In Table I are set out the influenza admission rates in the uninoculated and in the various vaccine groups. Those inoculated in 1954 only had significantly less influenza than the uninoculated $\left\{ \frac{\text{Difference}}{\text{Standard error}} = \frac{8}{3.7} = 2.2 \right\}$, and those inoculated in 1955 or in both years fared even better. Though the figures are small they suggest that those inoculated twice gained more protection than those inoculated in 1955 only. The virological results supported the clinical findings, all 44 strains being isolated from boys either uninoculated (40) or inoculated in 1954 only (4).

In Table II are shown the admission rates from causes other than influenza and surgery attendance rates of illnesses not requiring admission in the same groups of boys as in

TABLE II.—*Sickness Experience From Causes Other than Influenza*

	Admission Rate		Surgery Attendance Rate	
	Other Respiratory Illness	Non-respiratory Illness	Re-spiratory Illness	Non-respiratory Illness
Uninoculated ..	6%	4%	11%	34%
Inoculated 1954 only ..	3%	10%	9%	35%
" 1955 ..	4%	10%	10%	50%
" 1954 and 1955	7%	6%	7%	35%

Table I. The figures for all four groups are fairly similar apart from a high rate for non-respiratory illness attendance in those inoculated in 1955 only. The reason for this high rate is not known, but there is no evidence that it was related to vaccination. There is nothing in Table II to suggest that the lack of influenza in the inoculated was due to cases being diagnosed as something else.

Summary and Conclusions

An outbreak of influenza A occurred in Wellington College in February, 1956. Of the 664 boys present, 120 had been inoculated in December, 1954, with a vaccine containing influenza virus A and B strains, 100 had been inoculated in November, 1955, with a vaccine containing the A/Eng/19/55 strain, and a further 100 had been inoculated on both occasions. The admission rate to the sanatorium with influenza in these three groups was 12%, 8%, and 2% respectively, compared with 20% in the 344 boys who had not been inoculated. Throat swabs were taken from 73 of the 92 patients with clinical influenza, and influenza virus A was isolated from 44 of them. Forty of the strains were from uninoculated boys and the remaining four from boys inoculated in 1954 only. No strains of virus were isolated from boys who had received the 1955 vaccine.

Though the investigation did not constitute a controlled trial reasons are given for believing that the above rates are comparable.

It is concluded that some protection still remained from the 1954 inoculations and that a high degree of protection was obtained from the 1955 inoculations, particularly in boys who had also been inoculated a year earlier. The virus A strains isolated during the epidemic resembled the strains (A/Eng/1/54 and A/Missouri/303/52) used in the 1954 vaccine, but differed from the strain (A/Eng/19/55) used in the 1955 vaccine.

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MERCURY ABSORPTION AND PSORIASIS

BY

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Mercury compounds in ointments and pastes have been used for many years in skin diseases. Mercury ointments are still widely used in the treatment of psoriasis, and such applications often contain varying proportions of salicylic acid and tar. Absorption of mercury through the skin is known to occur, but is not commonly stressed in textbooks. Thus Goldsmith and Hellier (1954) state that "mercurials . . . are especially easily absorbed." They state that the literature is "very confused" and distinguish between "penetration" and "absorption."

Toxicity due to mercury absorption in the treatment of psoriasis must be rare, and has not been recognized in this clinic. Psoriasis is uncommon before the age of 4 years. This investigation resulted from the appearance of a child of 2 years with widespread psoriasis. As mercury is the probable cause of most cases of pink disease, the question arose of how much was absorbed. With ordinary applications it was important to obtain this information, since the local action of mercury in the treatment of psoriasis is imperfectly understood—in contrast to that of dithranol, tar, and ultra-violet light, which probably involve a process of oxidation or burning of the lesion.

That poisoning can occur from external use of mercury is well known. Not so long ago it was considered necessary in the treatment of syphilis to produce by mercury inunction gingivitis, loosening of the teeth, and excessive salivation. Such inunctions were performed with friction on areas where the skin was thin, the anterior forearm being a favourite site. However, applying mercury compounds to diseased skin without friction is a different matter. It might be expected that mercury would be more easily absorbed through damaged skin, as in eczematous or ecthymatous lesions, than through intact skin. In psoriasis, absorption might yet be different for two opposing reasons. On the one hand, thick psoriatic scaling could be expected to retard absorption of ointment. On the other hand, the histology of psoriasis shows the skin papillae to be greatly thinned and elongated. So there is only a much-thinned epidermis between the summit of any individual papilla and the horny layer; this explains why grattage of a psoriatic plaque causes small bleeding-points—due to damage to the superficially placed papillary loops. This feature of the psoriatic structure might well facilitate absorption of ointment.

Literature

Some findings of the more important recent papers on cutaneous absorption of mercury in humans not suffering from psoriasis, and in experimental animals, are summarized below.

Wild and Roberts (1926), studying mercury absorption from different ointment bases after massage into an area of skin of 20 sq. in. (139 square cm.), found that it was greatest from a lard base, and was much less from both hydrous wool fat and paraffin bases. Mercuric oxide was the most readily absorbed compound, calomel the least. The amount of mercurial absorbed was proportional to the amount of mercurial in the ointment.

Cole *et al.* (1930) studied mercury excretion in syphilitics. Their figures are difficult to understand, but they found that the total excretion was 25% greater with simple inunction than with "clean inunction," in which after the massage the excess of mercury ointment was cleaned off by benzene. They noted that "after discontinuance of the administrations the excretion continued high for a considerable time" (p. 374). They also found absorption and excretion of mercury after inunction to be directly dependent on the concentration of the metal in the base (p. 391). They cite the microscopical study of Zwick (1924), who had shown that mercury was absorbed via the hair follicles and sweat duct openings.

Gibbs *et al.* (1941) applied, with a flat steel spatula without undue rubbing, ammoniated mercury ointment to the flexor surface of the forearms of 17 medical students daily for four weeks, excluding Sundays—to 11 of them a 10% ointment and to 6 a 2%. As a result of measuring the mercury content of the urine and faeces they conclude "with reasonable certainty that the unbroken human skin does not permit the absorption of ammoniated mercury at all readily" (p. 867), and that (p. 872) "the application, even continued, of such ointments to the unbroken skin is not likely to cause general poisoning, providing oral ingestion is strictly prevented." This conclusion applies to the 2% and 10% strengths of ammoniated mercury ointment, but the bases used are not mentioned.

Robert (1946) applied 10 g. of 10% hydrarg. ammon. ointment daily to the intact and ulcerated skin of nine patients, but the base does not seem to have been regarded as of importance. Like Cole *et al.*, he found that increased urinary mercury excretion lasted for several months after the application of the ointment. No clinical poisoning was seen, and, curiously, no difference was found in the absorption through intact skin (three patients) as compared with ulcerated wound surfaces (six patients). From torpid chronic ulcers mercury absorption seemed to be less than from the intact skin of the thigh. He felt that mercury poisoning was possible with the use of greater quantities of ointment over a longer period.

Laug *et al.* (1947a), studying mercury absorption from the clipped backs of rabbits and rats, observed that the mercury contents of exsanguinated rats' and rabbits' kidneys gave a true index of the cutaneous penetrative ability of different compounds. Their finding that removal of excess ointment from the skin, "clean inunction," reduced the amount of penetration agrees with the findings of Cole *et al.* quoted above. An important observation was that covering the inunction site increased penetration nearly fourfold; this result is especially significant in view of the mercury absorption findings in psoriatics reported below.

In a second paper Laug *et al.* (1947b), using the same techniques, studied the absorption of 30% calomel from different ointment bases, and found the vehicle to be the most important factor in the absorption of mercury through the skin. To this extent, their observations support the earlier clinical findings of Wild and Roberts (1926). The vehicles most often incorporated in ointment—namely, petrolatum, mineral oil, and lanolin—were found to be the poorest media for the absorption of mercury in their animals—whereas oleic acid and propylene glycol allowed the greatest penetration. In contrast to the findings of Cole *et al.* and of Wild and Roberts, they found cutaneous penetration little affected by the concentration of mercury in the ointment, but they believed this discrepancy was because their animals survived only twenty-four hours after inunc-

tion, whereas the human assay method employed by other workers extended over many weeks.

So far the consideration of absorption from the skin has been confined to mercury in ointment. Absorption from the skin in other forms is difficult to estimate, since absorption by ingestion or inhalation may also be present. Thus, mercury poisoning is known to occur in police officers engaged in fingerprint detection.

Agate and Buckell (1949) investigated 32 policemen and one officer of the Lancashire Constabulary who used hydrarg. cum cret. for developing fingerprints. Of these men, seven showed a coarse and distinctive tremor affecting hands, lips, tongue, or eyelids. Four showed erethism. The authors considered that the absorption of mercury was probably by inhalation. An interesting finding was that clinical toxicity was not related to the amount of mercury excreted in the urine. But they found that the more time spent on this work the greater the chance of poisoning; 250 hours a year seemed to be the threshold of toxicity. Forbes and White (1952), however, investigating five policemen engaged on this work, concluded that absorption through the skin or accidental ingestion was more likely than inhalation. But Blench and Brindle (1951), in a discussion about two police officers who had been engaged in the same work "for years," assumed that ingestion was the route of absorption.

In chronic mercury poisoning there seems to be very wide variation in the reported levels in the urine. Professor Lane (1954) states, "the level of mercury in the urine gives a useful indication of the quantity being absorbed," and regards the normal range of urinary mercury as up to 80 μg . per litre of urine, values in excess of 100 μg . being abnormal. He states that values exceeding 1,000 μg . per litre have been found in workers exposed to metallic mercury, and in "isolated cases" values exceeded 2,000 μg . Although all these men were at work, many of them showed the rather indefinite clinical picture associated with chronic mercury poisoning. Professor Lane believed that symptoms should be looked for when the urinary mercury level persistently exceeded 300 μg . per litre.

In five cases of mercury nephrosis in young children, Wilson *et al.* (1952) found urinary levels varying between 220 and 2,000 μg . Their only fatal case had the lowest level of 220 μg ., but this might have been due to failure of the kidney to excrete mercury.

Farquhar (1953) reported two fatal cases of mercury poisoning in children. A male child of 16 months developed fatal nephritis (clinically nephrosis, histologically glomerulonephritis) following temporary recovery from mercury poisoning eleven months previously. The urine mercury level two days after admission of this case was 900 μg . per litre, and fell to 150 μg . per litre after twenty-three days. He states that "the former quantity indicates severe mercurial poisoning." In the second case a male child of 6 months died with a mercury level of 4,040 μg . per litre of urine. The poison in both cases was a calomel teething powder, which in the first case apparently had been given in two courses with an interval of 11 months between.

Bidstrup *et al.* (1951) found chronic mercury poisoning in 27 out of 103 men engaged on repairing direct-current meters. Here the route of entry was clearly by inhalation. A twenty-four-hour excretion of urinary mercury greater than 300 μg . (perhaps corresponding to 200 μg . per litre of urine) was generally accompanied by symptoms of chronic mercury poisoning "which in some cases had been attributed to neurosis."

In Warkany and Hubbard's (1951) investigation of 41 children with pink disease 38 had increased mercury in the urine. As a rule the mercury was found on repeated examinations; but in a few cases the amount in the urine varied greatly from sample to sample. The authors were not able to correlate the amount of the urinary mercury excretion with the severity of the disease. On the other hand, 85% of their controls "had no mercury in the urine."

In 20 of the 41 cases the first urine specimen examined contained more than 101 $\mu\text{g.}$ per litre. Only four had more than 400 $\mu\text{g.}$ per litre, in eight there was a concentration of between 51 and 100 $\mu\text{g.}$, and in 10 of between 1 and 50 $\mu\text{g.}$ In only one of the 60 controls was there more than 50 $\mu\text{g.}$ of mercury per litre, although eight had between 1 and 50 $\mu\text{g.}$ They also quote Lewin (1893) that "children frequently react to mild mercurial ointment with stomatitis and enteritis."

In 94 cases of pink disease in Manchester, Holzel and James (1952) found that 65% had increased urine mercury ranging from 200 to 2,500 $\mu\text{g.}$ per litre, whereas 35% had no detectable increase.

Dathan (1954), in discussing levels of urine mercury in acro-dynia, gives values varying from 300 $\mu\text{g.}$ per litre on admission (Case 13) up to 3,900 $\mu\text{g.}$ after death (Case 12); but although Case 13 had the least value quoted it was one of the two fatal ones. One particular brand of teething powder had been administered, and the level of mercury in the urine was high or very high in all of Dathan's 13 cases.

Present Investigation

It was decided to study the output of mercury in the urine of 24 patients with psoriasis who were to be treated by mercury ointments. These patients were divided into two groups of 12, each group to be treated exclusively by a commonly used mercury application for six weeks, during which time no baths were to be taken.

The ointment for group 1 was:

Hydrarg. ammon. ...	10 gr. (0.65 g.)
Liquor picis carb. ...	30 min. (1.8 ml.)
Paraffin molle ...	ad 1 oz. (31 g.)

and for group 2 (Vickers, 1950):

Hydrarg. ox. flav. ...	1 part
Picis carb. prep. ...	2 parts
Adeps lanae hyd. ...	10 parts
Paraffin molle ...	10 parts

The patients selected were mostly children or women who were able to attend hospital regularly for some months. They were shown how to apply the ointments twice daily. All had occlusive dressings of tubular stockinet on the affected limbs, and stockinet vests and pants were worn by those in whom the trunk was affected. Each case was examined weekly for six weeks, and at varying intervals subsequently up to twelve months. At the beginning of treatment the area of skin involved by psoriasis was noted. Where there were several patches on a limb, instruction was usually given for the ointment to be applied to the whole or the affected half of the limb, and similarly with the trunk. From the tables of Meeh (1906) the percentage of body surface under treatment could then be calculated. In a few cases, however, where they were not numerous, only the individual plaques were treated by ointment and dressings, although, of course, some ointment must have "spilled over" on to adjoining normal skin. In these cases the surface area to which mercury was applied was calculated by direct measurement.

For the six-weeks period of initial observation one 24-hour specimen of urine was examined for mercury content each week. Originally the patients were provided with large winchesters for this purpose. However, transportation of the filled winchesters proved difficult, and later the patients passed all their urine for 24 hours into a receptacle, and brought a representative sample. In most cases a control 24-hour specimen of urine was examined before treatment was started.

At each visit of the patient the urine was tested for albumin and a brief clinical assessment made. Questions were always asked about general health, intestinal function, and state of the mouth.

At the end of the six weeks, cases showing a substantial rise in urine mercury levels were kept under further observation, although in no case was mercury ointment applied

for more than six weeks, after which any local application was free of mercury.

Toxic Effects

There were no toxic effects in the patients studied: no gingivitis, sialorrhoea, stomatitis, or oral ulcers. One child had had aphthous ulcers of the mouth before treatment, but developed none while under supervision. There was no case of diarrhoea or evidence of erethism. In three cases there was albuminuria, on one occasion only, and almost certainly orthostatic.

Urine Mercury Levels

The urine mercury levels are set out in Tables I and II, but the following points are worthy of note.

Control 24-hour specimens of urine were studied in 17 of the 24 psoriatic cases. In 14 of these the urine mercury levels were 60 $\mu\text{g.}$ per litre or less. In the remaining three a history was subsequently elicited of casual and intermittent treatment of the psoriasis by mercury preparations at varying periods during the preceding year.

Of the 24 cases, only two (Nos. 3 and 4 of group 2) failed to show at some time a urinary excretion of mercury greater than the 80 $\mu\text{g.}$ regarded as the upper limit of normal by Professor Lane (1954). There seems to be a marked individual factor in the absorption of mercury, since the technique of application was carefully supervised and followed.

The percentage area of the total body surface (see Tables) was calculated from the tables of Meeh (1906) in all cases except the first four of group 2, in which the psoriasis was less extensive, and the ointment was applied to the patches only, although with an occlusive dressing. The areas of each patch were then added together and the percentage of body area involved calculated, allowing a total surface area of 17,500 square cm. (all these four cases were in women). The percentage areas of these are much smaller than those of the others, partly because the psoriasis was less extensive; since there must have been a spill-over of ointment on to normal skin, the figures are likely to be proportionately rather too low compared with the others. There is, however, a great difference between applying ointment to a few patches only and applying it to the whole of four limbs, including those parts not affected by psoriasis, as was done in the cases calculated according to Meeh's tables. In Cases 5 and 6 of group 2, however, 42% is a slight underestimation, since Meeh gives no figures to cover the back of the chest only.

Study of the tables will show that the absorption of mercury by no means depends in all cases on the percentage of skin area covered. Thus, in Case 1 of group 2 only 3½% of skin surface was covered, yet all seven of the urine mercury levels were high, the lowest 320 $\mu\text{g.}$, the highest 1,000 $\mu\text{g.}$ On the other hand, in the extreme Case 9 of group 1 in which 90% of the skin surface was treated, the figures, though above normal, failed to reach the high levels of several other cases. Generally the urine mercury levels were higher with the group 2 ointment than with the group 1. Although this might be due to the fact that part of the ointment base was lanolin rather than paraffin molle, yet the concentration of mercury in the former was a little more than twice that in the latter. Moreover, group 2 ointment contained yellow oxide of mercury, found by Wild and Roberts (1926) to be absorbed from the skin more easily than any other mercury compound.

Since Warkany and Hubbard (1951) pointed out the association between pink disease and mercury, interest in urine mercury levels has become widespread. Most authors, however, do not give the method of estimation employed, and it may be that variations in this are important. Wilson *et al.* (1952) state that "the method used for the mercury estimations was essentially that of Milton and Hoskins (1947). Warkany and Hubbard, however, seemed to employ Hubbard's method (1940), using di-beta-naphthylthiocarbazone. Holzel and James (1952) had the estimations performed in two different laboratories, one using heavy

TABLE I.—Group 1: Ointment No. 1

Case No.	Sex and Age	Area of Total Body Surface	Control Specimen	Urine Mercury ($\mu\text{g./l.}$)											
				After Week:						After Month:					
				1	2	3	4	5	6	1	2	3	4	5	6
1	F 43	86%	10	10	40	—	140	80	—	140	—	—	—	—	—
2	F 44	25%	20	100	60	40	60	50	—	60	—	—	—	—	—
3	F 14	28%	0-10	40	30	30	20	80	260	20	—	—	—	—	—
4	F 6	86%	—	180	500	520	460	360	480	460	380	210	180	20	60
5	M 21	28%	80*	—	80	110	200	210	—	200	190	—	350	100	60
6	M 11	86% and scalp†	30	110	90	30	40	180	180	40	—	110	150	—	—
7	F 10	86% and scalp†	90*	300	190	170	420	360	290	420	320	210	240	160	140
8	M 13	34%	20	300	780	820	1,300	—	1,500	1,300	1,000	560	—	190	570
9	F 24	90%	30	280	300	330	480	—	770	480	380	—	250	30	160
10	F 42	86%	20	70	120	180	210	250	260	210	170	160	170	150	—
11	F 12	86%	20	20	120	240	200	250	300	200	290	260	340	260	—
12	M 11	69% and knees†	20	20	1,200	240	120	110	210	120	90	120	240	—	—

* High level of control mercury probably due to the fact that mercury ointments had been used intermittently for this patient's psoriasis prior to the beginning of this investigation.

† Meek (1906) gives no figures for the scalp or knees.

TABLE II.—Group 2: Ointment No. 2

Case No.	Sex and Age	Area of Total Body Surface	Control Specimen	Urine Mercury ($\mu\text{g./l.}$)											
				After Week:						After Month:					
				1	2	3	4	5	6	1	2	3	4	5	6
1	F 44	31%	—	580	320	650	1,000	570	850	1,000	—	—	—	—	—
2	F 70	11%	—	200	60	20	40	40	70	40	60	—	—	—	—
3	F 26	4%	50	10	40	10	20	20	20	20	—	—	—	—	—
4	F 46	6%	—	10	10	30	—	20	0-10	20	—	—	—	—	—
5	F 28	> 42%	—	40	40	—	—	220	250	220	110	430	210	—	—
6	F 4	> 42%	—	1,500	—	760	720	1,200	2,200	720	1,050	860	400	320	220
7	F 60	86%	—	150	400	730	640	850	1,200	640	—	—	—	320	180
8	F 7	86%	60	2,000	3,300	1,050	1,050	—	—	1,050	630	—	100	200	190
9	F 50	86%	10	200	770	620	1,500	2,300	790	1,500	690	130	340	—	80
10	F 36	36%	20	60	30	90	70	80	150	70	110	120	—	150	200
11	M 10	28%	210*	430	360	1,050	560	1,000	930	560	460	500	260	—	—
12	F 12	86% and scalp†	20	150	110	310	—	400	930	400	110	360	—	—	—

* High level of control mercury probably due to the fact that mercury ointments had been used intermittently for this patient's psoriasis prior to the beginning of this investigation.

† Meek (1906) gives no figures for the scalp.

metal-free glass containers and the other ordinary glass bottles. The mercury levels were slightly higher in the latter, as might be expected, since ordinary glass contains traces of mercury. Agate and Buckell (1949) did their estimations by a modification of the dithizone extraction technique (Milton and Hoskins, 1947).

Since the technical details are important, we describe the method we used.

Method

Reflux under a double surface condenser for one hour 50 ml. of urine, 4 g. of potassium permanganate, and 10 ml. of 20 N sulphuric acid. Remove excess of permanganate by adding 30% w/v hydrogen peroxide (1-3 ml.) down condenser. Destroy excess of hydrogen peroxide by adding 0.5 ml. of 40% w/v hydroxylamine hydrochloride down condenser. After cooling, extract mercury by shaking digest with successive 5-ml. quantities 0.01% w/v di-beta-naphthylthiocarbazon (Eastman Kodak) in chloroform until chloroform extract changes from red to green. Shake combined chloroform extracts with 3 ml. of 10% w/v potassium bromide in N sulphuric acid to concentrate the mercury in the aqueous layer. Remove chloroform layer. Add 3 ml. of 40% w/v sodium acetate $\text{NaC}_2\text{H}_3\text{O}_2 \cdot 3\text{H}_2\text{O}$ to bromide-sulphuric acid layer. Titrate with successive portions 0.01% w/v di-beta-naphthylthiocarbazon in chloroform. Leave this solution to stand for two hours before use, then standardize against known amounts of mercuric chloride solution. Perform a blank on the reagents (usually 1 to 1.5 $\mu\text{g. Hg/determination}$). (1 ml. of commercial di-beta-naphthylthiocarbazon 0.01% w/v = approximately 6 $\mu\text{g.}$ of mercury.) With this method recoveries of 30 and 60 $\mu\text{g.}$ of mercury added to 50 ml. of normal urine were quantitative even when the urine was allowed to stand for seven days

after addition of the mercury. Rolfe *et al.* (1955) state that the recovery of mercury, using acid permanganate digestion methods, is only about 70% when urine is allowed to stand for five days after the addition of mercury. Quantitative recovery figures obtained, using Sunderland method for the investigation, were probably due to the very large amount of permanganate employed, compared with conventional permanganate oxidation methods.

Summary and Conclusions

The literature on absorption of mercury compounds applied to the skin is confused; opinion on the possibility of poisonous absorption of mercury, especially after application in ointment form, is sharply divided. Some of the salient features of the more important papers are noted.

Little consideration has been given to the likelihood of toxic absorption in psoriatics treated by mercury ointments. Two groups of 12 psoriatics were therefore each treated by twice-daily applications of one of two standard mercury ointments, and the mercury content of the urine was estimated weekly for a minimum of six weeks, when the ointments were discontinued. Where urine mercury had risen to high levels estimations were continued at varying intervals up to a maximum of twelve months. In this investigation mercury ointments were applied *with occlusive dressings* without cleaning or washing off the ointment. This is regarded as of great importance, not only because Laug *et al.* (1947a) showed that mercury absorption was four times as great if occlusive dressings were applied, but also for clinical

reasons. Thus, in our series of 24 patients a surprisingly high proportion of the psoriatics became completely free from eruption. (The provision of a pot of ointment without instructions in its use usually results in application of ointment at night only, and that erratically, with very little improvement in the psoriasis.) It seems that efficient occlusive dressings such as stockinet and tubegauze have increased the chances not only of effective local medication but also of cutaneous absorption and clinical toxicity. In this connexion it may be noted that for the successful treatment of extensive psoriasis large quantities of ointment are required, many of our patients using between 1 and 2 lb. (450 and 900 g.) weekly.

Of the 24 patients thus treated, 22 had levels of urine mercury above the limit generally accepted as normal. If urine mercury levels of 300 μg . per litre or above are considered to be in the range where clinical toxicity is likely, 13 of the 24 cases were in the toxic range: in one specimen the level was as high as 3,300 μg . per litre, and readings of 1,000 μg . or more occurred in eight cases.

Nevertheless there were no clinical signs of toxicity. Every patient was inspected and interrogated weekly for at least six weeks, but most of those showing high levels were followed for five or six months and a few for longer than this. There were no cases of albuminuria except in the three isolated specimens of orthostatic albuminuria. In spite of the clinical absence of toxicity, the earlier observations of others are confirmed that in many cases increased urine mercury levels take many months to subside to normal.

It is difficult to explain this lack of toxicity in view of the published cases of mercury poisoning in industrial workers, nephrosis, and pink disease since the second world war. Allergy to mercury applications in skin diseases is well known and may be acute. Possibly some such manifestations occur, though rarely, internally, producing mercury poisoning associated with urine mercury levels which are well tolerated by normal psoriatic patients. If this view receives support we may have to become wary of treating psoriasis for long periods by mercury ointment, since the allergic reaction cannot be forecast. On the other hand, some mercury compounds may be more poisonous than others. The cases of pink disease and mercury nephrosis referred to above nearly always followed the use of calomel ("calomel disease"). Calomel is less often used in skin applications, and the more widely used hydrarg. ammon. or yellow oxide of mercury may be less poisonous. Calomel was apparently used for cutaneous application in syphilis, and mercury poisoning from such treatment was then common.

There seems to be no reason to give up using mercury ointments in psoriasis if they are prescribed with discretion. But there is a need for clinical investigation to decide how important mercury is in the treatment of psoriasis. The same ointments containing the tar without the mercury might be found to be as effective. On the other hand, mercury ointments having been used so widely for so long, clinical experience would allow them to be generally non-toxic, apart from allergic reactions limited to the skin.

In spite of the relative safety of mercury ointments, our findings indicate that they should not be used for treating a psoriatic under 5 years of age. They should probably not be employed for any length of time in

anyone with a history of nephritis, or with albuminuria, or with impaired kidney function. Moreover, they should not be used in pregnant women, for mercury has been shown to pass to the foetus *in utero* through the placental circulation (Cushny, 1947).

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CONTROLLED TRIAL OF MEPROBAMATE

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Meprobamate is another of the recently introduced tranquillizing drugs. It has been tried out and used in the United States since 1952 and has temporarily become the fourth most commonly prescribed drug there. It is now also available in this country under the trade names of "equanil," "miltown," and "mepavlon" in tablets of 400 mg. for oral use. Sedative or tranquillizing drugs are now so commonly prescribed that their cost is a large proportion of the national drug bill. The expense of the newer preparations makes an early assessment of their true value a matter of considerable economic as well as medical importance.

Meprobamate was synthesized in 1950 by Ludwig and Piech in the search for compounds resembling mephensin chemically but having a longer therapeutic action. Meprobamate is 2-methyl-2-n-propyl-1,3-propanediol dicarbamate and has the following structural formula:

Berger (1954) has described meprobamate as a new interneuronal blocking agent, and showed that it acts,