Excretory irritation and the action of certain internal remedies on the skin / by David Walsh.

EXCRETORY IRRITATION

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AND

THE ACTION OF CERTAIN INTERNAL REMEDIES ON THE SKIN.

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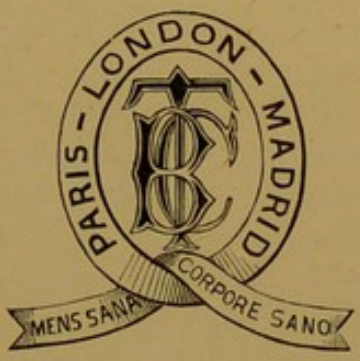

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PREFACE

This brief monograph reproduces the substance of a graduation thesis. It discusses somewhat more at length than was possible in the original the relation of certain inflammations of organs, especially the skin, to the excretory functions of the body. For many of the clinical and pathological facts advanced, the author has been indebted to the works of Kaposi, Malcolm Morris, Radcliffe Crocker, McCall Anderson, Jamieson, Unna, Pringle, and other well-known writers upon dermatology.

Note.—It may be noted here that little mention has been made of the nervous element in disorders of the skin, an omission that may be shortly explained as follows: Where the neurotic origin is central, the theory of irritation by skin elimination of course does not apply. On the other hand, when the origin is peripheral, the two pathological conditions (*i.e.*, of skin-cells and nerve-ends) appear to be inseparably dovetailed. In other words, the ultimate distribution of nerve-endings in relation to cells of the epidermis is so universal that it is hardly possible to conceive irritation of the one apart from the other. In the following pages, then, the phrase 'excretory irritation of the skin' will be taken to include irritation of either epithelial or nerve cells.

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I.

EXCRETORY IRRITATION.

EXCRETORY IRRITATION IN INFLAMMATION OF SKIN AND OTHER ORGANS.

APOLOGIA.

In 1890, at the Birmingham meeting of the British Medical Association, the present writer read a short paper upon 'Dermatitis as an Excretionary Symptom.'* His main object was to show the possible relationship of some forms of dermatitis to the excretory function of the skin. For that purpose a comparison was made of various rashes associated with internal causes, such as drugs, exanthems, gout, and other specific disorders. In each of these diverse conditions there were the common features of an inflamed skin and a blood-supply containing a well-defined irritant. Further inquiry showed that the irritant in almost every case affected the skin merely as one of a group of organs more or less actively engaged in excretion. In other words, the dermatitis was simply one of a general series of excretory irritations. The further application of this conclusion has led to results that in the present state of knowledge it seems impossible either to prove or to disprove. At the same time, if there be any truth in the theory of direct excretory

* *Medical Press and Circular*, October 22, 1890.

irritation as a cause of some forms of skin inflammation, it seems difficult to avoid the further proposition that a similar process may affect other excretory organs.

EXCRETION.

In the following pages the term 'excretion' will be taken to mean the process which results in the throwing off by different organs of certain normal and abnormal substances from the body. By 'normal substance' is meant any material found in the products of excretory glands, such as water, salts, etc.; 'abnormal' is applied to unusual or accidental materials, as, for instance, urea in milk, albumin in urine, mercury in sweat.

The modern view is that the products of excretion are chiefly the result of the metabolic activity of the essential cell. As Dr. Lionel Beale says: 'The characteristic substances present in the secretion are not merely separated from the blood, but are actually formed by the so-called secreting cells.'* Elsewhere he states that water is not passed on by the excreting cell as water, but is elaborated by the cell. That assumption may or may not be correct, but the specific micro-organisms of some infectious diseases must pass through the excretory cells alive and presumably unaltered, if we are to judge from the generally assumed after infectivity of the skin. But if a living micro-organism be able to pass through the excretory cell unaltered, why not urea, water, and other substances circulating in the blood? At any rate, we know that urate of soda and the pigments of jaundice may be sometimes seen upon the skin surface. Still, it seems likely that few substances pass unaltered through the excretory epithelium, and that all, or nearly all, the

* *Lancet*, 1896, vol. i., p. 986.

characteristic materials of the various excretions are elaborated in the cells. Any material taken up from the blood must become for the time being a factor in the metabolism of the cell, upon which it may or may not act as an irritant, and by which it may or may not be modified.

INTERNAL IRRITANT.

This term will be used to signify any substance circulating in the blood which has the power of irritating the excreting cell, or, more generally, of setting up an inflammation in any organ by which it may be eliminated from the body.

The main channels of exit of matters from the body are, of course, the lungs, skin, alimentary canal, and kidneys. Each throws off water, carbonic acid, and nitrogenous products of more or less complex composition. In our present state of knowledge we may assume that their epithelial structures exert a selective action upon the materials brought to them by the blood. To a great extent the function of the various eliminating organs is interchangeable, so that they may act vicariously the one to the other.

The foregoing statements are readily illustrated by the observations of everyday life and medical practice. By taking active exercise we throw the stress of elimination upon the skin and lungs. A compound colocynth pill excites copious excretion from the alimentary canal. Ample draughts of water or of broom tea increase the flow from the kidneys. Indeed, it is hardly too much to say that until recent years practical medicine was mainly based upon the interchangeable function of the excretory organs, which were relieved at each other's expense by

the familiar processes of purging, sweating, and diuresis. Even at the present time the control of the excretory functions may be regarded as the corner-stone of curative medicine.

But while the physician is thus able in many instances to determine the activity of various excretory channels, it is often by no means clear how unaided Nature avails herself of the interchangeability of excretory function. So far as the elimination of normal substances (water, carbonic acid, and nitrogenous matters) is concerned, the process by which the balance of excretion is maintained seems fairly intelligible. In the case of a labourer in a hay-field, the maintenance of a standard body-heat appears to be intimately connected with the result, through a complex nervo-vascular apparatus. The increased tissue heat and the high external temperature, acting directly and indirectly, charge the surface of the skin with blood ; there is copious sweating, which reduces the body-temperature by evaporation, and to a certain extent lessens the kidney excretion. The amount of material vicariously given off by the skin is represented by the difference between the scanty urine and the amount of urine that the labourer would have passed had he not been in the hay-field, but under ordinary conditions. If the same man took a Turkish bath, he would lose about two pounds in weight, but that loss would only in part represent vicarious kidney elimination, as the actual amount of urine excreted during the bath would not be very materially reduced. On the other hand, it should be noted that the flow from the kidneys is increased by the exposure of the skin to cold, while it is markedly lessened by free purging.

In the cases mentioned, the stimulating influences of

the shifted eliminations are before us, but they are by no means so in the case of abnormal or accidental substances that have gained entrance to the system, or have been elaborated therein. There is a good deal of irregularity, for instance, in the elimination of iodine and of the poison of gout. This may no doubt be partly explained by the activity or sluggishness of various organs. Quantity is another point: a small amount of an accidental substance in the blood, *e.g.*, iodine, is naturally eliminated by its usual organ of exit, the kidney. When introduced in excess, however, one may easily imagine how it might overflow, as it were, into other channels of exit. A few grains of sulphur taken by the mouth would in the usual course be thrown off by the bowel or the kidneys, whereas a larger dose would escape in part by the lungs and skin. Nevertheless, in the majority of drug rashes the occurrence and the severity of the skin lesion appears to be little influenced by the amount of the irritant taken into the system. The state of the local blood-supply is probably another factor of importance in determining the excretory activity of any particular organ. The skin of an individual in the hot-room of a Turkish bath is reddened and full of blood. In his case the distended cutaneous capillaries are brought into close relation with the glandular and Malpighian epithelium, so that for the time being the vascular arrangements of the skin closely resemble those of the kidneys. From this passing glance, it will be evident that the subject of the vicarious excretion of abnormal or accidental substances from the blood is full of difficulties. The writer's view is that the determination of the excretion of normal as well as of abnormal substances depends upon a variety of circumstances in which idiosyncrasy, the functional activity,

selectiveness and competency of organs, the amount and nature of the material to be excreted, and the conditions of environment all play essential parts.

IDIOSYNCRASY.

It is not clear why one person should have a rash from an irritant, external or internal, while another, apparently under similar conditions, escapes any such trouble. Nor can we always account for an eruption clearing up in one individual, while it becomes chronic in another. A depressed state of health may, of course, predispose to invasion, and also delay the reaction of healthy tissues, whereby noxious material is got rid of by phagocytosis and in other ways. Such explanations, however, obviously do not cover the whole of the ground, and we can only say that there seem to be personal predisposing factors which we are unable to explain, and these we sum up under the convenient term 'idiosyncrasy.' Formerly, many authorities assumed a vulnerability of skin, which they called the 'eczematous' or 'dartrous' diathesis. That there is a difference in the resistance of individual epithelial structures seems certain. Thus, to most folks a flea-bite is a mere trifling puncture, but in a few it gives rise to an acute circumscribed œdema as large as a shilling or a florin.

THE FUNCTION OF NORMAL EXCRETION.

This subject need not be discussed here at any length. It is mainly effected by organs that excrete by virtue of epithelial structures variously arranged, but which all agree in having active epithelium cells on a basement membrane, closely connected with the blood-supply.

THE EXTENT OF NORMAL EXCRETION.

In the light of many clinical and pathological facts it seems likely that physiologists hardly recognise the full nature and extent of the process of excretion. Any mucous membrane of the body, for instance, may take on an active eliminatory action in the presence of many of the substances circulating in the blood to which we have given the name of 'internal irritants.' Thus, the lining of the nasal cavity, under ordinary circumstances, is a simple mucus-forming membrane, but when the blood is charged with iodine it may, presumably by the excretion of that drug, give rise to acute coryza. Or take the intestine of a person suffering from chronic nephritis; the accumulated urinary products in his system seek exit by the bowel, and diarrhœa results, or they may in a similar way inflame the bronchi. In both instances a simple mucous membrane is for the time being converted into a vicarious excreting membrane. In the case of a gouty person we may see every mucous membrane in the body thus attacked in turn, so that he may suffer from conjunctivitis, coryza, pharyngitis, laryngitis, bronchitis, dyspepsia, diarrhœa, cystitis, or urethritis, while his ordinary excretory organs are prone to severe recurrent and chronic inflammations. Turning to drugs, we may take the example of mercury absorbed through the skin and excreted by the salivary glands and bowel, with attendant salivation and purging.

A kind of vicarious excretion, moreover, appears to affect the serous and synovial cavities. That is to say, the external irritants have the power, not only of irritating the excretory outlets, but also of inflaming the lining membranes of joints, bursæ and serous cavities.

Recently the writer's theory of excretory irritation has been applied by Mr. Sydney Stephenson* to the iris, which most ophthalmic surgeons regard as the organ that secretes the aqueous humour. It will be noticed that the terms 'secretion' and 'excretion' are used here as practically synonymous. Whether the products of glandular activity are or are not thrown off from the body immediately is simply an accidental particular. Moreover, from what has been already said, it seems certain that almost any of the so-called secreting membranes may become changed into excreting membranes. In the present article 'excretion' will be used in a wide sense, so as to include the less general term 'secretion.'

SKIN DISEASES—CLASSIFICATION.

Diseases of the skin may be divided, after Kaposi,† into (1) *Idiopathic* and (2) *Symptomatic*.

1. This division, the *Idiopathic*, includes lesions 'produced by some agency affecting the skin directly,' as scabies, heat, parasites, friction.

2. *Symptomatic*, described by Kaposi as 'those which are caused by the conditions of the blood and fluids in the organism itself, or by the state of the general system, or are caused by disease of individual organs or systems, or come from hereditary conditions. Such diseases are the essential or incidental symptoms of these states and conditions . . . symptomatic skin lesions.'

Kaposi here recognises the casual connection between

* 'The Excretory Origin of Certain Forms of Iritis and Cyclitis': *Lancet*, February 29, 1896.

† Kaposi's 'Diseases of the Skin,' pp. 63, 64, English translation.

symptomatic skin lesions and morbid conditions of other parts of the body, whether of blood or of organs, whether acquired or inherited. So far as one knows, however, he has not attempted to trace any actual bond between the skin symptoms on the one hand and the associated morbid conditions of blood and excretory organs on the other.

The following rough plan of etiology has been adopted by the writer to assist in the present inquiry :

A. **Predisposing Causes.**—Sex, age, and other special conditions of the individual or his environment.

B. **Determining Causes**, which may be summed up in the one word 'irritation.' The nature of the irritant is often obscure, but it seems probable that the greater number of skin diseases may be traced ultimately to the action of irritants, which may be classified into (1) external and (2) internal.

Class I. **External Irritants**: subdivided into (*a*) *mechanical*, (*b*) *chemical*, (*c*) *mechanical and chemical combined.*

(*a*) *Mechanical*, such as heat, which is the exciting cause of a rash induced by a Turkish bath or by working in front of a furnace; friction, as from clothing; parasites, such as scabies or *Tinea tricophyton.*

(*b*) *Chemical*, *e.g.*, lime or sugar (bricklayers' and sugarbakers' itch) ; medicinal applications, for example, cantharides, mustard, croton-oil, iodoform, tar ; soaps, especially the commoner sorts, in which there is an excess of free alkali.

(*c*) *Mechanical and chemical irritants combined.* Take the case of a scabies eruption, scratched by the patient into an eczema, raw and weeping, and followed by suppuration. In this way a dermatitis started from purely local causes may be spread all over the body by means

of the nails. This train of symptoms, it may be noted, would probably occur only in those persons who have what is sometimes called the 'eczematous tendency.' Under this heading may also be included micro-organisms which have attacked the epidermis, either as a primary invasion or a secondary complication of a dermatitis due to some other cause.

Class II. **Internal Irritants.**—These include all substances circulating in the blood capable of setting up a dermatitis.* They may be discussed under the headings of:

A. *Drugs.*
B. *Accumulation of normal excretory products in blood.*
C. *Specific disease poisons.*
   1. Pathogenic micro-organisms (and their products).
   2. Products of micro-organisms used as drugs.
   3. Poisons produced in the body.

Class III. **Other Internal Determinants:**

(*a*) *Mechanical*, chiefly vascular, such as blood-stases due to varicose veins, or to the œdema of chronic nephritis. This class does not fall within our definition of an internal irritant. Neither does the next.

(*b*) *Nervous.*—In many cases skin lesions are undoubtedly due to nerve influence, although that, again, may sometimes be referred to a remoter irritant, as, for instance, in herpes zoster following the administration of arsenic.†

* A better classification of Class II. would be into: (1) Drugs, (2) Vital irritants, the latter being further divided into: (*a*) Micro-organisms, (*b*) Products of micro-organisms, (*c*) Chemical substances produced otherwise in the body. The classification above adopted, however, has some advantages in the present inquiry.

† See note to Preface.

The present inquiry is concerned only with Class II., 'The Internal Irritants,' and discusses skin or other organic lesions produced by drugs and specific poisons (other than drugs) circulating in the blood. Few people, whether dermatologists or general physicians, would dispute the proposition that a dermatitis is the invariable result of some *causa irritans;* the moot point is how the local irritation is brought about, and its exact relation to other morbid phenomena. To ascertain, or to attempt to ascertain, the common underlying factor between symptomatic skin diseases and blood-borne irritants is the primary object of the present thesis.

The three subdivisions of (A) Drugs, (B) Accumulation of Normal Excretory Products in Blood, and (C) Specific Disease Poisons, include all substances that have the power of producing eruptions of the skin when circulating in the blood, and which, therefore, fall under our definition of 'internal irritants.'

CLASS II.

INTERNAL IRRITANTS.

Subdivision A.—DRUGS.

The following, taken from Gould's 'Dictionary of Medicine,'* is a fairly full and accurate list of drugs that, when taken internally, have been known to cause eruptions of the skin:

'*Antifebrin* produces a kind of cyanosis; *antipyrin*, an erythema that may be general or partial, but symmetric, affecting the extensor aspects in preference to the flexor, and the limbs more than the trunk: papules, vesicles, and bullæ have been noted; *arsenic* produces

* Gould's 'Dictionary of Medicine,' art. 'Dermatitis Medicamentosa.' New York.

an urticaria, erysipelatoid dermatitis of the face and eyelids, a papular rash on the face, neck, and hands, herpes zoster, and in large doses pustular, ulcerative, or gangrenous eruptions; *belladonna*, a diffuse erythematous blush and a scarlatiniform eruption; *boric acid*, an erythema; *borax*, psoriasis, eczema and erythema; *bromin* and *bromides*, pustular erythematous, urticarial, and squamous eruptions; *cannabis indica*, a vesicular eruption; *chlorate of potash*, a fiery, erythematous and papular eruption, and cyanosis; *chloroform*, purpuric spots; *chloral hydrate*, erythema, scarlatiniform, bullous, erysipelatous eruptions; *chloralamid*, scarlatiniform; *chrysarobin*, erythema, vesicles; *cod-liver-oil*, vesicular eruption, acne; *copaiba*, erythematous, urticarial, papular eruption; *cubebs*, papular erythema; *digitalis*, scarlatiniform, papular erythema; *iodin* and *iodides*, pustular, vesicular or bullous, purpuric, erythematous, urticarial; *iodoform*, punctiform, papular and erythematous; *mercury*, erythematous, exfoliative dermatitis; *morphin*, erythematous; *phosphoric acid*, bullous, purpuric; *quinine*, eczema, erythematous, urticarial, purpuric, vesicular, bullous; *resin*, urticarial; *rhubarb*, hæmorrhagic and pustular bullæ; *salicylic acid*, erythema, urticaria, bullæ, petechiæ, vesicles, pustules; *santonin*, urticaria; *stramonium*, erythema; *strychnin*, scarlatiniform pruritus, miliaria; *sulphonal*, erythema, purpura; *tannin*, urticaria; *tar*, erythema, vesicles, and bullæ, acne; *terebene*, papular erythema; *tuberculin*, scarlatiniform; *turpentine*, erythema, papules, vesicles.'

We shall next consider in detail a few of these symptomatic drug rashes:*

* See also second article of this pamphlet, 'The Action of Certain Internal Remedies on the Skin.'

Arsenic.

Multiform rashes often attend the internal use of arsenic ; and herpes zoster appears to develop with undue frequency either during or after a course of the drug. Unna* quotes Wyss to show that the basal prickle layer of the epidermis was deeply pigmented in a choreic child treated with the drug. In his 'Smaller Clinical Atlas,' Mr. Jonathan Hutchinson† has three interesting plates, showing arsenic psoriasis, keratosis and cancer. The multiform and extensive nature of these lesions has been summed up by Dr. C. Rasch, quoted by Wood,‡ of Philadelphia, as follows : '1. Pigmentation. 2. Erythematous and desquamative eruptions. 3. Urticaria and subcutaneous œdema. 4. Vesicular eruptions. 5. Bullæ. 6. Papules. 7. Pustules and ulcers. 8. Purpura. 9. Shedding of the hair and nails. 10. Keratosis.' The chief path of exit of arsenic from the system is by the kidneys, but it also escapes through the mucous membranes of the alimentary canal (*e.g.*, after cutaneous absorption), through the skin, and even in the secretions of the lachrymal and salivary glands. Wood§ quotes a case, reported by Dr. Pinkham (*Boston Med. and Surg. Journal*, 1878, p. 358), in which the liver, kidneys, and epithelial lining of the peptic glands were almost destroyed. Salkowsky, of Moscow, showed that in rabbits poisoned by small doses of arsenic the liver was enlarged and fatty, with degeneration of the central

* Unna's 'Histopathology,' p. 974. English edition, 1896.'

† 'Smaller Atlas of Clinical Surgery,' Plates XVIII., XIX., XX. 1895.

‡ Wood's 'Therapeutics,' p. 559. Ninth edition, 1894.

§ Wood, *op. cit.*, p. 548.

cells of the acini. The renal tubules were choked with fat globules, and their epithelium destroyed.*

From these statements, it appears that arsenic is an internal irritant capable of inflaming the chief excretory organs (except perhaps the lungs), and that it is highly damaging to their epithelium. Lastly, it may be noted that externally arsenic acts as a powerful irritant and caustic.

Mercury.

The internal use of mercury may be followed by various forms of dermatitis, varying from a mild fugitive erythema to papular and severe desquamative lesions. The drug is eliminated by many channels of exit, a fact which holds good whether it is taken by the mouth or introduced into the system in other ways, as by inunction. Wood,† who gives a capital account of drug eliminations, observes: 'Mercury has been found in the blood, urine, the serum and pus of ulcers, saliva, fæces, seminal fluid, the milk of nursing women . . . indeed, in every conceivable secretion and tissue. Haller, of Vienna, found it in the aborted fœtuses of salivated women, and Mayençon and Bergeret in the urine of a baby whose nurse was taking calomel; and both of these observations have been confirmed by Wellander.'‡ Mercury is capable of causing considerable damage to excretory organs, as proved by the diphtheritic colitis, the skin lesions, and the renal mischief found after death from poisoning by corrosive sublimate.

Mercury, then, acts as an irritant to all the excreting organs, with damage to their epithelium. It may also act as an external irritant.

* Virchow's 'Archiv.,' Bd. xxxiv., p. 77.

† Wood, *op. cit.*, p. 566.

‡ Hutchinson, *op. cit.*, Plates III., IV.

Iodine and Iodides.

The internal use of iodine and its compounds may cause erythematous rashes about the arms, face and neck; an eczematous state of the scalp; a pustular, acne-like rash, besides bullous tubercular eruptions. Hutchinson has two excellent coloured illustrations in his 'Smaller Atlas'† of a patient thus affected. The eruption consisted of scattered tuberous fungating masses, due to large doses of iodide of potassium. Iodine is usually eliminated by the kidney, but it may also escape by any of the mucous membranes or by the skin. Many observers have reported albuminuria during its administration, and have even asserted it to cause true tubular nephritis. In any case there can be no doubt that iodine exerts an irritant effect when excreted by the skin. Its direct escape from the latter organ has been maintained by Dr. R. W. T. Taylor (*American Journal of Syphilography and Dermatology*, April, 1893), and has also been reported by Adamkiewicz and Guttman, quoted by Dr. Pye-Smith.* The group of symptoms known as 'iodism,' namely, dermatitis, coryza, and gastro-intestinal trouble, follows when iodine is thrown off by channels other than the kidney. Any or all of these symptoms may ensue when the iodine is introduced into the system otherwise than by the mouth, as by painting the skin or by injection into an ovarian cyst. Some writers assert that iodism is more apt to occur when kidney action is defective. Thus, Dr. Pringle says: 'Renal disease and cardiac weakness strongly predispose to the occurrence of bromide and iodide rashes owing to the deficient elimination of the drugs in

* Pye-Smith's 'Diseases of the Skin,' p. 154. London.

the presence of such conditions.'* Dr. Radcliffe Crocker remarks: 'Iodide eruptions, especially the severer forms, are very liable to occur when there is any renal inadequacy, whether that is due to disease of the kidney itself or to a weakly acting heart. . . . Iodide of potassium is a powerful diuretic, and as long as diuresis is kept up there is often no eruption, but when the drug is stopped for a few days the diuresis stops, and the iodine, not being removed fast enough, excites an eruption.'† A simple explanation of the renal inadequacy would be found if we assume the iodine to irritate the excretory epithelium of the kidney, as it certainly does that of the skin and mucous membranes. The disturbance to the kidney would hinder its function, so that the stress of subsequent elimination of the irritating iodine would be thrown upon other excretory organs.

Iodine, then, is excreted chiefly by the kidneys. It is capable of irritating other excretory organs, chiefly the skin and mucous membranes, with damage to their epithelium. Externally it acts as a severe irritant and caustic.

Subdivision B.—ACCUMULATION OF NORMAL EXCRETORY PRODUCTS IN BLOOD.

(That is, practically, substances usual in certain excretions, but accumulated in blood, and vicariously excreted.)

Uræmia.

This condition is caused by the accumulation within the system of substances that should be eliminated by

* Fowler's 'Dictionary of Medicine,' art. 'Medicinal Rashes.'

† Crocker's 'Diseases of the Skin,' p. 304. Second edition, London.

the kidneys; these may be called for convenience 'uræmic products.'

These uræmic products are in reality composed of a number of poisons. That they act as irritants to various excretory outlets is shown by the accompanying vomiting and diarrhœa. Dr. Carter* says that in uræmic vomiting there is a direct and free excretion of urinous products by the gastric membrane. The peculiar odour of the skin of uræmic patients points to the excretion by the skin of some volatile abnormal substances. Moreover, urea has been found in the sweat and the breath of such patients. Landois and Stirling state: 'In uræmic conditions urea has been found crystallized on the skin. When the secretion of sweat is greatly increased, the amount of the urea in the urine is diminished, both in health and in uræmia.'†

Jaundice.

In this condition bile is sometimes excreted through the skin, as shown by the peculiar colour of the sweat. The fact is noteworthy that its early stage is often marked by irritation of the skin. In one instance that came under the writer's observation, a woman complained of intense general prurigo, and a week later presented herself at hospital deeply jaundiced.

The most common excretory outlet of the bile in jaundice is by the kidney. In some cases it has appeared to the writer that it may be to some extent excreted by the bowel, and thus give a yellowish colour to fæces that would otherwise be white. This method of excretion

* Fowler's 'Dictionary of Medicine,' art. 'Uræmia,' by Dr. Carter.

† Landois and Stirling's 'Physiology,' pp. 352, 353.

would certainly explain the intermittent faint colouring of the fæces that sometimes occurs in obstructive jaundice.

Subdivision C.—SPECIFIC DISEASE POISONS.

1. Pathogenic micro-organisms (and their products).
2. Products of micro-organisms used as drugs.
3. Poisons produced in the body.

1. PATHOGENIC MICRO-ORGANISMS (AND THEIR PRODUCTS).

Of these we shall consider two only with special relation to the skin eruption and to accompanying affection of other excretory organs. Both will be exanthems.

Measles.

Before the rash appears there is catarrh of the conjunctiva and of the mucous membranes of the nose, pharynx and larynx. About the fourth day a papular rash appears on the face, and soon involves the body and limbs. During the crisis the rash may suddenly disappear, an occurrence which Kaposi* says is always the result of a febrile complication. The same observer states that the rash may now and then be altogether absent. In some cases the eruption may be multiform. Complications are: inflammatory affections of the lungs, air-passages, eye and ear, intestines, or rarely the kidney.

In measles, then, we have a specific poison that may inflict slight or severe damage on excretory epithelium. The inflammatory process may not affect the skin at all, or it may be suddenly shifted (disappearance of the rash) from the skin to other organs.

* Kaposi's 'Diseases of the Skin,' p. 157. English edition, Baillière, 1895.

Scarlatina.

The rash of scarlet fever begins as a punctate eruption on the upper part of the chest about the second day of the fever. It rapidly becomes diffuse, lasts about three days, and is followed by desquamation, a process which may extend over six weeks.

The rash may be multiform, and sometimes is altogether absent. The tongue and fauces are always inflamed. The intestinal tract may be affected, causing diarrhœa or croupous enteritis, the latter being sometimes accompanied with fatal hæmorrhages. Albumin is present in the urine at an early stage in nearly all cases; indeed, renal disease, in the shape of catarrhal or glomerular nephritis, during desquamation is the most frequent complication. There is a marked tendency to inflammation of serous and synovial membranes. At times the rash may suddenly and entirely disappear, an occurrence which usually points to serious disease of internal organs, such as the lungs or brain.

Thus, in scarlet fever we have a specific virus, or its products, which attacks all the excretory outlets, causing much damage to their epithelium. In the case of the skin we note that there may be no rash, and that the eruption may suddenly disappear; these facts probably point to a shifting of the usual channel of elimination of the virus to other organs.

2. PRODUCTS OF MICRO-ORGANISMS USED AS DRUGS.

Note.—It is still a moot point how far the rashes of the exanthems are to be ascribed to the influence of toxins and other products of micro-organisms, apart from the actual organisms themselves. In treatment by

tuberculin, and by antitoxin, however, there can be no such doubt, as the products of specific micro-organisms are in each case introduced directly into the system.

Tuberculin.

It is a familiar observation that tuberculin, injected subcutaneously, often gives rise to a transitory scarlatiniform rash. This fact was observed by the writer in a fair proportion of cases out of a large number treated by tuberculin in the year 1890 at the Birmingham Workhouse Infirmary. For the most part the fleeting eruptions in question were at first minutely punctate, but afterwards passed into a diffuse erythematous form.

Antitoxin.

An eruption of the skin occurs in a large number of cases of diphtheria treated by the hypodermic injection of antitoxin. Thus, an erythematous rash was reported by Drs. Washbourn, Goodall and Caird* in 25 per cent. of 80 cases. In 231 cases Dr. Moisard† noted fourteen instances of urticaria, nine of polymorphic erythema, nine of scarlatiniform erythema, and one of purpura. In a collected series of 110 antitoxin cases in private practice recently published in the *British Medical Journal*,‡ a skin complication is mentioned in 39. Dr. Tidswell,§ Medical Officer of the New South Wales Board of Health, out of 55 cases found 18 had rash. The Metropolitan Asylums Board report as follows: 'Among the undesirable effects of the use of antitoxin,

* *British Medical Journal*, p. 1418. December 23, 1894.

† *Medical Press and Circular*, p. 34. January 9, 1895.

‡ *British Medical Journal*, 'Diphtheria and the Antitoxin Treatment.' January to April, 1896.

§ Report, Dr. Tidswell, *British Medical Journal*. February 1, 1896.

by far the most common was a rash, usually urticarial, but sometimes erythematous or scarlatiniform. A rash was observed in 45·9 per cent. of the cases treated with antitoxin, and was often accompanied by fever, which was observed in 29·6 per cent. of all the cases. In some it persisted for several days. Joint pains were observed in 4·7 per cent. of the cases. They were rarely severe or accompanied by effusion, and almost invariably passed off in a few days.'*

In both tuberculin and antitoxin we have bacterial products which sometimes inflame the skin when introduced into the blood. At times they affect both serous and synovial membranes.

3. POISONS PRODUCED IN THE BODY.

Gout.

This condition is due to some poison, presumably uric acid, which, so far as we know, is developed in the system. The injury it causes to excretory organs is illustrated in those who inherit the gouty tendency and who suffer from what is known as 'irregular gout.' Persons affected in this way are liable to dyspepsia and various disorders of the alimentary canal, to skin troubles, to kidney mischief, and to inflammation of various mucous membranes.

'Crystals of urate of soda are found deposited in the tubules and inter-tubular tissue of the kidneys, in the sputa of gouty bronchitis, and as an efflorescence on the surface of the body in cases of gouty dermatitis.'†

* Report, Metropolitan Asylums Board, 1896. See also 'Manual of Infectious Diseases,' p. 359, by Drs. Goodall and Washbourn. 1896.

† Fowler's 'Dictionary of Medicine,' art. 'Gout,' by Dr. Shelley

The gouty poison, then, appears to affect all the excretory outlets, with severe damage, at any rate in chronic cases, to the epithelial structures.

Rheumatism.

This condition is no doubt due to a specific poison circulating in the blood. The exact nature of the virus is not yet known, for the generally accepted view that it is a chemical poison, lactic acid, has been disputed by some modern authorities, such as Newsholme, who maintain it is a specific micro-organism. In either case it falls under the general definition of an internal irritant.

The poison of rheumatism appears to be partly eliminated by the skin, if we may judge from its association with erythematous and urticarial rashes, and with the remarkable purpuric manifestation *peliosis rheumatica*. Besides these definite eruptions, there can be little doubt that rheumatism is obscurely connected with a number of skin lesions. During the past few years the present writer has made a point of systematically inquiring into the history of patients under his care at a special hospital, and has found a large proportion of patients either directly or indirectly tainted with rheumatism.

The poison of rheumatism seemingly expends most of its violence upon the mesoblastic tissues, having a marked tendency to attack serous and synovial membranes. Upon the ordinary excretory organs it appears to inflict only a moderate amount of damage. At times bronchitis, pneumonia and glycosuria develop during acute attacks.

GENERAL REMARKS ON THE INTERNAL IRRITANTS.

In the foregoing summary a few types only have been chosen to illustrate each of the three divisions of internal irritants. They agree in the following cardinal points:

1. They are specific substances circulating in the blood.
2. They may set up a dermatitis.
3. They may cause inflammation of any of the other excretory organs, although their action is, as a rule, selective. In other words, internal irritants have the power of irritating any or all of the excretory organs.

These propositions are true of every kind of internal irritant. Some of the specific substances, such as arsenic and the virus of scarlatina, are highly injurious to excretory epithelium, but it seems that all of them possess the same faculty to a greater or less extent. As a rule, each irritant affects its own peculiar channel or channels of exit, but exceptions are common. Thus, there may be scarlet fever without rash, or long-continued gout without kidney mischief.

The majority of drugs cause little or no irritation while being eliminated from the system. A typical instance of this class is sulphur, which is excreted by lungs, skin, bowel, and by various mucous membranes, so far as we know, without causing any damage.

In the irritant drugs the power of damaging epithelial structures is shown, whether they gain access to the cells from without or within. For example, arsenic, which externally is a powerful irritant and caustic to the skin, acts as a strong internal irritant to all the excretory organs.

Arsenic has been shown by Murrell and Ringer* to cause separation of the epidermis from the dermis when administered hypodermically in minute doses to frogs. This result Nunn† traced to disturbance of the basement cells of the rete Malpighii. Cantharides applied to the skin causes a blister, and the clinical fact is familiar that after absorption into the blood it may set up inflammation and hæmorrhage in its passage through the kidneys. Dr. Murrell‡ states that the majority of purgatives derived from the vegetable kingdom belong to the class of cutaneous irritants, and among them he cites croton-oil, gamboge and elaterium. Of these drugs, it is yet undecided whether any except elaterium is capable of purging after absorption through the skin. If that be the case, then croton-oil and gamboge must act as purgatives by virtue of their direct irritant action on the mucous lining of the intestines. Castor-oil, so far as the writer has been able to ascertain, does not inflame the skin, but it sometimes acts as an aperient when rubbed into the skin of the abdomen, especially in children, though this might of course be due to the massage. The case of elaterium, at any rate, if not of castor-oil, appears to point to a power of selective excretion of the drug possessed by the bowel. Certainly mercury, whether administered by inunction, fumigation, or hypodermic injection, may cause purging which it would be difficult to explain on any other theory than that of direct excretory irritation of the bowel.

The foregoing facts suggest a wide excretory function

* Ringer's 'Therapeutics,' p. 277.

† Nunn, *Journal of Physiology*, vol. i., p. 247.

‡ *Medical Press and Circular*, art. 'The Pharmacological Action of Purgatives,' by Dr. W. Murrell. January 8, 1896.

for the intestine. It seems not impossible that the action of some purgatives, especially the delayed ones, may be accounted for by bowel excretion following absorption from the stomach. Moreover, a similar action may afford a key for results other than purgative. Morphia when injected subcutaneously has been detected in the gastric juice and other secretions.* In this way a dose of opium absorbed from the stomach might possibly be in part excreted through the intestine, with consequent disturbance of function.

In the case of specific disease poisons, just as with drugs, many pass off from the body and cause little organic mischief, as, for instance, the virus of chicken-pox, mumps, vaccinia, rheumatism, or mild ptomaine poisonings. On the other hand, a certain number, like scarlatina, lead to severe, and sometimes permanent, damage of excretory organs. Lastly, no organ engaged in excretion is exempt from attack. In all these points there is an exact analogy between the drugs and the specific disease poisons associated with skin lesions. Any individual member of either group may do little or much damage to organs during its elimination from the blood, and all appear to be at times equally erratic in their choice of exits.

So far as drugs are concerned, the theory of excretory irritation has been endorsed by Kaposi.† After speaking of reflex toxic phenomena, he goes on: 'In other cases the toxic substances, being excreted through the cutaneous capillaries, have a direct irritant and paralytic action upon the peripheral vessels and adjacent tissues, so that the erythemata and the more intense inflammations

* *Klin. Wochens.*, xxvi., art. by Dr. K. Orlt. Berlin, 1889.

† Kaposi's 'Diseases of the Skin,' p. 224, English edition.

(iodine and bromine acne) develop only at those points.' He also quotes a similar opinion advanced by Behrend.

In an able and philosophical address on 'Bacteria in Diseases of the Skin,' Dr. J. F. Payne,* after speaking of external infection, said: 'There is only one other possible source for the staphylococci of the skin. It has been suggested by M. Leloir that organisms contained in the blood may be excreted by the sebaceous and sudoriparous glands, and thus produce local suppuration. Dr. Walsh has drawn attention to the excretion of toxic bacterial products. These explanations are quite possible, but cannot be said to be actually proved.'

This paper of Leloir,† quoted by Dr. Payne, was written in 1890. He dealt with suppurative lesions of the skin following influenza, and appears to have suggested that the actual elimination of the specific bacteria through the skin was the cause of the local inflammations. As against this theory, however, we have the following definite opinion of Drs. Goodall and Washbourn.‡ 'In view of the fact that the bacillus does not multiply in the blood or organs, we must consider that influenza is a local disease, usually of the respiratory tract, and that the symptoms are due to the absorption of the toxines.' It will be noted that this view does not exclude the possibility of a local invasion of the skin by the particulate virus of influenza. From the author's point of view the skin lesions might be set up by the specific bacterial products as well as by the actual organisms. In the year 1890, when Leloir advanced

* 'Presidential Address of Dermatological Society of Great Britain and Ireland,' by Dr. J. F. Payne. *Lancet*, May 20, 1896.

† Leloir, 'Lésions Suppuratives de la Peau à la Suite de l'Influenza,' *Bull. Méd.*, iv. 117; Paris, 1890.

‡ Goodall and Washbourn, *op. cit.*, p. 261. 1890.

this theory of irritation of the skin by the elimination of microbes, the author* published the wider view that some forms of dermatitis might be due to the excretory irritation (*a*) of micro-organisms, (*b*) of bacterial products, (*c*) of drugs, (*d*) of the virus of various blood-borne diseases (*e.g.*, gout).

The proofs, direct and indirect, of the actual influence upon the skin of the internal irritants are chiefly:

1. Some irritant drugs, as iodine, bromine, arsenic, mercury, have been detected in the excretions of the inflamed skin, as well as of other excretory organs.

2. Some non-irritant drugs, as sulphur, are excreted by the skin, and can be found in the sweat.

3. In gouty eczema (*i.e.*, eczema in a gouty person) urates have been found as an efflorescence on the skin surface, and urea in uræmic conditions.

4. In the case of some exanthems it seems probable that the specific micro-organisms themselves, apart from their products, are directly excreted by the skin, thus accounting for the infectiousness of affected individuals, which is generally assumed to be greater in the desquamating stages.

5. In the excretions of organs other than the skin, the presence of the internal irritants, whether chemical or bacterial, has been often demonstrated by chemists and bacteriologists.

The cause of the rash in the exanthems is a subject that raises points of much interest as well as of practical importance. Hitherto it has been usual to regard the desquamated skin of a scarlet-fever patient as infectious. If so, the actual specific micro-organisms of the disease must necessarily have been eliminated by the skin.

* *Medical Press and Circular*, October 22, 1890.

Lately, however, there seems to be some doubt amongst sanitary experts as to the infectivity of a desquamating scarlet-fever patient. Whatever the exact method of exit of the virus, it is clear that the living germs must in some way be eliminated from the body. Scarlet fever would cease to exist did not the specific micro-organisms escape from the human body in a condition capable of spreading the disease. As this particular virus flourishes in the blood, it follows that it must be excreted in a living state by the skin or other excretory organs of successive individuals. The question is, Through what particular channels of exit do the active germs escape? If through the kidney and bowel discharges, then it is tolerably certain that effective measures are not taken in one case out of a hundred, even in our best-ordered fever hospitals, to disinfect those evacuations. So, too, with the lungs—if the active germs are given off in the breath, what is done in the direction of aërial disinfection? Indeed, the only attempt at systematic disinfection of scarlet-fever cases appears to be directed to the skin, the clothing, and other objects that have been in contact with the skin. Upon logical grounds there seems to be good reason for regarding with grave suspicion all excreta from a scarlet-fever patient.

In typhoid fever the rash most commonly consists of small rose-coloured papules on the abdomen. At other times it appears on the general skin surface; thus, in a case under the writer's care, the rash began on the legs and soon involved both upper and lower limbs. The reason of the almost constant localization of the rash on the abdomen is not easy to conjecture. There may possibly be some lymphatic channels by which either the organisms themselves or their products might

reach the surface of the abdomen. At any rate, we know that typhoid bacilli are by no means confined to the intestines, but are found in the abdominal cavity and in various parts of the body. De Grandmont,* quoted by Stephenson, found them in the anterior chamber of the eyeball of a convalescent from the disease. He further introduced a pure culture of the organism into the vitreous humour of a rabbit, which, when killed three weeks later, was found to have numerous typhoid-fever bacilli in the liver and intestines.

The direct excretion of pathogenic bacteria from the body has been definitely stated by Dr. Anton Weichelsbaum in the following passage: 'Bacteria circulating in the blood may be excreted through the kidneys, probably in cases where, owing to some changes in the walls of the vessels and the membrana propria of the urinary tubules, the passage of the bacteria through them is rendered possible or favoured. They may also, under analogous conditions, traverse the membrana propria of the mammary glands and appear in the milk, or during pregnancy may travel through the placenta into the fœtus.'†

Professor Unna,‡ again, speaks of certain infectious exanthems, 'due to a chemical, locally active poison, produced by a specific germ. Such are the roseola-like spots in typhoid, typhus, dysentery, diphtheria, pneumonia, recurrent fever, acute rheumatism and influenza.' These roseolæ he regards as areas of reaction around

* 'Archives d'Ophthalmologie,' p. 623. 1892.

† Weichelsbaum's 'Elements of Pathological Histology,' p. 116. English translation (Dawson), 1895.

‡ Unna's 'Histopathology,' p. 12. English edition, translated by Dr. Norman Walker.

more or less scattered emboli of the specific germ, upon which they are performing the office of 'undertakers.' From this passage it is clear that Unna has no doubt that many rashes are due to the localizing of specific micro-organisms in the skin.

Referring once more to De Grandmont's experiment, in which he injected a pure culture of the typhoid bacillus into the vitreous of the rabbit, and three weeks later found the specific bacilli in the intestine: if those organisms can be excreted by the bowel, there is no reason, so far as one can see, why they should not be likewise eliminated by the skin and other excretory organs, seeing that the latter are all formed on a common anatomical and physiological basis. In addition to this logical possibility, however, we have direct evidence of the existence of active *bacilli typhosi* in the urine. Dr. Weichelsbaum* states definitely that the organisms of typhoid may be found in the urine sometimes even on the third day of the disease. At the same time it should be stated that, in common with most experimenters, he is opposed to De Grandmont's conclusion, which may be taken to assert the reproduction of enteric fever in the rabbit by injection of the specific bacillus into its tissues. 'Typhoid fever,' writes Weichelsbaum, 'cannot be set up in animals by inoculation with typhoid bacilli. Injection of cultures into the blood or digestive tract may indeed kill rabbits, but this takes place, as it appears, not by infection, but merely by intoxication.'

The drift of modern opinion points to the conclusion that the rashes of specific fevers are for the most part connected with bacterial products rather than with the organisms themselves. The night-sweats of phthisis are

* Weichelsbaum, *op. cit.*, p. 145.

probably due to some toxic bacillary product which acts either on the sweat centres directly or the glands of the skin. Malcolm Morris writes: 'Profuse sweating may be the result of nerve exhaustion, or of the presence of toxic matters in the blood calling for elimination.'* The view of bacterial-product origin is supported by the frequent occurrence of eruptions after the hypodermic injection of tuberculin and antitoxin, which are both obtained from micro-organisms. The usual assumption appears to be that these particular rashes are the result of reflex nervous origin. The writer's suggestion is that they are the result of the excretion, or the attempted excretion, by the skin of an irritant bacterial product. This explanation is borne out by the exactly analogous action of certain drugs and chemical irritants in the system. This theory of excretory irritation, be it noted, remains unaffected whether the rash of exanthems be traced ultimately to the influence of the organisms themselves or of their products.

ANTITOXIN RASH.

In a paper read before the Dermatological Society of Great Britain and Ireland in 1895, the present writer† suggested that the multiform rash commonly met with during the antitoxin treatment of diphtheria might be due to excretory irritation. This view was supported by the analogy with tuberculin rash. The possibility of a nerve origin of this and other eruptions connected with internal irritants was discussed as follows: 'In the case of scarlatina both the dermatitis and the nephritis

* Malcolm Morris's 'Diseases of the Skin,' p. 2. London, 1894.

† D. Walsh, 'Note on Antitoxin Rash,' *British Journal of Dermatology*, February, 1895, p. 59.

are presumably due to a common cause. If the skin lesion be regarded as of nervous origin, then a similar explanation should also apply to the kidney complication. However, I have never heard that anyone claimed a neuritic origin for either symptom in scarlatina. A similar line of reasoning applies to the skin and kidney inflammations following the injection of antitoxin. Both rash and nephritis are clearly due to a common cause, and if one be a neurosis, so probably is the other. From my point of view, the more likely explanation appears to be that both are caused by direct irritation of excretory epithelium.' (See note to Preface.)

This passage has been quoted in full because it deals with the chief alternative theory to excretory irritation in the class of skin inflammations under consideration. Crocker, who admits the close relationship between gout and eczema, yet asserts that the skin conditions are 'all instances of irritation of the alimentary canal with reflex capillary dilatation.'* This explanation, however, is not altogether satisfactory, as it omits to state how the uric acid reaches the intestine from the gouty tissues.

Bouchard, in his work on Auto-intoxication,† makes the following statement, which appears to bear on the theory of excretory irritation: 'Je suppose que, comme après l'ingestion de ces divers médicaments, les vaso-moteurs cutanés sont impressionés par l'action directe du poison, ou que leur perturbation est le résultat d'un réflexe du système nerveux. Pourtant, quand il s'agit de sécrétions morbides comme l'acné, l'eczéma, il

* Radcliffe Crocker's 'Diseases of the Skin,' p. 123. Second edition.

† Bouchard's 'Auto-intoxication,' p. 176. Paris.

est difficile d'admettre la médiation du système nerveux. Ne vaut-il pas mieux incriminer l'élimination d'acides gras volatils ? Quelle que soit d'ailleurs l'interprétation, le fait empirique de l'enchaînement entre la dilatation de l'estomac et un grand nombre de manifestations cutanées reste certain, c'est bien un enchaînement et non une association fortuite. Comme explication pathogénique, je vous propose provisoirement l'intoxication.'

CHLORAL RASH.

The eruption due to the internal use of chloral may be mentioned here as one of a class that can hardly be explained by any theory of excretory irritation. There is an excellent figure in Hutchinson's 'Smaller Atlas,'* showing both hands of a gentleman, aged thirty-four, with dusky-red erythematous patches, fairly symmetrical, and lasting about three weeks. The patient experienced fifteen attacks, which were definitely connected with the taking of chloral. He was gouty, but otherwise in good health.

This particular eruption is almost certainly connected with nervo-vascular disturbance. It does not follow, however, that the drug should not be able to cause direct excretory as well as reflex irritation. Indeed, we find that various scarlatiniform and bullous rashes have been traced to chloral. Arsenic behaves in a precisely similar way, for while we find it at one time causing a nervous lesion, like herpes zoster, at another it sets up various forms of local irritative skin eruptions.

It may be well to point out that the theory of excretory irritation as the cause of some forms of dermatitis would not be vitiated were it shown that certain other

* Hutchinson, *op. cit.*, Plate V.

drug eruptions were of nerve origin. The affirmative proposition is particular only, and would not be falsified by the production of a particular negative.

POLYMORPHISM OF DERMATITIS DUE TO INTERNAL IRRITANTS.

Multiformity of lesion is the rule rather than the exception in the rashes connected with internal irritants. This variability of result does not strengthen the case for existing classifications, which are chiefly based on morphological grounds. Indeed, it seems likely that in the near future the nomenclature of dermatology will be considerably altered.

As to the anatomical elements of the skin involved in the excretory irritation, the process may begin in the glands, papillæ, or rete mucosa—in short, over as wide a field as that suggested by the multiform lesions. Anatomically, there is a striking resemblance between the ultimate structure of the skin and the kidney. Elsewhere the writer* has pointed out: 'The Malpighian tufts are very similar to the sweat glands, while the renal tubules may be compared with the palisade layer of mucous cells overlying the papillæ.'

This common structural plan is well described by Waller,† who says of the kidney: 'As in all secreting or excreting glands, the essential elements are a thin sheet of blood separated by a membrane from a layer of epithelial cells.'

Once started, the dermatitis may go on to resolution, suppuration, abscess, gangrene, or may become chronic.

* Walsh, *British Journal of Dermatology*, p. 62, February, 1895.

† Waller's 'Human Physiology,' p. 224.

Its survival may be due to the continued excretion of the original irritant, or to a secondary local development of micro-organisms. If these explanations be true in the case of the skin, why should they not be true of other excretory organs? From the facts that have been advanced, it is clear that internal irritants, capable of inflaming the skin, may inflame any or all of the rest of the excretory organs. An acute inflammation is often the starting-point of chronic disease in any given organ. If these premises be true, and if certain drugs be included among the internal irritants, as they are by our original definition, then it follows that certain drugs are often the starting-point of chronic disease in excretory organs.

In other words, we arrive at the somewhat startling proposition that any of the drugs we have placed among the internal irritants, if introduced into the blood, may be the starting-point of more or less serious disease in any of the excretory organs. This possibility, therefore, applies to arsenic, mercury, cantharides, antimony, iodine, bromine, salicylic acid, and many other drugs commonly used in medicine. With regard to the point thus raised, we may at once recall two facts: (1) the origin of an enormous amount of organic disease is absolutely unknown; (2) modern pathology has taught us that in morbid processes the first step is the all-important one. Again, we know that in gouty persons the long-continued elimination of an irritant by the kidneys gives rise to chronic nephritis. Why should not the long-continued excretion of arsenic, then, a drug which is intensely irritant to excretory epithelium, also give rise to chronic nephritis? Yet arsenic is administered daily as a medicine, apparently with hardly a thought as to its possible ill

effects upon internal organs. The same thing happens with many other irritant drugs used in medicine. It is clear, logically, that if the theory of excretory irritation be true, then the use of any drug that inflames the skin should be carefully watched and safeguarded by careful regulation and intermission of dosage. For some years the writer has acted upon this deduction from the general law of excretory irritation.

There are many facts to illustrate the occasional disastrous effects of drugs used as curative agents. Instances are found in iodine and bromine rashes, and in arsenical keratosis and cancer. Hutchinson,* with characteristic acumen, detected opacity of the vitreous humour in patients who had been taking long-continued courses of arsenic.

Of late years there has been a reaction against the indiscriminate use of arsenic. Crocker,† for instance, writing of the use of arsenic in psoriasis, states that on account of its toxic and irritant effects, and of its 'uncertainty of action,' he uses it less and less every year. Experience varies greatly as to its value in skin practice, and we are lost in wonder how so many good observers can arrive at totally different conclusions. From a consideration of the facts of erratic elimination, it seems not unlikely that the arsenic is often excreted by the kidneys and does not reach the skin at all, just as the virus of scarlet fever now and then fails to produce a rash. Many other drugs have an equally uncertain and disappointing action in diseases of the skin, and it may be that they also are excreted by other organs.

* Hutchinson, *Ophthalmic Review*, vol. viii., No. 87, January, 1889.

† 'Twentieth-Century Practice of Medicine,' vol. v., p. 274, art. 'Squamous Affections,' by Crocker.

It is a common practice to prescribe a small dose of arsenic—say, three minims of Fowler's solution—to a patient suffering from a skin affection. There is no guarantee, however, that the drug does not pass away by the kidneys. Moreover, after a time the arsenic begins to accumulate in the system, and is eliminated by various channels other than the kidney, yet it may still avoid the skin. The question arises—Supposing arsenic to benefit the skin by its direct action, would it not be possible in the first place to determine its action to the surface of the body by the aid of a drug like pilocarpin? Some sort of natural determination probably takes place when the skin is previously irritated, which would explain the familiar observation that arsenic often acts adversely upon an acute eczema.

The reader has now had in review a mass of clinical and other evidence tending to show that inflammations of the skin and of other excretory organs may result from certain irritants circulating in the blood. There appears to be a further remarkable connection between the organic inflammations and those of serous and synovial membranes. In a sense the latter affections may be regarded as a sort of attempt at vicarious excretion.

In many cases specific pathogenic organisms have been detected in the effusions of inflamed cavities. Stephenson* has quoted instances where the micro-organisms of enteric fever, of erysipelas, of tubercle, and of leprosy, have been found in the anterior chamber of the eyeball, associated with iritis. He quotes Mazza, who saw pleurisy, pericarditis, and poly-arthritis during an attack of gonorrhœa, and found the characteristic cocci in the

* Stephenson, *loc. cit.*, *Lancet*, February 29, 1896.

pleuritic effusion. He also mentions Poncet, Clement Lucas, Fendick, and others who detected gonococci in the joint effusions following purulent ophthalmia, a disease dependent on Neisser's gonococcus. Moreover, some skin diseases, as erythema multiforme and dermatitis herpetiformis, are often associated with articular pains and effusion.

NERVE SYMPTOMS CAUSED BY INTERNAL IRRITANTS.

Inquiry shows that nerve symptoms of a more or less severe nature are at times associated with all, or almost all, of the internal irritants. In this connection it should be remembered that both nerve cells and excretory cells are in close relation to their vascular supply, so that both are readily exposed to the action of blood-borne irritants. Consequent irritation both of cutaneous and nerve structures may be shown by (*a*) disturbance of function, (*b*) inflammatory changes of varying intensity.

Take the action of arsenic as a general internal irritant:

Organ.	*Effect.*
Skin	Multiform dermatitis.
Kidney	Nephritis.
Stomach	Gastritis (*i.e.*, when absorbed through the skin).
Bowel	Enteritis, hæmorrhages.
Brain	Depression, vertigo, convulsions, etc.

Compare this with the effect of the scarlet-fever poison on similar organs.

Organ.	*Effect.*
Skin	Desquamative dermatitis.
Kidney	Nephritis.
Stomach	Gastritis.
Bowel	Diarrhœa (sometimes).
Brain	Delirium, coma, convulsions.

The effects of alcohol, a powerful internal irritant, may be taken for further comparison.

The liver is acted upon more or less injuriously by nearly every member of the group of internal irritants. Indeed, its action as an excretory organ can hardly be appreciated without a full consideration of the bile in relation to varying blood conditions. In the present inquiry, for the sake of simplicity, it has not been considered among the excretory organs. There can be no doubt, however, that if our conclusions be right as to excretory irritation in general, they will apply to the liver in particular.

SUMMARY AND CONCLUSIONS.

Taking the skin as one of a group of excreting organs, we find it suffers from various forms of inflammation in the presence of a number of specific substances circulating in the blood, to which we have given the name of 'internal irritants.' In some cases the relationship between the excretions of the skin and an underlying pathological condition is evident to our senses. Thus, we can sometimes see urates on the skin surface, and bile in the sweat. In other instances we detect by means of chemical and biological tests the presence of an internal irritant in the matters given off by the skin. Besides which, we have daily before our eyes the objective rash that gives unerring evidence of a specific irritant within the body. But these symptomatic skin eruptions are so constantly associated, not only with internal irritants, but also with inflammations of other excretory organs, that it seems impossible to avoid the conclusion that whole series of these phenomena are due to a common cause. The origin of the general process

we take to be the disturbance set up by the eliminatory passage of the internal irritant through the essential cells of the excretory organs.

CONCLUSIONS.

The main conclusions arrived at in the course of this inquiry may be summed up as follows :

1. That some forms of dermatitis are due to the irritation set up by the excretion from the blood of certain specific substances (here called ' internal irritants ').

2. That the skin suffers as one of a group of excretory organs; and that all those organs may be similarly affected by the internal irritants.

3. That the internal irritants sometimes inflame the serous and synovial membranes.

4. That proof is afforded, by means of chemical and biological tests, of the frequent passage of some of the internal irritants from the blood into the excretions, and into serous and synovial effusions.

5. That the internal irritants often affect the nerve centres.

6. That any internal irritant which inflames the skin may be suspected of inflaming other excretory outlets.

7. That any drug which inflames the skin should be administered with great caution, owing to the possibility of damage to other organs.

8. That it may be possible at times to guide the action of a remedy to the organ it is wished to affect.

9. That, conversely, any particular organ may be relieved of the stress of elimination.

10. That the law of excretory irritation has a wide application to general pathology.

APPENDIX I.

The attempt to present the theory of excretory irritation within the limits of a graduation thesis led to a terse literary treatment, which has been little expanded in the present monograph. However, the reader who admits the main principle of the theory will have little difficulty in recognising its further applications. For the sake of brevity, no mention has been made of alcohol, which may be regarded as an internal irritant, with a most damaging effect on excretory outlets. Nor, again, has Savill's* disease been discussed —an epidemic dermatitis where the desquamative lesion has all the appearance of resulting from the cutaneous excretion of an intensely irritant product of obscure origin. Although as yet no positive evidence on the point has been forthcoming, yet the balance of suspicion has pointed towards the milk-supply as a source of infection.† It is suggestive that a similar type of exfoliative dermatitis is known to exist in cattle.‡ The amyloid degeneration of organs associated with long-continued suppuration may also possibly be of irritant excretory origin. Inflammation has been claimed as the broad basis of modern pathology; but if the law of excretory irritation be true, we go a step further back to the starting-point of a great class of inflammations arising from the disturbed metabolism of the excreting cell.

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* Savill, 'A New Form of Skin Disease.' London, 1892.

† *British Medical Journal*, 'Milk and Epidemic Skin Disease,' May 2, 1896.

‡ Eddowes, *British Journal of Dermatology*, p. 54, Feb., 1895.

APPENDIX II.

In an able paper discussing the causation and treatment of mammary abscess, Mr. Marmaduke Sheild writes: 'In accordance with the view that all cases of acute mammary abscess are due to the entrance of organisms from the neighbourhood of the nipples, I must view with doubt those cases of so-called idiopathic abscess that occur in the unimpregnated condition.'* He quotes Baum, that in most cases *staphylococcus*, sometimes *streptococcus*, and even *gonococcus*, is found in the pus of acute mammary abscess. His proposition is that organisms gain an entrance from the skin to the gland by the lymphatic channels, and also along the milk ducts. In chronic mammary abscess where tubercle is found, he appears to think that the specific organism has either entered through an abrasion in the skin, or has been previously latent in the tissues.

It will be seen that in mammary abscess Mr. Sheild advocates local invasion, to the exclusion of any theory of internal or excretory infection. Without in any way attempting to deny the importance of external infection, attention may be drawn to the following points in favour of an internal origin in some cases:

1. The *gonococcus* has been found in the eyeball, as well as in pleural and joint effusions, situations to which it could have gained access only through the blood-stream.

2. Where mammary abscess is accompanied by concurrent inflammations of other organs. On this point Mr. Sheild quotes Spiegelberg's view—that cases where the abscess is part of a general septic infection must be very few.

3. It is known that a tubercular abscess may occur in the kidney, where the probability of infection from the blood-stream seems greater than from outside. There is an obvious analogy between tubercular abscess of the kidney and of the mammary gland.

4. The milk of cows infected with tuberculosis may contain the tubercle bacillus. Professor Wynter Blyth† states that it is only by biological methods that such diseased milk can be detected; that the milk of a cow suffering from a most mortal and virulent malady may be chemically unaffected.

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* *Lancet*, 'The Causation and Treatment of Mammary Abscess,' May 2, 1896, p. 199.

† Wynter Blyth, 'Foods.' Fourth edition, 1896.

5. Many drugs are excreted in milk. There is a direct excretion of such substances as arsenic, iodine, and mercury. If drugs, why not organisms (and their products)?

6. The mammæ are most commonly affected during pregnancy and lactation (out of 200 cases, Mr. Sheild found 169 during lactation); that is to say, the glands are attacked at the very time when their activity would be likely to invite the excretion of any irritant circulating in the blood. Such activity, on the other hand, would be most unfavourable to local invasion; any micro-organisms gaining entrance from outside would stand less chance of survival in tissues charged with blood, and roused to a full state of functional activity. In other words, if mammary abscess be the result of local invasion, one would expect the greater number of cases to occur when the gland was inactive. Clinical experience shows that the reverse really happens.

(NOTE.—Weichelsbaum,* quoted on p. 37 of this pamphlet, says that bacteria circulating in the blood may be excreted through the kidneys, the mammary glands, and the placenta.)

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* Weichelsbaum, 'Pathological Histology,' p. 116. English edition, 1895.

II.

THE ACTION OF CERTAIN INTERNAL REMEDIES ON THE SKIN.

[This short article is added here as it deals with some practical outcomes of the irritation of organs by the elimination of blood-borne irritants from the body. Written upon another occasion, it necessarily repeats some of the facts and arguments advanced in the foregoing thesis.]

THE ACTION OF CERTAIN INTERNAL REMEDIES ON THE SKIN.*

Of late years external remedies have assumed a position of first importance in the treatment of diseases of the skin. However, they have not driven out of the field such drugs as arsenic and mercury, which dermatologists give internally both for their general and their specific curative effects. At the same time, little appears to be known as to the exact method of action of internal remedies upon the skin.

The internal drugs most commonly used in dermatology are arsenic, mercury, and iodine. Attention may be drawn to the following points regarding them :

ARSENIC.

In small doses arsenious acid is an alterative, and in large doses an irritant poison. Rideall† states that it is a 'mild antiseptic,' and Koch‡ found that a 1 per cent. solution in water killed spores in ten days. It is a strong epithelial irritant. Externally, it vesicates and

* Paper read at the Third International Congress of Dermatology, London, 1896.

† 'Disinfection and Disinfectants,' p. 133.

‡ *Vide* Brunton's 'Pharmacology.' Third edition, p. 93.

acts as a caustic. Internally, it was shown by Murrell and Ringer* to cause separation of the epidermis from the dermis of frogs. This result Nunn† traced to disturbance of the basement layer of the *rete Malpighii*. In man arsenic may set up multiform eruptions, and it was long since shown by Mr. Jonathan Hutchinson to be answerable for chronic dermatitis of various kinds. Salkowsky,‡ of Moscow, found that in rabbits poisoned in three to six days by arsenic the kidneys were choked with fat globules, and their epithelium almost completely destroyed. Arsenic may leave the body by any ordinary or vicarious channel of excretion, as by the kidneys, stomach, intestines, skin, or mammary glands. It has been repeatedly detected in the sweat and other excretions. Thus, Bergeron and Lemaître§ found it in sweat, and Chatin in the serum of a blister. In large doses it often causes strangury, hæmaturia, and suppression of urine.

Susceptibility to arsenic varies both in the individual and in the species. Murrell and Ringer‖ found the frog very susceptible, as $\frac{1}{30000}$ part of the weight of the animal in arsenious acid produced complete paralysis in 108 minutes, while $\frac{1}{80000}$ part killed the frog on the third day. Dogs are susceptible. Ringer says the horse and sheep can take large doses. That statement, however, is not confirmed by such veterinary authorities as Wallis Hoare,¶ who writes: '. . . that the toxic dose in the horse is liable to great variations has been proved

* Ringer, 'Therapeutics,' p. 277.

† *Journal of Physiology*, vol. i., p. 247.

‡ Virchow's 'Archiv.,' Bd. xxxiv., p. 77.

§ *British and Foreign Medico-Chir. Rev.*, xlviii., 1871.

‖ Murrell, 'Pharmacology and Therapeutics,' p. 235.

¶ Wallis Hoare, 'Veterinary Therapeutics,' p. 281.

experimentally. In some instances even medicinal doses produce serious effects.' A similar result sometimes follows a moderate dose in the human subject, as pointed out by Farquharson* and others. Dr. Hunt showed that girls often required a larger dose than boys; while a child of five can take as much arsenic as an adult. Susceptibility also appears to vary in the same individual at different times.

MERCURY.

Mercury is an alterative, and most of its salts are germicide, antiseptic, and poisonous. It is an irritant to epithelium. Externally, blue ointment sometimes sets up a local dermatitis, while more irritant preparations are apt to vesicate. Given internally, it may cause dermatitis. Ringer† states that 'mercury salts are to some extent eliminated by the urine, by the mucous membrane of the intestines, and with the bile; indeed, they have been found in every secretion, physiological and pathological.' When absorbed through the skin it may cause diarrhœa. Small doses of blue pill and of calomel are said to be diuretic. The effects of mercury on the kidney are thus summarized by Professor Wood,‡ of Philadelphia: 'After death from irritant preparations of mercury, as first shown by Salkowsky, structural alterations abound in the kidneys. That the renal lesions may be produced by the non-irritant preparations of mercury has been shown by Dr. B. Silva (*Central. f. Klin. Med.*, vol. xix., 1888), who found true desquamative nephritis in dogs to which calomel had been given. For

* Farquharson, 'Therapeutics.' Fifth edition, p. 113.
† Ringer, *op. cit.*, p. 250.
‡ Wood, 'Therapeutics.' Ninth edition, p. 568.

a full discussion of the subject and its literature, see Virchow's 'Archiv.,' cxviii., 1889, where Dr. Felix Klemperer concludes that the successive changes in the kidneys are: excessive hyperæmia, parenchymatous nephritis, hæmorrhagic nephritis, with widespread degeneration of the epithelium.'

Susceptibility to mercury varies greatly in the individual. Brunton* mentions a case where salivation occurred from as little as a grain and a half of calomel, and from one-fiftieth of a grain of corrosive sublimate.

IODINE AND THE IODIDES.

Iodine is alterative, antiseptic, and poisonous. Applied externally, it acts as a strong epithelial irritant. It is eliminated from the body by the various organs of excretion, although its chief channel of exit is through the kidneys. It has been found in the sweat by Dr. R. W. Taylor,† Adamkiewicz, and others; and in the saliva by Professor Sèe.‡ Ringer§ says: 'Iodine has been detected in the blood, saliva, milk, and urine, even in the urine of the sucking child, whose mother was taking iodide of potassium.' As to the dermatitis due to the internal use of iodine, Nevins Hyde,‖ of Chicago, observes: 'There is no group of medicaments which is so often responsible for a cutaneous exanthem, and none in which the results are so dissimilar and severe.' As to the kidney, Wallis Hoare¶ mentions that large doses

* Brunton, *op. cit.*, p. 648.
† *American Journal Syph. and Dermat.*, 1873.
‡ *London Medical Record*, vol. i., p. 757.
§ Ringer, *op. cit.*, p. 137.
‖ 'Twentieth Century Practice of Medicine,' vol. v., p. 240.
¶ Wallis Hoare, *op. cit.*, p. 295.

sometimes cause hæmaturia in the dog. In small doses, as pointed out by Ringer and others, iodide of potassium has a diuretic action. Individual susceptibility to the action of iodine varies considerably. The clinical observation is familiar that extremely small doses of iodide will cause iodism in some persons.

From these facts we may draw the following general conclusions as to arsenic, mercury, and iodine, or of their compounds as used in practical medicine:

1. They are alterative, antiseptic, and poisonous.
2. They are epithelial irritants.
3. They are eliminated from the body by one or all of the various excreting organs.
4. They may cause multiple dermatitis.
5. In moderate doses they may cause diuresis or transient albuminuria; and in large doses, albuminuria, hæmaturia, and suppression of urine.
6. In large doses they have been shown experimentally to disorganize the kidneys in the lower animals, and a similar result often follows poisonous doses in man.
7. Their action appears to be greatly influenced by the susceptibility of the individual.

To which we may add:

8. They exercise an undoubted control over some skin diseases.

These drugs probably affect the skin in two ways: (1) *Indirectly*, through the influence of the general nutrition, or through the nerves. (2) *Directly*, by local action.

1. The *indirect* action on the skin through the general nutrition will not be dealt with here.

2. The *direct* local action on the skin of drugs given internally does not seem to have engaged the serious

attention of writers upon either dermatological or general therapeutics. If we may assume that a local effect is produced, the explanation may possibly be found in the antiseptic and irritant properties common to these drugs.

(*a*) *Antiseptic local action*, by the direct excretion of the drug through the cutaneous glands or papillæ; or, short of excretion, by its presence in the blood or lymph. In either way the antiseptic remedy may be assumed to control both primary and secondary invasions of microbes.

(*b*) *Irritant local action*.—We know that either arsenic, mercury, or iodine introduced into the system is capable of exciting a multiform dermatitis, and that in each case the drug may be detected in the excretions of the skin. It seems reasonable to suppose that the irritation set up by their local presence or by their actual excretion may give rise to reflex neuro-vascular activity. The resulting hyperæmia might destroy locally-developed micro-organisms by phagocytosis, and by flushing the skin with blood bearing an antiseptic drug.

In the particular case of arsenic, Dr. Radcliffe Crocker* says: 'That the action is mainly a local one is shown by the action in the treatment of psoriasis; for while under its use old patches often get well, new ones may form, even when the patient is fully under the influence of the drug. Its local action is further illustrated by its deposition in the form of a brownish-black pigmentation limited to the site of the diseased area. Possibly the greater instability of the diseased area may to some extent account for the apparent elective affinity of the arsenic.' Crocker also says, that in his belief 'arsenic acts directly on the skin, picking out and acting especially, if not entirely, on the diseased tissue, *i.e.*, in what

* Crocker, 'Diseases of the Skin.' Second edition, p. 36.

one may call a local manner ; or it may act as a stimulant to the peripheral nerves, and perhaps to the vaso-motor and trophic centres.'

The general position of dermatologists with regard to arsenic is expressed by Dr. Dühring,* of New York, as follows : ' Arsenic has long been used and held in high esteem as a remedy in the treatment of cutaneous diseases. It is proper to state, however, that at the present day there exists a great diversity of opinion concerning its actual value as a therapeutic agent against this class of diseases. Certain dermatologists claim to derive marked good from its employment in quite a large number of affections, while others of equal experience are inclined to place but little reliance upon its curative powers. Without entering at all into this discussion, it may be unhesitatingly said that it is a remedy of real worth and service in several very important cutaneous diseases, and that it may be combined with other remedies and used with good effect in certain other diseases of the skin, acting in those cases as a general tonic. It is the dermatologists' most valuable internal remedy in a large number of cases. But it must be skilfully employed, and the cases, moreover, must be selected, if we would expect satisfactory results.'

This uncertainty of arsenic in skin diseases may, to some extent, be explained by its varying elimination —that is to say, if we assume that its therapeutic effect is partly due to direct local action. Suppose we give a patient five minims of liquor arsenicalis, we have no guarantee that it will not all be carried out of the body forthwith by its usual channel of exit, the kidney. The question then naturally arises, whether it would

* Wood, *op. cit.*, p. 556.

not be possible to ensure that the drug should reach the organ it is desired to affect. We may seek to attain that end by exciting the action of the skin in two ways: (1) by drugs, such as jaborandi; and (2) by local determinants and stimulants, such as the wet pack, hot baths, frictions, and various stimulating applications.

There can be little doubt that mercury has a direct local action on the lesions of syphilis. When given internally, one would think it a simple matter to determine its action to the skin by baths and stimulating frictions. The clinical observation is familiar that a tar or a chrysophanic ointment often has a good effect upon syphilides. Although this good result may be due to a variety of causes, such as the local destruction of non-specific microbes, yet it would be to some extent explained if we imagine a determination to the skin of the mercury circulating in the blood. In some of the German spas, again, a main feature is the prolonged hot bathing. The success of that method of treatment of syphilis may perhaps be partly due to the determination of internal specific remedies to the skin.

In the case of iodine the efforts of the physician will probably be to guide the excretion of the drug to channels other than the skin, upon which it often has disastrous effects.

It may be here noted that the exact etiology of the iodine rash is still doubtful. Pringle* says that renal disease and cardiac weakness strongly predispose to the occurrence of such rashes, owing to the deficient elimination of the drug. If we accept that view, it seems hardly possible to avoid the conclusion that the skin is damaged by the vicarious elimination of the

* Fowler, 'Dictionary of Medicine;' art., 'Medicinal Rashes.

iodine. Professor Unna* admits that traces of iodine or iodides may be found in the sweat, saliva, and other excretions. He rejects the idea, however, that there is such a thing as a follicular dermatitis set up by iodine. But while he denies a primary alteration of follicles, he affirms the existence of a local and somewhat superficial inflammatory focus. This histological condition might be accounted for if we assume excretion of the irritant iodine to have taken place through the epithelial covering of a dermal papilla. Active hyperæmia, stasis, exudation, and the local development of micro-organisms, would explain the further development of the iodine rash.

Stimulation, it need hardly be said, is a right-hand weapon of the dermatologist. Under ordinary conditions the application of a stimulus to the skin causes a local determination of normal blood. But when a drug is circulating in the system the stimulated skin becomes flushed with blood bearing an agent which may be remedial or otherwise. In this way the writer has sought to emphasize the action of thyroid gland upon the skin by the addition of sudorifics. Thus, four cases of moderate but well-marked congenital ichthyosis in children have been treated thrice daily with fifteen minims of tincture of jaborandi, together with five to fifteen grains of the dried gland. For the sake of convenience, a tabloid has lately been substituted containing one-tenth of a grain of pilocarpine to five grains of gland. Results have been so far rapid and excellent, and in one case the skin has returned to its normal appearance, except for a tendency of the face to get dirty and a shiny look of the palms, which, however, feel soft and perspire freely.

* Unna, 'Histopathology,' p. 107.

Another point suggested in the course of this inquiry is whether the internal drugs used in skin practice may not have an injurious effect upon other organs. We know that, as a rule, arsenic acts on the skin only after it has been administered for some time, or, as the phrase goes, has 'accumulated' in the system. May it not be that the kidney, the usual channel of exit, has ceased to eliminate the drug owing to some form of epithelial disablement? We know that the long-continued excretion of the gouty poison is able to set up kidney disease. Arsenic is obviously a more powerful irritant of epithelium than the poison of gout, and there is no apparent reason why the long-continued elimination of arsenic should not also cause a nephritis. On account of its irritating nature, few dermatologists would venture to use arsenic externally, except as a caustic. Yet the drug is given daily as an internal remedy, and when once introduced into the body, must be sooner or later eliminated by organs not a whit less delicate than the skin—organs, moreover, which are constructed upon a similar anatomical type, and which are known to be invariably damaged by poisonous doses of the drug. Nor is there any reason, so far as one can see, for assuming any essential difference between the epithelium of the skin and of the kidney in their response to irritants. Cantharides raises a blister when applied to the skin, and often sets up a hæmaturia during its after-elimination from the body. Here skin and kidney react to a common irritant, just as happens in the case of many other specific drugs and poisons capable of causing dermatitis.

Nor is it easy to see how the long-continued excretion of so irritant a drug as iodine can be thrown upon the kidneys with impunity. As already pointed out, many

writers have attributed iodism to defective kidney action, but hitherto it does not appear to have been suggested that the iodine may have irritated the kidney, as it were, into a state of revolt, so that the vicarious elimination of the drug has been thrown upon other organs. Ringer says some writers hold that iodide of potassium given in large doses for long periods may produce albumen in the urine, and even Bright's disease. Wood* also remarks that 'during its passage through the kidneys iodine undoubtedly exerts an influence upon those organs, as is shown by its producing albuminuria at times.' Indeed, it is a matter of common observation that albuminuria may occur also during a course of mercury or of arsenic. May it not be that we too readily assume that the albuminuria in these instances is purely functional? When albumen occurs in the course of scarlet-fever it is commonly regarded as a possible symptom of impending kidney change.

A minor proposition of the foregoing paper is that certain internal remedies used in skin practice, being of a powerful irritant nature towards epithelium, may in some instances damage, not only the skin, but other eliminating organs as well. Its main proposition, however, is that the action of internal remedies upon the skin might perhaps be made more energetic and more constant by stimulating the activity of that organ. It seems not unlikely that many of our present methods of treatment act by the determination of blood, or of blood-borne remedies, to the skin. If such be the case, then, as so often happens, empirical practice has found out for itself the path of true knowledge.

* Wood, *op. cit.*, p. 585.

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