

MISS E. E. CHAMPION : *W/O emulsions*. I refer to the stability of hand stirring with a glass rod against the instability of an American experiment using a mechanical stirrer. Had any air been incorporated during the manual action using a glass rod, hence any bearing on the stability ?

THE LECTURER : I have never observed the inclusion of air in hand-stirred emulsions. With a high-speed mechanical stirrer air might well be included in the emulsion but I do not believe that it would affect its stability.

MR. K. H. STEINITZ : At what temperature were the hand-stirred emulsions prepared ?

THE LECTURER : All emulsification experiments have been conducted at room temperature. I have observed that some emulsions break very readily as the temperature is raised. Moreover, the breaking temperature is fairly reproducible which suggests the possibility of a phase change in the system.

DR. J. J. MAUSNER : Please comment on the relative stabilities of cholesterol versus cholesterol/ester emulsions.

THE LECTURER : There is nothing to choose between them. Both types of emulsion are stable for four weeks at room temperature.

PHOTO-CONTACT DERMATITIS FROM SOAPS

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A lecture delivered before the Society on 26th January 1962.

The studies which led to the discovery of the photo-contact sensitizing property of tetrachlorosalicylanilide are described.

ABNORMAL HYPERSENSITIVITY to light is a phenomenon that has interested biologists, veterinarians and physicians for at least a century, although the most intensive studies have been made over the past twenty or thirty years. It has been appreciated for a long time that certain chemicals have the capacity to make animals and men more sensitive to light, not as an exceptional phenomenon but as a normal inherent property. The use of some such chemicals has been discontinued in medical therapeutics entirely because of their photosensitizing properties. The first medicaments to be used on a large scale in recent years which frequently produced light sensitivity were the sulphonamides. Various sulphonamide derivatives used for other than anti-bacterial action have been found to have a similar effect.

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The list of drugs with recognised photosensitizing properties has lengthened considerably in the past decade.

Nearly two years ago, a number of dermatologists in England noted a group of patients with an unusual pattern of dermatitis, for which they could find no ready explanation. The clinical picture was more or less identical in all the patients, making them recognisable with ease. Their skin eruption came on relatively suddenly, usually in persons who had no previous history of eczema or dermatitis. It consisted of a diffuse redness affecting the whole of the head and neck areas, including the forehead, eyelids, in and around the ears, and the neck down to the collar line. The webs, sides and backs of the fingers and hands, as well as the backs of the wrists and forearms were often involved. It was sometimes accompanied by considerable swelling, particularly of the eyelids and of the loose tissues of the face. Some areas developed blisters which would burst and produce considerable serous exudation, which was followed by crusting, fissuring and dry scaling. The main symptoms were a burning sensation, soreness, and irritation.

Although occasional patients showed a more widespread eruption, in the vast majority it was confined to the light exposed areas of the head and neck and the hands and forearms. The sharp limitation at the collar line or the "V" of the front of the neck in men who wore open shirts, or a deeper "V" in women corresponding to the shape of their dresses, were persistent and striking features. We felt no doubt that this pattern of dermatitis had a close association with light, although paradoxically we were seeing most of them in December, January and February of an English winter! We carried out a number of skin tests and other investigations without gaining any clue. The majority of the patients were men, but a few women were also affected. Their occupations varied and, in fact, almost none of the patients believed that their work was responsible. The problem was solved, however, principally by the detailed investigation of an "epidemic" of patients with this dermatosis seen by Wilkinson¹ in an engineering factory at Maidenhead. While looking for fluorescent material in the factory which could give a clue to a photosensitizing substance, he found in a very thorough study that a solution of the toilet soap from the wash rooms fluoresced. Although he did not perhaps at once appreciate the significance of this fluorescence, the immediate co-operation of the research department of the soap manufacturer laid bare the whole story.

A new chemical germicide, tetrachlorosalicylanilide, had been introduced by one large soap manufacturer some months before into two of their toilet soaps; and by other manufacturers into a number of toilet goods. (The germicide had only been incorporated in the soap for a period of three months when continuing research by the manufacturers suggested

a potential hazard, and production of new tablets had already ceased before Wilkinson's request for assistance in connection with the factory at Maidenhead.) Although an advertising campaign indicated that the formulation of two widely used soaps had been changed, I believe it true to say that no more than one or two dermatologists were aware of a change, or appreciated that it could be significant. The main reason for this failure appeared to be that dermatologists, in this country at least, do not think that toilet soaps are causes of allergic sensitivity reactions. In Denmark, Hjorth² has shown that soap perfumes may produce reactions in patients primarily sensitized to Balsam of Peru, but the latter is used much more frequently there than in Great Britain.

On going back to question all the patients we had previously seen with this striking clinical picture, we found that virtually all of them admitted to having used one of the toilet soaps which we now knew to contain tetrachlorosalicylanilide. However, we have since seen a number of patients who appear to be typical cases, but who deny that they have used any of these soaps. One knows, of course, that patients are fallible and some may not know what soaps they have used. Presumably most of the patients affected used the same soap for bathing as they did for washing their face and hands, and hence it was puzzling that the covered parts remained so completely spared; more so because some patients readily reacted to a skin test with the chemical on their backs.

When carrying out patch tests with a photosensitizing substance special precautions are needed. The tests should be duplicated so that one can be exposed to light and the other used as a control. In these patients, my method was to test with tetrachlorosalicylanilide as a 1% solution in methyl ethyl ketone, applying two identical patches on the skin of the back. They were left in place for fortyeight hours, after which they were removed and any positive results recorded. If the test was negative, one patch was covered with black paper and the other irradiated (over a wider area than the actual test site) with a suberythema dose of ultraviolet light from a Hanovia mercury arc lamp. In practice, an exposure of thirty seconds at a distance of thirty inches was found to be adequate. The results were then recorded after a further fortyeight hours. If both tests were positive fortyeight hours after first application, no light exposure was usually given. The results showed that about one-third of the cases gave a positive patch test at the fortyeight hours or ninety-six hours reading, without the addition of ultraviolet light, but that about two thirds of them required the addition of the light exposure to obtain a positive test. It is surprising that the patients who gave a positive test without exposure to light, did not produce dermatitis on their trunks when bathing with the soap containing the chemical.

All doctors are becoming increasingly concerned with skin infection and skin carriage of bacteria, particularly staphylococci since antibiotic resistance is spreading. Hospitals especially are much interested in ways and means of preventing staphylococcal crossinfections. Hence, there is considerable interest in germicidal soaps. The social mores of our times also demand the effective control of axillary and body odour, which is produced by the action of skin bacteria on apocrine gland secretion. It was the need of more efficient germicides which resulted in the introduction of tetrachlorosalicylanilide into soaps and other toilet products. The range of substances which remain active in soap solutions is limited. The present choice is shown in *Table 1*.

Table 1. Germicides suitable for use in soaps.

Hexachlorophene (G11, AT7)
Dichlorophenol (Bithional, Actamer, horothidol)
Dichloro-m-xylene (DCMX)
p-Chlormethylxylene (PCMX)
Tetramethylthiuramdisulphide (TMTD, Puralin)
Trichlorosalicylanilide (Anobial)
Tribromosalicylanilide (TBS)
Tetrachlorosalicylanilide (TCSA)
Trichlorcarbanilide (TCC)

A number of these compounds were tested by Hurst *et al*³ against *Escherichia coli* and *Staphylococcus aureus*, and tetrachlorosalicylanilide was found to be the most effective, as shown in *Table 2*.

Table 2. Bacteriostatic levels (ppm.) of different disinfectants.

Disinfectant	<i>Staph. aureus</i>	<i>E. coli</i>
G11	0.5	50.0
Actamer	1.0	50.0
DCMX	2.5	50.0
TMTD	0.25	25.0
TCC	0.2	25.0
TCS	0.1	12.5
TBS	1.0	25.0

Any new product for use in man must undergo a testing programme for toxicity and sensitivity. The manufacturers of tetrachlorosalicylanilide had a number of tests carried out on the skin of the guinea pig and man, and the substance was passed by the Food and Drug Administration of the United States, as satisfactory for use in soaps. The guinea pig tests consisted of repeated applications to the skin with solutions of the chemical,

followed in one series by exposure to ultraviolet light. Only irritant effects were seen, without evidence of allergic sensitization. (This substance is irritant in concentrations of about three to five per cent.) As regards man, routine patch tests and repeat insult patch tests of various types in over four hundred subjects were also negative except for a few irritant reactions again. The chemical was then incorporated into toilet soap at a concentration of 0.2% and used for the routine washing of children, and of dermatological patients at three centres in the United States. In two of them, over three hundred children and nearly two hundred skin patients showed no adverse reactions at all; but at the third centre three per cent of over two hundred skin patients became sensitized. The crux of the problem of evaluation is to know how much weight to put on a single positive result as in this case. It could be disregarded as being unrepresentative. Perhaps the most relevant factor is how the particular chemical is going to be used. If it is being developed as a pharmaceutical for the treatment of infective disease, certain risks are justifiable when they could not be accepted for a substance which is to be utilised in an everyday toilet requisite or article of clothing or foodstuff. When products are being developed it is not usually possible to forecast how they will be used, so that the mere fact that a substance has a known sensitization index should not negative its use in any form.

Tetrachlorosalicylanilide has been used in soaps in several countries without ill-effects, and perhaps it continues to be used safely. The reasons for such variation are obscure, but in experimental sensitization, the results obtained in different countries, or in different parts of the same country, may vary enormously. In the case of this compound under consideration the incidence of dermatitis appears to have been very much greater in the south of England than in the north, and in Scotland.

A dermatological colleague in the United States has told me that he has seen no cases of contact dermatitis from soaps containing tetrachlorosalicylanilide (at a concentration of 0.2%), but when using it as a 1% solution for the treatment of fungus infections of the feet, he encountered an incidence of allergic sensitization of up to 20% of cases treated. An interesting property of this chemical is its ability to be adsorbed on to the skin surface and on to clothing. It has been estimated⁴ that when the skin is washed in soap containing tetrachlorosalicylanilide, as much as 20% may remain on the surface after rinsing. The concentration may increase with repeated washing several times a day, and this factor is likely to be an important one in facilitating both allergic contact sensitization and photosensitivity. At the same time, of course, if it is germicidal the persistence on the skin surface will be beneficial, provided that no adverse reaction is induced.

With most substances the genetic "state of preparedness" or susceptibility plays a major part. Only a proportion of the population at risk will become sensitized when all are equally exposed. How this susceptibility is determined is not known. That it exists can be demonstrated in both man and in guinea pigs. I believe that dermatitis from tetrachlorosalicylanilide has been a problem in England only because the soaps containing it have been used by such a large number of people, and almost all of the patients have been among those who use the soap with the largest sales. It is interesting that I have not seen, and do not know of any instance of more than one proven case in a family, even though the same soap has been used by the whole household. I have heard of alleged familial cases, but have not had the opportunity to prove any of them.

From the study of these patients, dermatological knowledge has been enriched, but, as usually happens, many further problems have been posed. Perhaps the most pertinent one is this: Could any animal or human studies have detected the photo-contact sensitizing property of tetrachlorosalicylanilide sufficiently accurately to have recommended to the soap manufacturers that it should not have been used? In the present state of knowledge and experience, I doubt it.

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