1979; August 21st, 12.
_____ 1979 (c) *Medical Hypotheses* 1979; 5; 1237.
Wynne-Griffiths G. *Lancet* 1982; i; 399.
Zimmerman H.M. and Netsky S.M. 1950 *In Multiple sclerosis and the demyelinating diseases* Williams and Wilkins Ltd., Baltimore, p. 271.

In Memoriam

Roger Wyburn-Mason, M.D., Ph.D. October 2, 1911–June 16, 1983

By Anthony di Fabio, June 18, 1983

When I was at last cured of the dreaded, crippling rheumatoid arthritis, I never dreamed of embarking on a worldwide challenge to professional rheumatologists, the gigantic and ineffective Arthritis Foundation, and the American petrochemical industry that siphons S15,000,000,000 a year in the United States of America from the sick and the lonely, chiefly for aspirin substitutes that simply treat symptoms, and not causes.

Somehow the Good Lord has seen fit to successfully guide my path -- along with other determined, sincere people to bring the good message to all: there is a cure! it is simple! it is cheap! it is available everywhere!

My book *Rheumatoid Diseases Cured at Last* was monitored by Professor Roger Wyburn-Mason, and based on his original work, *The Causation o/ Rheumatoid Disease and Mann Human Cancers (1978).* My first book was designed for the ailing to find hope, to convince them, to be carried to their family physician for further interpretation where they would be treated.

My small book,also launched *The Roger Wt burn-Mason & Jack M. Blount Foundation for Eradication of Rheumatoid Disease (AKAs: The Arthritis Trust of America and The Rheumatoid Disease Foundation),* which is now successfully off and running, millions of messages having already spread the word. Many fine humanity-conscious physicians and non-physicians are now members, or practitioners of life-saving, pain-relieving treatments, and working toward common goals set by Professor Roger Wyburn-Mason.

Some six weeks before his death I wrote to Roger, asking that he please include a summary of his professional life and writings. I argued that while his work ought to stand on its own two feet, professional humans, like other humans, simply were more impressed with the number of "brownie points" and "merit badges" than with whether or not the work was "scientifically valid" -- not meaning, of course, to disparage either the Boy or Girl Scouts, (I was an active Boy Scout) but rather to emphasize the sad state in which the so-called professional scientific community finds itself -- where "altitude" and "prestige" is of more consequence than scientific validity.

Reluctantly, Professor Roger Wyburn-Mason sent this, his last letter, before the Good Lord called him on June 16, *1983.*

> "I was born in Monmouthsire, England. On my mother's side I am a descendent of Bishop Stephen Gardiner, who was Lord Chancellor of England, that is the most powerful person in the country after the Monarch in the reign of King Henry VI11, King Edward VI, Queen Mary the first and Queen Elizabeth the first. He conducted the marriage of King Philip II of Spain to Queen Mary the first of England in Winchester Cathederal, where he is buried in a magnificent tomb. My mother's cousin was the former Prime Minister of New Zealand, Mr. Nash. My godfathers were the greatest English Composer, Dr. Ralph Vaughan Williams of Cambridge University and now buried in Westminster Abbey, and the historian H.A.L. Fisher, the head of New College Oxford, both of whom held the decoration of Order of Merit (O.M.), the highest honour that can be bestowed by the Monarch.
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> "I attended a public school (a public school in England is the opposite of one in the United States, being privately as opposed to state owned and includes such distinguished Institutions as Eton, Harrow and Winchester Colleges). At the end of school years I took the necessary final examinations and gained the top marks in the whole of Great Britain and was awarded a State Scholarship and an Open Scholarship to Christ's College, Cambridge (founded in 1405 A.D.), where the poet John Milton and the great scientist Charles Darwin were also students. Here I occupied the same rooms as those of Darwin himself.
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> "At Cambridge I obtained double first class honours in the final examinations for the B.A. (Bachelor of Arts) degree. I also represented my University at Rugby football and Athletics. At the end of my period as an Undergraduate I remained in Cambridge as a Bachelor Fellow of the College and did research in pathology and particularly protozoology. I afterwards was awarded the degree of M.A. (Master of Arts) a higher degree and the only University scholarship awarded to graduates completing their clinical studies at a London Hospital where 1 finally obtained my M.B. (Bachelor of Medicine) and B. Chir. (Bachelor of Chirurgerie). 1 afterwards held the posts of Registrar (the equivalent of Instructor in America) in the foremost hospitals in London, namely the Middlesex Hospital, the Brompton Hospital for Chest Diseases, the National Heart Hospital, the National Hospital for Nervous Diseases and the Royal Marsden Hospital for Cancer. While at the Middlesex Hospital I took part in the first Clinical Trials of the first sulphonamide Antibiotics. While working at the National Hospital for Nervous Diseases I wrote my thesis for the M.D. (Cambridge Degree -- This is a higher degree unlike it is in the United States and other countries). I also sat for M. R.C. P. (Member of the Royal College of Physicians) examination in which 1 obtained the top marks of all the candidates. My M.D. thesis was entitled "The vascular tumours and abnormalities of the spinal cord and its membranes" and received with acclaim as it was the first description of these matters. It was published as a monograph and has remained the standard work on this subject. While working at the National Hospital for Nervous Diseases 1 published a number of papers in Medical Journals and two of these described new diseases which have since been named after me and I am the only living doctor who has such a distinction. One of these conditions describes the presentation of cancer as a peripheral neuropathy, that is a disturbance of the nerves of the limbs before any other evidence of cancer is present. The other describes a congenital blood vessel disease of the skin of the forehead, the fundus of the eye, the optic nerve and the brain.

"I later was elected Research Fellow at the Royal Marsden Hospital for research into cancer and later Research Fellow at the Royal College of Surgeons of England, where I continued my research into the nature of cancer and first isolated from all human malignant tumours and from cases of rheumatoid arthritis an hitherto unknown, very small free-living amoeba. For this 1 received the Ph.D. degree.

"While working at the Royal Marsden Hospital I discovered that human tissues affected by herpes zoster (shingles) and by herpes simplex (cold sores) which are both due to virus infections, were liable to develop cancer of the skin at a later date. This was the first description of human cancer caused by a virus and it resulted in my invitation by the late Professor Duran-Reynals, who was working at Yale University on the viral cause of human cancer, to Yale to work with him as his assistant where I continued after his death. I later travelled to the Mayo Clinic and worked with [my friend] the late Dr. J.W. Kernohan, the neuropathologist.

"I became convinced that while viruses cause cancer in animals, they rarely do so in man. During these years I published many papers and monographs (books) on my researches, and as a result of these I was awarded the degree of Doctor of Science of Cambridge University (a rare honour) and elected a Fellow of my old College.

"After twenty years work on the new organism which I had discovered I was able to show that this was the cause of rheumatoid arthritis. Furthermore, infection with species of this organism in susceptible subjects seemed to be the cause of a large proportion of cases of human cancer, which can be prevented by taking appropriate substances which kill the organism. This work has all been described in a book entitled *The causation of rheumatoid disease and many human cancers - A new concept in Medicine,* and it has caused worldwide interest.

"After a time it became necessary for me to return to England where 1 continued my work in the laboratories and wards of the National Health Service.

"Among my publications are the following -

Books

The vascular tumours and abnormalities of the spinal cord and its membranes. Henry Kimpton, London, 1943.

Trophic nerves. Henry Kimpton, London, 1950.

Reticulo-endothelial system in growth and tumour formation. Henry Kimpton, London, 1958.

A new protozoon, its relation to malignant and other diseases. Henry Kimpton, London, 1964.

The causation of rheumatoid disease and many human cancers -a New concept in Medicine. Iji Publishing Co. Tokyo, Japan, 1978.

A précis and addendum to the above. AC Publishing Co., Rt. 4, Box 137, Franklin, TN 37064, 1983.

Some Papers

"On some anomalous forms of amaurotic idiocy and their bearing on the relationship of various types". Brit. *Journ. Ophthalmol.,* April/May 1943, p. 145-187.

"Arterio-venous aneurysm of midbrain and retina, facial naevi and mental changes". *Brain,* 1943, 66, 163-203. (This is known as *WyburnMason Syndrome l).*

"On some pressure effects associated with cervical and the rudimentary and 'normal' first ribs and the factors entering into their causation". *Brain,* 1944, 67, 141-177.

"A new conception of angina pectoris". *Brit. Med. J.,* 1948, i, 972.

"Bronchial carcinoma presenting as polyneuritis". *(Wyburn-Mason's Syndrome II). Lancet,* 1948, i, 203.

"The significance of the reference of anginal pain to the right or left side of the body". *Amer. Heart J., 1950, 39, 315-335.*

"The nature of tic doulourux". Brit. Med. J., 1953, iii, 119.

"Costo-clavicular compression of the subclavian vein and its significance in relation to post operative oedema in carcinoma of the breast". *Brit. Med. J.,* 1953, iv, 1198-1200.

"Nature of Bell's palsy". *Brit. Med. J.,* 1954, iii, 679-681.

"Malignant change arising in tissues affected by herpes simplex". *Brit. Med. J.,* 1955, iv, 1106-1109.

"Malignant change following herpes simplex". *Brit. Med. J.,* 1957, ii, 615-161.

"Visceral lesions in herpes zoster". *Brit. Med. J.,* 1957, i, 678-681.

These last three articles are the first reports of a viral cause of human cancer.

"Association of gastroduodenal lesions with Me'nie're's syndrome". *Brit. Med. J.,* 1959, i, 78-83.

"Clotrimazole and rheumatoid arthritis". *Lancet,* 1976, i. 489.

"The free-living amoebic causation of rheumatoid and auto-immune diseases". *International Medicine,* 1979, 1, 20-25.

"New views on the aetiology of rheumatoid arthritis". *British Medicine,* August 21st, p. 12-14.

"The Naegerial causation of rheumatoid disease and many human cancers - A new concept in medicine". *Medical Hypotheses,* 1979, 5, 12371249.

"SLE and lymphoma". *Lancet,* January 20th, 1979.

"ROGER WYBURN-MASON June 10th, 1983"

Professor Roger Wyburn-Mason solved the riddle of one of man's oldest curses, and in so doing, discovered a vast panorama of formerly, and socalled, uncurable diseases. He strived with every ounce of his great, God-given intellect to bring to all humanity his discoveries. We prayed to be there when he walked across the stage to receive his Nobel Prize, and other prizes that were his due - but God, in his great wisdom, decided otherwise for us, and we must accept.

To the famous names of Semmelweis, Jenner, Koch, Harvey, Ross, Lister, Pasteur, Ehrlich, Sister Kenny, and Roentgen add Wyburn-Mason -a most brilliant, brave, humanity-loving man who pursued evil forces causing them to acknowledge that humanity need not always feel pain, suffering, depression, disillusionment