A Preliminary Report of 2-Mercapto-3-Hydrazinoquinoxaline (MHQ) in the Treatment of Leprosy in Cambodia.

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Introduction

Historical review of chemotherapy in the treatment of leprosy reveals a gradual transfer from a purely empirical approach to a more rational one. A long and futile search for anti-leprosy agents has at last given rise to an extensive and systematic research method, which has, in turn, led to the discovery of the present standard drugs.¹⁻⁴⁾ These drugs have proved to be effective agents against clinical as well as experimental leprosy. But the problems such as the optimal regimen of administration of the drugs, the best and shortest duration of treatment, the optimal daily dosage, the side-effects of the drugs, the clinical significance of drug-resistance, the relapse of disease and the management of far advanced leprosy, still await further research for the successful and satisfactory solutions, which we have not attained yet.

In order to overcome these problems, studies in pursuit of newer, more powerful drugs (in any type), as well as those of more effective combination of chemotherapeutic agents have been incessantly launched.

Properties of MHQ

Dr. Kazuo Asano et al.⁷⁾ in 1957 synthesized MHQ from 2, 3-dimercaptoquinoxaline and hydrazine hydrate, which showed marked antibacterial activity, with only little toxicity. This compound was introduced in the chemotherapy of leprosy by Dr. Sadae Tsutsumi et al.⁶⁾

Appearance of MHQ: By the chemical reaction, it occurs as a yellowish needle from hot ethanol, m.p. 254°C (decomp.), and is soluble in hot ethanol, methanol, or propylene glycole but it is only slightly soluble in hot water. The chemical formula is as follows:

The MHQ-ointment is consisted of 1% W/W MHQ (α -form), 5% V/W Propylene glycol, and water soluble base. It is odourless and non-irritant.

Antibacterial action: The antibacterial spectrum of MHQ⁷⁾ is very broad as shown in Table 1, and it has not only bacteriostatic, but bactericidal action. It is notable that MHQ showed complete inhibition on the growth of *M. tuberculosis* in the concentration of 0.78 mcg./ml. in the serum Kirchner medium for four weeks.

Table I
Antibacterial action of MHQ

Strain	Minimum Inhibitory Concentration mcg./ml.	Minimum Bactericidal Concentration mcg./ml.
<i>M. tuberculosis</i> H37 Rv	0.78	
" 607	0.78	0.78
<i>E. coli</i>	1.56	1.56
<i>Pseud. aeruginosa</i>	12.5	25.0
<i>Sal. paratyphi</i> H ₉₀ IW	3.12	3.12
<i>Sal. dysenteriae</i> Siga	0.78	1.56
" Komagome A	0.39	0.78
" " B 111	0.78	1.56
<i>Vibrio comma</i> Inaba	0.78	1.56
<i>Staph. aureus</i>	3.12	6.25
<i>Staph. albus</i>	3.12	3.12
<i>Streptococci</i> J ₁₇ A ₄	0.78	0.78
<i>B. subtilis</i> Pcl 219	0.78	0.78
<i>C. albicans</i>	6.25	6.25
<i>Asp. niger</i>	6.25	6.25

Toxicity : Behren-Körper's test of acute toxicity showed as described follows : Mouse, per os, LD₅₀ 240 mg./kg. (base) ; Mouse, intravenously, LD₅₀ 155 mg./kg. (hydrochloride).

Clinical Results

Following the very encouraging reports by the Japanese clinicians who indicated that this drug was very effective with no side-effects on the important internal organs such as kidney, liver, and haematopoietic organs, a trial of the ointment alone in Cambodian patients was started and continued for six months trial at the Troeung National Leprosarium. This program was conducted through the courtesy of the Cambodian Government starting on October 12, 1966, when the author was sent to Cambodia under the Colombo-plan. Each of the patients chosen for trial had a long history of the disease and had received the standard drugs before the applications of this ointment. The preparation was rubbed in the skin, five days a week, in 5 to 10 gm. doses each time. Five to six hours after the inunction, it was washed out.

The following ten case reports serve to show the effectiveness of the new preparation.

Case 1. An 8-year-old child had a 7 year history of the disease at the beginning of which whitish infiltrated macules appeared in the left cheek and right popliteal fossa. The

treatment of Disulone (antileprosy specificum made in France) showed no regression of the lesions; because Disulone was ineffective there was question as to whether the child was born of parents who had been both leprosy. A marked improvement was observed in about one week after the application. And the macules disappeared about two weeks after the treatment.

Case 2. A 27-year-old male had a 17 year history of the disease at the beginning of which he had an anesthesia in the posterior part of the right thigh. Lepromas appeared on the face, trunk and four extremities. Prior to the treatment by MHQ, lepromas could be found on the face, back, hips and four extremities. There was swelling of the face. A half month after the treatment, the swelling was reduced, the lepromas became soft and smaller in size, the nodules became flat, and by the end of the trial, they disappeared.

Case 3. A 28-year-old female had a 12 year history of the disease at the beginning of which she had red flecks on the abdomen. After two years, an expansion of the red flecks occurred. She received Chinese drugs at home, but the lesions became worse. At the onset of treatment, she had lepromas on the face, ears, thighs and nodules on the face, trunk, hips and four extremities. One month after the treatment, swelling of the face and hyperpigmentation were improved to normal, and the lepromas and nodules were beginning to become soft. By the end of the trial, they disappeared.

Case 4. A 30-year-old male had a 30 year history of the disease. At the beginning, he had an anesthesia in the exterior part of the right foot. After two years, reddish flecks appeared on the face, ears, trunk abdomen, back and four extremities. At the onset of treatment, he had lepromas on the face, ears, trunk, abdomen, back and four extremities. Two months after the treatment, the lepromas and nodules were gradually reduced. By the end of the trial, the lepromas and nodules disappeared. The nodules of the feet were gradually resolved to become flat in 3 to 4 months, merely leaving dark brown pigmented spots at these resolved nodular parts, and the pigmented spots were improved to normal.

Case 5. A 35-year-old male had a 17 year history of the disease at the beginning of which lepromas appeared on the back, face and four extremities. For five years after the appearance of the disease, he began to have home-treatment by eating grains in the fruits of a tree called "Krabao" (Cambodian name which is probably equivalent to *Hydnocarpus Kurzii*), resulting in the regression and disappearance of the lepromas. Twelve years after the interruption of the home-treatment with the grains of the "Krabao", lepromas and nodules reappeared in the same parts. At the onset of the topical treatment, the lepromas and nodules could be found in the same parts. One week after the inunction, there was regression of the lesions and in two months they completely disappeared.

Case 6. A 35-year-old male whose disease began with the right plantar ulcer at the age of 5 years. After six months, reddish spots occurred on the face, abdomen, hips, thighs and four extremities. At the commencement of MHQ drug treatment, she suffered from lepromas on the face, papules and nodules on the abdomen, two forearms, hips and

thighs and the right plantar perforative ulcer. One and half months after the application of the ointment, the lesions were almost improved.

Case 7. A 42-year-old male whose disease began with an ulceration in the anterior part of the ankle of the left foot at the age of about four years. After one year, paresthesia and reddish flecks appeared on the two forearms. At the commencement of treatment, there were lepromas on the face, right ear, hips and four extremities with right plantar ulcer, and papules on the arms, back and feet. Three months after the external use of the ointment, swellings became normal, the lepromas became soft and they disappeared by the end of the trial.

Case 8. A 59-year-old female whose disease began with red flecks on the chin at the age of 6 years. After one year, reddish flecks appeared on the back and four extremities. At the time of the inunction, she had lepromas on the face, ears, back, hips and four extremities. Two months after the external use of this drug, the lesions were reduced, complete regression or disappearance taking place by the end of the trial.

Case 9. A 17-year-old female whose disease began with reddish flecks on the ears at the age of about 7 years. After two years, infiltrated macules appeared on the face, trunk, four extremities and all over the back. At the onset of treatment, she had lepromas on the ears, waist and abdomen; macules and nodules on the forearms, which were edematous. One week after application of the ointment, she had a high fever the cause of which was unknown. The inunction was stopped for a while, and then the perfriktion was continued until end of the trial. Almost all the leprous symptoms disappeared.

Case 10. A 23-year-old female whose disease began with leproms on the face, back and four extremities at the age of 20 years. She took grains of the "Krabao" at home but the result was unsuccessful. At the onset of inunction, she had lepromas on the cheeks, ears, forearms and fingers, nodules on the feet. At the beginning of treatment, a lepra reaction took place and the inunction was stopped. Then, in several days, she was found to be free of the side-effect. She declined to take the drug any more.

Discussion

A total of ten cases were treated with this drug, one case being of tuberculoid type and the others being of lepromatous type. Although only a small number of patients were treated, the disappearance of infiltration, redness, pigmented spots and swellings could be observed in a relatively short time. The nodules disappeared rapidly after the application of the ointment, smaller nodules became flat in 1 to 2 months and larger ones gradually subsided to become flat in 3 to 4 months, and finally lepromas disappeared by the end of the trial. The application of the ointment, in nearly all cases, was carried out for six months without dermatitis. In Japan, dermatitis occurred frequently at a rate of 70 to 80% with the treatment of diethyl-dithiol-isophthalate (Etisul)⁵⁾. Japanese doctors, in their experience of the ointment-treatment,^{8,9)} reported the MHQ ointment was also effective against drug-resistant and relapsed diseases.

This trial work in Cambodia lacks microscopic examination of the skin smears. But in Japan,⁶⁾ in the treatment of leprosy patients, it is well known to be the fact that, even though no remarkable changes can be found in bacillary index, leprosy bacilli are often, disintegrated or fragmented, and further, some of granular type appeared, in process of the chemotherapy with some of the stopical drug.

Conclusion

The ointment of a derivate of mercaptan, 2-mercapto-3-hydrazinoquinoxaline was used for external inunction and was proved to be very effective against leprosy. It has no undesirable property such as odour and did not cause any incidence of dermatitis during the course of the trial. Further investigations are necessary to determine whether this drug can be applied as a long-term chemotherapeutic agent, but it is notable that a new and different type of antileprosy drug has now been added in the field of leprosy treatment.

Résumé

Voici une présentation de dix cas de lèpre au Cambodge traités avec les excellents résultats, par la pommade de MHQ synthétisée au Japon. Il faut beaucoup plus d'investigations afin qu'on puisse utiliser cette drogue longtemps, mais il est remarquable qu'un médicament du nouveau type a été ajouté dans le traitement de la lèpre.

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MHQ のカンボジアらい患者への治療略報

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らいに関する薬物療法の歴史を通覧するに、経験的方法論より次第に理論的アプローチを通じて、より科学的方法論をもって、その道の変遷をたどっている。かかる努力が近代の光輝かしい標準的な薬物治療の発見を促し、らい治療の分野に相当の見るべき治療効果をあげつつある。しかし一面、薬物の副作用、最適量、薬剤耐性の臨床的意義、重度難治らいの諸問題などは、いまだ十分に解決されたとは言いがたい。これらの諸問題を解決するため、薬物のよりよい併用療法の研究はもちろんであるが、さらに強力な新薬の発見に不断の努力がなされている。

1957年日本の浅野らにより新しく合成され堤らによりらい化学療法に導入された MHQ は該新物質の化学的性状、生物学的毒性試験、抗菌スペクトルらにおいて、優れた特性を有し、ことに抗酸菌中、結核菌に対しては、低濃度において完全にその発育を阻止すると報告されている。それだけに、これを軟膏として外用使用することにより、らいが皮膚に好発するだけその効果が速効直達的であるであろうことが想像される。

著者は、日本におけるらい臨床医の数種の治療効果の報告を総合して、相当の効果を期待できうと思われ、かつこれらの報告に勇気づけられたので、著者が日本国厚生省より、コロンボ計画に基づき、医療協力のためカ

ンボジア国に1カ年半にわたり派遣されたのを機会にして、同国唯一の国立らい療養所において、MHQ 軟膏の単独療法を6カ月間試みた。

臨床実験に選ばれた患者は10名で1名はT型(case 1)で、他はすべてL型患者であり、全例この疾病に関して長い病歴を有し、過去において、ズルホン剤を投与されていた者ばかりであったが、1例(case 10)を除き、実験終了後、特に認むべき副作用もなく、好成績をあげることが出来た。

籲って、Etisul は、いむべき悪臭があり、これを日本のらい患者に使用した場合、70~80%の皮膚炎を惹起する難点があったが、MHQ にいたっては、かかる好ましくない臭気もなく、ほとんど全例においてかかる副作用はなく、患者らは常夏の国で裸体に近く、外用薬とし、衣服を汚染することも少なく、患者達は MHQ は、優れた薬剤だと言っていた。

本実験においては、例症が少なく、これが長期間、治らい剤としての資格を獲得するには、さらに例症を積みかさねる必要があるものの、らい治療外用薬として、らい治療界に新しいしかも従来よりも病巣に対し、直達的にも効果をおよぼすという形の変った薬剤を追加したことは注目に値する。