THESIS

for the Degree of

Doctor of Medicine

of the

University of Edinburgh.

1934

WILLIAM EDWARD ORCHARD, M.B. Ch.B.

ARSENICAL DERMATITIS.

A study of its causes, with a review of 96 cases occurring during treatment at the Salford Municipal Clinic.

"The skin is the largest and most exposed organ of the body. It and the lungs, therefore, share two common weaknesses: each is always open to irritation by external attack, as well as by internal toxins."

(Prosser-White, Occupational Affections of the Skin. 1928)

Historical.

When Columbus wearily warped his travel-stained vessels at Palos, on the Ides of March, 1493, he brought with him the news of the discovery of America. As the immediate evidence of the gallantry of his crews, there was introduced into a factious and warring Europe a new peril, which was to add to the armoury of nations a weapon which not all the mamelons and javelins of the contentious armies could equal in effectiveness, a new disease. Its very novelty was its chief menace, and with the passage of time although the problem of diagnosis and classification has been solved, there still remains the greater problem of its treatment. Since the first therapeutic gropings of the early syphilidators, which led to the foundation

of the modern attack on the disease, until the present day, the variety of the drugs has only been exceeded by the variety in the methods of applying them. The result of the patient endeavour of these four centuries, has been to establish the drug Arsenic in the first place in the armamentarium of the syphilographer. While it does not stand in relation to the treatment of syphilis as Cinchona Bark does to malaria, yet its proved efficiency and its ease of administration has entitled it to the distinction of being called "the Golden Drug of Syphilis".

The extensive use of Arsenic as a poison has given to the toxicologist and the general public a knowledge of its lethal action on the body. Its therapeutic use has also been followed by ill-effects and with its universal use in the treatment of syphilis, the knowledge and understanding of these ill-effects becomes increasingly important.

Bechet (1) in a review of the history of the arsenical eruptions, mentions that Fowler was the first to record the frequency of urticarial eruptions after the use of his Liquor Potassii Arsenitis, and in 1857 Devergie was the first to realise tnat cutaneous lesions might result from the internal administration of arsenic. The

lesions he called "taches arsenicales" were examples of arsenical pigmentation. Erasmus Wilson drew attention to the local and systemic poisoning from dyes containing arsenic, and Jonathan Hutchinson described arsenical keratosis and arsenical cancer.

Hutchinson (2) noticed the occurrence of Herpes Zoster following the use of arsenic, and further he mentions that patients who were being given the drug tended to show other signs of cutaneous and systemic intolerance, in the form of a dry, earthy skin, and a dull eye. He demonstrates the recurrent eruption then known as "arsenical eczema", and states that the herpetic eruption of arsenic was not usually a symmetrical lesion. In confirmation of the effect of the internal administration of arsenic on the nervous system, he describes a case of peripheral neuritis, and frequently mentions the lesions of herpes which follow these signs of intolerance. In another volume he illustrates the development of Arsenical Keratosis and "Arsenic-Cancer" in patients on long-continued arsenic. He describes typical keratoses of the palms and soles in such a case, and a case of arsenical pigmentation.

Pharmacology of Arsenic in Relation to its Cutaneous Toxicity.

Cushny (3) in his description of the action of Arsenic upon the skin, states that it accelerates growth and proliferation of epithelium, and in severe cases this goes on to atrophy and degeneration. The skin eruptions are due directly to the action of arsenic on the cutaneous structures, and discussing chronic arsenical poisoning, he mentions that these occur in various forms in the second phase of the toxic process. In prolonged poisoning the skin lesions simulate almost any form of skin disease. Later stages of the poisoning process are characterised by disturbances of sensation and motion in localised areas, generally in the hands and feet in the form of peripheral neuritis.

The skin disturbances take the form of papules, either vesicular or erythematous, a flaking of the epidermis and keratosis. Pigmentation is also noted and conversely depigmentation.

Prosser-White (4) quotes Fischer and Schmidt's experiments on the excretion of certain substances which when introduced into the body are voided with the skin secretions. Fischer(5) states that this excretion is responsible for the production of dermatoses, which he

calls "excretion dermatoses", and they are characterised by proliferation of the cells of the horny layer, and those lining the follicles, the falling out of the hair, and ultimately of cancer.

Butler (6) describes the effect of arsenic in chronic poisoning (even with minute doses) on the nervous system, which is markedly affected, particularly the peripheral nerves, both motor and sensory. With prolonged use arsenic tends to accumulate to a greater extent in nervous than in other tissues. Butler goes on to say that chronic arsenical poisoning is followed by eruptions, herpes, pigmentations, increased growth of hair and nails, paraesthesiae, peripheral neuritis, and neuralgic pains.

Kolmer (7) considers that the action of arsenic on the skin in the production of the "arsenical dermatoses" lies in its action on the capillaries, which he classes as primary toxic effects.

The Distribution

The distribution of the arsenic in the various tissues of the body is of prime importance, since the inter-dependability of function of the different structures of the human frame is a primary physiological fact. Stokes (

in a table of the comparative distribution of arsenobenzole compound after injection, quotes the findings of Boegtlin and Clausen and Jeans, which give the arsenic content in the different tissues in the following order:

Urine, bile, liver, spleen, stomach, intestinal tract, blood, lungs, heart, kidneys and skin.

It is noteworthy that the skin is mentioned last. He states that the high arsenic content of the urine and bile shows the rapidity with which the kidney and liver deal with the drug, and the fact that the kidneys show, next to the skin, the lowest content of arsenic, points to the rapidity with which this organ eliminates the drug.

Kolmer (9) describing the distribution and storage of the arsphenamines after injection, states that the arsenic has been found largely in the liver, spleen and lungs.

Bulmer (10) found that after the intravenous injection of the arsphenamines in rabbits, the arsenic was found chiefly in the liver, lungs, kidneys and long bones.

In further observations of the effect of arsenic on rabbits Osborne, Putnam and Hitchcock (11) based their findings on micro-chemical studies of the arsenic in the tissues, as they state that a quantitive estimation of

the drug from various sites is no indication of the storage of the drug. The arsenic is deposited in the tissues as the trisulphide. They observed that in rabbits which had received a course of eight therapeutic injections of arsenic:

1. The drug is rapidly metabolised in the liver.
2. No evidence was present that there was any appreciable amount of storage in the tissues.
3. There was a rapid elimination of the drug.

They went on to show, however, that there was storage of arsenic in the liver in cases where a fatal dose was given, but that other tissues did not show any great degree of retention. The kidneys especially showed very little storage, and they concluded from this that the kidneys played a minor rôle in the elimination of the drug. The intestinal tract, the stomach, colon and small intestine were the greatest factors in the elimination, and that no other organs were involved in the storage of arsenic, except when it occurred in and around the smaller blood vessels.

Fordyce, Rosen and Myers (12) have shown that arsenic has a marked affinity for epithelial cells.

Elimination of Arsenic.

The study of the elimination of the drugs used in the treatment or syphilis depends upon the "usability" (Burke) of the drug, i.e. the amount which can be taken up by the body and converted from the therapeutically inactive form in which it is injected (as proved by in vitro tests) into the potent oxide of the organic arsenical compound. The rapidity with which this is accomplished is one factor, another is the rapidity with which the drug is passed out of the system either as the "oxide" or the therapeutically inactive arsenites and arsenates. This latter factor is of special interest to the syphilographer, in his assessment of the particular line of treatment of any particular patient as it concerns him greatly if his patient cannot tolerate the generally accepted efficient dose of the drug chosen. He cannot assess the amount of wastage which occurs with the elimination of the therapeutically active portion of the drug.

Kolmer (13) in his studies of this aspect of the administration of the arsphenamines in the treatment of syphilis, has shown that the rate of absorption of the arsphenamine series depends upon the route of administration.

The intravenous route is favoured with a rapid rate of absorption, but it is offset by a greater rate of elimination, and consequent shorter period of therapeutic activity, and in addition toxic effects are more likely to occur.

After intramuscular injection, on the other hand, the rate depends upon the amount of tissue injury, the greater the tissue injury the slower the absorption.

By whatever method the drug is administered, the ultimate fate is the same. After an intravenous injection the blood receives all the drug, and with a varying interval, after intramuscular injection it eventually passes almost in its entirety into the blood stream, either via the lymph channels, or by being directly absorbed at the point of entry by the blood itself. Little or none is fixed by the tissues at site of injection.

Disappearance of the arsenic from the blood occurs in a very variable manner. It has been shown by Fordyce, Rosen and Myers (14) that this variation is due to personal idiosyncracy or predisposition to intoxication, and also upon the rate of excretion. In certain individuals examination of the blood immediately after an injection revealed that from 37.9% to 66.1% of arsenic

had already disappeared from the blood-stream.

Elimination in the urine was first studied by Abelin in 1911, and he developed a method for the detection of arsenic by the diazo colour reaction. Numerous observers have used his method, or devised modifications of it, and have reported on the rate of elimination. In spite of a general agreement that the test was not extremely accurate, it was almost unanimously discovered that arsenic began to appear in the urine within five minutes and that excretion went on for twenty-four hours.

Lloyd and Lloyd (15) in a contribution on the urinary excretion of Novarsenobillon, noted that the excretion of arsenic did not proceed evenly. In general there was a maximum elimination in the first few hours, followed by a gradual diminution in the amount of arsenic in the succeeding 12-15 hours. It was not claimed, however, that the Lloyd's modification of Abelin's test demonstrated the cessation of the eliminatory process, for by other means it was proved that arsenic was present in the urine for some considerable time afterwards. It was noticed also that the patients themselves showed variations in their capacity for elimination, for in some cases there was no elimination in the first twenty-four hours, while in others the presence of arsenic was demonstrable up to several days.

They were able to show that a close association existed between inefficient urinary elimination and the development of toxic effects, for in 17 out of 34 cases of major or minor complications arising out of the toxic nature of the drug, defective urinary elimination was present.

The discovery that large amounts of arsenic were present in the faeces led to the discovery that the bile was the vehicle in which the greatest amount of arsenic was eliminated. It was found later that from three to five times as much arsenic is to be recovered from the faeces than from the urine. The time for the appearance of the drug in the bile is however later than in the case of the urine, being three or four days after an injection of either "606" or "914" preparation.

Some investigators showed that the quantity increased with each succeeding injection, and attributed this to the fact that the liver bore the brunt of the storage when the quantity of drug was in excess of that which the body was able to metabolise.

The Intestinal Mucosa is also concerned in the elimination of arsenic. Analyses have shown the presence of arsenic in those tissues and arsenic has been demonstrated as the cause of cloudy swelling and fatty

degeneration of the lining cells, as well as hyperaemia of the submucosa.

To conclude, the various secretions which share in the elimination of the drug are the saliva, the milk, the perspiration, and finally the vomitus, found in a case who vomited four hours after an injection of arsphenamine intravenously: but this was due more to regurgitation of bile than from actual excretion by the gastric mucosa.

Variation in the Rate of Elimination. Voegtlin and Thompson (quoted by Kolmer (16)) found considerable variation in the excretion of arsenic in different rats, after intravenous injection with various organic arsenicals. These variations occurred not only in animals with impaired renal function, but also in those whose kidneys were normal. They showed also that the pentavalent arsenicals were excreted more rapidly than the trivalents. This fluctuation in the rate of excretion was evidently an individual variation, and the authors believe that there is no reason to doubt that these fluctuations occur in the human being, especially when his eliminatory mechanism is still further affected by his disease.

Variation in the chemical and physical constitution of the arsenical preparations used in the treatment of syphilis was also studied by these authors, and they

concluded that the difference in the rate of excretion, toxicity and therapeutic activity of the various trivalent arsenicals was due to the difference in their physical properties. Kolmer (17) in commenting upon the work of Voegtlin and Thompson mentions their findings that arsphenamine is eliminated largely by the liver in the bile, and that neoarsphenamine and atoxyl are chiefly excreted by the kidneys. He submits the hypothesis that by relieving the strain on one already overloaded eliminatory organ, it is possible that the body tolerates another form of the drug, which calls into play an entirely different route.

Histology.

In 1905 Justus (18) described a method for the microchemical detection of arsenic in the tissues, and by its means he found that the deposition of arsenic occurred around the nucleus in the cell cytoplasm. The organs chiefly affected were the skin, kidneys, liver and intestines, and that the deposits were finer in the kidney and intestine, and coarser in the muscles, coil glands and epidermis.

Brunnauer (19) saw the deposition of arsenic trisulphide as fine, rounded, prolongated granules, yellow

brown in colour, and practically all of it was situated extracellularly. He was unable to say that any of it was definitely intracellular.

Osborne (20) using a modification of Brunnauer's method, noted the characteristics of arsenic trisulphide in the tissues, and gave a chemical proof of the identity of the arsenic. His researches were concerned with the action of the pentavalent forms of the drug, the materials used being potassium arsenite (Fowler's solution), solution of arsenious acid and mercuric iodide (Donovan's solution), arsenic acid, sodium and iron cacodyllate. None of the patients had received the trivalent arsenicals, such as the arsphenamines.

In describing Keratosis he made the following observations:

1. The arsenic (as the trisulphide) was evenly distributed in the horny layer between the cells, none being intracellular. It was not only present in the keratosis but also in the corneum of the normal skin surrounding the keratosis, but to a lesser degree.

2. The arsenic was present in the stratum granulosum and stratum spinosum, down to and including the basal layer. The deposits were particularly marked surrounding the areas of necrosis.

3. The area of greatest deposit was in the basal layers of the epidermis and in the papillae of the corium, especially under the areas of necrosis.

4. A small amount of arsenic was present in the intercellular spaces, around the coil glands, but not in the coil glands themselves. It was evenly distributed throughout the walls of the ducts as in the epithelium, and very little was seen in the lumen of the ducts. Commenting on a case described by Brunnauer, in which there was an associated hyperidrosis, and in which arsenic was found in the coil-glands and ducts, in addition to the papillae and epidermis, he states that the bulk of the arsenic is apparently deposited in the areas of greatest vascularity and gradually passed out intracellularly. In a case of his own, in which there was hyperidrosis together with keratosis, he saw arsenic in the coil-glands, but states that they need not necessarily be involved.

The mechanism of the production of arsenical keratoses would seem to be the speeding-up of the keratinization cycle, by the deposition of an irritant in the form of arsenic in the upper corium, papillae, and epidermis.

In a case of Arsenical Pigmentation the summary of the pathological findings was:

1. A general thickening of the epidermis, owing to an increase in the stratum spinosum, stratum granulosum and particularly in the horny layer, which in some areas was exfoliating. Oedema and inflammatory changes were present in the papillae.

2. Marked perivascular infiltration of the upper part of the cutis, of round cells and mast cells, extending up into the papillae, with increase and dilatation of the small arterioles and lymph spaces, together with oedem of the entire upper part of the corium.

3. Pigment chiefly in the papillae and upper half of the corium, located around the arterioles and capillaries and in cells arising from them. Infiltration was also present around these areas. No pigment was seen

intracellularly. In the epidermis there was an increase in pigment in the basal layer, and here and there in the stratum spinosum and stratum granulosum, and this pigment was granular, situated intracellularly around the nucleus. The bulk of the pigment was in the corium.

The arsenic findings in this case were as follows:

1. The entire epidermis contained a great deal of arsenic. In the lower layers some of it was apparently inside the cells, was evenly distributed, but in no relation to the amount of pigment.

2. The upper half of the corium contained large amounts of arsenic, particularly in the papillae and in the intercellular spaces surrounding the arterioles. The arsenic was separate and distinct from the pigment.

3. The coil-glands and ducts contained small amounts of arsenic, while the sebaceous glands and their ducts contained a comparatively large amount.

4. Considerable amounts were present in the follicles and sheaths of the hairs, and in the hairs themselves.

He concludes with suggesting that the formation of pigment is due, not to the reaction of the cells themselves to the irritant action of the arsenic, but to the direct action of the arsenic on the melanin to form finished pigment.

The same observer (21) continuing his studies in the deposition of arsenic in the skin in cases of arsenical dermatitis investigated the differences between the dermatoses produced by the trivalent arsenicals and those resulting from the pentavalents. His study comprised a review of cases of varying severity, from a simple erythema to a severe, exudative dermatitis, with

intense oedema, thickening, fissuring and crusting.

His findings were as follows:

1. At no stage in the dermatitis could any but the most minute traces of arsenic be found in the epidermis, nor could any appreciable amount be found in the sub-papillary layer of the corium.

2. The bulk of the arsenic was deposited deep in the corium around the arterioles and capillaries, in the walls and lumen of the sweat and sebaceous glands and their ducts, in the hair follicles and in the hairs themselves.

3. The amount of arsenic was proportional to the severity of the dermatitis, provided the biopsy was performed before the administration of sodium thiosulphate.

4. Section of the normal skin removed from patients receiving arsphenamine showed the arsenic in the same location, but in relatively small amounts.

It appears that the actual distribution of the arsenic in the sections was intercellular.

Summing up, Osborne states that arsenic in the pentavalent form shows a definite predeliction for structures of ectodermal origin, e.g. the sweat and sebaceous glands and their ducts, as well as for the hairs and hair follicles, and little for the blood vessels in the corium.

In the case of the trivalent compounds, the arsenic had a special affinity for the vascular structures, e.g. the small arterioles and capillaries below the papillae. He remarks that this confirms the clinical opinion that arsphenamine is vasculotoxic. (This was first stated by Ricker and Knape in experiments on animals.) This special

affinity of the pentavalent arsenicals for the ectodermal structures may account for the greater affinity of atoxyl and tryparsamide for the central nervous system. Clinically these facts are borne out by the production of the neuro-cutaneous types of lesion, e.g. wristdrop and optic atrophy, pigmentation, whereas in the typical lesions following the trivalent aresenicals, severe dermatitis, haemorrhagic encephalitis and purpura are examples of the effect of a vasculotoxin.

Cannon and Karelitz (22) do not agree with Osborne. In an investigation on the development of vitiligo in the skin of a negro patient after a severe exfoliative dermatitis, they were able to demonstrate the absence of pigment in the vitiliginous areas. The tissue changes were not limited to the cutis, as reported by Osborne. In this and two other cases which they examined microhistologically, the epidermis was markedly thickened and irregular. Marked changes were present in the rete, where acanthosis, disorganisation of the basal-cell layer and granular degeneration, as well as disturbances in keratinization (hyper- and parakeratosis), Arsenic was present in the tissues as arsenic trisulphide at all stages of the dermatitis, and was to be found throughout the epidermis including the horny layer, in the papillary

layer of the corium, especially round the capillaries, and in the lumen of the sweat glands and their ducts. An interesting feature was that different parts of the skin in the same patient yielded varying amounts of arsenic, when the dried tissue was examined. They state that this might well signify nothing more than the irregular distribution of arsenic throughout the skin, even in closely adjacent areas, possibly contingent upon the vascular supply and the cut of the section, whether straight or oblique.

In reviewing the causes of vitiligo, why it should appear in some cases and not in others, or why hyperpigmentation should follow arsenical dermatitis and depigmentation in others, they find that the action of the sun's and X-rays give the same paradoxical effect. They agree with Kyrle (23) who postulated a "congenital inferiority of certain circumscribed areas of the skin," and suggest that the factor of defective elimination in susceptible cases produces a breakdown in the skin. The arsenic they describe as the exciting force, but not the only one.

An interesting point that they bring out is that the size of the dose has little to do with the onset of arsenical dermatitis, and that personal idiosyncracy

plays a larger part.

Kyrle, whose views on the micro-chemical picture they quote, says that the primary point of attack is in the epidermis. The vascular response (erythema) is a reaction in the epidermis to the toxic arsenic. This vascular response he holds to be transitory and the symptoms recede, but if the irritation is maintained changes take place in the structure of the cells in the form of a parakeratosis, to be succeeded by passive hyperaemia, exudation of serum and further infiltration of cells into the cutis.

Moser (quoted by Jaffein in (24)) found that cornification and parakeratosis had taken place in two cases of terminal lesions resulting from sulphoxalate arsphenamine. The most striking change was a vascular degeneration. In all the specimens the cutis showed perivascular infiltration, especially in the subpapillary layers, and most showed cellular infiltrates around the sweat glands.

The vascular damage is clinically demonstrable in the obliteration of the radial artery in a case of Robinson's (25) and in a case of Kraetzer's with Raynaud's disease following chronic arsenic retention. (26) This he attributes to the specific action of the arsenic upon

the endothelium of the arteries and also to the action on the sympathetic nervous system. Both factors evidently operate to produce the syndrome he describes. Ronchese (27) further demonstrated a case in which there was definite obstruction to the blood flow in the leg in a case which had had an acute dermatitis.

Theories of the Causation of the Dermatoses.

With the pharmacology and histo-pathology of the skin eruptions as a basis, it is possible to use these to arrive at some conception of the causation of them. The importance of etiology has been recognised since the earliest observers correlated cause and effect while using arsenic as a therapeutic agent. In 1879 Binz and Schultz conceived the theory that the occurrence of cutaneous intolerance might be due to the change in the body of the pentavalent arsenicals to a trivalent form. This induced a tissue instability which manifested itself with eruptions on the skin. Since the introduction of the organic arsenicals and their universal application in the treatment of syphilis, it was noticed that they were followed by a variety of skin lesions, and in an attempt to arrive at some explanation of these phenomena, numerous theories have been advanced.

The report of the Salvarsan Committee, 1922, of the Medical Research Council gave a general resumé of the types of dermatitis following the use of salvarsan, and attempted to give a line of guidance to those whose duty it was to treat syphilis with this drug. Their tabulation of observed facts, however, was no more than a record of the toxicity of the arsenicals, and they did not give a reason why these skin manifestations should occur.

Moore and Keidel (28) in a review of the skin reactions following the organic arsenicals, grouped all skin reactions and attributed them directly to the use of arsenic. They summarised the causes in two main groups:

1. Simple reactions. These include the urticarias, herpes simplex and erythemata, due to the liberation of toxins from latent foci.

2. Reactions of a graver type, in which the causes may be: (a) Damage to the haematopoetic system. Describing the blood changes during an acute dermatitis, they found that there was present a leucocytosis, together with an eosinophilia. Where the reaction increased in severity there occurred a state of aplasia of the bone marrow and haematogenous tissues, with leucopenia and finally death from aplastic anaemia. (b) Where normal excretion is interfered with there is a cumulative effect of arsenic. (c) Damage to the liver preventing the normal change of arsenic from a toxic to a non-toxic form. (d) The expression of an anaphylactic phenomenon.

In a later communication, representing ten years of further observation on this subject, they concluded that

postarsphenamine dermatitis was the result of direct sensitization to arsphenamine, to the products of its metabolism, or to a state of general allergic instability or hypersensitiveness, not necessarily specific for arsphenamine. This sensitization is proved by the recurrence of the dermatitis after exhibition of the drug, no matter in how small a dose or how long the interval between the injections.

They point out that there is clinical evidence that certain cases of dermatitis may be drug-specific, in that neoarsphenamine or silverarsphenamine may be given without recurrence of the rash. In this connection, a similar drug-specificity was noted by the same observers in their earlier paper, by Stokes and Cathcart (29) and by Ireland. (30)

Milian (31) considered that the influence of toxic foci was indisputable, and considered that the onset of all skin lesions, not of the exfoliative type, was due to the action of toxins from latent bacterial foci, stirred into activity by a general lowering of resistance temporarily by an injection of arsphenamine.

The exfoliative type, whether maculo-papular, vesicular, or scarlatiniform, is definitely due to the action of arsenic per se, and he notes particularly the association

of oedema with these reactions.

From the "infective" theory of Milian, Stokes and Cathcart (32) proposed an allergy or hypersensitiveness, not necessarily specific for arsenic, due to continued absorption of bacterial proteins from a focus of infection, with perhaps the added changes in the blood and tissues induced by the injection of the drug, or of the sudden liberation of such proteins from a focus following the administration of arsenic. There is also present an acute shortage of adrenalin, as suggested by Harris (33), the effect of which is to inhibit the vaso-dilator mechanism in the skin. The site of the lesion is determined by local application of irritants (e.g. iodine or mercury, as suggested by Auer (34)), and increased amounts of bacterial protein or antigen brought to these sites of irritation or vasodilatation excite the skin cells to inflammation.

The liver, they consider, plays a part in that injury to this organ, either by syphilis or by large doses of drug, perverts the metabolism of the arsphenamine, with the throwing into the blood stream of quantities of toxic proteo-chemical compounds.

Stokes and Kulchar (35) have summarised the "etiologic background" of arsenical dermatitis as having the following elements:

1. Drug injury to the skin, in addition to other organs connected to it in the metabolic processes, e.g. the liver.

2. A general allergic reactivity, due to bacterial sensitization, (the infective theory of Milian), or an example of the atopic state.

3. A local sensitivity due to the application of nonspecific irritants or from foci of infection in the skin itself.

He stresses the importance of Osborne's findings of the vascular injury due to the distribution of arsenic around the vessels of the trivalent compounds, and considers that there is an undoubted element of true specific allergy to the drug. They postulate the interaction of the drug-allergy and bacterial-allergy, and state that either may induce a dermatitis, by influencing the allergic mechanism of either sensitization.

Discussing dermatomycotic infections, they consider that these influence the dermatitis process by localising the lesions, or by setting up an allergic state for themselves and so increasing the general allergic instability. Whatever non-specific factor may be present, the exhibition of arsphenamine aggravates the condition, and in the cases where as yet no dermatitic element has developed the administration of the drug predisposes the patient to the onset of dematitis.

Other factors are proposed by Lees (36), who found

that alcoholism and pre-existing dermatoses predisposed to the development of dermatitis. He agrees with Stokes that in every case of exfoliative dermatitis a dermatoses existed at the commencement of treatment, and in patients with the "seborrhoeic diathesis" there was a noticeable tendency for eruptions to occur during treatment. Lees also considers that nervous, highly strung patients are more prone to skin accidents.

In his conception of the etiology of these dermatoses, Schiff (37) is of the opinion that an anaphylactin or similar toxic product is produced by injection of the drug, which lowefs the vascular threshold to an unknown antigen. The distribution of the arsenic in the skin acts as a local irritant, and in addition it finds its way into the bone marrow, there to set up changes in the haematopoietic function.

That there is a definite sensitization process at work is shewn by the work of Sulzberger (39), Nathan and Munk (40) and Frei (38). These observers all found that intradermal injection of arsphenamine produced sensitization as a rule rather than as an exception. Kauder (41) called attention to the frequency with which infiltration of the drug into the tissues during an injection was followed by a dermatitis. In Frei's cases, out of 66

patients who had never received arsphenamine, he succeeded in sensitizing 8. Schoch (42) reviewed the literature of the production of sensitization from percutaneous injection quotes the results of Fuhs and Riehl who passively sensitized a normal individual with the fluid from a vesicle following a percutaneous test. The positive reaction also showed itself at a distant point on subsequent testing, and showed that the whole skin had become sensitized. The phenomenon of reactivity at the distant point is a proof of the specific allergic nature of the process, and means that it depends upon an antigen-antibody reaction. In discussing this, Schoch suggests that the sensitivity produced by the injection of blister fluid was really due to the introduction of minute amounts of arsphenamine present in the testing dose remaining in the fluid and being re-introduced into the subject. Other workers, Templeton and Skilling (43) were unable to produce sensitivity either in human beings or experimental animals by the methods of passive transference. It would thus appear that the allergic state can only be produced by active means.

Description of the Lesions produced by Cutaneous Intolerance to the Arsphenamine Series.

From the historical survey, it will be seen that it was realised that certain affections of the skin were characteristic of the effect of arsenic. With the advent of the salvarsan series into anti-syphilitic therapeutics, additions were being constantly made to the list of these, and so much so, that practically any type of dermatoses can be produced by the action of these drugs on the cutaneous structures. Ireland (44) tabulated these, and assessed them in terms of their dermatological equivalents. He found that they might be classified as:

1. Urticaria, indistinguishable from other types of the same dermatoses and doubtless a response to cutaneous vascular injury.

2. Erythema Multiforme is not common, and occurs about the third day after injection, and he states that the cause may be either a peripheral vascular injury or the stirring up of a bacterial focus by the injection, with the production of a protein or minute emboli.

3. Lichenoid simulating Lichen Planus.

4. Herpes, usually labial, but occasionally zosteriform.

5. Fixed Exanthemata, as noted by Fuchs (45) he considered uncommon.

6. Keratoses, which he also found uncommon.

7. Ninth-day erythema as described by Milian and Thesleff he noted as a transient erythema occurring about the ninth day after injection and usually passing off without complications.

8. Pruritus, either a fleeting condition or as a prodrome of exfoliative dermatitis.

9. Rarer toxic manifestations, such as Lichen Spinulosus Stauffer (46), Psoriasis, Spicca and Bennett (47).

10. Lastly what he describes as Arsphenamine Dermatitis, in which he classes all cases of dermatitis varying from the mild, transient pruritic scaling erythema to the severe oozing generalised exfoliations.

He concludes that a survey of the literature reveals a diversity of reactions, but the number of fatalities are few.

In a contribution on Herpes Zoster, Wollheim (48) quoted Butler's views on the action of arsenic on the nervous system, particularly the peripheral nerves. Under prolonged use the drug tends to accumulate in the nervous tissues to a greater extent than in others, so much so that Stokes considers that herpes arises from the irritation of the peripheral nerves. Lees was of opinion that it was a common symptom of "tubing reaction" and Stokes agrees with him. Lees also states that the occurrence of this lesion is a serious warning of hypersensitiveness. Wollheim however thinks that the lesion is as frequent in cases who have been given their injections by the syringe, and so far from being a prodromal warning of importance, he found that suspension of treatment temporarily cleared up the condition, and that it never recurred even on further exhibition of the same drugs, nor did serious manifestations of cutaneous intolerance develop.

Fixed Exanthemata.

With regard to this condition of the skin, several observers have noted and commented upon it. That it is a rare condition is generally agreed, an explanation of its etiology is varied. Naegeli (49) in describing a case which occurred in a naevus, and another in a chronic conjunctivitis considered that the localisation of the lesion to these areas was due to the hyperaemia and vascularisation. Fuchs (50) in the case of a woman with a florid secondary syphilide, who noted a brown spot on her leg, sharply circumscribed, which itched intolerably, and which "flared-up" with each injection of "914" or on the application of a solution of this drug offered no explanation. The essential condition is as Fuchs described, namely a sharply circumscribed area, which showed an exacerbation of inflammation with each injection or when a solution of the same drug is applied to it. It is not common, and subsides when treatment with the exciting agent is discontinued. The most satisfactory explanation is that of Whitfield (51) who points out that when the skin is sensitized to a protein, and an eczematous lesion develops, the whole body is rendered more susceptible to other irritants. In the case of an

eczema, itself the product of sensitization to a bacterial protein, the area of the eczematous lesion is the precise spot at which the response to another irritant will show itself. The fact that none of these fixed exanthems ever develops into a generalised dermatitis is probably due to the maintenance in the particular patient of a balance of the antibody-antigen mechanism, the flare-up being merely a localisation in the skin at a point where a definite weakness exists.

The study of the pharmacology, distribution and elimination of the arsenobenzoles following injection, yields the information that from the point of view of toxic effects, the organic compounds and the inorganic salts are identical in their action, and that therefore all the effects are due to the arsenic radical.

Pick (52) demonstrated the specificity of the arsphenamine molecule in the production of a dermatitis in a patient who had become sensitized to both arsenic and mercury. A local reaction followed the local application of arsphenamin. The reports of the Salvarsan Committee of the Medical Research Council in 1922, concluded that dermatitis could follow the administration of arsenic in whatever form it was given. In so far as deposition

and storage in the various organs of the body is concerned, those structures in which there is the greatest metabolic activity show the largest amount of the drug. Elimination naturally follows, the presence of arsenic beyond the normal amounts inducing an effort on the part of the organs to regain their normal state. The kidneys are primarily affected, since the blood receives the whole of the injection, and as they are the principal regulators of balance they are easily stimulated to restore it. They may be regarded as filters and they possess very little tissue to retain any arsenic that is not immediately disposed of. The liver, as the principal detoxicating agent is then called upon, and hence the bile receives a large proportion of the arsenic injected. The spleen, as the clearing house of the blood, is bound to contain a considerable amount, both from circulating arsenic and from the breakdown of humoral elements. It would be natural to expect that the lungs, through which all the blood must pass, would be found to have retained a share in proportion to their size, and that they have an undoubted eliminatory function is proved by the well-known clinical fact that after an injection of meta-arsenargenticum the odour of the patient's breath advertises his presence for a considerable time afterwards.

Without doubt it is with the liver and kidneys that we are most concerned, and efficient functioning of these organs is essential for the proper disposition of the drug during treatment. The work of the Lloyds showed that inefficient urinary elimination was associated with the development of toxic effects. Storage in the liver occurs with each injection, and it is natural that constant irritation due to overloading of this organ would induce toxic effects, at first in the liver itself, and later in the other tissues by the suspension of its function. As seen by the work of various authors, where the drug is retained, overloading of the tissues results, and Diasio (53) in a very complete summing up of the causes of dermatitis gave the local irritation of a storage overload as one of the main factors.

It is well-known that the liver can carry on with only a very small portion of its substance acting, and it is only in those cases where gross damage by gummata or by the action of specific liver poisons, of which arsenic in certain circumstances is one, that the liver function is disorganised, and in these cases e.g. acute yellow atrophy, death follows from this reason alone.

Kolmer found that the long bones stored the drug in appreciable amounts, and this may be the foundation of

the observed haematopoietic effects noted by Moore. On the other hand the leucopenia may develop from the exhaustion of the blood forming tissues due to the intensity of the reaction.

With regard to the deposition of arsenic in the skin, it is most natural to expect to find it in or near the blood vessels, since it is carried by the blood stream. We agree with Cannon and Karelitz that the micro-chemical picture may be likened to a snapshot of the process, since the taking of a continuous picture presents very great difficulties. That the pentavalent arsenicals show a definite affinity for the ectodermal tissues is granted, but that they localise their effects to this part of the skin is not entirely proved, for the observed skin lesions following tryparsamide or Stovarsol therapy are in no way different from those following the tri-valents. That the exhibition of these drugs is not followed by toxic cutaneous manifestations so frequently as the trivalent arsenicals, is most probably due to their comparatively low arsenic content. The explanation of the concentration of arsenic around the blood vessels of the corium when trivalent arsenic is used, is that the sections were taken at a stage when this had been but lately deposited, and had no time to be dispersed, since death had taken place.

Kyrle's views that the persistence of the irritation produces the changes in the skin appears to be the correct one, the parakeratoses which have been observed being one manifestation, while another, depigmentation, is due to the destructive action on the pigment cells.

That arsenic is a vasculo-toxin is indisputable. Its effect in producing an endarteritis in the cases recorded by Robinson and Ronchese, as well as those of Meser, show that degeneration does actually follow. It is probably one of the chief localising factors in those eruptions which are not directly attributable to the specific sensitization phenomena, since the anaemia and malnutrition of local areas of the skin is the ideal nidus for the action of toxic proteins, whether of bacterial or chemical origin. The reason for the selection of certain areas of the body for the exertion of this vasculotropic effect is that in those areas a congenital weakness does exist (Kyrle). They are analogous with the formation of multiple aneurysms, for while the vis a tergo factor in the production of these is admitted, it does not explain why that part of the artery wall should have been selected for the action of the syphilitic toxins.

In the brief review of the literature presented above, the views of various observers are given in an

attempt to arrive at a working hypothesis of the causation of skin complications. The factors operating in the production of the dermatoses are either: (1) specific sensitivity of the body cells to the arsenical element of the various compounds, or to the different radicals of which the compound is made up, and (2) the effect of infection upon the individual.

Idiosyncracy to the drug or to the elements in its composition is a factor which might show itself in the skin or elsewhere in the body c.f. arsenic asthma.

The effect of infection is a complex one, and the factors operating to produce this effect will be more easily understood when the lesions themselves are being considered.

These factors are not alone the cause of a dermatosis for it is the summation of several elements which go to produce the lesion on the skin, in addition to certain predispositions on the part of the patient.

The best summary of the theories advanced to explain the dermatoses is the work of Diasio (53) which he tabulates as follows:

General or Systemic Factors.

1. Lowered resistance to infections.
2. Lowered tolerance to the arsenicals.

3. Functional abnormalities, e.g. seborrhoea, etc.

4. Vascular injuries caused by the metal.

5. Altered metabolism of the drug.

6. Subnormality of other storage depôts, such as the liver.

7. Presence of sensitizing products inducing a state of allergy.

Local.

1. Irritation produced by external irritants, such as chemical agents applied to the skin, and occupational hazards.

2. Irritation locally due to storage overload of the arsenic.

3. Localisation due to the presence of an independent dermatosis.

A Review of 96 Cases of Arsenical Dermatitis, Occurring during Treatment for Syphilis at the Salford Municipal Clinic.

In compiling this review it was felt that a mere record of the total number of injections during the time that they occurred would be unnecessary. It is not intended to give an appraisal of the toxicity of the various compounds used, nor the percentage of cases of dermatitis in a series of treated cases of syphilis. In the former, unless the patients are being treated exclusively with one drug any attempt to evaluate the toxicity is useless,

and percentages can mean anything or nothing. It is however, useful to know that the exhibition of a certain class of compound has a greater or less dermo-toxicity, and in this connexion the arsenicals are referred to as trivalent or pentavalent.

Type of Arsenical Preparation and Relation to Dermo-Toxicity.

No difference was noted in the incidence of dermatitis according to the type of preparation used, since both these classes of the arsenicals produced skin lesions.

With stovarsol (a pentavalent arsenical given by mouth) dermatitis was observed in seven cases, and in five of these the eruptions developed during the administration of the drug. In two of these cases the trivalents had also been exhibited, but changed in one case because of prodromal symptoms of intolerance, and in the other, while the stovarsol did not have any ill-effects, change to sulpharsenol produced an eczematous lesion on the leg.

Sulpharsenol was less frequently used than the other "914" preparations, but it produced a greater incidence of skin intolerance. 16 cases were observed, and while the dermatitis developed during the actual exhibition of the drug in only four of these, we are of the opinion, in common with Belding and Goldman(54) and Fordyce, Rosen

and Myers (55) that this form of trivalent arsenical predisposes to the onset of dermatitis. The effect of sulpharsenol in bacterial infections is to produce a marked improvement in the condition. In gonococcal epididymitis and prostatitis, the exhibiton of this preparation is sometimes dramatic. It is assumed that the action is two-fold, partly a chemotherapeutic one, and partly the effect of protein shock. The latter may be effected either by stirring up the gonococcal focus to liberate more gonotoxin, or by tissue destruction at the site of injection with the production of a non-specific protein, which acts as a stimulant to antibody formation. It may be assumed that the chemotherapeutic part played by this drug is small, since the exhibition of other trivalent arsenicals by the intravenous route is not followed by any ameliorating effect (based on personal observations, to be published), and moreover it has not been noticed that in cases of gonorrhoea which are being treated co-existently with syphilis, that there is any shortening of the period during which the active gonorrhoea shows itself. It follows, therefore, that this preparation must exert its principal action by the stimulation of toxic foci to produce more toxin. The reaction of the healthy body is an equal and opposite one, with the

result that antibody (antitoxin) is formed. In a patient who has both a toxic focus and in whom there is the added effect of the depressant action of arsenic, it follows that lesions will develop at the point of maximum irritation, namely in the skin, where a combination of forces, e.g. the seborrhoeic diathesis, or the deposition of arsenic where elimination by other routes is deficient, or local areas of diminished resistance, are in action.

With the other arsenical compounds this overloading of the tissues must produce a constant depressant effect, which tends to permit unchecked the toxic action of bacterial poisons, whether acquired or inherent.

Influence of the Stage of the Syphilis when Treatment was Commenced on the Occurrence of Dermatitis.

The degrees of syphilis at this clinic are divided into eight groups, viz.:

1. Sero-negative primary syphilis.
2. Sero-positive primary syphilis.
3. Sero-positive secondary syphilis, with early skin rash.
4. Sero-positive secondary syphilis, with fading skin rash.
5. Latent syphilis with no demonstrable lesions.
6. Tertiary or Visceral syphilis.

7. Neuro-syphilis.

8. Congenital syphilis.

In the first four degrees of syphilis, where the action of the syphilitic toxin is the cause of skin lesions, the incidence of dermatitis during treatment was no greater than in the later or tertiary (visceral and neuro-syphilis) and in congenital syphilis the lowest incidence of all was noted. The figures for the incidence of dermatitis are as follows:

1. = 12·5% e.g. 12 cases
2. = 12·5% " 12 "
3. = 10·4% " 10 "
4. = 12·5% " 12 "
5. = 19·8% " 19 "
6. = 12·5% " 12 "
7. = 12·5% " 12 "
8. = 6·25% " 6 "

In fact they show a remarkable uniformity. The "latent" degree of syphilis, where no demonstrable lesions due to the disease are present, shows the highest incidence, being twice as great as those where an early skin rash had developed. In this stage (5) the action of spirotoxin is not sufficient to cause a reaction, but yet the cutaneous tolerance to the arsenicals is less than

in the other types. These are patients in whom, while the disease processes are not sufficiently active to produce a suspension of function of vital organs, (liver, kidney, etc.) yet the additional strain of arsenic storage may be enough to cause a temporary suspension of their function, or at least to modify it. Yet since there was no increase in the incidence in the other late stages, it cannot be said that this is a factor which is of primary importance.

It might be expected that in congenital syphilis (8) where the patient may be said to be in a state of super-saturation with treponemata, the effect of the killing of large numbers of the organisms would precipitate the effects of an added toxic substance, but Nabarro (56) has shown that children tolerate the arsenicals much better than adults, except where personal idiosyncracy exists, when they are just as liable to exfoliative complications.

It can therefore be said that the onset of dermato-logical accidents is in no way comparable with the degree of the syphilis.

Type of Skin Lesion and Factors Associated with their Production.

The factors which were specially considered were as follows:

Type of Reaction	Ery-thema	Urti-caria	Eczema	Exfo-liative	Herpes Zoster	Herpes Simplex	Herx-heimer	Xero-dermia	Sebor-rhoeic Dia-thesis	Pity-riasis Rosea	Remarks
Total No. of cases	39	6	18	6	9	=	7	3	5	1	Represents total no. of cases with lesions of the type named.
Average no. of injections	8	9	10	7	12	=	2	8	13	32	
No. of times treatment was resumed	21	5	5	Nil	7	=	7	1	2	1	i.e. resumed with out ill-effects.
Recurrences	9	1	12 persistent	2	2	=	-	2	3	-	

1. Average number of injections given before the lesion appeared.

2. Whether treatment was resumed after the lesion had disappeared, or when it was felt that it was safe to do so, using the same agents.

3. Whether the dermatitis recurred.

The types of dermatoses observed were:

a. Erythematous.

b. Urticarial.

c. Eczematous.

d. Exfoliative.

e. Herpetiform (Zoster or Simplex).

f. Other types e.g. Xerodermia, Seborrhoea, Pityriasis Rosea.

g. Herxheimer (skin).

It will be convenient to tabulate the "Reactions" under the three headings above, and it becomes immediately evident that except for the eczematous and exfoliative types, the others show a very strong resemblance to each other in the light of these headings.

In certain cases treatment was not resumed with the same drug, as it was felt at the time that the element of risk was too great.

With the exception of the "explosive" types of reaction, e.g. the exfoliative and the Herxheimer, it will be seen that no very great differences exist in the number of injections given before the onset of dermatitis.

It is when one considers the results of resumption of treatment that the various types become of value as a guide to their causation. It will be noticed that in all the cases above, except the exfoliative, the eczematous, xerodermic, and seborrhoeic, treatment was resumed in the great majority without recurrence, and when this did occur, the lesion was repeated, and there was no tendency to the later development of exfoliative dermatitis. In the case of exfoliative dermatitis itself, while it is surprising that the average number of injections figure is so high, it can be explained by the inclusion of one case in which no less than 12 injections were given. That this condition may occur during the 1st-3rd injection was noted by several observers, but in this series it was somewnat later. On the basis of induced hypersensitiveness this would be easily explained, as some time must elapse for the condition to develop.

There are cases, however, in which there is an apparently congenital predisposition to arsenical toxic reactions, and in these this develops with the first or second injection.

The Xerodermic and Seborrhoeic types are in all probability analogous to the eczematous, but the seborrhoeic factor in one and the peculiar dry, hard condition of the skin in the other were too pronounced to include them in that group. The results of continued treatment with arsenic was the same, as the majority of these lesions persisted, and tended only to become cured when arsenic was withheld. They never developed into the severe type.

Included in the eczematous lesions was one undoubted case of a "fixed exanthem", who developed a seborrhoid after 10·35 grammes of trivalent arsenic, in 22 injections. This lesion invariably showed an exacerbation with each arsenical injection, but always remained circumscribed and never showed any tendency to spread and involve other areas. Lees (in a personal communication) is of opinion that these are probably psoriasis lesions, but their disappearance after cessation of treatment is proof of their specific nature, and arsenical in origin. The Herpetic lesions were with two

exceptions Zosteriform. In the true condition of herpes zoster, local prodromal signs are present, and it is assumed that a neuritis is an early sign. Certainly the great master of syphilology, Hutchinson, sought to establish the true toxic effect of arsenic upon the peripheral nerves and correlate the later appearance of herpes. In none of the cases under review were signs or symptoms of peripheral nerve involvement present. That peripheral neuritis does follow the exhibition of the arsenicals is indubitable, but there appears to be little or no connection between the onset of dermatitis and this complication. In three cases of neuritis prior to dermatitis, the types of lesion they preceded were erythema in two cases and the other was an exfoliative dermatitis.

Robinson (57) in a review of postarsphenamine dermatitis found that the majority of patients (70%) gave a history of prodroma. In this series the number was 5 (5·2%). These were of the nature of pruritus 2·1%, vasodilator 2·1%, pains in the bones and in the joints 1% each. Neither Kyrle nor Cannon and Karelitz believe that any relationship exists between the occurrence of prodroma and the onset of dermatitis, and from this they argue that they have no common origin. Nevertheless the

fact that these conditions are present in cases under treatment with arsenic, and that they develop dermatitis at a later state must surely indicate that if they in themselves have no common origin, they are at least pointers to the instability of the patients' tolerance to arsenic. The types of lesion which they preceded were:

1.	Vasodilator...	Eczematous, and Xerodermia, which tends to support Kyrles view that the angio-neurotic patient (early nitritoid crisis) did not develop actue dermatitis.
2.	Pruritus	Herpes Zoster, and Erythema.
3.	Bones	Herpes Zoster.
4.	Joints	Eczematous.

The Herxheimer Reaction and its Relation to Dermatitis.

Seven cases of cutaneous Herxheimer reaction were noted and these developed on an average after the second injection. In every case treatment was resumed and in only one did a dermatosis develop at a later date, in the case of a "bad reactor" to the arsenobenzoles.

The mechanism of the Herxheimer reaction is assumed to be the result of the sudden liberation of "spirotoxin" from large numbers of killed treponemata following an

injection of arsenobenzole. The rash in secondary syphilis is the external evidence of an intense toxic process, each minute focus in the skin being the reaction around one or more of the actual organisms. The destruction of these organisms and the liberation of spirotoxin would be expected to intensify the skin eruption, but it was observed that only one of the cases where a Herxheimer reaction developed was a "florid secondary" syphilide. Five were primary syphilis, and one was a latent case. The reaction is therefore a true provocative one, and it has been repeatedly observed that the Serology, even in seronegative cases at the outset, almost invariably increases to give a positive result, after one or two injections. (Burke, in a personal communication.) The skin Herxheimer must therefore be analagous to the secondary rash, in that it is due to an increase in the amount of circulating "spirotoxin". The serology in both is the same, as the body reacts with the production of lipo-protein reagent, whether it be a true antibody or a breakdown product of spirochaetal action on the tissues. We conclude by stating that there is no relationship between the occurrence of a Herxheimer reaction and later onset of dermatitis.

The Effect of Bismuth in the Production of Dermatitis.

As a large number of cases in all groups had bismuth alternately with arsenobenzole, it is not possible to fix on the arsenical as the causa causans of the dermatoses. The toxic effect of bismuth is chiefly on the kidneys, and Stokes considers that skin lesions resulting from bismuth therapy are rare. In this series, twenty-seven cases of dermatitis occurred while the patient was receiving bismuth. The probable etiology is that the effect of the bismuth is to displace the arsenic, and where this is present in large amounts in any organ e.g. skin or liver, a greater toxic concentration is produced in the organ. Irritation of the surrounding cells then follows and so dermatitis is produced, and certain cases of jaundice. The jaundice in this case is the type of true toxic jaundice, where there is inflammation and swelling of the hepatic cells, with increase in size of the liver. This is distinct from the most usual catarrhal type, due to a concurrent duodenitis.

Relationship of Jaundice and Dermatitis.

The majority of observers are agreed that no definite relationship is present between these two toxic manifestations. In one case jaundice and dermatitis were

co-existent, but in the majority, jaundice developed after the dermatitis, in 15·6% of the cases. Jaundice preceded the dermatitis in 3·1%. At the same time there is present in some of these cases a definitely toxic element, and the effect is bound to be the creation of an added strain upon the hepatic function. This, however, can be grossly damaged without breaking down, but eventually the "storage overload" becomes too much for it, elimination is forced more and more on to other organs and their inherent weaknesses are thus exposed.

Previous Dermatoses and the Onset of Dermatitis.

In 13·5% of the cases under review skin lesions were present before treatment was commenced, and only two subsequently developed dermatitis. In neither of these was the dermatitis compatible with direct arsenobenzole intolerance, one case incurring an impetiginous, the other an eczematous skin eruption, neither of which persisted.

Seasonal Incidence of Dermatitis.

A factor which has been overlooked by all workers on this subject has been the seasonal one. They have

stressed the occupational factor, but this is one which can only have a remote bearing on the real cause of the condition, since in those trades where dermatitic hazards are operating, the mere fact that a patient is receiving injections of arsenic will not inflict him with a skin complication to the exclusion of his fellow-workers. The seasonal factor, however, has a distinct bearing upon skin respiration and it is tne importance of this function which it is desired to stress.

Where deficient elimination is present by the more rapid channels in the body, it is agreed that an added strain is thrown upon those whose action is not so spectacular. The skin respiration is the simplest physiological means of maintaining a healthy tone on the surface of the body, and where this is hampered, the natural discarding of dead epithelim, and the removal with it of irritant substances is retarded to such an extent that accumulation of these foreign substances occurs. It was observed in this series that in the Autumn and Winter months more skin complications occurred than in the Spring and Summer. The actual figures are:

Autumn (September, October, November) 30.4%

Winter (December, January, February) 32·6%

Spring (March, April, May)	16·4%
Summer (June, July and August)	20·6%

In the Winter months it is the custom for the inhabitants of these islands to clothe themselves to the fullest extent, and in addition the incentive to indulge in exercise and free movement is diminished. There is a definite tendency to hug the fire and spend as much time as possible within doors. The skin respiration is thereby damped down, and the accumulation of waste products of all types, be they bacterial or arsenical, is encouraged. If to this is added any cause whereby elimination in other ways is also at a disadvantage the optimum conditions for irritation (mental or cutaneous) are produced. In the Spring there is a physiological resurgescence, and it is reflected again in a lower incidence of dermatitis, being half that of the preceding six months. The slight rise in Summer is due to the external influence of solar rays, and this is reflected in the onset of a severe erythematous dermatitis in a case receiving stovarsol, and involving the face, trunk, arms and legs. It appears, therefore, that the free interchange of air at the skin surface is essential to maintain a healthy tone in this organ, with its constant stimulation to excretory activity.

As further proof that this surface respiratory and metabolic activity is of vital importance in the conception of the etiology of the dermatosis, it has been shown by Nabarro (56) that children do not suffer so frequently from skin complications during treatment for syphilis. This may be attributed to the greater cutaneous metabolic activity of these ages, together with a free surface respiration, promoted by general muscular activity and the rapid metabolic processes.

Conclusions.

Dermatitis occurring during treatment with the arsenicals is therefore attributable to a variety of factors, or to the combination of several of them. Summarised, they are as follows:

1. Exfoliative, an expression of a true antigen-antibody reaction, with the element of cutaneous sensitization due to a specific allergic response to arsenic.

2. Predisposition; where the patient would have developed a dermatitis (given the requisite stimulus of trade hazards, emotion, drugs, foci of infection, etc.) in any case. These lesions are the approximation to the type of Erasmus Wilson, with symmetrical lesions, showing lichenification, weeping, etc.

3. Transient early erythemata, where after 5-9 injections the patient develops a dermatitis, which after treatment never returns, and to whom arsenic may be given with impunity. These cases may be explained as the restoration in elimination - intake balance, or as the balance between an antigen-antibody reaction.

4. Failure of Elimination; where the dermatitis is the expression of the breakdown of one or more of the excretory organs of the body. In all cases of overloading of an excretory mechanism, the evidence of failure of function follows. The natural respiration of the skin carries with it the elimination of foreign substances, and the retention of this is bound to cause irritation. The type of eruption is merely an expression of the particular reaction of the patient, their very multiplicity and diversity being a proof of this, for what in one patient would be a streptococcal fissure, in another it becomes an impetigo.

The empirical use of such toxic drugs as arsenic is always bound to be followed by reactions, whether he be sensitive to the drug itself, or whether he be in addition the cockpit of a fierce bacterial war. Even to-day we are no nearer the discovery of the therapia sterilisans magna of Ehrlich, and in the meantime we

continue to use the tree-trunk of modern therapy to pick out the acarus which stands for the syphilitic process. We may destroy it wholly, but in so doing we are bruising the tissues of the host to such an extent that sometimes the last state of the patient is worse than the first.

In no other disease more than syphilis is the aphorism that we are "treating a patient, not a disease" more true, for the action of the arsenicals is not primarily as a sterilising agent. The Treponema Pallidum exposed in vitro to the drugs are not materially affected (Levaditi (58)). It is necessary that the living tissues combine with all or part of the drugs to produce from these comparatively inert substances a compound lethal to the organism, whether it be as the "arsenoxyl" of Levaditi, by oxidation and reduction as postulated by Voegtlin and Smith or by the abstraction of oxygen from the Treponema by the arsenobenzoles as Schumacher (59) has tried to show. Burke (60) has pointed out that the manufacture of the toxalbumens (arsenoxyl) throws a strain upon the producing-tissues of the patient, and it is evident that where this function is deficient, a quantity of unused drug is circulating in or being eliminated from the blood stream. The elimination of

arsenic can never be an indication of the effect of the drug upon the invading organisms, since the amount of combined arsenic in the tissues must remain for a varying length of time, until the body finally discards it, its work done.

The future will give us a drug, a more rational equivalent to Ehrlich's effective sterilizing dose, which when introduced into the body produces an equal and opposite effect upon the invading organism, and each moiety will be utilised in the production of the effect for which it was intended, the final and complete destruction of the Treponema Pallidum.

REFERENCES.

1. Bechet, P. E. — Archives of Derm. and Syph. 23: 114: 1931.
2. Hutchinson — Archives of Surgery.
3. Cushny — Pharmacology. 1928.
4. Prosser-White — Occupational Affections of the Skin. 1928.
5. Fischer, H. — Derm. Wochenschr . 1926. p.805.
6. Butler — Mater. Med. 1906.
7. Kolmer — Chemotherapy. 1926.
8. Stokes — Mod. Clin. Syphilology. 1927. 168.
9. Kolmer — ibid.
10. Bulmer — Journ. Pharm. and Exper. Ther. 1923. 34: 301:
11. Osborne, Putnam & Hitchcock — Arch. Derm. & Syph. 25: 3: 1932.
12. Fordyce, Rosen & Myers — A. J. Syph. 1923. 19: 209:
13. Kolmer — ibid.
14. Fordyce, Rosen & Myers — A. J. Syph. 1923. 7: 225 and 528. ibid 1924. 8: 34: and 264.
15. Lloyd and Lloyd — Brit. Journ. Ven. Dis. Jan. 1930. VI: 1.
16. Kolmer — ibid
17. Kolmer — ibid
18. Justus — Derm. Ztschr. 12: 277. 1905.
19. Brunnauer — Arch. f. Derm. u. Syph. 129. 186-198. 1921.
20. Osborne — Arch. Derm. and Syph. 12. 773. (Dec) 1925.

21. Osborne — ibid. 18. 37 (July) 1928.

22. Cannon and Karelitz — Arch. Derm. and Syph. 28. 658: 1933.

23. Kyrle — Vorlesungen uber histobiologie der meuschlichen Hant und ihrer Erhraukungen. Berlin. Julius Springer. 1925: vol. 1. p.118.

24. Moser — (quoted by Jaffein in Der Handbuch der Salvarsantherapic. Berlin 1925. vol. 2. 259.)

25. Robinson, H. M., — Amer. J. Syph. Octo. 1929. p.536.

26. Kraetzer, A. F., — J. A. M. A. 94: 1035. 1930.

27. Ronchese, F., — A. J. Syph. xv. 1931. p.368.

28. Moore and Keidel — Arch. Int. Med. 22. 716: 1921.

29. Stokes and Cathcart — Arch. Derm. and Syph. 7: 14: 1923.

30. Ireland, F. M., — A. J. Syph. 16: 22: 1932.

31. Milian — Bull. et mem. d. Hop. de Paris. 43: 1055: 1919.

32. Stokes and Cathcart — ibid.

33. Harris — quoted by Stokes and Cathcart. ibid.

34. Auer — " " " " " "

35. Stokes and Kulchar — Brit. J. Derm. and Syph. XLVI: 3. 134. 1934.

36. Lees — Diagnosis and Treatment of V. D. 202. 1931.

37. Schiff — Ann. d. mal. vener. 16. 257: 1921.

38. Frei — Klin. Wehnschr. 7. 1928.

39. Sultzberger — Arch. Derm. and Syph. 20: 669: 1929.

40. Nathan and Munk — Klin. Wehnschr. 7: 1125: 1928.

41. Klander — Arch. Derm and Syph. 5. 486: 1922.

42. Schoch, A. G., — A. J. Syph. Jan. 1930.

43. Templeton and Skilling — A. J. Syph. Oct. 1930.

44. Ireland, F. M., — ibid.

45. Fuchs — Deutsche. Med. Wochen. 46: 11: 1920.

46. Stauffer — Arch. f. Derm. und Syph. 154: 217: 1929.

47. Spicca and Bonnett — Arch. ital. di dermat. sif. 4: 241: 1929.

48. Wollheim — A. J. Syph. 1. 1931.

49. Naegeli, O., — Cor-Bl. f. Schweig. aerzte. 39. 1917. (quoted by Fuchs)

50. Fuchs — ibid

51. Whitfield, A., — viii International Congress of Derm. and Syph. p.112. 1930 Copenhagen.

52. Pick — Dermat. Wehnschr. 78: 15: 1924.

53. Diasio, F. A., — A. J. Syph. Oct. 1930. 483.

54. Belding and Goldman — Boston M. and S. Journal. 193: 19. 1925.

55. Fordyce, Rosen & Myers — A. J. Syph. 1925. 9: 1.

56. Nabarro, D., — B.J.V.D. Jan. 1934.

57. Robinson, H. M., — Southern Med. Journ. 23: 711: 1930.

58. Levaditi — Ann. l'Inst. Pasteur. 1909: 23: 604.

59. Schumacher. — Arch. f. Dermat. und Syph. 1925: 149: 13.

60. Burke, E. T., — Lancet. 1931. 1127.