only a small proportion of the total attendance for that disease, but these records, mostly of Ganda patients, were chosen for their relative completeness. In 173 of these 190 cases (all young adult males) the serum Kahn was positive or spirochaetes were found. In 7 the serum Kahn was negative. Penile sores were present in 60 cases; 41 admitted and 6 denied having had any penile lesions. Among these 190 cases the following frequency of lesions was recorded: condylomata, 91; "secondary rashes," 21; macules, 20; papules, 14; maculo-papules, 9; circinate lesions on scrotum, 8; buccal mucous membrane lesions, 8; papulo-squamous, 3; squamous, 2; circinate, 2. The condylomata were described as scrotal, perineal, and anal. No mention was made of any framboesiform lesions. At Lira the atypical secondary yaws lesions, and genital lesions, in the absence of typical lesions were infrequent. Loewenthal (1939) reported syphilitic aortitis and aneurysm, meningo-vascular lesions, choroiditis, and gummatous iritis in patients at Mulago, but stated that visceral gummata were rare. Such lesions were not seen among the Lango.

Serological Surveys

Sera collected in January, 1939, from 100 consecutive male Lango prisoners, aged 18 to 35 years, in the Erute (Lira) Gaol gave the following Kahn reactions: + + + +, 46; + + +, 21; + +, 14; +, 2; ±, 7; and -, 10. If reactions of +, ±, and - are regarded as negative, then 81 were positive. The ages of these subjects were: 18-20 years, 32; 21-25, 36; 26-30, 23; 31-35, 9. Other findings in this group and in 130 station labourers are given in Table VI.

TABLE VI.—Clinical Findings in Two Groups of Adult Lango Males at Lira

	100 Prisoners	130 Station Labourers
	%	%
History of having had yaws ..	94	90
Scars of previous secondary yaws ..	78	79
Enlarged epitrochlear glands ..	72	69
Bone changes	68	62
Palmar changes	51	60
Plantar changes	61	73
Bone pain	49	41

One case each of dorsal ganglion of the wrist, Dupuytren-like contractures of the fingers, and aortic systolic murmur was seen among prisoners under 30 years of age; the sera from these were Kahn + + + +. Among the labourers were 4 cases with ganglion and 12 with Dupuytren-like contractures. Bone changes consisted mainly of bowing, thickening, or irregularity of tibiae. Palmar and plantar changes comprised thickening, localized or generalized erosion, fissuring, pitting, and laminar desquamation.

Among the prisoners no statistical association was found between any of the items in Table VI and the reaction of the serum Kahn. The six prisoners who denied having had yaws were under 25 years of age; the serum from two was Kahn + + + +, from another two it was Kahn + + +, and from the remaining two Kahn -. The last two subjects were 20 years of age, both complained of bone pain, one had enlarged epitrochlear glands, and the other had indefinite minor plantar changes. Of 120 male Lango prisoners in the Erute (Lira) Gaol, in October, 1938, 8 denied having had yaws. Their ages ranged from 17 to 33. Sera from four were Wassermann + + + + and Kahn + + + +, those from the remaining four were Wassermann -; from one of these it was Kahn +, from another Kahn ±, and from the remaining two Kahn -.

Summary and Conclusions

In 1931 a survey showed that 3.9% of 24,249 children under 15 years of age were suffering from secondary yaws.

At Lira, in a "yaws area," yaws was a frequently diagnosed disease (20% of 14,707) and was 19 times as frequent as syphilis. At Masaka, in a "syphilis area," syphilis was a frequently diagnosed disease (17% of 16,207) and was 11 times as frequent as yaws. At each locality coughs, colds, and traumatic lesions were the most frequent diagnoses. Malaria was probably of nearly universal incidence in both localities. At Lira females were proportionately more numerous among the yaws cases than among the total attendances. A quarter of the yaws cases were under 10 years of age. There

was a smaller proportionate excess of females among the syphilis cases at Masaka as compared with the total attendances. Syphilis cases at Masaka were older compared with the age distribution of the other attendances.

In 1939, 81 of 100 consecutive male Lango prisoners, aged 18-35, had positive Kahn reactions. Of the six of this series who denied having had yaws, only two had completely negative Kahn and Wassermann reactions in their sera.

It may be concluded that the incidence of yaws in Lango was high, and that probably very few adults died without having contracted the disease. On the other hand, in Lango the incidence of venereal disease was very low.

The material for this paper was obtained during 1937-40 while holding a Senior Fellowship in Tropical Medicine of the Medical Research Council. I am indebted for much help received to Dr. W. H. Kauntze, then D.M.S., Uganda, and his medical officers. All serological tests were carried out by the staff of the pathological laboratory at Mulago Hospital. Dr. W. J. Martin, of the Statistical Department of the Medical Research Council, has kindly carried out the statistical analyses.

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EFFECT OF ORGANIC MERCURIAL PREPARATIONS ON DISEASES OF THE SKIN

BY

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A preliminary report on organo-mercurial treatment of the dermatomycoses and of infected skin lesions, including "jungle sores," was published in the *Indian Medical Gazette* in August, 1944 (Byrne and Croxon). This present report is an amplification, and is based on the treatment of 500 cases of skin lesions in the Tropics with organo-mercurial compounds. Three preparations were used—phenyl mercuric chloride, acetate, and benzoate; they will be referred to subsequently as P.M.C., P.M.A., and P.M.B.

The toxic action of mercury on bacteria depends on the free concentration of Hg ions in solution (Paul and Prall, 1907), and it has been shown that the Hg cation is the most effective of the heavy metal cations (Woodruff and Bunzel, 1909; Winslow and Hotchkiss, 1922); but though the inorganic salts of mercury have a powerful action *in vitro* their bactericidal effect is greatly diminished *in vivo*, especially in the presence of organic matter. Chick and Martin (1908) consider that this is due to the fact that the Hg cation combines with protein to form an insoluble albuminate, hence the concentration of free ions is greatly diminished. The same workers reported that the addition of 3% of faeces to a solution reduced the activity of mercuric chloride by 90%. The activity of certain organo-mercurials under these conditions is reduced only by 20-25%, for it appears that the formation of an insoluble albuminate does not obtain to any marked degree with drugs of this group. It therefore follows that in the presence of organic protein matter the organo-mercurials possess a far greater bactericidal effect than do the inorganic salts of mercury.

An exceptional toxicity towards all forms of life is exhibited by those compounds of mercury which structurally are the most simple, and this lethal action is markedly selective in highly organized animals: the effect is determined largely by the character of the hydrocarbon radicle—aromatic or aliphatic—associated with the mercury atom, aliphatic compounds being particularly virulent. On the other hand, aromatic derivatives have a relatively low local and systemic toxicity, and, provided the hydrocarbon is an unsubstituted phenyl radicle (C₆H₅), a very high bactericidal potency.

It is important to record in connexion with specific action that the aliphatic organo-mercurials exemplified by mercury dimethyl and diethyl—(CH₃)₂Hg and (C₂H₅)₂Hg—and derivatives thereof, such as the chloride (CH₃HgCl) and nitrate (CH₃HgNO₃), have a specific effect on the C.N.S., causing rapid degenerative lesions in cerebral and cerebellar areas. These compounds are most interesting in human toxicology,

in view of the long latent period between their application or ingestion and the development of signs and symptoms in the C.N.S. This characteristic has received much attention in industrial medicine, as the pathological symptoms differ from those associated with ordinary mercurialism (Hunter *et al.*, 1940; Hill, 1943).

Preference for P.M.C.

The aromatic aryl compounds (phenyl mercuric chloride, nitrate, borate, acetate, benzoate, and picrate) have been investigated chiefly in the United States, but Biskind (1935) has given a detailed account concerning them in the English literature. Certain of the above-mentioned compounds find extensive application in horticulture and agriculture for the control of fungous disease of plants, and the fungicidal action of P.M.C. was investigated by Shaw and Montgomery (1941; Shaw and Moore, 1944). They showed that this substance is one of the most powerful fungicides known, and acts rapidly and effectively in high dilution, destroying both spores and vegetative forms.

For medical purposes the bactericidal and bacteriostatic action of P.M.C. was first investigated by Weed and Ecker in 1933. These workers found that the concentration necessary to inhibit the growth of *Str. haemolyticus* and *Staph. aureus* was of the nature of one part in several millions. This effect is due to the C_6H_5Hg ion, and though the solubility of P.M.C. is very low this does not detract from its effectiveness. The lethal effect is due to the action of mercury in combining with and blocking essential thiol groups in the cytoplasm of the infecting fungi or bacteria. The gross disturbance of metabolic function so caused leads to the rapid death of the infecting agents.

P.M.A. and P.M.B. have a marked affinity for chlorine; as NaCl is an invariable constituent of tissue fluid it was felt that the change to P.M.C. would be a rapid one, and that the direct application of this ultimate chemical product should be made whenever possible (FitzGibbon, personal communication). This report therefore deals mainly with the action of phenyl mercuric chloride.

As in all bactericides, the reaction velocity of P.M.C. depends on its concentration in the area in which it is to exert its action, but owing to its tendency to produce a vesicant effect on tissue or skin (although strikingly less than other compounds in the series) the concentration used must be carefully limited. In practice it has been found that 0.25% P.M.C. or P.M.A. represents the maximum concentration which can be used without producing these effects. Applications of a much lower strength were used in the majority of cases treated. A strength of 0.5% P.M.C. precipitated on a calamine filler was used in the preparation of an adhesive lotion for moist skin lesions; but the physicochemical mechanisms obtaining when the drug is presented in this way are entirely different from those which occur when emulsifying or aqueous vehicles are used. The use of a colloidal solution was considered, but the grave disadvantage of this method is that in using colloidal solutions of a drug the activity of which is an ionic property the protective colloid removes the charge from the active cation, and hence nullifies its effect.

Preparation for Use

In order to deal with the varying types of skin lesions requiring treatment it was decided to present P.M.C. and P.M.A. in three types of base: (1) in "eucerin" and distilled water; (2) in an adhesive lotion of the lotio calaminae type; (3) in simple solution in distilled water. As P.M.A. is soluble in hot distilled water up to a concentration of 2.5% the ointment is made by dissolving the drug in distilled water at a temperature of 85° C. This solution while still warm is slowly added to the "eucerin," previously melted and kept at a temperature not exceeding 55° C. The mixture is continuously stirred until cool, when a white homogeneous cream is produced which is absorbed by the skin with the minimum of friction. In the earlier cases treated a strength of 0.2% was used, but it was later found that 0.125% ointment gave equally good results, and this was employed in the majority of cases.

As the solubility of P.M.C. in water is only 1/20,000, the most efficient method is to incorporate the drug in the melted

"eucerin" at 55° C., using careful trituration, and keeping the contents of the mortar heated to 55° C. by means of a water bath. It is essential that the P.M.C. be as evenly dispersed as possible in the melted "eucerin" before adding the distilled water (heated to 85° C.) in small quantities, with rapid stirring. The whole is now allowed to cool rapidly, stirring until a white homogeneous cream is obtained. In the preparation of large quantities the use of a homogenizer would be a great advantage.

For moist surface lesions an adhesive lotion was prepared, designed to fulfil the following requirements: (a) Sufficient concentration of P.M.C. to exert the maximum fungicidal and bactericidal effect; (b) contact with the affected area for a prolonged period, in spite of excessive perspiration or moistness of the skin; (c) ease of application. It was found that the P.M.C.-calamine preparation was much more "dense" than calamine B.P. and required a large amount of zinc oxide and glycerin to maintain an even suspension when shaken and sufficient adhesiveness when applied to the infected area. The following lotion was found to be the most satisfactory:

P.M.C. 0.5% precipitated on calamine	gr. 15 (1 g.)
Zinc oxide	gr. 30 (2 g.)
Glycerin	ml 30 (1.8 ml.)
Distilled water	to 1 oz. (28.4 ml.)

For large infected areas of deep-seated origin and for "jungle sores" application of a solution of P.M.A. had the desired effect. A concentration of 1/8,000 was found to be the most efficient. Solution is effected by heating up 2 g. of P.M.A. in 250 ml. of hot distilled water, and pouring the almost boiling solution into 750 ml. of cold distilled water. This stock solution can be regarded as 0.2% w/w or w/v for all practical purposes. The desired strength of solution may then be obtained by further dilution with distilled water. The concentrated solution is self-sterilizing.

Method of Application

At the beginning of the investigation cases were treated as out-patients, attending twice daily for inunction. Though results were very satisfactory, it was found that this method was wasteful in the use of the limited amount of ointment available at the time. As the reaction velocity of P.M.C. depends on the concentration applied and the duration of application, it was obvious that a great saving in the amount of ointment used would be effected by applying it on lint and bandaging it on to the affected part for a fixed period. Investigation showed that three to four hours' application of 0.125% strength was sufficient to overcome the infection in all cases of tinea cruris, corporis, and capitis. The affected areas were slightly red and itching for about 24 hours after the treatment; at the end of this time the lesion began to fade out, and in five to six days the skin became normal in appearance, though some slight desquamation usually occurred. In a few resistant cases a second application (of 0.2% strength) was used for three hours.

The types of mycotic infection seen varied enormously, presumably due to the nature of the infecting fungi and the skin reaction of the patient. Dry superficial circinate lesions of large extent and rapid spread alternated with those producing agminate folliculitis, and maculo-papular lesions of both guttate and punctate varieties were found. Epidermophyton infections affecting the groins, palms, and soles were extremely common, as the warm humid climate of S.E. Bengal and the Arakan areas kept the skin continually moist, providing optimum conditions for the growth of fungi.

For all lesions which were reasonably dry a three- to four-hours application of P.M.C. ointment on lint was used. At the end of this time the excess of ointment was wiped off. Where the lesions were moist, application of the ointment was followed by the P.M.C.-calamine lotion. In two to three days the infection was controlled, and rapid healing ensued.

Treatment of Various Infections

The following is a classification of the diseases treated by organic mercurial compounds:

Ringworm of trunk and limbs	200
Epidermophyton inguinale	110
Epidermophytosis of feet	90
"Jungle sores"	50
Infected wounds of various types	50

Epidermophytosis of Feet.—The interdigital spaces were thoroughly cleaned, and all dead skin removed; 0.5% P.M.C.—calamine powder was applied if the affected area was very moist, and when drying had occurred 0.125% ointment was applied twice daily.

Epidermophyton Inguinale (Dhobi Itch).—A single application of ointment was used for four hours' contact. After thorough inunction into the affected area, paying special attention to the infected spreading edge, strips of lint coated with the ointment were applied to the lesion, and fixed in position with pads of cotton-wool and a double T-bandage. The skin became normal in five to six days.

Regarding epidermophyton infection of the toes, recurrences are mainly due to (1) fresh infection from an outside source; (2) reinfection from the patient's own socks or footwear. To overcome the latter, socks should be steeped for an hour in 1/20,000 P.M.A. solution before washing; the boots or shoes can be treated by spraying the interior with a 1/2,000 alcoholic solution of P.M.A.

Jungle Sores.—In forward areas and where the sores were small or of recent origin, compresses of 1/8,000 P.M.A. were applied for 24 hours. This brought about complete disinfection of the sore. Elastoplast was then applied, after painting the surrounding skin with the solution, and very good results were obtained. In base areas, where large chronic sores were seen, the following technique was adopted. (1) Disinfection with 1/8,000 compress of P.M.A. for 24 hours; (2) normal saline compress for a further 24 hours; (3) skin-grafting on the third day. In some of the early cases the grafts did not take well, and it was considered that excess of the C_6H_5Hg ion was the inhibiting factor. The saline lavage and compress for 24 hours did away with this side-effect. It is suggested (Fitz-Gibbon) that a rapid lavage with a 1% thiourea solution would produce the same effect, as the —SH group in thiourea would neutralize any excess of the compound ion.

Toxic Effects

No cases of sensitivity to organo-mercurials were encountered. In some patients, especially those of fair or auburn colouring, slight and temporary vesication occurred, mainly around the spreading edges of the skin lesions. This disappeared in 24 to 48 hours, leaving a clean healthy skin beneath. There appears to be no possible danger of toxic effects due to absorption through the skin. The work of the U.S. External Products Research Institute has shown that the body can deal with daily several thousand gamma of Hg in the form of a soluble mercurial, and that the human skin absorbs only 1/3,800 of that applied to it (*American Perfumer and Essential Oil Review*, 1943; Stock, 1938). No dangerous mercury reservoirs are formed, as in the case of lead. Ten grammes of 0.125% P.M.C. contains about 6,000 gamma of Hg, and the amount absorbed is minute. In this connexion it is interesting to note that all U.S. reconstituted plasma contains 12.5 mg. of phenyl mercuric borate to each 250 ml. unit; this is equivalent to about 8,000 gamma of Hg. No toxic effects have been reported in cases which have had large plasma transfusions, in spite of the considerable intake of organic mercury.

Summary and Conclusions

A report is presented of the successful treatment of 500 cases of skin disease by organic mercurials.

It is pointed out that phenyl mercuric compounds in plant mycology are recognized as possessing specific and rapid fungicidal effects in high dilution, and that similar effects can be obtained in fungus infections in man.

The bactericidal potency of these compounds is extraordinarily high, and as surface antiseptics they were found to be extremely satisfactory.

The method of preparation is described, with the results of treatment in certain infections.

It must be emphasized that the method of application and duration thereof must be strictly adhered to in order to effect rapid cure.

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Medical Memoranda

Lethane 384 on Clothing as a Mosquito Repellent

In 1942 during field tests with various antimosquito repellents a few tests were carried out with "lethane 384." They were only preliminary tests and were never followed up, but they showed that lethane 384 applied locally to clothing—for example, stockings—may have its uses as a mosquito repellent in civil life when dimethyl phthalate either is not procurable or its use is undesirable because of its solvent properties on plastics, paint, etc. Lethane 384 is of course unsuitable as a skin application on account of its irritant and toxic properties.

METHOD

All tests were made in a wood at Brookwood, Surrey, during August, 1942. The mosquitoes biting were mainly *Aedes cantans*, *Ae. punctor*, *Ae. annulipes*, with an occasional *Ae. cinereus*, *Ae. geniculatus*, and *Anopheles claviger*. Treated volunteers and untreated controls sat together in the wood, usually for 15 minutes, and counted the number of bites experienced. Controls and treated men sat a few feet apart. There were two sets of experiments.

Test 1.—Men wore thin cotton stockings (A.T.S. issue), which were sprayed with 50% lethane 384 (25% actual; solvent; a light oil; spray base 775) from a hand-spray held at a distance of 1 ft. (30 cm.). Six pumps were given to the front and six to the back of the legs of each man—23 ml. was used to spray four men. The men then rolled up their socks over the stockings at the ankles, pulled down the trouser legs of the battle dress and waited, strolling about, till the testing times. At the test, the trouser legs were rolled up above the knees and the socks turned over below the ankles, and the men sat on the bank of a dry ditch, together with controls (stockings untreated), and counted the mosquitoes which bit the legs from knee to ankle. The hands and face were covered with gloves and veils.

Test 2.—Men wore denim overalls, which were sprayed thoroughly all over so that the overalls could be seen to be wetted. The spray was held at a distance of about 18 in. (45 cm.). The mean dosage was not less than that delivered on the legs in the first test. In this test the sleeves were rolled up to above the elbow and the number of bites on hands and forearms were recorded. The exposed parts were in no way treated.

RESULTS

Table I summarizes the results for sprayed stockings. The figures in brackets show the number of men in each group.

TABLE I

Time after Spraying (hours)	Period of Test (mins.)	No. of Bites		Biting Rate (No. of bites in control = 100%)		% Protection
		Treated	Control	Treated	Control	Treated
1 -1½	15	3 (4)	6 (4)	50 } 11.7	100	} 88.3
1½ -1	15	1 (4)	28 (4)		3.6	
4 -4½	15	1 (4)	35 (4)	2.9 } 22	100	} 97.1
5 -5½	15	6 (4)	22 (4)		27.3	
5½ -5	15	3 (4)	19 (4)	15.8	100	} 78
Total ..		14 (20)	110 (20)	12.7	100	87.3
Stockings removed : rolled up and put on again next morning :						
24	15	24 (3)	23 (3)	104.3	100	Nil

No. of bites per man :

Mean .. 0.70 5.50
S.E. of mean .. 0.2012 0.7159
Difference of means is statistically significant.