

Agreement for Assignment of Invention

THIS AGREEMENT made and entered into this 22nd day of November
, 1975 by and between Dr. Roger Wyburn-Mason, residing
at 2 Hillbrow, Richmond Hill, Richmond, Surrey, England,
(hereinafter referred to as "Inventor"), and Dr. Tsuneyoshi Koba,
residing at 73, 1-1-7arita Nishi, Suginami-Ku, Tokyo, Japan
, (hereinafter referred to as "Assignee").

WITNESSETH:

WHEREAS, the Inventor has researched and developed a certain
drug, generically known as ^{Metronidazole, Tinidazole, Nimerazole, & Ornidazole} Clotrimazole, as fully described in the
specifications prepared by the Inventor and attached hereto, (such
drug hereinafter being referred to as "Drug Invention"), which drugs
^{are} effective for the treatment for rheumatoid disease;

WHEREAS, the co-inventor, _____, has
transferred his rights and interests to apply for and acquire patents
on the Drug Invention in Japan to the Inventor;

WHEREAS, the Inventor represents that he is now the sole owner
of the rights to make applications for patent registration on the
Drug Invention in Japan; and

WHEREAS, the Assignee is desirous of acquiring all rights
to apply for patent registration on the Drug Invention in his
own name in Japan, and acquiring the Japanese patents to be
obtained therefrom.

NOW, THEREFORE, for and in consideration of the premises and the mutual covenants herein contained, the parties agree as follows:

Article 1. Assignment

The Inventor hereby assigns and transfers to the Assignee the full and exclusive right to make applications to the Japanese Patent Office for patent registrations on the Drug Invention and to receive the patent registrations on the Drug Invention from the Japanese Patent Office under and in the name of the Assignee.

It is understood that the Inventor will also assign to the Assignee the right to apply for and acquire all patents on any modifications, improvements or deviations made or acquired at any time by the Inventor in connection with the Drug Invention.

Article 2. Consideration

1. So long as the Japanese patents on the Drug Invention have been registered and are existing in the name of the Assignee, the Assignee hereby agrees to pay to the Inventor a royalty equal to two percent (2%) of the bulk price of the Drug Invention used in the manufacture of all "per os form" products sold in Japan incorporating the Drug Invention upon which Japanese patents have been issued and registered and are existing in valid in the name of the Assignee (hereinafter referred to as "Products").

The bulk price shall mean the price paid by a manufacturer for purchasing the Drug Invention in bulk to manufacture the

Products in per os form, or if a manufacturer itself prepares the Drug Invention in bulk for manufacturing the Products, then the bulk price shall be determined from the manufacturer's selling price of the Products less an amount to be deducted to reflect the value of other ingredients, wrapping, profit, added value, costs, etc., on the basis of the manufacturer's calculations.

2. The timing, frequency and other conditions for the payment and remittance of royalties on the Products shall be separately agreed upon by the parties, when the decision to register the Japanese patents on the Drug Invention is made by the Japanese Patent Office.

Article 3. Information

1. Upon execution of this Agreement, the Inventor agrees to provide the Assignee, at the Inventor's expense, with any and all documents, papers, affidavits and other tangible or intangible information necessary for applying for patents on the Drug Invention to the Japanese Patent Office or for the fulfillments of any governmental requirements concerning this Agreement or any other incidental agreements hereto executed by the parties.

2. The Inventor further agrees to provide the Assignee, at the Inventor's expense upon the request of the Assignee, with any tangible or intangible information necessary for obtaining, maintaining and enforcing the Assignee's patent rights on the Drug Invention, and to assist the Assignee in protecting the patents on the Drug Invention from infringements by third parties during the life of any of the Assignee's patents on the Drug Invention.

Article 4. Expenses

The Assignee agrees to pay all expenses necessary for obtaining and maintaining the Japanese patents on the Drug Invention, other than the expenses incurred by the Inventor in accordance with Article 3.

Provided however, it is understood that the Assignee shall not owe any responsibilities or shall not represent to any person to obtain, maintain and protect the Japanese patents on the Drug Invention.

Article 5. Miscellaneous

1. The validity, effect and construction of this Agreement shall be governed by the laws of Japan.
2. This Agreement is written in English and interpreted in accordance with such language.
3. This Agreement shall become effective upon the execution of this Agreement by the parties.

IN TESTIMONY WHEREOF, the parties hereunto set their hands and affixed their seals in duplicate as of the date first above written.

Inventor:

R. Wyburn-Mason

Assignee:

Isuneyoshi Kasa

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Chemotherapy - London. With Compliments - Rhyfion - Mason

In rheumatoid disease 70-80 per cent of cases develop rheumatoid factor (RF) in the serum, which often also contains antinuclear factor (ANF) and auto-antibodies against various tissues. Most workers favour an unknown infective aetiology for the condition. Rheumatoid factor and auto-antibodies to various tissues may also be found in the serum, though in low concentration not comparable to the level in rheumatoid disease, in many infections, including subacute bacterial endocarditis, infective hepatitis, tuberculosis, syphilis, leprosy, etc. Arthritis is not a feature of these conditions and successful treatment of the underlying disease causes the serum factors to disappear. They appear as a response to an infection, suggesting a similar mechanism in cases of rheumatoid disease.

Certain observations are consistent with the possibility that rheumatoid disease may perhaps be due to a protozoal infection.

Firstly, RF occurs in the blood in high concentration comparable to that in rheumatoid disease and accompanied by auto-antibodies to various tissues in chronic infections with many protozoa, including malaria, trypanosomiasis, kala-azar and visceral leishmaniasis, in which arthritis is not a feature. These blood changes also gradually disappear on treatment with appropriate anti-protozoal drugs.

Secondly, in amoebic dysentery due to infection with the protozoon, *Entamoeba histolytica*, an arthritis practically identical with that occurring in rheumatoid disease may be

observed.

Thirdly, a high proportion of cases of rheumatoid disease respond, usually slowly, to various anti-protozoal drugs of widely differing chemical constitution. These include the 4-aminoquinolines, chloroquine, hydrochloroquine and amodiaquin, but also pyramethamine and mepacrine. They are unique in their effect on rheumatoid disease in that, unlike other anti-rheumatoid drugs, they result in complete reversal of all the phenomena of active disease. No explanation of the effect of chloroquine in such ~~cases~~ ^{cases} has been forthcoming. The similar action of these antiprotozoal drugs of different chemical structure and active against a spectrum of protozoa in completely abolishing evidence of activity could be explained if the disease was of protozoal origin.

Fourthly, the nitro-imidazole derivative BT 985 E. Merck AG, which is related to naxogin, is protozocidal to amoebae, giardia, trichomonas, leishmania and trypanosomes. The drug cures infections with the first three organisms. It has been reported as dramatically relieving all evidence of activity in 9 of 10 cases of rheumatoid disease.

Clotrimazole, also an imidazole derivative and thus chemically related to the above is an antimycotic agent with a broad spectrum as well as being inhibitory to certain moulds and aspergillus, and to protozoa, such as histoplasma, flagellates, and small free-living amoebae, such as Naegleria fowleri. The possible protozoal nature of rheumatoid disease and the inhibiting

effect of clotrimazole on a number of protozoa seemed to warrant a trial of the drug in cases of active rheumatoid disease. An attempt at a double blind trial with a placebo had to be abandoned because the beneficial effect of the drug was so dramatic that after two days it was obvious to the observer which drug was being used on which patient.

It was given orally to 12 successive cases of rheumatoid disease in an active state as evidenced by pyrexia, pain, swelling, heat and restriction of joint movements, oedemas, morning stiffness, rise in the blood sedimentation rate, sweating, etc. All cases fell into the "classical" or "definite" categories of rheumatoid arthritis as defined by the American Rheumatism Association. The cases had all been treated previously often for years with various drugs, frequently in combination, including aspirin, phenylbutazone, indomethacin, ibuprofen, ketoprofen or cortico-steroids, without controlling the activity of the disease. They were hospitalized at first, but not confined to bed. The drugs were discontinued. If taking steroids, these were tapered off completely. This resulted in an exacerbation of the symptoms, often severe. Serial investigations were carried out before and repeatedly during and after treatment. In 7 cases RF and in 4 thyroid and gastric parietal cell auto-antibodies were present in the sera. Clotrimazole was administered by mouth in as near a dosage of 100 mgms. per kilogram per day as possible, taken in divided doses immediately after meals with milk. It may cause nausea, vomiting and

diarrhoea. The former were controlled by an anti-emetic, which often allowed the full dose of the drug to be taken. When it induced diarrhoea, this could usually be prevented by a kaolin mixture.

Details of the cases are shown in the table (Slide 1). Four were males and 8 females, their ages ranging from 47-77 years. Symptoms had been present for 2 months up to 23 years previously. In 2 cases the gastro-intestinal side effects of the drug were so severe as to prevent continuation of treatment for more than 2-3 days. All of the other 10 cases, especially when taking the full dose of the drug, there was a dramatically favourable response to treatment. This often began within 24 hours, when the oedema, pain, joint swelling, stiffness and restricted movements began to subside. The temperature settled. In one case disappearance of all clinical evidence of active disease was complete in 3 days. In other cases it took 2-4 weeks for all evidence of activity to disappear according to dosage of the drug and severity and duration of the disease. In one case bilateral olecranon bursitis resolved completely in 3 weeks. It was found that administration of the drug had to be continued for 8-12 weeks before it could be left off without a return of symptoms.

Before treatment was commenced most cases exhibited a rise in the ESR and 7 of them some degree of anaemia and a reversal of the albumin-globulin ratio in the serum, while electrophoresis showed excess of alpha 2 globulin. In every case administrat-

ion of the drug caused an increase in the ESR and a fall in the red blood cell count and haemoglobin content of the blood after about 7-10 days. This was sometimes associated with transient eosinophilia of up to 10 per cent of 7,500 W.B.C. per cu. mm. In 2 cases at the time of the eosinophilia there developed slight transient painful lymphadenopathy and in 3 cases an itchy generalized erythematous rash lasting about a week. The ESR and blood count returned to normal in about 6 weeks. In 4-6 months the albumin-globulin ratio returned to normal and electrophoresis now showed no abnormality. The cases were followed up for 12 to 15 months and remained well. At the end of this time the RF and auto-antibodies had disappeared from the blood. In those cases tolerating it the drug thus completely reversed all the manifestations of activity in rheumatoid disease and its effects were so rapid in appearance as to resemble that of an antibiotic in cases of bacterial infection. Moreover, it was completely effective when all other antirheumatoid drugs, including cortico-steroids, had failed to control the disease. It appears to be the most potent antirheumatoid drug known.

Rheumatoid disease must be an infection with an organism which is killed or inhibited by clotrimazole, which has anti-protozoal properties, and the various auto-antibodies and RF in the serum are produced as a response to this infection, just as they are in cases of malaria, trypanosomiasis, kala-azar and leishmaniasis. Coupled with the effect of other anti-protozoal drugs of totally different chemical constitution

mentioned above, in abolishing evidence of activity in this disease this points to rheumatoid disease as being a protozoal infection and is ^{probably} curable by clotrimazole.

Slide 2. Case 1. Pitting oedema of the feet and attempted dorsiflexion of the ankle (above) and (below) 2 weeks after treatment with the drug. Note the disappearance of the oedema and ankle swelling and recovery of normal ankle movements.

Slide 3. Case 2. showing appearance of wrists and hands before (above) and (below) 10 days after beginning treatment. Note complete disappearance of joint swelling.

Slide 4. Case 3. showing swelling and an attempt at full flexion of the left knee before (above) and the appearance (below) 9 days after beginning treatment.

Slide 5. (a) Case 5. Attempting to make a fist with the right hand before (left) and (right) 2 weeks after beginning treatment with the drug. Note the disappearance of swelling of the hand and return of finger movements to normal.

Slide 5. (b) Case 5. Same case showing appearance of hands at corresponding times.

Slide 6. Case 6. Appearance of hands before (above) and (below) 2 weeks after treatment with the drug. Note disappearance of ~~e~~ oedema and joint swelling.

Slide 7. Case 9. Maximum attempt to make fists before (left) and (right) two weeks after treatment with the drug. Note the improvement in the joint mobility and disappearance of swelling of wrists and digits.

Slide 8. Case 10. Appearance of legs before (left) and (right) 2 weeks after treatment with the drug showing disappearance of oedema and joint swelling.

The reason for using the drug Clotrimazole was not a fluke or "an inspired guess", but the result of scientific deduction. In 1964 I described the isolation of a free-living amoeba from all the body tissues in cases of rheumatoid disease (see "A New Protozoon", 1964, C.C. Thomas, Springfield, Illinois). Since then the organism has been found to belong to the family, Naegleria. Early in 1964 in the "Lancet" this family of organisms were reported to be killed by Clotrimazole in vitro and this was the reason for trying the drug in rheumatoid disease. The result, therefore, was not totally unexpected.